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Non-invasive brain stimulation in psychiatric disorders: From bench to bedside

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Non-invasive brain stimulation in psychiatric disorders: From bench to bedside

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Editorial: Non-invasive brain stimulation in psychiatric disorders: From bench to bedside

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noninvasive brain stimulation, transcranial magnetic stimulation, transcranial direct current stimulation, non-regional specificity, rTMS, tDCS

Editorial on the Research Topic
Non-invasive brain stimulation in psychiatric disorders: From bench to bedside

The development of effective treatment modality for psychiatric disorders is an enduring goal of translational research and evidence-based medicine. In recent decades, progress in neuroscience has identified the dysfunctional brain circuits and networks that may underpin the pathogenesis of psychiatric disorders (1). Non-invasive brain stimulation (NIBS) is a set of techniques that can modulate the excitability of large-scale networks in the brain (2). Studies have shown promising results in circuit-based psychiatric treatments in either diagnosis- or symptom-based clinical conditions (3–5).

The current Special Issue, *Non-invasive brain stimulation in psychiatric disorders: From bench to bedside*, in Frontiers in Psychiatry, is dedicated to collect high-quality studies that explore the possible mechanisms for the therapeutic effects of NIBS, including molecular, genetics, neuroimaging, and neurophysiological aspects. The relevance for application of transcranial magnetic stimulation (TMS) in treating psychiatric disorders is driven by the development of new protocols and sequences (2). The Food and Drug Administration agency of the United States approved rTMS as a treatment for medication-resistant patients with MDD in 2008 (6). The therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) were also observed in other psychiatric conditions, including MDD (Harika-Germaneau et al.; Spitz et al.), suicidal ideation (Huang et al.), smoking cessation (Chen et al.), and methamphetamine use disorder (Mikellides et al.). Unlike TMS, TES uses low intensity currents to modulate the excitability of targeted networks in the brain. TES is an umbrella term for a variety of different stimulation modalities, such as transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation.

Evidence supports TES as a therapeutic tool in depression (Chang et al.), attention-deficit/hyperactivity disorder (Sobral et al.), and social cognition in schizophrenia (Kannen et al.). These findings from clinical trials and practical experiences suggest that one of the strength of NIBS may lie in its non-regional specificity.

The circuit-based neuromodulation of NIBS may explain the heterogeneity of psychiatric disorders than can be treated with TMS/TES (Figure 1). For example, high-frequency rTMS over left dorsolateral prefrontal cortex (DLPFC) or low-frequency rTMS over right DLPFC are usually applied in the treatment of MDD (Yamada et al.); however, targeting other brain regions also revealed therapeutic effects for MDD, such as ventromedial prefrontal cortex (PFC), orbitofrontal cortex, and ventrolateral PFC (7). The magnetic stimuli applied may regulate the activity of local circuits in the interneurons including fibers projecting to other distant brain regions, which depend on the intrinsic properties and geometrical orientation of the fibers within the stimulated brain region (8). The interconnection between networks of the brain may thus also

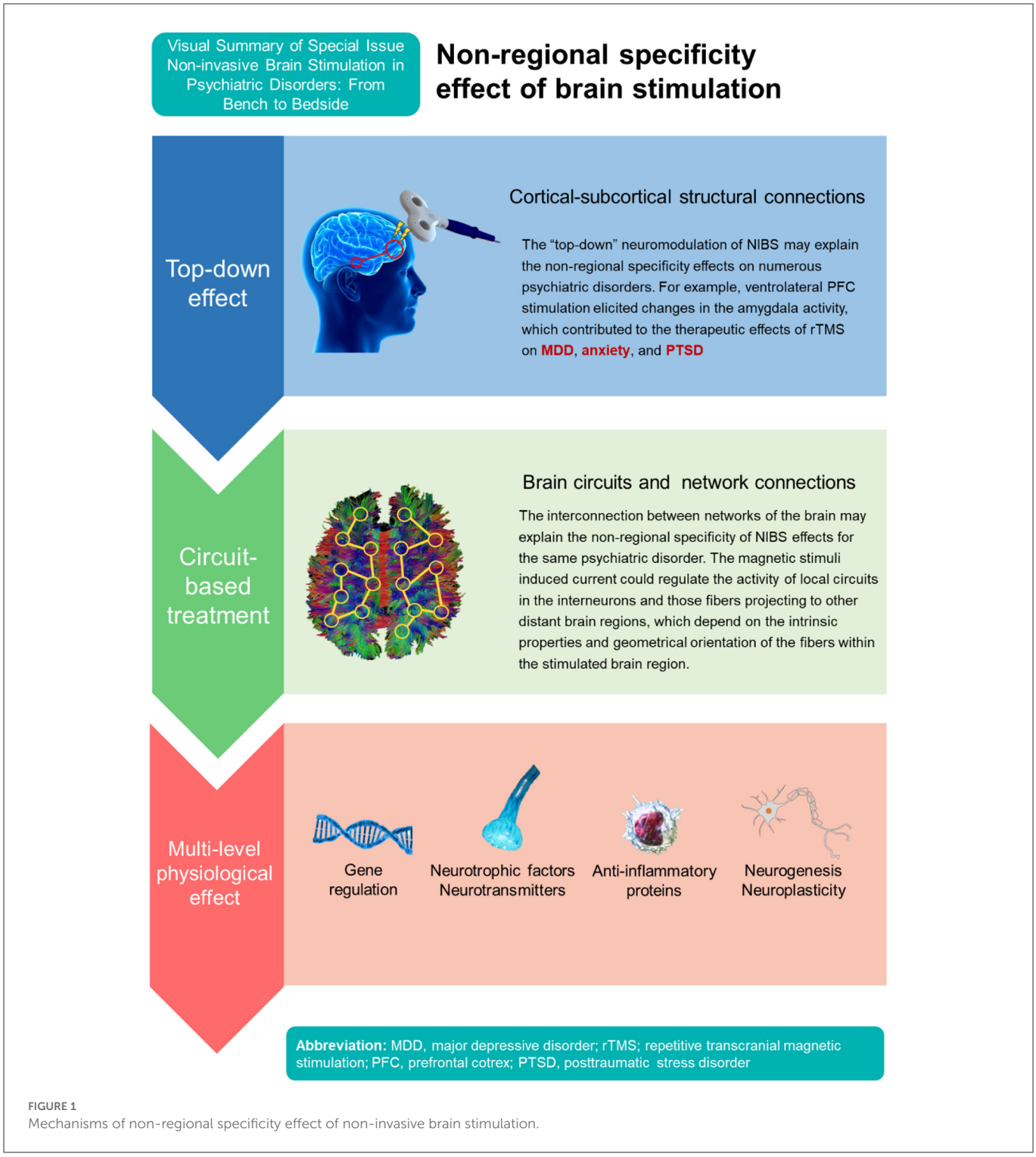

FIGURE 1
Mechanisms of non-regional specificity effect of non-invasive brain stimulation.

explain the non-regional specificity of NIBS effects for the same psychiatric disorder.

In addition, stimulating left DLPFC showed therapeutic effects not only for MDD but also in obsessive-compulsive disorder (9), suicidal ideation (Huang et al.), and methamphetamine use disorder (Mikellides et al.). The neuromodulation can be considered a "top-down" intervention, working at the level of brain networks and then affecting neurogenesis, neuroplasticity, and neurocircuitry (8, 10). For example, a recent study using TMS applied to the ventrolateral PFC elicited changes in the amygdala activity (11). The amygdala processes valenced stimuli, influences emotion, and contributes to a wide array of behavioral and brain disorders (12). Therefore, the top-down neuromodulation of TMS on the amygdala may enable a specific brain region stimulation for the treatment of numerous psychiatric disorders showing aberrant activity in the amygdala, such as MDD, anxiety, and posttraumatic stress disorder (11). Importantly, the therapeutic mechanisms of rTMS also involve neurotransmitter systems (e.g., serotonin, dopamine), neurotrophic factors, anti-inflammatory protein, and various molecular pathways (e.g., extracellular signal-regulated kinase 1/2, endocannabinoid systems) (8, 13, 14). Therefore, the cortical-subcortical structural and functional connections as well as various gene/protein expression and pharmacological modulation may all support the non-regional specificity of NIBS effects for various psychiatric disorders.

Take genetic molecular mechanisms for example, preliminary evidence suggests that the neurobiological effects of gene activation/regulation, *de novo* protein expression, synaptic morphological changes, homeostatic processes and glial function might underlies the long-term after effects of NIBS (15). Althoufh the effects of rTMS may produce long-term therapeutic effects on various psychiatric disorders (15), evidence suggests that rTMS pattern, intensity, frequency, train duration, intertrain interval, intersession interval, pulse and session number, pulse width, and pulse shape can alter motor excitability, long term potentiation-like facilitation, and the clinical antidepressant response (16). The response of rTMS varied widely among depressed patients. A study including 1,132 participants reported that around a half of patients could not achieve treatment response after rTMS treatment (Caulfield and Brown). Therefore, exploration of treatment predictors could help guide the choice of NIBS protocols that are more effective in precision medicine. A naturalistic observational study found that early improvement of depression can be a useful predictor for treatment response for rTMS treatment (Harika-Germaneau et al.). Another study examined clinical and neuroimaging biomarkers of treatment response with rTMS among treatment-resistant depression (6). The reported predictors included depression type, gender, depression severity, and the average volume of the left part of the superior frontal and the caudal middle frontal regions (6).

Advances in psychiatric practice lie in translating evidence from bench to beside. A better understanding of the neurobiological mechanism of NIBS has become an important piece in modern psychiatric practice. The non-region specificity of NIBS provides a window into circuit-based treatment for numerous psychiatric disorders. We believe the findings of the Special Issue could inspire future research to improve psychiatric treatment with precision NIBS applications.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Increased Prefrontal Activation During Verbal Fluency Task After Repetitive Transcranial Magnetic Stimulation Treatment in Depression: A Functional Near-Infrared Spectroscopy Study

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Background: Previous studies have shown the clinical effect of 2 Hz repetitive transcranial magnetic stimulation (rTMS) for depression; however, its underlying neural mechanisms are poorly understood. The aim of this study was to examine the effects of rTMS on the activity of the prefrontal cortex in patients with depression, using functional near-infrared spectroscopy (fNIRS).

