ORIGINAL ARTICLE

Efficacy of Intermediate Theta Burst Versus High-Frequency Repetitive Transcranial Magnetic Stimulation in Treatment-Resistant Depressive Patients Using Electroencephalography

Mahmoud Bagheri [1], Javad Hosseini Nejad [1*], Hassan Tavakoli [1, 2, 3*], Seyed Abbas Tavallaie [4], Aliakbar Karimi Zarchi [5, 6]

[1] *Neuroscience Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran*

[2] *Radiation Injuries Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran*

[3] *Department of Physiology and Biophysics, Baqiyatallah University of Medical Sciences, Tehran, Iran*

[4] *Behavioral Sciences Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran*

[5] *Health Research Center, Life Style Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran*

[6] *Department of Epidemiology and Biostatistics, Baqiyatallah University of Medical Sciences, Tehran, Iran*

*Corresponding Authors: Javad Hosseini Nejad, Hassan Tavakoli
Email: javadhoseini1360@gmail.com, tavakoli6402@gmail.com

Received: 25 November 2023 / Accepted: 26 December 2023

Abstract

Purpose: This study was conducted to evaluate the comparative effectiveness of repetitive Transcranial Magnetic Stimulation (rTMS) and intermittent Theta Burst Stimulation (iTBS), in Treatment-Resistant Depression (TRD) patients using resting-state Electroencephalography (EEG). iTBS is a novel form of magnetic stimulation with the potential to produce similar anti-depressant effects but in a much shorter time.

Materials and Methods: In two stimulation protocols, 78 patients with TRD received 20 sessions. Depression symptoms were assessed based on the changes in the Hamilton Depression Rating Scale (HAM-D) and Beck Depression Inventory (BDI-II) scores at baseline, after the last session, and at 4 weeks after treatment. Resting-state EEG was measured at baseline and after the last session. EEG power spectrum was extracted and power changes were evaluated statistically.

Results: There was no significant difference in response and remission rates between the two groups. Following 10 Hz rTMS and iTBS, the clinical indexes improved by 48.5 ± 19.8 % (p-value < 0.05) and 50.4 ± 21.7 % (p-value < 0.05), respectively. There was a significant reduction in the mean depression scores for both treatment groups ($p < 0.05$). Following treatment, TRD patients showed considerable enhancement in gamma power at the left DLPFC site (F3, F5, and F7 electrode) in the iTBS group and significant increases in delta power at the F3 and F7 electrode sites in the 10 Hz rTMS group.

Conclusion: iTBS provides clinical advantages, which showed that the results did not contrast altogether with results from a standard course of rTMS treatment. It might be invaluable from a clinical, benefit, and understanding perspective. Biomarkers of clinical outcomes such as resting-state brain activity measured with EEG may save individuals worthless treatment and moderately limited clinical assets.

Keywords: Transcranial Magnetic Stimulation; Treatment-Resistant Depression; Intermittent Theta Burst Stimulation; Electroencephalography.

DOI:

1. Introduction

Depression is a range of mental health disorders characterized by decreased mood and loss of interest or pleasure that affects about 3.4% of the world population [1]. Today, the first-line medication for depression includes pharmacotherapy and psychotherapy. However, antidepressant drugs do not have the efficiency to relieve about one-third of patients and they are bearing Treatment-Resistant Depression (TRD) [2]. TRD refers to when a patient does not respond to at least one antidepressant trial of adequate duration and doses. Thus, TRD patients need new alternative management [3].

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive method for the stimulation of the human brain [4]. The process of stimulation is evoked by inducing a transitory and robust magnetic field through the application of a brief electrical current within a magnetic coil. rTMS is used for mental disorders diagnosis and treatment [5]. rTMS delivers repeated localized electrical pulses across the scalp in fully conscious human subjects [6]. These pulses change the excitability of cortical neurons and enhance or suppress neural activity, change the release of neurotransmitters, and change in blood flow of the targeted site which causes a change in related functions and behaviors and generates short and long-acting therapeutic effects [7, 8].

The Dorsolateral Prefrontal Cortex (DLPFC) is an area accepted in the treatment of rTMS in depression [9]. For example, Corlier *et al*. reported that a 30-session treatment course of 10 Hz rTMS in left-side DLPFC improves psychomotor speed and cognitive control in Major depressive Disorder (MMD). Similarly, high-frequency (20 Hz) rTMS decreased the depression severity, enhanced accuracy, and decreased reaction time in the MMD [10]. The conventional, US Food and Drug Administration (FDA)-approved protocol requires about 37.5 min of stimulation per session. Long session lengths restrict treatment capacity and increase the cost per session. Reduced session lengths could therefore improve the accessibility and cost-effectiveness of rTMS [11].

Intermittent Theta Burst Stimulation (iTBS) is an alternative rTMS protocol that may have the potency of effective treatment for TRD was approved by the FDA and showed beneficial effects in several studies. iTBS as a novel TMS protocol induces more rapid and long-lasting effects on neural excitability especially synaptic transmission enhancement in a shorter time than rTMS. The iTBS protocol entails the administration of bursts of gamma frequency (~50 Hz) pulses, lasting only a few cycles, interspersed at regular intervals of theta frequency (5 Hz). Treatment utilizing iTBS requires approximately 180 seconds per session, which is significantly shorter in comparison to the 2400 seconds per session required for traditional rTMS and, as a result, presents a potential avenue for cost-effectiveness [12-14].

Despite its clinical progress, the effect of rTMS on neuroplasticity remains unknown. In addition, clinicians prescribe rTMS after thorough assessment and extensive trial and error testing to improve diagnosis and manage outcomes. Resting-state EEG spectral power in different frequency bands may be useful for depression diagnosis [15]. Previous studies demonstrated a robust relationship between EEG markers of TRD and rTMS administration. For example, EEG spectral features especially alpha and theta frequency bands have been the most frequent features in previous research [16]. Therefore, EEG acquisitions before and after treatment may yield novel observations that enhance our understanding of the mechanisms underlying magnetic stimulation. These observations may inform novel treatment protocols. Furthermore, the identification of brain-based biomarkers of early therapeutic response remains an important and unanswered question in the field. In addition, less clear evidence for iTBS electrophysiological neural effects in TRD has been provided. Therefore, the present study investigated the neural correlates of rTMS and iTBS based on resting-state EEG in TRD patients.

The aim of the present study was to detect the neuroplasticity effects of rTMS on patients diagnosed with TRD using a clinical EEG system. Furthermore, the effects of the two different rTMS protocols (10 Hz rTMS, and iTBS) on EEG power spectral analysis were assessed in patients with TRD.

2. Materials and Methods

2.1. Participants

Seventy-eight depression patients (36 males and 42 females; 47.46 ± SD 12.65 years old) participated in this retrospective experiment. All patients had a primary diagnosis of TRD (defined as at least two failed responses to antidepressant medication) during the current major depressive episode. No patients

started any new medications in this experiment period. The exclusion criteria for this experiment consisted of a documented medical history of drug abuse or addiction within the preceding three-month period, implantation of any medication pump in the body such as a cardiac pacemaker, active suicidal intent, and the diagnosis of any mental or neurological disorder. Patients were randomly divided into two groups: 10 Hz rTMS, and iTBS over the left DLPFC. The two groups were not fundamentally different for relevant parameters (age, gender, and depression severity).

2.2. Clinical Assessments

All participants were selected with a major depressive episode by their recourse to the psycho-therapist or it was introduced by their own doctor. 17-item Hamilton Depression Rating Scale (HAM-D), and Beck Depression Inventory (BDI-II) were used to assay the severity of depression [17, 18]. All participants who had HAM-D and BDI-II scores ≤20 before rTMS were excluded from the experiments. Participants were assessed at baseline, after completion of treatment, and 4 weeks after treatment.

2.3. Treatment Procedure

The rTMS was used through an expert rTMS operator using a Neurosoft MS/D stimulator with the FEC-02-100 coil (Neurosoft, Ivanovo, Russia). A liquid-cooled figure-eight-shaped magnetic coil was used to deliver biphasic 280 μs impulses for all patients. All subjects underwent 20 treatment sessions (5 consecutive days per week for 4 consecutive weeks) over left DLPFC. The stimulation parameters of the two protocols used in the study are presented in Table 1. The total duration of the 10 Hz rTMS protocol lasted 37 min and 30 seconds, and iTBS was just over 3 minutes. DLPFC of the left hemisphere was localized according to the international 10-20 system equivalent to F3 electrode location, respectively. The coil was positioned tangential to the scalp at 45° relative to the midline. Stimulation intensity for both rTMS and iTBS, before the commencement of treatment, was determined at 120% Resting Motor Threshold (RMT) over the primary motor cortex for every subject. RMT for the Abductor Brevis (APB) muscle was measured using single-frequency TMS using standard published methods and visual visualization of APB movements. MT is defined as the minimum stimulus intensity necessary to elicit an overt motor response in the APB for ⩾50% of applied stimuli [19].

2.4. EEG Acquisition Procedure

The brain waves were recorded at baseline and after treatment for 10 minutes while the person had their eyes closed. EEGs were measured from 32-channel eWave32 amplifier electrodes. These electrodes are made of Ag/GgCl and are passive. They follow the 10-20 system and have a reference electrode at the FCz spot and a ground electrode at the AFz spot. The amplifier, created by ScienceBeam, can collect 1,000 samples every second. This lets us accurately examine how the brain processes information over time. The impedances were lower than 5,000 ohms. We used EEGLAB, running on MATLAB [R2021b (9.11), The Mathworks, Inc.] to remove unwanted sounds and distortions from the EEG signals. The rate at which data was collected was decreased to 250 times per second. The information was filtered using a special filter to allow only certain frequencies between 0.5 Hz and 50 Hz to pass through. Then, the faulty channels