Methods: Forty patients with major depressive disorder (MDD) and 40 healthy controls were enrolled in this study. Patients underwent 4 weeks of 2 Hz TMS delivered to the right dorsolateral prefrontal cortex (DLPFC). fNIRS was used to measure the changes in the concentration of oxygenated hemoglobin ([oxy-Hb]) in the prefrontal cortex during a verbal fluency task (VFT) in depressed patients before and after rTMS treatment. The severity of depression was assessed using the Hamilton Rating Scale for Depression-24 item (HAMD-24).

Results: Prior to rTMS, depressed patients exhibited significantly smaller [oxy-Hb] values in the bilateral prefrontal cortex during the VFT compared with the healthy controls. After 4 weeks of 2 Hz right DLPFC rTMS treatment, increased [oxy-Hb] values in the bilateral frontopolar prefrontal cortex (FPPFC), ventrolateral prefrontal cortex (VLPFC) and left DLPFC during the VFT were observed in depressed patients. The increased [oxy-Hb] values from baseline to post-treatment in the right VLPFC in depressed patients were positively related to the reduction of HAMD score following rTMS.

Conclusion: These findings suggest that the function of the prefrontal cortex in depressed patients was impaired and could be recovered by 2 Hz rTMS. The fNIRS-measured prefrontal activation during a cognitive task is a potential biomarker for monitoring depressed patients' treatment response to rTMS.

Keywords: major depressive disorder, repetitive transcranial magnetic stimulation, prefrontal cortex, functional near-infrared spectroscopy, verbal fluency task

INTRODUCTION

Major depressive disorder (MDD) is a common psychiatric disease, with over 300 million individuals worldwide suffering from the disease (1). Unfortunately, as yet there is no specific biomarker for diagnosing and monitoring the progression of depression. Moreover, although pharmacotherapy is the first-line antidepressant treatment, about a third of patients with MDD are failed to achieve satisfied response to the initial antidepressant treatment because of the ineffectiveness or side effects of antidepressant medications (2).

For patients with MDD, repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising treatment (3, 4). rTMS is a safe and non-invasive brain stimulation techniques for stimulating specific cortical regions and modulating neuronal activity (5). During the last decades, a great number of studies have demonstrated encouraging results about the utility of rTMS in neuropsychiatry (6–9). And the U.S. Food and Drug Administration has approved the rTMS applied over the dorsolateral prefrontal cortex (DLPFC) for MDD in 2008. However, the neural mechanism of rTMS treatment in depression is not very clear. The current application principle of rTMS is based on human neurophysiological experiments using motor evoked potential (MEP), i.e., high-frequencies rTMS (typically 5 or 10 Hz) demonstrates an excitatory effect on the stimulated motor cortex (M1), while low-frequencies rTMS (typically 0.2 to 1 Hz) suppresses cortical excitability of the stimulated M1 (10). The knowledge learned from stimulation of M1 are assumed to be applicable in other cortical regions, such as the prefrontal cortex (PFC), where the physiological response of stimulation is difficult to measure using MEP-related outcomes. Due to the lack of an objective marker, it is difficult to determine the optimal stimulation parameters in the PFC regions and evaluate the immediate and long-term responses to rTMS treatment.

Along with the rapid development of recent neuroimaging technologies, the brain activity in patients with MDD has gradually come to be visible. Previous functional neuroimaging studies have shown the dysfunction of the PFC in patients with MDD, which may be related to their clinical symptoms, including both depressive mood and cognitive impairment (11–13). Therefore, it is reasonable that the combined use of rTMS and neuroimaging will provide a reliable evaluation of neurobiological state, and their combination will facilitate understanding of potential modulation over the time course of rTMS treatment in a depressive brain. Functional near-infrared spectroscopy (fNIRS) is an emerging optical neuroimaging technology that can measure changes in concentrations of oxygenated hemoglobin [oxy-Hb] and deoxygenated hemoglobin [deoxy-Hb] in the brain cortex (14). Compared with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), fNIRS has several advantages in that it is easy to use and has a low cost. Accordingly, fNIRS has been widely used in clinical application and medical research to assess cortical functions of patients with psychiatric disorders.

The verbal fluency task (VFT) is a frequently used cognitive task in the fNIRS studies, in which participants are asked to generate as many words as possible beginning with a certain semantic category or letter within a limited time. The VFT mainly reflects the executive function, which is associated with some basic neurocognitive activities, such as working memory, motivation and attention. Many studies have reported that neurocognitive impairments are associated with PFC dysfunctions in numerous psychiatric disorders (15, 16). Accordingly, VFT has been widely employed in psychiatric disorders as a sensitive indicator of deficits in cognitive and executive domains that depend on the activation of prefrontal regions. A large number of fNIRS studies (17) reported that the [oxy-Hb] activation in the PFC during VFT was lower in MDD patients than in healthy controls, suggesting the executive dysfunction in patients with MDD may be caused by the impairment of the PFC functioning. Based on these findings, fNIRS is a promising technique for evaluating cortical functional changes in real time.

In past decades, two main rTMS strategies for depression treatment have been developed: high-frequency rTMS on the left DLPFC and low-frequency rTMS on the right DLPFC (6, 18, 19). Although both protocols have been shown be equally antidepressant effective as standard antidepressant medications (20–22), their therapeutic effects appear to be moderate. Therefore, an increasing number of studies have explored novel rTMS protocols for achieving better therapeutic efficacy. Among them, Fitzgerald et al. (23) reported that 2 Hz right DLPFC protocol was slightly superior to 1 Hz right DLPFC protocol in reducing the depressive symptoms in MDD patients. The finding led us to explore the antidepressant effect of 2 Hz rTMS over the right DLPFC and its possible neural mechanism.

In our study, fNIRS was used to examine the hemodynamic changes in the PFC in both patients with MDD and healthy counterparts during VFT, and then patients were treated with 4-week of 2 Hz right DLPFC rTMS treatment. We compared the change in the PFC before and after rTMS treatment. We hypothesized that (1) patients with MDD demonstrate a reduced activation of the PFC area during VFT, compared with their healthy counterparts, and (2) the level of activation in the PFC and the severity of depressive symptoms can be improved by using 2 Hz DLPFC rTMS treatment.

MATERIALS AND METHODS

Participants

Patients were recruited from the outpatient department of West China Hospital, Sichuan University from May 2021 to December 2021. We included 40 patients aged 20–59 years who were diagnosed with moderate MDD according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorder (DSM-5) with a Hamilton Rating Scale for Depression-24 item (HAMD-24) total score between 20 and 35. All patients had to be right-hand dominant. In order to eliminate the influence of antidepressant medications, we included the patients who had not taken antidepressants at least 1 month before treatment start. Considering that it is common for patients with depression comorbid with anxiety and insomnia (24, 25), the use of

benzodiazepines was allowed in this experiment since it can alleviate anxiety and insomnia but not depression. The exclusion criteria were as follows: (i) severe and unstable physical illnesses; (ii) antidepressants have been used within 4 weeks before enrollment; (iii) had a score ≥3 on item 3 (suicidal thoughts) of the HAMD-24 or had made a suicide attempt in the previous 6 months; (iv) presence of other mental disorders; (v) severe auditory dysfunction; (vi) pregnant or breastfeeding women; and (vii) contraindications for undergoing rTMS treatment, such as metallic implants or a history of epileptic seizure.

Forty healthy controls (HCs) were recruited from the local community and matched to the MDD patients in terms of age, gender, level of education. They were required to be right-hand dominant and in a good healthy condition with no any known history of neurologic and psychiatric diseases, or a family history of psychotic disorder.

Before this study, all participants provided written informed consent. This study was approved by the West China Hospital Clinical Trials and Biomedical Ethics Committee of Sichuan University (No. of ethical approval: [2021]-428) on April 30, 2021 and registered in the Chinese Clinical Trials Registry (registration No. ChiCTR2100046806) on May 29, 2021.

Study Overview

Major depressive disorder patients received rTMS treatment for 4 weeks. Depression severity was assessed by HAMD-24. Before and after 4 weeks of rTMS treatment, all patients were assessed with HAMD-24 and fNIRS by a trained research staff to ensure consistency. In addition, considering acute cognitive enhancing effects of rTMS, which were typically observed when the test was administered immediately following stimulation, usually within several minutes (26), we thus set the interval between the last rTMS session and fNIRS test after treatment more than 24 h in this study. Healthy controls were only assessed with fNIRS at baseline.

Repetitive Transcranial Magnetic Stimulation Intervention

Repetitive transcranial magnetic stimulation was performed with a CCY-I Magnetic Stimulator (YIRUIDE Medical Co., Wuhan, China) with an air-cooled, figure-of-eight 70 mm coil. At the first TMS session, the resting motor threshold (RMT) of the right abductor pollicis brevis muscle was determined as the lowest strength of transcranial magnetic stimulation needed to elicit at least 5 electromyographic responses in the form of motor evoked potential (EMG/EP Measuring system, Nihon Kohden, Tokyo, Japan) ≥50 μV in 10 trials (27). The site of stimulation during the TMS treatment sessions was right DLPFC defined by a point 5 cm anterior to the motor hotspot (28). Treatment parameters were standardized for each session at the treatment location with the following stimulation parameters: 90% of individual RMT, frequency in 2 Hz, train duration of 10 s, inter-train interval of 3 s and 130 trains per session, leading to a total of 2,600 pulses delivered in 28.7 min. The treatment was performed 5 days per week for 4 weeks for a total of 20 sessions.

Clinical Assessment

The 24-item HAMD (29, 30) includes 24 items rated on either a 2-, 3- or 4- point scale with total score range from 0 to 76 points. Patients who achieve a HMAD-24 total score of 8–19 points are regarded as mild depression, total score of 20–35 points are regarded as moderate depression, total score of >35 points are regarded as severe depression (31). As a note, HAMD was used to evaluate the level of depression, but rather to offer a strict diagnostic guideline.

The primary outcome measure for this study was the total score of HAMD-24. Clinical response was defined as a reduction in HAMD-24 scores of at least 50% from baseline.