Table 1. Treatment parameters

Treatment Group	Stimulation frequency	Train duration (s)	Trains per session	Inter-train Interval (s)	Stimulation intensity (%RMT)	Stimulation location	Pulses per session	Total Sessions	Total pulses
10Hz rTMS	10 Hz	4	75	26	100	Left DLPFC	3000	20	60000
iTBS	3 × 50 Hz bursts; repeated at 5 Hz	1.8	20	8	80	Left DLPFC	600	20	12000

DLPFC: Dorsolateral Prefrontal Cortex; Hz: Hertz; iTBS: intermittent Theta Burst Stimulation; RMT: Resting Motor Threshold; rTMS: repetitive Transcranial Magnetic Stimulation; s: Seconds.

were automatically found and fixed by filling in missing data. The Independent Component Analysis (ICA) method was used to automatically get rid of unwanted things like eye movements, heart activity, and muscle activity. Additionally, a machine was used to reject periods that had signal strengths greater than 100 μV or less than -100 μV. In the end, the data was adjusted to compare it to a typical value. After removing the redundant information from the data, absolute power analysis (μV2) was performed using a custom MATLAB script. The frequencies we focus on are delta (1 to 4 Hz), theta (4 to 8 Hz), alpha (8 to 13 Hz), beta (13 to 30 Hz), and gamma (30 to 45 Hz). Frequency bands were analyzed individually for each electrode of interest. Simply put, brain data is used to calculate changes in the power of different brain cells after an rTMS session. For fast Fourier transform (FFT) analysis, the Bonferroni method is applied to correct for multiple comparisons across four frequency bands. Following the procedure based on the previous research (ref), to reduce the amount of data and statistical analysis of frequency power, electrodes from the left DLPFC region (F3, F5, F7) were selected for band power analysis. The power change for each bandwidth relative to the baseline value is calculated using the following formula: [(post X - pre X)/pre X] × 100, where X is the frequency power value at the electrode site. The average electrode force around F3, F5, and F7 was calculated for statistical analysis [20].

2.5. Statistical Analysis

Differences in TMS effects between two conditions (i.e. before and after TMS), and between the two stimulation methods, were analyzed separately. Therefore, the statistical analysis of critical energy images is divided into the first level (subject level) and the second level (group level). Data were found to meet the normality assumption using the Kolmogorov-Smirnov test. We performed the Chi-Square test ($\chi 2$) and independent sample t-tests to compare demographic characteristics and baseline depression severity. Clinical improvement was compared between the two treatment groups using the Pearson chi-square test. Paired t-tests were performed to determine changes in the HAM-D and BDI-II from baseline to week 4 in both treatment groups. For all analyses, the statistical significance was set at $P < 0.05$.

To analyze the long-term changes in the power value of the frequency band in each electrode before and after each treatment group, a t-test with Bonferroni correction was applied to 3 electrodes between the pre and post- EEG data.

3. Results

3.1. Changes in Clinical Indexes

There were no differences in demographic (age and gender) as well as clinical characteristics (HAM-D, BDI-II). Demographic characteristics between 10 Hz rTMS and iTBS groups are summarized in Table 2.

Table 2. Demographic characteristics between 10 Hz rTMS and iTBS groups

Treatment Group / Factor	Total	10 Hz rTMS	iTBS	p-value
Number (F/M)	78(42/36)	43(22/21)	35(20/15)	0.76
Mean ± SD age [years]	47.46 ± 12.65	47.02 ± 9.27	48.01 ± 14.01	0.62

Adverse events did not happen in this study. Specifically, there was no admission of seizures or manic episodes in the subjects. Headache was a common side effect in subjects, followed by mild neck pain. No neck pain was reported after starting to use the air-travel style pillow. Side effects are self-limiting and do not require any therapy.

Differences in baseline HAM-D and BDI-II scores were not clinically significant across the two groups (Table 3). For patients who had undergone both 10 Hz rTMS and iTBS protocols, the average HAM-D BDI-II scores significantly reduced after treatment. Following 10 Hz rTMS, the HAM-D score (28.8 ± 5.9 → 15.5 ± 6.8) and the BDI_II (32.1 ± 6.9 → 15.8 ± 5.9) improved by 46.2 ± 17.3 % (p-value < 0.05) and 50.8 ± 21.2 % (p-value < 0.05), respectively. Also, for iTBS group, the HAM-D score (27.6 ± 6.3 → 14.2 ± 6.2) and the BDI_II (31.2 ± 8.3 → 14.9 ± 6.9) improved by 48.5 ± 19.4 % (p-value < 0.05) and 52.2 ± 23.6 % (p-value < 0.05), respectively. There was no

Table 3. Difference between HAM-D, and BDI-II scores in 3 studies groups before, after, and 4 weeks after treatment

	TMS	Baseline		After Treatment		4 Weeks after Treatment	
		mean	SD	mean	SD	mean	SD
HAM-D	iTBS	27.6	6.3	13.9	5.6	14.2	6.2
	10 Hz	28.8	5.9	15.2	6.5	15.5	6.8
P value		0.32		0.28		0.31	
BDI-II	iTBS	31.2	8.3	14.5	6.6	14.9	6.9
	10 Hz	32.1	6.9	16.2	5.5	15.8	5.9
P value		0.29		0.27		0.32	

significant difference in response status between the 10 Hz rTMS group and the iTBS group.

Responders were patients who had a decrease of 50% or more from their starting scores to their scores after treatment. Remitters were patients with a HAM D post score of 7 or less, and BDI II of 13 or less [21]. Table 4 displays the rates of how well the treatment worked and how many people got better after completing it. There was no significant difference in response rates or remission rates between the groups in any of the analyses.

Table 4. Treatment outcomes for the standard 10 Hz rTMS group and iTBS group

		10 Hz rTMS n(%) n=43	iTBS n(%) n=35	P value
HAM-D	Response	21 (48.80%)	16 (45.70%)	0.32
	Remission	13 (30.20%)	11 (31.40%)	0.39
	No response	9 (21.00%)	8 (22.90%)	0.22
BDI-II	Response	20 (46.50%)	17 (48.60%)	0.35
	Remission	13 (30.20%)	10 (28.50%)	0.42
	No response	10 (23.30 %)	8 (22.90%)	0.26

3.2. TMS Related Power Changes

Paired t-tests demonstrated significant increases in delta power at the F3 ($t43 = -4.928$, $p < 0.0001$) and F7 ($t43 = -3.809$, $p < 0.0001$) electrode sites following 10 Hz rTMS. Resting delta powers pre- and post-10 Hz rTMS at these sites are depicted in Figure 1a. Also, significant increases of gamma power at the F3 ($t35 = -6.012$, $p < 0.0001$), F5 ($t35 = -4.152$, $p < 0.0001$), and F7 ($t35 = -3.768$, $p < 0.0001$) electrode sites following iTBS were demonstrated. Resting gamma powers pre- and post-iTBS at these sites are depicted in Figure 1b.

Correlation analysis between the average power changes (%) of left DLPFC three electrodes (F3, F5, and F7) for each frequency band and the change (%) in two clinical assessments of the HAM-D and BDI-II were explored. A statistically significant negative correlation was observed between the change in the clinical assessments (from baseline to week four) and the average power changes in the delta frequency band for the 10 Hz rTMS group. Similarly, for the iTBS group, a significant negative correlation was indicated between the change in two HAM-D and BDI-II scores and the average power changes in the gamma frequency band. Scatterplots of these two significant correlations are presented in Figure 2.

4. Discussion

This study was designed to compare the efficacy of 10 Hz rTMS, and iTBS in seventy-eight subjects suffering from TRD. The results showed that in the two treatment groups, demographic characteristics, diagnosis, and baseline disease severity were consistent with each other.

This research indicated that both types of therapy were effective in clinical settings. This resulted in a significant reduction in depressive symptoms as measured by the HAM-D and BDI-II. The response and remission rates were not significantly different in both groups. The results strongly indicate that iTBS is comparable to standard 10 Hz rTMS in decreasing depressive symptoms. This is consistent with Blumberger's earlier discovery of the equivalence between iTBS and 10 Hz rTMS [11].