Activation Task (Verbal Fluency Task)

The task procedure in the present study was a Chinese-language phonological VFT developed by Quan et al. (32) for Chinese participants. Previous research (33) has shown evidence that patients with MDD are associated with reduced brain activation in the prefrontal cortex during this version of VFT in comparison to the healthy controls. Each trial consisted of a 30s pre-task rest period, a 60s task period and finally, a 60s post-task rest period (see **Figure 1**). During the pre-task and the post-task rest period, participants were asked to verbally count the numbers from one following the voice prompts from the fNIRS machine. The 60s task period was divided into four sequential 15s blocks. During each 15s block, one of four Chinese syllables "shang (上)," "shi (时)," "shuo (说)," and "jia (家)," which indicate upper, time, speak and home, respectively, was audibly presented to the subjects. And subjects were instructed to generate as many words as possible which began with the same syllable. All the participants were given the same syllable cues and no changes were made to the order of presentation. We provided all participants with a practice session before the formal testing, in order to ensure the participants fully understand the tasks. During the task, an investigator monitored the performance of the participants, in order to ensure the participants were fully engaged in the assessment.

NIRS Measurement

The 37 multi-channel fNIRS instrument (BS-3000, Wuhan Union Medical Technology Co., Wuhan, China) measures the concentration changes of [oxy-Hb] and [deoxy-Hb] in cerebral cortex using two wavelengths (695 and 830 nm) of infrared light, based on the modified Beer Lambert law (34). The absorption of those infrared light emitted by dual wavelength laser diodes could distinguish the deoxyhemoglobin and oxyhemoglobin (35). This system consists of 12 light emitters and 12 light detectors, and the distance between each emitter and detector is 3 cm. A channel (ch) was defined as the measurement area between a detector and source probe pair. The sampling rate was set to 20 Hz. The probe set was positioned on the participants' prefrontal areas and the lowest probes were positioned along the Fp1–Fp2 line in accordance with the International 10–20 System of electroencephalogram electrode placement. Thus, the waveforms change of [oxy-Hb] and [deoxy-Hb] in PFC were acquired from all 37 channels.

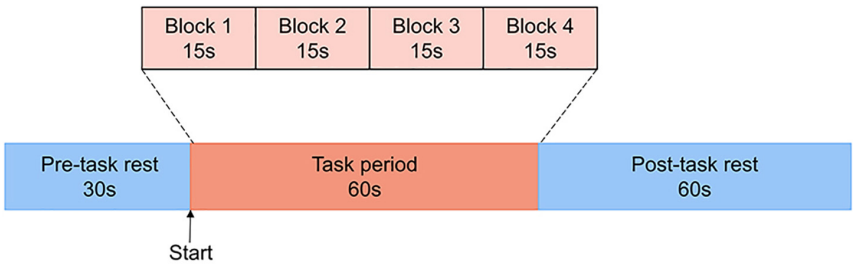

FIGURE 1 | The VFT protocol used for near-infrared spectroscopy. Each trial consisted of a 30s pre-task rest period, a 60s task period subdivided into four 15s blocks and finally, a 60s post-task rest period.

According to a previous study of anatomical craniocerebral correction via the international 10–20 system (36, 37), we confirmed the correspondence between the NIRS channel and the measurement position on the cerebral cortex. Thus, according to the international 10–20 system, the approximately positions of the 37 channels were as follows: ch4, 7–12, 16,19–21, 26, 28, 29, and 32–34 are located over the DLPFC (BA 9 and 46), ch1-3, 5, 6, 30, 31, and 35–37 are located over the ventrolateral PFC (VLPFC; BA 44, 45, and 47) and ch13-15, 17, 18, 22–25, and 27 are located over the frontopolar PFC (FPPFC; BA 10), based on Brodmann's area (BA) (38) (see **Figure 2**).

NIRS Data Analysis

The toolbox HOMER2, a MATLAB-based graphical user interface program was used to analyze the NIRS data (39). First, the raw data were filtered using a Band-pass filter within the range of 0–0.1 Hz to remove high frequency noise. Similar to study of Lee et al. (40), the threshold signal-to-noise ratio in our study was 30 dB, which was used to qualify the noise of the detected channels after band-pass filtering and eliminate the slow drift of physiological and environmental noise. Then, a processing method based on moving standard deviation and cubic spline interpolation was applied to remove motion artifacts (41, 42). Artifacts were distinguished by identifying the sliding window standard deviation above a certain threshold and were removed by cubic spline interpolation (43). Finally, the filtered optical data were translated to [oxy-Hb] concentrations by applying the modified Beer-Lambert law (44). We focused on [oxy-Hb], since the change of [oxy-Hb] could better reflect cortical activity as it is assumed to more directly response to cognitive task-related brain activation and more strongly correlated with blood oxygenation level dependent (BOLD) signals measured by fMRI (45). And we took the final 10 s of the pre-task rest period as the baseline. The mean [oxy-Hb] values of the task period and baseline in each channel for each participant were calculated separately. The [oxy-Hb] values during the VFT, i.e., the mean [oxy-Hb] change between the baseline and task period., was finally calculated by subtracting the baseline mean [oxy-Hb] values from the task period mean values.

Statistics

Statistical analysis was performed using SPSS software version 26.0. Baseline demographic characteristics were assessed by means of a chi-squared test (sex), *t*-test (age) or Mann-Whitney test (education), comparing the MDD and HCs groups. Symptom change, i.e., difference between the two total HAMD-24 scores (pre – post over the full treatment course), was compared by paired *t*-test. To analyze our NIRS data, Mann-Whitney *U* tests were used to compare [oxy-Hb] values during the VFT for each channel between the MDD and HCs groups at baseline. Then, to assess [oxy-Hb] responses to rTMS treatment in patients with depression, the differences in [oxy-Hb] values during the VFT for each channel were compared between pre- and post-treatment in the MDD group, using Wilcoxon test.

To examine the relationships between [oxy-Hb] values before treatment during the VFT and HAMD-24 total scores and to test whether the former was related to clinical outcome, correlation analysis was carried for MDD patients. For channels showing a significant difference in [oxy-Hb] value in MDD group between pre- and post-treatment, we also examined the association between the [oxy-Hb] changes from baseline to post-treatment and the degree of improvement in depressive symptoms.

We adopted a false discovery rate (FDR) (46) in order to perform multiple comparisons for the neural activation in the probes of 37 channels. Significance level was set at a $p < 0.05$.

RESULTS

Demographic and Clinical Characteristics

There was no significant difference in gender (chi-square test: $\chi^2 = 0.621$, $p = 0.600$), age (*t*-test: $t = 0.247$, $p = 0.806$) or education (Mann-Whitney test: $z = -0.036$, $p = 0.971$) between the MDD patients and the healthy controls. For patients, the duration of illness was 5.80 ± 7.37 years. A 60% (24/40) patients were diagnosed with MDD with a first episode and 40% (16/40) had recurrent episodes. A 72.5% (29/40) patients were comorbid with anxiety and 75% (30/40) patients were comorbid with insomnia. A 67.5% (27/40) patients had never taken antidepressant medications. A 55% (22/40) patients were medicated with benzodiazepine drugs. The demographic and clinical characteristics of the participants are presented in **Table 1**.

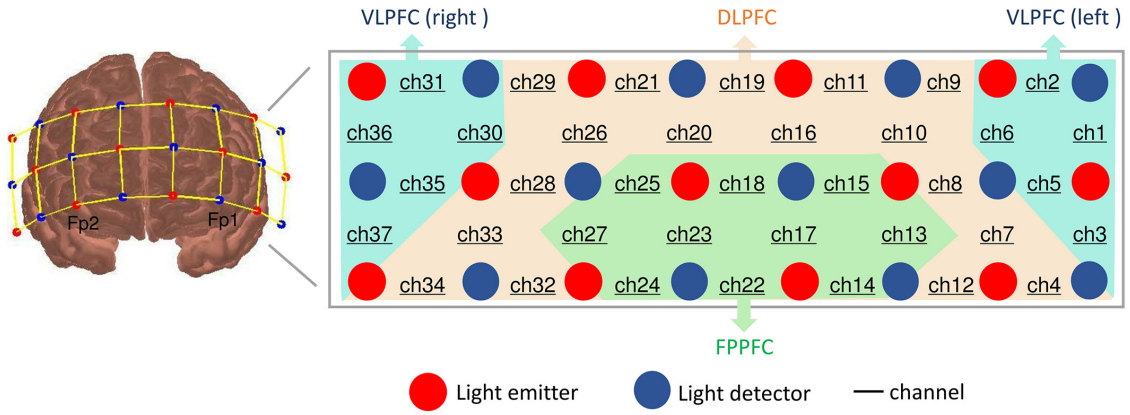

FIGURE 2 | Location of probes and channel settings in 37-channel near-infrared spectroscopy. Brodmann area showing 37 sensing areas (from Ch1 to Ch37) within the prefrontal cortex.

TABLE 1 | Demographic and clinical characteristics of participants.

	HCs	Patients with MDD		$t/z/\chi^2$	*p*
		Pre-treatment	Post-treatment		
n	40	40	40	–	–
Demographic					
Age, years	37.75 ± 4.72	38.18 ± 9.81	–	0.247	0.806
Gender, male/female, n	11/29	8/32	–	0.621	0.600
Education, years	13.93 ± 2.00	13.83 ± 3.01	–	−0.036	0.971
Clinical					
Duration of disease, years	–	5.80 ± 7.37	–	–	–
Number of episodes, n (%)					
Single episode		24 (60%)			
Recurrent episode		16 (40%)			
Comorbidity, n (%)					
Anxiety		29 (72.5%)			
insomnia		30 (75%)			
Previous antidepressants history, yes/no		13/27			
Current benzodiazepine use, yes/no		22/18			
HAMD-24 scores	–	26.08 ± 4.66	17.73 ± 8.12	6.700	0.000

Clinical Outcomes

After 4-weeks of rTMS treatment, the HAMD-24 scores in the MDD patients significantly decreased, from 26.08 to 17.73 (paired *t*-test: $p < 0.001$). A 27.50% (11/40) of MDD patient were responded to treatment in our study.