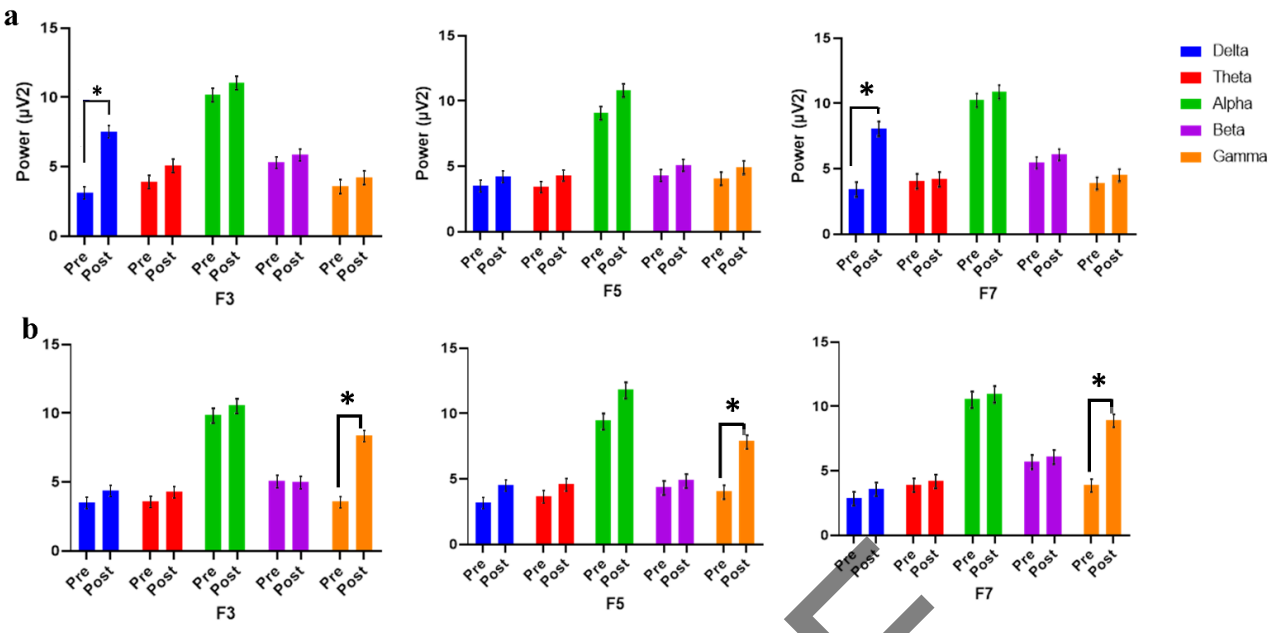

Figure 1. TMS-related power changes at F3, F5, and F7 electrodes. (a) the power pre- and post-treatment with 10 Hz rTMS to the left DLPFC. (b) the power pre- and post-treatment with iTBS to the left DLPFC. *: significant findings

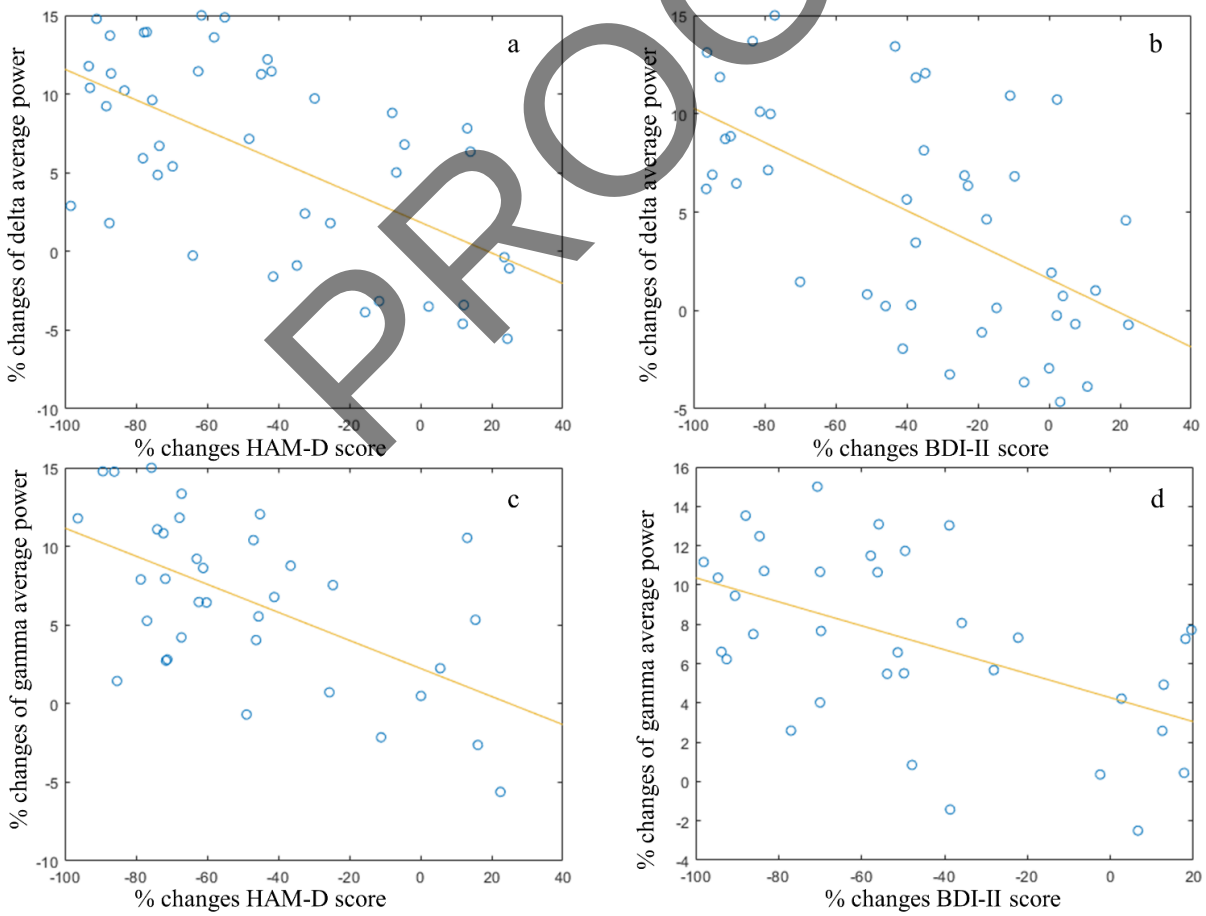

Figure 2. Scatterplots showing clinical correlations. (a and b) correlations between the average delta power changes (%) at F3, F5, and F7 electrodes sites and the score in HAM-D (r = -0.57, p = 0.004) and BDI-II (r = -0.53, p = 0.006) after 10 Hz rTMS treatment. (c and d) correlations between the average gamma power changes (%) at F3, F5, and F7 electrodes sites and the score in HAM-D (r = -0.56, p = 0.003) and BDI-II (r = -0.51, p = 0.004) after iTBS treatment

Similarly, a recent study by Giam *et al.* gave patients iTBS and standard rTMS treatments for 4 weeks and checked if their condition improved after 4 weeks [22]. They observed considerable improvement, and it remained the same after 8 weeks. The current study shows that iTBS treatment helped patients, and the results were similar to regular rTMS treatment on most measures. Equivalence like this would allow iTBS shorter treatment sessions. This means we could treat more patients without affecting treatment effectiveness. It would also make treatment more cost-effective. Overall, these findings show that rTMS and iTBS may have positive effects on treating depression, offering alternatives to traditional treatment.

Neuroimaging evidence showed abnormal brain activity in several brain regions and neural circuits during depression. These activities may be due to abnormality in the neurotransmitter cycle such as serotonin reuptake thus antidepressant approaches target these molecules and pathways to normalized brain activity. Thus, depression is an interesting disease for rTMS administration because depression is related to changes in the brain network activity especially in the frontal region [23]. For example, George *et al.* showed that rTMS administration by changing in left DLPFC activity improves the depression scales in HMA-D and BDI-II compared to the sham-operated group [24]. These results are in line with Tuinstra *et al.* who reported that anxiety in TRD was reduced after rTMS which indicated the critical role of left DLPFC in symptoms of TRD, especially anxiety [25]. Isenberg *et al.* reported that symptoms of TRD in attention to HAM-D score alleviated through low and high-frequency rTMS in right and left DLPFC, respectively, after 4 weeks of treatment [26]. On the other hand, rTMS of the DLPFC with high frequency leads to modifying the activity of neural circuits. It also affects the deeper regions of the brain with synaptic connections and modulates the mesolimbic function of the neural circuit involved in mood [27]. In addition, stimulating the inhibitory neurons of the right posterior prefrontal cortex of the brain with low frequency due to the influence of the subcortical areas related to the limbic structure, such as the amygdala, leads to hyperpolarization and a decrease in neuronal activity, so induced an antidepressant effect [28]. It is proved that iTBS can similarly improve depression symptoms. Our results confirmed these findings and showed that the administration of 10 Hz rTMS and iTBS to left DLPFC ameliorated depression symptoms. It seems that either rTMS or iTBS, due to its potential for DLPFC pathways modulation, induced therapeutic effects.

4.1. TMS-Related Power Changes

The effects of two types of magnetic stimulation on brain activity in patients with treatment-resistant depression were measured. They were either relaxed or awake during the investigation. From looking at the scalp, the areas that responded the most were found near the rTMS target spot. In past research, Valiulis *et al.* found that using 1Hz rTMS on the right prefrontal area caused a significant increase in brain wave activity in the alpha, theta, and beta frequency ranges in patients with depression [29]. Another study by Noda *et al.* also observed similar results. The study showed that using a specific type of brain stimulation called 20Hz rTMS on the left prefrontal area increased brain activity in a certain frequency range (gamma power) in depressed patients. This increase in brain activity was found at the site where the stimulation was applied and also linked to an improvement in depressive symptoms [30].

Previous studies reported a direct correlation between depression and band power and depression symptoms. For example, Lin *et al.* demonstrated a positive relationship between depressive symptoms and alpha band power in patients with depressive disorders [30]. Additionally, some previous studies have reported that resting-state EEG-recorded theta, alpha, and gamma band powers predicted therapeutic response to antidepressants in patients with depressive disorders [31]. Our results were in line with these findings. We show a significant increase in delta power following 10 Hz rTMS gamma power following iTBS. The pathological conditions inhibit the neural activity in the cortex and delta wave as a marker of normal brain activity will be suppressed. Thus, we can hypothesize the increase in delta power is due to the therapeutic effect of rTMS in TRD patients. However, changes in EEG power also have been impacted by TMS treatment. Our findings indicated that the improvement in TRD symptoms was related to an increase in delta power from the initial EEG compared to the follow-up EEG. These findings were in agreement with Voetterl *et al.* [32]. This effect may have been caused by higher stress levels before the first rTMS session. This would activate the sympathetic nervous system and reduce low-frequency power.

The lack of significant effects in other bands after rTMS and iTBS may be due to the overall highly interindividual changes in all of the powers of the EEG bands except for the delta and gamma bands with respect to the increase in power after 10 Hz rTMS and iTBS stimulation, respectively.