Effects of Repetitive Transcranial Magnetic Stimulation on [oxy-Hb] Signals During the Verbal Fluency Task

At baseline, the [oxy-Hb] values in the MDD group during the VFT were significantly lower than that of HCs group in the 31 channels located over the bilateral FPPFC, DLPFC and VLPFC (HCs vs. MDD-pre: ch1-18, 20–28, 32–34 and 37; Mann-Whitney test: $z = -5.965$ – -2.212, FDR $p = 0.00001$–0.032). After 4-weeks of rTMS treatment, the significant increase in [oxy-Hb] changes were observed in the MDD group compared with the pre-treatment levels in the 7 channels located over the bilateral FPPFC, left DLPFC and bilateral VLPFC (MDD-pre vs. MDD-post: Ch1, 3, 7, 22, 23, 27, and 37; Mann-Whitney test: $z = -3.669$ – -2.594, FDR $p = 0.0002$–0.047). The prefrontal cortical activation during the VFT in different group are shown in **Figure 3**. **Figure 4** shows the waveforms of [oxy-Hb] values during the VFT in 37 channels over prefrontal regions in different group.

Correlation Between NIRS Data and Clinical Data

In the MDD group, the increased [oxy-Hb] values from baseline to post-treatment was positively related to the total HAMD-24 score reductions in the right VLPFC in 37 (Pearson's $r = 0.381$, $p = 0.017$; see **Figure 5**).

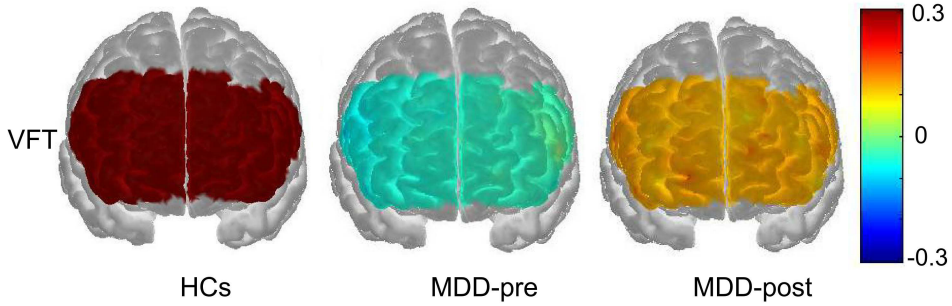

FIGURE 3 | Prefrontal cortical activation during the VFT in patients with MDD before (pre) and after (post) rTMS treatment and HCs. The color scale depicts the change of [oxy-Hb] value range from −0.3 to 0.3 in μmol × mm.

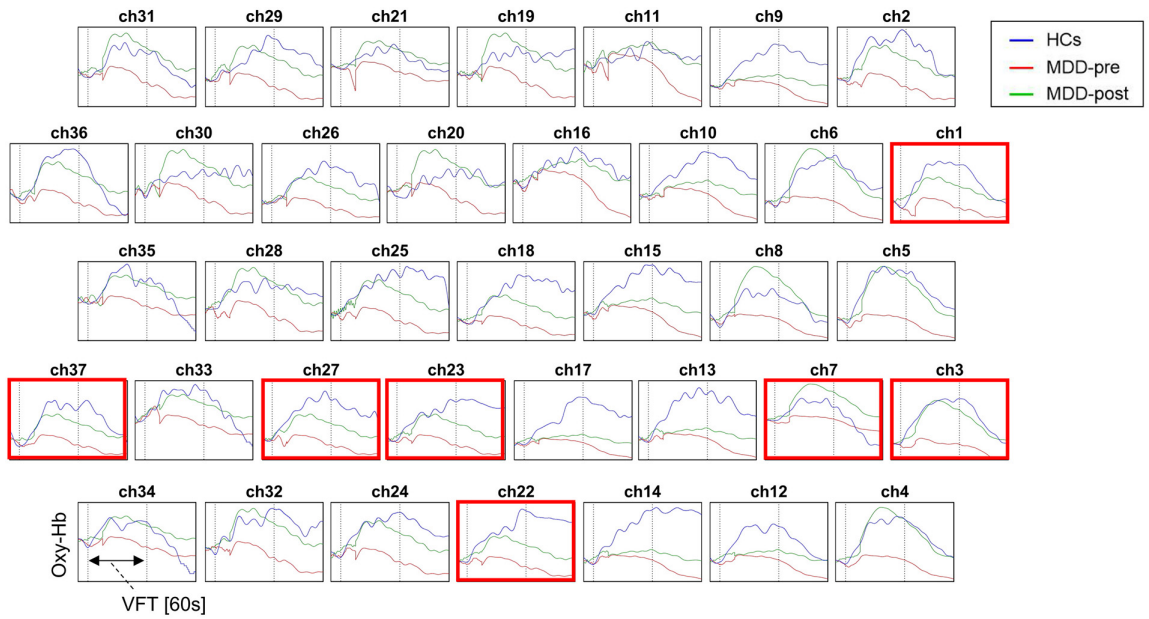

FIGURE 4 | Waveforms of [oxy-Hb] values during the VFT in the 37 channels over prefrontal regions in patients with MDD before (pre) and after (post) rTMS treatment and HCs. Red box indicates significant increase in [oxy-Hb] value from baseline to post-treatment in patients with MDD in this channel.

However, the [oxy-Hb] values before treatment were not significantly correlated with baseline HAMD scores, nor the total HAMD-24 score reductions after treatment (all $p < 0.05$).

However, after FDR correction, there was no significant correlations between NIRS data and clinical data.

DISCUSSION

To the best of our knowledge, this is the first study to examine the effects of DLPFC rTMS on modulating to cognitive task in MDD patients using fNIRS. We found that patients with MDD had significantly less activation in the PFC in response to the VFT compared to their healthy counterparts, whereas that the level of the activation in patients was not related to their depression severity. After 4-weeks of 2 Hz DLPFC rTMS treatment, the decreased depressive severity and the increased activation in response to the VFT were observed in MDD patients, and the increased activation in the right VLPFC from baseline to post-treatment was positively related to the improvement of depressive symptoms.

The overall results of previous NIRS studies of the VFT revealed reduced PFC activation in MDD patients compared with HCs (33, 40, 47, 48). Akiyama et al. (49) demonstrated that the hemodynamic response to the VFT in MDD patients was significantly reduced compared with HCs in the bilateral DLPFC (BA 9, 46), VLPFC (BA 44, 45, 47), and FPPFC (BA 10) cortical surface regions. Consistent with those previous studies, our study also found less activation in the different PFC areas (the bilateral FPPFC, DLPFC and VLPFC) in MDD patients during the VFT was, suggesting the functional hypofrontality in the bilateral PFC in patients with MDD.

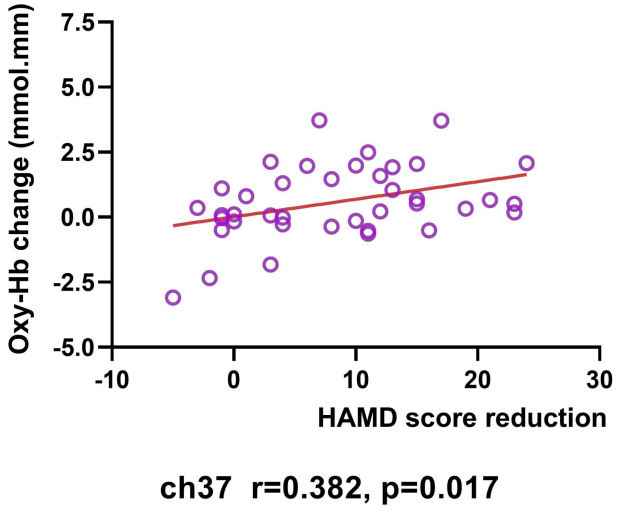

FIGURE 5 | Correlation between HAMD score reduction and changes in [oxy-Hb] value (from baseline to post-treatment) in Ch37.

Similarly, several fMRI studies show that the MDD patients had a reduced response in the PFC, particularly in the left DLPFC, during the VFT compared to the healthy controls (50, 51). The findings may be attributed to neuronal dysfunction through the mechanism of neurovascular coupling (52), or a decreased cerebral vasoreactivity (53). In accordance with the study of Tsujii et al. (54), our study observed no significant correlations between HAMD scores and oxy-Hb concentrations. However, the results about the clinical correlations between [oxy-Hb] change on NIRS and depression symptom severity were still controversial as several studies (55–57) suggested that a correlation existed, while others did not. The difference between these results may be related to the inconsistency in the patient characteristics between studies and differences in the methods used to analyze the [oxy-Hb] variations measured by fNIRS.

We found that the [oxy-Hb] values in the bilateral FPPFC, left DLPFC and bilateral VLPFC during the VFT were gradually increased after 4-weeks of 2 Hz rTMS applied on right DLPFC than before rTMS. Our results suggest that 2 Hz rTMS could evoke an increased cerebral cortex activation during a cognitive task. Similarly, previous study using fMRI indicated that 2-week of rTMS applied on the DLPFC had focal and remote effects on several brain areas involved in working memory in healthy subjects during an n-back task (58). Also, Cao et al. (59) investigated the effect of 5s trains of 1, 2, and 5 Hz stimulation delivered at the left DLPFC on twelve healthy participants, showing a decrease in blood oxygenation after 1 Hz compared to the [oxy-Hb] increases observed in both the 2 and 5 Hz stimulations. Although several NIRS studies (60, 61) have also investigated the effects of rTMS on the MDD patients and described a modulation of the blood oxygenation response over the PFC that was built up during the course of rTMS treatment in depression, these studies measured the oxy-Hb response during TMS, not during a cognitive task. Given the interest in using rTMS to influence high-level cognitive function, the changes in functional measures during task-related activity are particularly important. Moreover, the present study differed from previous studies in that the patients we included were not taking antidepressant. In addition to the uncertain effects on cognition, studies have found that antidepressant can affect the NIRS signals (62). Thus, a strength of our study is that fNIRS data we collected was not interfered by medicine.

In the present study, 2 Hz right DLPFC rTMS was effective as a monotherapy for MDD who were not undergoing any antidepressant medication. The finding was consistent with previous studies (63, 64), which demonstrated the improvement of depressive symptoms in patients with treatment-resistant depression after 2–4 weeks of rTMS treatment. In the study of Fitzgerald et al. (23), 42% patients in the 1-Hz group and 53% patients in the 2-Hz group achieved response criteria. A meta-analysis reported response rates of 45% (144/320) in patients treated with low frequency right-sided TMS and 48% (148/307) in patients treated with high frequency left-sided TMS (65). The lower response rate in our study was 27.5% which was relatively lower than the findings of previous studies. It may be because the patients in our study were undergone monotherapy treatment of rTMS without medications, or the differences in the characteristics of our sample (i.e., moderate depression) and stimulation protocol applied.