In the correlation analyses, an increase in resting delta and gamma power at the left prefrontal area was significantly correlated with the improvement of clinical symptoms measured with the HAM-D and BDI-II following 10 Hz rTMS and iTBS treatments, respectively. The lack of significant effects in other bands after rTMS and iTBS may be due to the overall highly interindividual changes in all of the powers of the EEG bands except for the delta and gamma bands with respect to the increase in power after 10 Hz rTMS and iTBS stimulation, respectively

4.2. Limitation

The limitation of the research is the lack of a placebo control group, the lack of blinding subjects, and the operator, thus suggesting that randomized controlled studies be conducted in future studies. Also, one of the limitations is the small sample size. Among the reasons for these limitations, we can list the ineligibility of the entry criteria, uncertainty about the treatment method, lack of coordination with the process of the sessions, or the simultaneous use of other treatment methods.

In this study, the analysis focused only on the F3, F5, and F7 electrode sites. Therefore, we couldn't investigate the effects of rTMS on other areas. Finally, this study looked at what happens after rTMS stimulation

5. Conclusion

rTMS is a safe and effective treatment for treatment-resistant depression. It has very few negative side effects. This study examined how rTMS affects brain activity in patients with TRD, using two different ways of stimulating the brain, called 10 Hz rTMS and iTBS, both targeting the left DLPFC. To sum it up, the iTBS treatment is just as effective and acceptable as the standard 10 Hz rTMS treatment for TRD. An ordinary iTBS treatment session, including setup, lasts about 5-10 minutes. In contrast, a standard 10 Hz rTMS session takes about 40 minutes. Hence, iTBS can increase the number of patients treated per machine, per day by up to four times.

Acknowledgments

The authors received no financial support for this research, authorship, or publication of this article.

References

1- Eugene S Paykel, "Basic concepts of depression." *Dialogues in clinical neuroscience*, (2008).

2- Dawn F Ionescu, Jerrold F Rosenbaum, and Jonathan E Alpert, "Pharmacological approaches to the challenge of treatment-resistant depression." *Dialogues in clinical neuroscience*, (2015).

3- Maurizio Fava, "Diagnosis and definition of treatment-resistant depression." *Biological psychiatry*, Vol. 53 (No. 8), pp. 649-59, (2003).

4- Mahboubeh Masoumbeigi *et al.*, "Altered Amplitude of Low-Frequency Fluctuations of rs-fMRI Signal followed by rTMS Analgesic Effects in Non-Specific Chronic Low Back Pain (CLBP) Patients." *Journal of Biomedical Physics and Engineering*, (2022).

5- Mahboubeh Masoumbeigi *et al.*, "rTMS Pain Reduction Effectiveness in Non-specific Chronic Low Back Pain Patients using rs-fMRI Functional Connectivity." *Journal of Medical and Biological Engineering*, Vol. 42 (No. 5), pp. 647-57, (2022).

6- Hassan Tavakoli and Arsalan Heidarpanah, "Designing a circular coil of repetitive transcranial magnetic stimulation at frequencies of 0.5 and 1 Hz using CST studio suite software and comparison of results with theoretical calculations." *Biomedical and Biotechnology Research Journal (BBRJ)*, Vol. 6 (No. 3), pp. 382-86, (2022).

7- Janna Marie Hoogendam, Geert MJ Ramakers, and Vincenzo Di Lazzaro, "Physiology of repetitive transcranial magnetic stimulation of the human brain." *Brain stimulation*, Vol. 3 (No. 2), pp. 95-118, (2010).

8- Hassan Tavakoli and Arsalan Heidarpanah, "Literature review of the efficacy of repetitive transcranial magnetic stimulation on epilepsy." *Iranian Journal of Child Neurology*, Vol. 17 (No. 1), p. 9, (2023).

9- Yoshihiro Noda *et al.*, "Neurobiological mechanisms of repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex in depression: a systematic review." *Psychological medicine*, Vol. 45 (No. 16), pp. 3411-32, (2015).

10- Fatemeh Asgharian Asl and Ladan Vaghef, "The effectiveness of high-frequency left DLPFC-rTMS on depression, response inhibition, and cognitive flexibility in

female subjects with major depressive disorder." *Journal of Psychiatric Research*, Vol. 149pp. 287-92, (2022).

11- Daniel M Blumberger *et al.*, "Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial." *The Lancet*, Vol. 391 (No. 10131), pp. 1683-92, (2018).

12- Romain Duprat *et al.*, "Accelerated intermittent theta burst stimulation treatment in medication-resistant major depression: a fast road to remission?" *Journal of affective disorders*, Vol. 200pp. 6-14, (2016).

13- Alexandria Pabst, Shannon Proksch, Butovens Mede, Daniel C Comstock, Jessica Marie Ross, and Ramesh Balasubramaniam, "A systematic review and meta-analysis of the efficacy of intermittent theta burst stimulation (iTBS) on cognitive enhancement." *Neuroscience & Biobehavioral Reviews*, Vol. 135p. 104587, (2022).

14- Adriano H Moffa, Tjeerd W Boonstra, Ashley Wang, Donel Martin, Colleen Loo, and Stevan Nikolin, "Neuromodulatory effects of theta burst stimulation to the prefrontal cortex." *Scientific data*, Vol. 9 (No. 1), p. 717, (2022).

15- Mahsa Soufineyestani, Dale Dowling, and Arshia Khan, "Electroencephalography (EEG) technology applications and available devices." *Applied Sciences*, Vol. 10 (No. 21), p. 7453, (2020).

16- Elias Ebrahimzadeh, Mostafa Asgarinejad, Sarah Saliminia, Sarvenaz Ashoori, and Masoud Seraji, "Predicting clinical response to transcranial magnetic stimulation in major depression using time-frequency EEG signal processing." *Biomedical Engineering: Applications, Basis and Communications*, Vol. 33 (No. 06), p. 2150048, (2021).

17- Max Hamilton, "A rating scale for depression." *Journal of neurology, neurosurgery, and psychiatry*, Vol. 23 (No. 1), p. 56, (1960).

18- Aaron T Beck, Robert A Steer, and Gregory Brown, "Beck depression inventory–II." *Psychological assessment*, (1996).

19- Georgios Mikellides, Panayiota Michael, Lilia Psalta, Teresa Schuhmann, and Alexander T Sack, "A retrospective naturalistic study comparing the efficacy of ketamine and repetitive transcranial magnetic stimulation for treatment-resistant depression." *Frontiers in psychiatry*, Vol. 12p. 784830, (2022).

20- Premysl Vlcek, Martin Bares, Tomas Novak, and Martin Brunovsky, "Baseline difference in quantitative electroencephalography variables between responders and non-responders to low-frequency repetitive transcranial magnetic stimulation in depression." *Frontiers in psychiatry*, Vol. 11p. 83, (2020).

21- Frank P MacMaster *et al.*, "Repetitive transcranial magnetic stimulation in youth with treatment resistant major depression." *Frontiers in psychiatry*, Vol. 10p. 170, (2019).

22- Andrew Giam *et al.*, "Comparing theta burst stimulation with standard left high frequency transcranial magnetic stimulation in the treatment of depression in a randomized controlled study: a preliminary comparison study." *Journal of Affective Disorders Reports*, Vol. 5p. 100162, (2021).

23- Brendan D Hare and Ronald S Duman, "Prefrontal cortex circuits in depression and anxiety: contribution of discrete neuronal populations and target regions." *Molecular psychiatry*, Vol. 25 (No. 11), pp. 2742-58, (2020).

24- Mark S George *et al.*, "A controlled trial of daily left prefrontal cortex TMS for treating depression." *Biological psychiatry*, Vol. 48 (No. 10), pp. 962-70, (2000).

25- Dan Tuinstra *et al.*, "Treatment of anxiety symptoms in patients receiving rTMS for treatment resistant depression." *Psychiatry Research Communications*, Vol. 2 (No. 1), p. 100014, (2022).

26- Keith Isenberg *et al.*, "Low frequency rTMS stimulation of the right frontal cortex is as effective as high frequency rTMS stimulation of the left frontal cortex for antidepressant-free, treatment-resistant depressed patients." *Annals of Clinical Psychiatry*, Vol. 17 (No. 3), pp. 153-59, (2005).

27- PENG Zhengwu *et al.*, "Mechanism of repetitive transcranial magnetic stimulation for depression." *Shanghai archives of psychiatry*, Vol. 30 (No. 2), p. 84, (2018).

28- Marcelo T Berlim, Frederique Van den Eynde, and Z Jeff Daskalakis, "Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: a meta-analysis of randomized, double-blind and sham-controlled trials." *Neuropsychopharmacology*, Vol. 38 (No. 4), pp. 543-51, (2013).

29- Vladas Valiulis, Giedrius Gerulskis, Kastytis Dapšys, Giedre Vištartaite, Aldona Šiurkute, and Valentinas Mačiulis, "Electrophysiological differences between high and low frequency rTMS protocols in depression treatment." *Acta Neurobiol Exp*, Vol. 72 (No. 3), pp. 283-95, (2012).

30- Yoshihiro Noda *et al.*, "Resting-state EEG gamma power and theta–gamma coupling enhancement following high-frequency left dorsolateral prefrontal rTMS in patients with depression." *Clinical Neurophysiology*, Vol. 128 (No. 3), pp. 424-32, (2017).

31- Chiara Spironelli, Alessandro Angrilli, Antonino Calogero, and Luciano Stegagno, "Delta EEG band as a marker of left hypofrontality for language in schizophrenia patients." *Schizophrenia bulletin*, Vol. 37 (No. 4), pp. 757-67, (2011).

32- Helena Voetterl *et al.*, "Investigating EEG biomarkers of clinical response to low frequency rTMS in depression." *Journal of Affective Disorders Reports*, Vol. 6p. 100250, (2021).