Moreover, our study demonstrated, for the first time, the correlation of the increase of NIRS activation in the prefrontal region with improvements in the depressive symptoms of patients during the rTMS treatment. In our 4-week rTMS treatment period, the longitudinal increases in the right VLPFC were shown to be positively correlated with improvements in the severity of depressive symptoms for MDD patients. This finding is consistent with the previous study conducted by Shinba et al. (61) which investigated the relationship between cerebral blood flow changes during stimulation and the effectiveness of TMS. Their result showed that increased PFC oxy-Hb levels during TMS at the last day of treatment were linked to a larger reduction of depressive symptoms. As such, they also concluded that the maintenance of PFC activation during stimulation in the course of TMS series is related to the effectiveness in the treatment of depression. Although the significant result in our study did not survive FDR correction for multiple, our discovery partly suggested that fNIRS could be useful in monitoring treatment response of rTMS treatment in patients with MDD. Also, to some extent, our observations support the potential neuroimaging mechanism of DLPFC-rTMS treatment in MDD, namely increased metabolic activity and blood flow perfusion in frontal regions (66, 67).

LIMITATIONS

There are some limitations of our study. First, our fNIRS signals in typical source-detector channels were possibly contaminated

with systemic interference occurring in the superficial layers of the head (68). Although the brain hemodynamics response to a task without short channel separation has been used in depression assessment (69), it can be more precise to use an additional short source-detector separation optode in future study, to order to remove the systemic interference and improve the accuracy of fNIRS measurements (70). Second, the duration of follow-up in the present study was not long enough; Having more frequent fNIRS measurements in longitudinal studies (e.g., weekly) may oxygen hemodynamics provide us with a better understanding of the brain dynamics and minimize the influence of confounding factors. Third, longer longitudinal studies of at least 6 months to 1 year would be beneficial, considering that most depressive episodes last for at least a few months. Fourth, most of patients in this study comorbid with anxiety and dysthymia, which could affect the NIRS assessment results. Fifth, our sample size was small. Sixth, we did not employ a sham rTMS-control group. Considering these limitations, future studies with larger sample sizes and placebo-control participants are needed to confirm our preliminary findings for 2 Hz rTMS, especially with respect to an intensified PFC hemodynamic response.

CONCLUSION

Our study demonstrated that patients with MDD had significantly reduced brain activation in the PFC during VFT when compared with HCs, and these functional deficits can be improved after 4 weeks of 2 Hz right DLPFC rTMS treatment. Furthermore, there was correlation between improvements in the depression severity in MDD and increases of hemodynamic response to VFT in the right VLPFC during treatment. These results suggest that hemodynamic response to VFT in PFC, measured by fNIRS, is a potential biomarker for monitoring MDD patients' treatment response to rTMS. How to improve the cognitive and brain function of MDD and how to predict the prognosis of the patients are important issues that need more exploration in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the West China Hospital Clinical Trials and Biomedical Ethics Committee of Sichuan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZZ conceived and designed the experiments. JH performed the experiments and data analysis. TZ checked the processed experimental data. JZ and JH wrote the manuscript with input from all authors. PW supervised the project. All authors discussed the results and contributed to the final manuscript.

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Mechanical Affective Touch Therapy for Anxiety Disorders: Feasibility, Clinical Outcomes, and Electroencephalography Biomarkers From an Open-Label Trial

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Background: Most external peripheral nerve stimulation devices designed to alter mood states use electrical energy, but mechanical stimulation for activation of somatosensory pathways may be harnessed for potential therapeutic neuromodulation. A novel investigational device for Mechanical Affective Touch Therapy (MATT) was created to stimulate C-tactile fibers through gentle vibrations delivered by piezoelectric actuators on the bilateral mastoid processes.

Methods: 22 adults with anxiety disorders and at least moderate anxiety symptom severity enrolled in an open-label pilot trial that involved MATT self-administration using a simple headset at home at least twice per day for 4 weeks. Resting EEG data were acquired before and after a baseline MATT session and again before the final MATT session. Self-report measures of mood and anxiety were collected at baseline, week 2, and week 4, while interoception was assessed pre- and post-treatment.

Results: Anxiety and depressive symptoms improved significantly from baseline to endpoint, and mindfulness was enhanced. EEG metrics confirmed an association between acute MATT stimulation and oscillatory power in alpha and theta bands; symptom changes correlated with changes in some metrics.

Conclusion: Open-label data suggest MATT is a promising non-invasive therapeutic approach to anxiety disorders that warrants further development.

Keywords: peripheral nerve stimulation, acoustic stimulation, therapeutic neuromodulation, anxiety, EEG

INTRODUCTION

Therapeutic non-invasive peripheral nerve stimulation is being investigated for conditions such as gait disorders (1), pain (2), anxiety, and depression (3, 4). Nerve activation can be achieved by delivering electrical or mechanical energy directly to the area of the dermis that is innervated by the target nerve(s). The majority of potentially therapeutic externally applied devices to date

have used electrical stimulation to alter mood states (3–5), address pain (6), and treat diseases (7). Fewer studies have examined the effects of mechanical (acoustic) stimulation; nonetheless, ultrasound (>20 KHz) has been shown to successfully activate peripheral nerves (8, 9) and low-frequency acoustic vibrations (<20 KHz) can activate somatosensory mechanoreceptors. Mechanical stimulation offers a more robust safety profile than electrical stimulation (which itself is considered very low risk) (10, 11), yet somatosensory pathways remain largely unexplored as potential mechanisms for therapeutic neuromodulation.

C-tactile fibers (CT) are specialized unmyelinated Group C peripheral nerve fibers which conduct afferent signals relatively slowly from hairy skin to the insula. CT are mechanoreceptors that show particular sensitivity to gentle touch (12). They fire when stroked at velocities perceived as pleasurable or comforting and prefer temperature ranges that correspond with skin-to-skin interpersonal contact. CT generate signals that mediate emotional rather than discriminative properties of touch (13). This is the target for stimulation by an investigational device called "Mechanical Affective Touch Therapy" (MATT) which delivers gentle vibration on the bilateral mastoid processes.

The acute anxiolytic effect of stimulation observed during device development was presumed to arise from mechanoreceptive signals to the insula, a cortical brain region associated with interoceptive awareness and socio-emotional processing. Insula function and interoception have long been linked to anxiety and mood disorders (14). Interoceptive training has been shown to reduce both somatic symptoms and anxiety states in healthy volunteers (15).

MATT prototype devices use MP3 signal generators wired to a set of digital amplifiers and 3 cm round ceramic piezoelectric actuators which translate the signal to gentle vibrations on the areas of application behind the patient's ears. Two tractors are mounted on disks and connected by ball joints to a metal headset which also has a cable for attachment to an electronics housing (similar in appearance to a small off-the-shelf MP3 player) enabling the patient to control the amplitude of stimulation. Initial development of the MATT stimulation parameters included various biometric assessments and behavioral questionnaires during tests with different waveforms. Ultimately, an isochronic 10 Hz wave, cycling 2 s on and 2 s off, was chosen for subsequent clinical trials; this stimulation pattern was observed to induce a state of relaxation and increase occipital alpha oscillations in pilot study subjects (data on file Affect Neuro Inc.).

To inform further development of MATT, this open-label pilot study was designed to confirm the preliminary efficacy and feasibility signals in a clinical sample with anxiety disorders and to explore changes in brain activity associated with use. Based on a presumed role of insula in the therapeutic mechanism of action, we assessed interoception (mindfulness) and obtained several electroencephalography (EEG) metrics and resting-state functional magnetic resonance imaging (fMRI) data to elucidate potential MATT mechanisms of action following acute (a single 20-min session) and chronic (4 weeks of twice-daily use) therapy. We hypothesized that chronic therapy would result in reduced anxiety, enhanced mindfulness, and neuroimaging changes that correlated with clinical changes.

Based on preliminary EEG findings that guided the selection of the stimulation parameters during device development, enhanced alpha oscillations were anticipated following acute stimulation. Previous studies have reported power increases in the theta and alpha frequency bands as markers for enhanced mindfulness (16); these metrics were examined in our participants to evaluate the hypothesis that MATT exerts it actions through interoceptive pathways. fMRI data from this study is published separately (17).

MATERIALS AND METHODS

Study Design and Subjects

This was a single site, open-label, 4-week mechanisms-focused study using a prototype device (Affect Neuro Inc.) in outpatients with anxiety disorders recruited through local advertisements. The study was approved by the Butler Hospital Institutional Review Board (IRB) and conducted between 2/13/19 and 10/02/19. Eligible participants were 18–60 years old, determined by a trained clinical rater to meet DSM-5 criteria for an anxiety disorder according to a modified version (updated for DSM-5) of the Mini International Neuropsychiatric Interview (MINI) (18). Eligibility also required a moderate to severe level of current anxiety severity [Generalized Anxiety Disorder 7-item (GAD-7) score $\geq$ 10] (19). Bipolar I and primary psychotic disorders were exclusionary, as were contraindications to MRI, significant neurological conditions, hospitalization for a psychiatric disorder within the past 6 months, change in psychotropic medication within the past 1 month, and dermatological conditions on the scalp that might be exacerbated by using the device. Eligible participants could be free of psychotropic medications or alternatively remaining on stable regimens; if the latter, they were required to continue the same stable agents and doses for 1 month prior to and throughout the duration of the study. All cases were reviewed by a study psychiatrist for confirmation of eligibility.

Mechanical Affective Touch Therapy Device and Treatments

The MATT prototype device appears in **Figure 1**. At baseline, research staff demonstrated how to self-administer the stimulation and helped participants adjust the intensity of the vibrations to a threshold that was consistently detectable but not uncomfortable. Participants were instructed to remain on stable medications/doses throughout the entire study (if applicable) and report any deviations. The first two sessions occurred in the context of baseline biomarker collection procedures and were observed by research staff. Following the second MATT baseline session and demonstration of satisfactory competence in self-administering the treatments, participants were issued a MATT device for home-use and instructed to use it at least twice daily for 20 min at each session. All stimulation was active, and no parties were blinded. Participants were given the option to use MATT for additional sessions each day, if desired. Time of use each day, reason for additional stimulation and/or

FIGURE 1 | Mechanical Affective Touch Therapy (MATT) prototype device. Stimulating actuators (connected to the MP3 signal generator) are attached to an adjustable metal headset.

missed sessions, adverse effects, and technical problems were recorded by participants in daily diaries provided by the study and discussed at an in-person research clinic assessment visit following 2 and 4 weeks of MATT self-administration.

Assessments

A timeline of study assessments is displayed in **Figure 2**.

Electroencephalography

The first MATT stimulation took place in the MRI research facility, between two scan sessions. Several days later, participants had their second MATT session in the laboratory, with collection of resting EEG immediately before and after a 20-min stimulation session; the vibrating actuators were detached from the headset for the EEG recording session and manually placed on the bilateral mastoid processes beneath the BrainVision neoprene cap which held 32 recording electrodes. For 5 min immediately before (T1 = pre-MATT baseline) and after (T2 = post-MATT baseline) this MATT session, EEG data were acquired with eyes closed in 30 channels. Electrodes Tp9 and Tp10, located in the area of the actuators, were removed to allow for placement of the MATT device during this session. Following 4 weeks of self-administered daily MATT, participants returned to the laboratory for a repeat (endpoint) EEG-MATT session (T3 = pre-MATT endpoint). Acute EEG changes were represented by T2-T1 and chronic changes by T3-T1.

Symptoms

Anxiety, depression, and stress symptoms were assessed at baseline, after 2 and 4 weeks of stimulation using several self-report scales: GAD-7, Beck Depression Inventory (BDI) (20), the Perceived Stress Scale (PSS) (21), and the Depression, Anxiety, Stress Scale (DASS) (22).

Interoceptive Awareness

The Multidimensional Assessment of Interoceptive Awareness (MAIA) (23) is a 32-item self-report scale developed to measure interoceptive body awareness within eight domains: Noticing, Not-distracting, Not-worrying, Attention Regulation, Emotional Awareness, Self-regulation, Body Listening, and Trusting. MAIA was administered at baseline and endpoint.

Feasibility/Side Effects

A paper daily treatment log sheet was given to each participant for recording the time of device use each day, along with any adverse effects or problems. A modified version of the Systematic Assessment for Treatment Emergent Events (SAFTEE) (24) was also used to detect possible side effects at all three assessment visits. A feasibility questionnaire was administered at the final visit. Details of these measures appear in **Supplementary Material**.

Data Processing and Statistical Analyses

Overall Analytic Plan

The goals of this project included assessment of clinical outcomes associated with MATT and their association to change in biomarkers. We tested change in EEG alpha and theta power associated with an acute (1 session) MATT treatment to confirm signals detected by the device developers in healthy volunteers. Exploratory aims included testing for changes in alpha and theta band metrics following chronic (4 weeks) MATT, and change in EEG markers associated with clinical outcomes. Feasibility, acceptability, and safety of MATT were evaluated to inform future clinical trial designs.

For analysis of symptoms and interoception, participants who were treated with MATT and completed a post-baseline assessment were included in the intent-to-treat (ITT) sample. Last-observation-carried forward (LOCF) values were used for all ITT analyses where week 4 data were missing. Participants who completed week 4 symptom and endpoint EEG assessments comprised the "completer" sample that was used for all EEG analyses.

Statistical tests were two-tailed with an alpha of 0.05. Given the highly exploratory nature of this work, the small sample size, and our goal for detection of potential EEG biomarkers associated with MATT, *p*-values were not adjusted for multiple comparisons on tests of EEG metrics (changes over time or their relation to symptoms). After the application of the Bonferroni factor, significance was defined by $p < 0.008$ on two-tailed tests for measures of mood and anxiety (GAD-7, BDI, PSS, DASS-Depression, DASS-Anxiety, and DASS-Stress). There was only one interoception measure (MAIA total); all *post hoc* tests of individual MAIA subscales (several of which comprised only three items) were considered exploratory and not corrected for multiple comparisons. Results are reported with uncorrected *p*-values below.

Analysis of Clinical Outcomes

Features of completers versus drop-outs were compared with independent samples *t*-tests and chi-squares to explore potential baseline differences. Simple descriptive statistics and paired *t*-tests were used to characterize symptom severity at baseline and to evaluate clinical change from baseline to week 4 endpoint (or LOCF) on total scores for each measure (GAD-7, BDI, PSS, and three subscales of the DASS: Depression, Anxiety, and Stress).

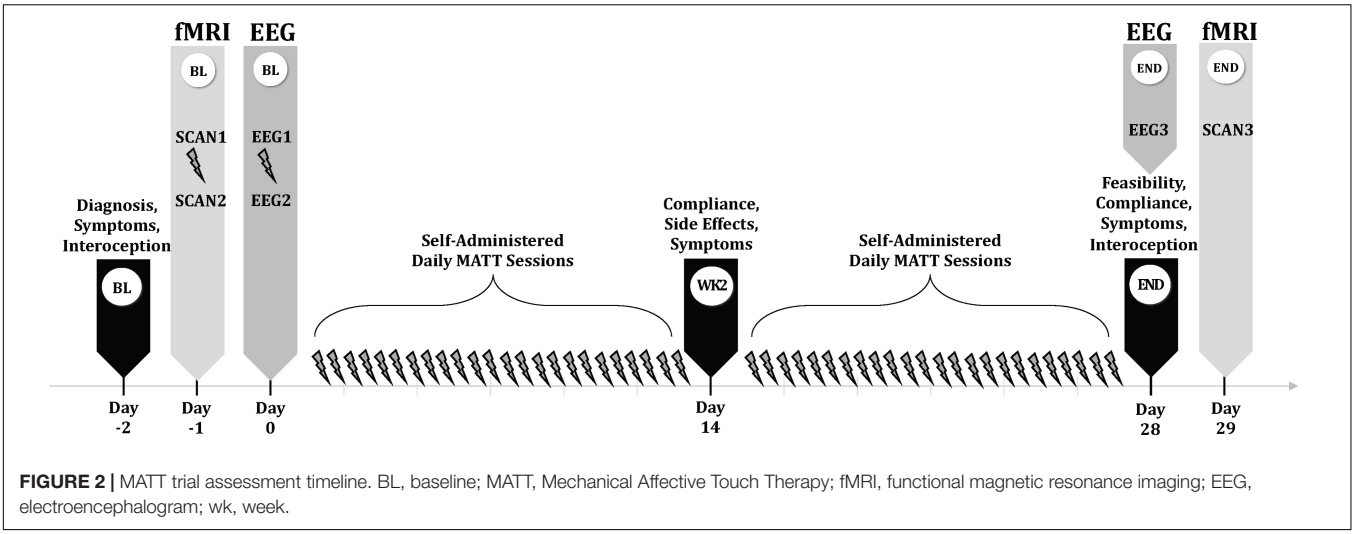

FIGURE 2 | MATT trial assessment timeline. BL, baseline; MATT, Mechanical Affective Touch Therapy; fMRI, functional magnetic resonance imaging; EEG, electroencephalogram; wk, week.

For each symptom measure, % Change values were calculated for week 4 (or LOCF) data, relative to baseline. Indices of interoceptive awareness (MAIA total, and for *post hoc* tests, 8 MAIA subscale scores) were analyzed similarly.

Electroencephalography Metrics

A priori EEG metrics of interest were alpha and theta power in frontal and occipital regions. We also explored other markers associated with anxiety: frontal alpha asymmetry (FAA) and individual peak alpha frequency (IAF) (see **Supplementary Material**). Baseline symptom severity (GAD-7, BDI, PSS, and DASS subscales) and interoception (MAIA) were first examined in association with T1 EEG metrics. Paired *t*-tests were used for EEG changes acutely (T1 vs. T2) and over time (T1 vs. T3). Pearson correlations compared acute (T2-T1) and chronic (T3-T1) change EEG metrics with symptom %Change.

Electroencephalography Data Processing

Analyzable EEG data were available from 18 participants at baseline; a subset of 16 had both baseline and endpoint EEG data. EEG data processing methods appear in **Supplementary Material**.

RESULTS

Clinical, Safety, and Feasibility Outcomes

A CONSORT flow diagram is presented in **Figure 3**. Baseline demographic and clinical characteristics for the ITT sample (n = 22) appear in **Table 1**. In the completer sample, mean scores on all symptom measures fell significantly (all $p < 0.01$), and MAIA total increased (p = 0.014) (**Table 2**). Based on diary entries (see **Supplementary Material** for details), mean MATT compliance with the prescribed dose for ITT ranged from 9 to 100%; among the 17 completers, compliance was 91 ± 13%. There was no significant correlation between compliance estimates and % Change on any symptom measure or any of the EEG metrics we evaluated.

There were no serious adverse events. Treatment-emergent events (at least moderate severity) were heart palpitations (n = 2, resolved by week 4), stuffy nose (n = 1), headache (n = 1; reported at week 2, attributed to device, and associated with study discontinuation), and weakness/fatigue (n = 1, reported at week 4). Feedback from participants confirmed feasibility and acceptability. The MATT device was found easy to use, with most of the treatments administered at home when alone. Out of 22 participants, 20 (91%) indicated that they would recommend MATT to others, and 17 (77%) indicated that they would request a prescription for MATT if it received regulatory approval.

Electroencephalography Markers

Alpha Power

At baseline, higher (absolute) T1 frontal alpha power (FAP) correlated with more severe symptoms on the DASS-Anxiety scale (r = 0.566; p = 0.017) and the DASS-Stress scale (r = 0.741; $p < 0.001$; **Supplementary Figure 1**); it was weakly associated with lower baseline values on the MAIA "Not-Worrying" subscale (r = −0.469; p = 0.049; **Supplementary Figure 1**).

Acutely, there was a non-significant trend toward increased mean FAP (t = 1.89; p = 0.076) at T1. A trend suggested larger FAP increases tended to correspond with greater increases in overall mindfulness (MAIA total) at week 4 (r = 0.480; p = 0.060). *Post hoc* exploration of MAIA subscales showed that the degree of acute FAP increase at T1 correlated with the extent of mindfulness increase after 4 weeks in Attention Regulation (r = 0.525; p = 0.037) and Self-Regulation (r = 0.636; p = 0.008) (**Figure 4**). While mean FAP from baseline to week 4 did not significantly change, greater reductions in perceived stress were associated with dampening of FAP following chronic MATT (r = −0.700; p = 0.003; **Supplementary Figure 1**).

Baseline occipital alpha power (OAP) did not correlate with any baseline symptom measures, and the group mean did not change following the baseline stimulation session. Chronic OAP decrease correlated with the degree of symptom improvement on BDI (r = −0.586; p = 0.017), DASS-Depression (r = −0.492; p = 0.053), DASS-Stress (r = −0.593; p = 0.015), and PSS

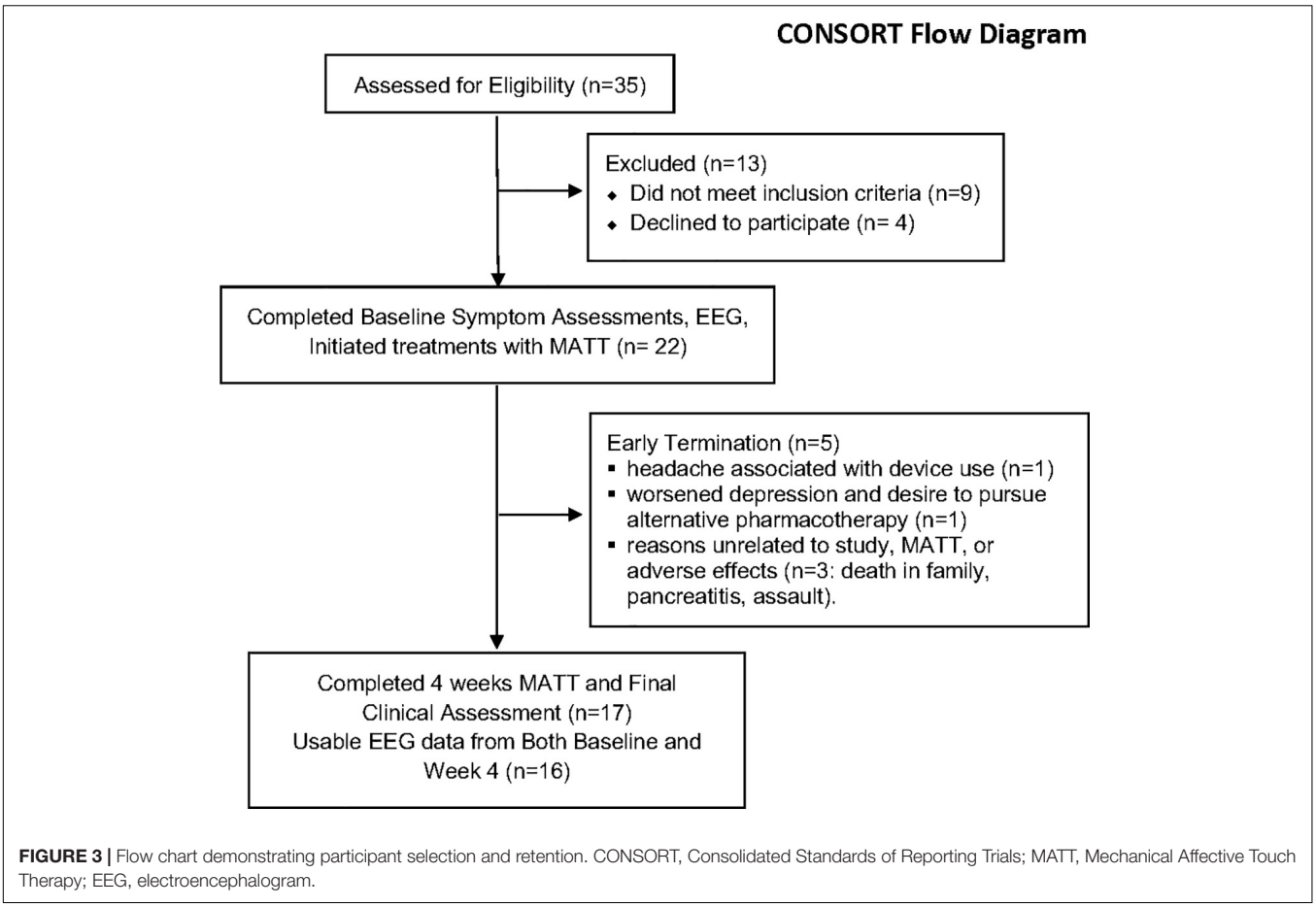

FIGURE 3 | Flow chart demonstrating participant selection and retention. CONSORT, Consolidated Standards of Reporting Trials; MATT, Mechanical Affective Touch Therapy; EEG, electroencephalogram.

($r = -0.650$; $p = 0.006$) (**Figure 5**). OAP decrease over 4 weeks was also found to be linked to the extent of mindfulness increase on the MAIA Noticing scale ($r = -0.612$; $p = 0.012$).

Theta Power

At baseline, frontal theta power (FTP) correlated only with perceived stress (PSS; $r = 0.616$, $p = 0.007$). Acute stimulation produced a significant increase in occipital theta power (OTP) ($t = 3.190$, $p = 0.005$), and the degree of change correlated with mindfulness enhanced attention regulation at week 4 ($r = 0.588$; $p = 0.017$; **Figure 4**). At week 4, the group mean for OTP was generally unchanged, but there were significant correlations between degree of OTP increase and symptom reductions with chronic MATT in depression (BDI $r = 0.507$, $p = 0.045$; DASS-Depression $r = 0.543$, $p = 0.030$), stress (DASS-Stress $r = 0.650$, $p = 0.006$), and anxiety (DASS-Anxiety $r = 0.533$, $p = 0.034$) (**Figure 5**).

DISCUSSION

In this report, we describe preliminary clinical outcomes, EEG biomarker data, and feasibility data from a 4-week, open-label pilot trial of a novel non-invasive neuromodulation therapy for individuals with anxiety disorders. We sought to replicate the EEG alpha power changes in association with acute MATT stimulation that were observed in healthy volunteers during device development and guided the selection of parameters for treating anxiety. Mindfulness techniques, which enhance interoceptive awareness, are associated with acute increases in alpha power, reflecting a relaxed state (16, 25, 26). Since interoception is a proposed pathway for MATT's anxiolytic and mood-improving effects, we expected stimulation would generate related signals in alpha EEG metrics. Generally consistent with early developers' observations, we found that an initial 20-min stimulation was associated with a non-significant trend toward enhanced FAP in our relatively small sample. There may have been a ceiling effect, as baseline resting alpha power was highly correlated with severity of stress and anxiety symptoms. After 4 weeks of daily MATT use, significant decreases in occipital alpha power (relative to baseline) were found among those who reported the greatest reductions in symptoms.

Increased theta power has also been shown to be a marker of a mindful state during meditation in a number of studies (16, 25). Researchers evaluating neuronal oscillations associated with somatosensory processes for pain versus touch found that, in contrast to EEG response to pain intensity, the intensity of brief touch was encoded only by theta activity (27).

Consistent with a potential mechanism that involves both CT and interoception, we observed increased theta power in the

TABLE 1 | Sample characteristics (n = 22).

Age [range; mean (SD)]	18–59; 37.3 (14.8)
Gender [*n* (%)]	
Male	5 (22.7%)
Female	16 (72.7%)
Non-binary or trans	1 (4.5%)
Race [*n* (%)]	
White	17 (77.3%)
Black	2 (9.1%)
Asian	1 (4.5%)
Other	2 (9.1%)
Employment status (not mutually exclusive) [*n* (%)]	
Student	7 (27.3%)
Disabled	3 (13.6%)
Employed full time	10 (45.5%)
Employed part-time	4 (13.6%)
Unemployed	3 (18.2%)
Current Diagnoses (not mutually exclusive) [*n* (%)]	
Generalized Anxiety Disorder	21 (95.5%)
Major depressive episode	10 (45.5%)
Panic Disorder	6 (27.3%)
Social Anxiety Disorder, Generalized	11 (50.0%)
Social Anxiety Disorder, Non-generalized	1 (4.5%)
Obsessive Compulsive Disorder	5 (22.7%)
Post-Traumatic Stress Disorder	3 (13.6%)
Baseline Symptom Severity	
GAD-7 [mean (SD)]	14.5 (2.2)
Perceived Stress Scale [mean (SD)]	36.2 (5.5)
Beck Depression Inventory [mean (SD)]	30.5 (7.6)
DASS-D Depression Scale [mean (SD)]	20.4 (9.0)
DASS-A Anxiety Scale [mean (SD)]	13.8 (7.9)
DASS-S Stress Scale [mean (SD)]	21.8 (7.9)
Interoceptive Awareness	
MAIA Scale Total [mean (SD)]	84.4 (18.0%)
Medications	
On stable doses of antidepressants/anxiolytics	16 (72.7%)
Not on any psychiatric medications	6 (27.3%)

TABLE 2 | Change in symptoms and interoception for completers (n = 17).

	Baseline mean (SD)	Week 4 mean (SD)	*t*-value	*p*-value
GAD-7	14.3 (2.2)	7.1 (4.5)	−5.62	0.00003*
Perceived Stress Scale	34.9 (4.5)	26.2 (6.0)	−5.92	0.00002*
Beck Depression Inventory	30.6 (7.7)	14.8 (11.5)	−5.59	0.00003*
DASS-D Depression Scale	19.7 (7.6)	10.1 (8.8)	−4.07	0.00079*
DASS-A Anxiety Scale	13.5 (6.8)	6.4 (4.6)	−3.87	0.0012*
DASS-S Stress Scale	20.6 (7.5)	10.6 (7.7)	−4.30	0.00048*
MAIA Interoceptive Awareness	83.1 (17.3)	93.5 (25.9)	−2.76	0.014

**Uncorrected for multiple comparisons; application of Bonferroni factor results in a corrected threshold of $p < 0.008$ for statistical significance in measures of mood, anxiety, and stress.*

occipital region immediately following a baseline MATT session. Of particular relevance to the therapeutic application considered here for MATT, acute enhancement of theta power, including or prominently in posterior brain regions, has also been shown to occur with transcutaneous trigeminal nerve stimulation (28), transcranial magnetic stimulation (29), and magnetic seizure therapy (30).

Enhanced interoception following 4 weeks of treatment was consistent with the proposed mechanism for MATT's anxiolytic effect and may implicate activation of insula. We observed increased mindfulness scores over 4 weeks corresponding with decreases in other symptom measures and EEG biomarkers, though some were trend-level findings and *post hoc* exploratory analyses. These preliminary signals define areas for subsequent inquiry and replication. More rigorously designed studies and analyses in larger samples are needed to further evaluate interoceptive processes as a putative therapeutic mechanism.

Though they must be interpreted in the context of an open-label design, the results also confirmed significant improvements in mood, stress, and anxiety symptoms over 4 weeks in a sample of adults with moderate baseline anxiety diagnosed with a range of anxiety disorders. Consistent with many naturalistically treated populations, GAD was prominent, and comorbid major depression characterized nearly half of the sample. The majority were on antidepressant or anxiolytic medications, but a notable portion was free of psychiatric medications and specifically seeking alternatives to pharmacotherapy for symptom management. Participants found use of MATT to be acceptable and were generally compliant with self-administering the 20-min sessions 1–2 times per day in the comfort of their home or other environment of their choice.

We gathered usability and feasibility data to guide further device development. Headache, reported by one subject at the mid-study assessment and associated with discontinuation, was the only notable side effect. Unfortunately, this subject did not report the event to the study team earlier, as the headache associated with MATT would likely have been resolved by turning down the intensity of the stimulation.

Future studies of devices like MATT which are self-administered at home would benefit from concurrent use of smartphone apps or online platforms through which participants can conveniently provide feedback about side effects after each session and receive additional instructions to troubleshoot technical difficulties or address adverse experiences with the device. Overall, the safety data collected in this small study confirmed MATT has a benign safety profile, supporting its further development as a treatment that can be administered with minimal medical monitoring.

A number of limitations characterize this study design and interpretation of the results. This was a single-arm open-label pilot study. As a critical goal of this pilot study was to detect preliminary biomarker signals associated with MATT through neuroimaging that might speak to its proposed therapeutic mechanisms, we employed a generally exploratory analytic approach that focused on magnitude of symptom change over time in relation to corresponding changes in biomarkers. While EEG metrics may be less vulnerable to placebo effects than mood/anxiety symptom change during a clinical trial, it will not be possible to know whether our biomarker observations are attributable to MATT until they are replicated with a

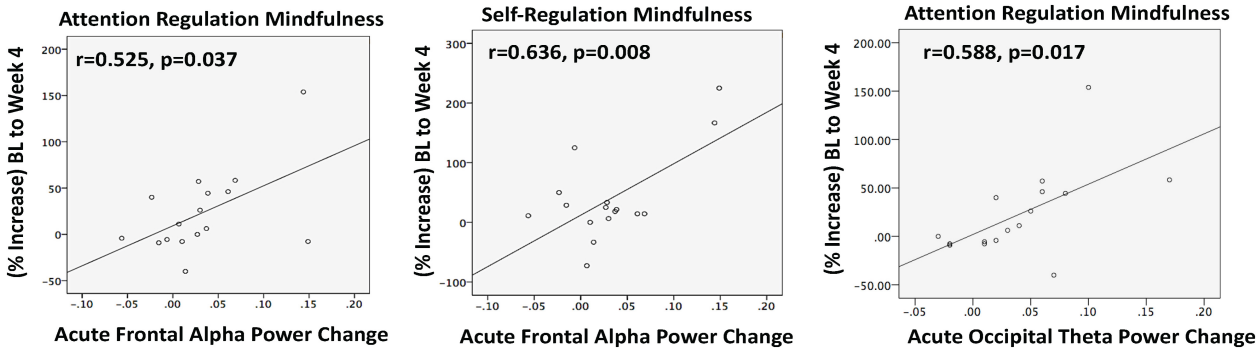

FIGURE 4 | Resting EEG was recorded immediately before and immediately after a 20 min stimulation session at baseline. In completers (n = 16), acute increases in frontal alpha power (left and center) and in occipital theta power (right) during the baseline MATT session correlated with enhanced mindfulness after 4 weeks of daily MATT (right). BL, baseline; MATT, Mechanical Affective Touch Therapy; EEG, electroencephalogram.

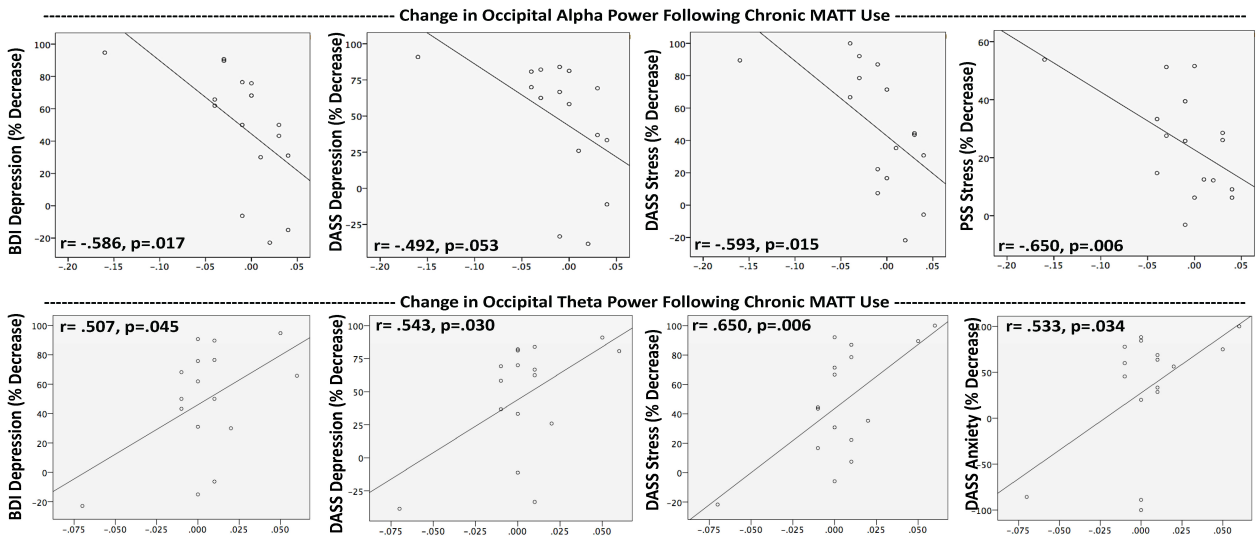

FIGURE 5 | Greater symptom improvement after a 4-week course of MATT was associated with reductions in occipital alpha power and increases in occipital theta power. In completers (n = 16) Resting EEG and symptom assessments were collected at baseline and after 4 weeks of daily MATT use. Negative values on the x-axes reflect decreases in resting power from baseline to study endpoint, positive values reflect enhanced power over time. Trend-level relationships are shown here to illustrate the reciprocal direction of change on the same measure for alpha vs. theta power. MATT, Mechanical Affective Touch Therapy; BDI, Beck Depression Inventory; DASS, Depression Anxiety Stress Scale; PSS, Perceived Stress Scale.

sham-controlled design. Given the large number of EEG metrics examined and the lack of p-value correction for EEG metrics, it is possible that we detected and reported oscillatory change signals which represent spurious findings. Nevertheless, the findings provide some preliminary support for further target engagement studies examining interoception pathways and anxiety/stress symptoms with MATT. Further supporting this conclusion are MRI data from this study showing that MATT was associated with acute and chronic connectivity increases in insula and posterior regions of the default mode network, respectively, particularly when there were decreases in stress and depression symptoms (17).

The data are also limited in their ability to elucidate relationships between MATT "dose" and other outcomes. We employed a relatively crude method for monitoring MATT dose, i.e., participants were told to self-record their daily use (minutes) of the device in a paper diary and return it at study visits; such data lack the level of accuracy and reliability that will be needed to properly investigate dose-response relationships. Evaluating feasibility was a goal of this study, so we did not compensate participants based on the number of self-administered sessions they logged or otherwise incentivize them to falsify their reports of MATT use. With our simple self-report method and through calculated estimates of each participant's dose received (relative to the optimal/prescribed dose of 20 min twice daily for 4 weeks), we found compliance was generally good but variable across subjects, as might be expected for an intervention that is self-administered outside of a medical setting multiple times per day. Future studies will benefit from more sophisticated methods for remotely monitoring daily MATT compliance, tracking cumulative dose

for individual participants, and capturing if/how use of the device on an "as needed" basis may be acutely anxiolytic.

Confirmation of a C-tactile afferent pathway for insula activation as a putative therapeutic mechanism of MATT would inform its potential applicability in a wide range of disorders where interventions such as meditation and mindfulness have shown promise. Notwithstanding the limitations described here, our results suggest that this specific "affective touch" pathway may provide a way to deliver neurostimulation in a novel manner that appears to have few side effects and does not entail electrical or electromagnetic energy.

CONCLUSION

Data from this open-label trial suggest MATT is a promising non-invasive therapeutic approach to anxiety disorders. Acute and chronic use of the investigational MATT device had reciprocal effects on alpha and theta oscillatory activity that corresponded with clinical improvement in this small pilot study. However, double-blind controlled trials and replication samples are needed to definitively establish efficacy and more rigorously replicate proposed therapeutic mechanisms.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Butler Hospital Institutional Review Board (IRB). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SH conceived the basic idea. LC and SH designed the study. LC directed the study at Butler Hospital and drafted the manuscript. ET, EK, FK, and AF collected the clinical and EEG data. EK, LC, SG, AF, and ST conducted the data quality control procedures and performed the statistical and data analyses. QB, LC, AF, and EK created the figures and tables. LC, EK, QB, SG, and ST provided input on data analysis and interpretation of results. All authors contributed to the revisions of the manuscript and read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.877574/full#supplementary-material

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SYSTEMATIC REVIEW
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Efficacy and Tolerability of Repetitive Transcranial Magnetic Stimulation on Suicidal Ideation: A Systemic Review and Meta-Analysis

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Objective: This study aimed to investigate the efficacy of repetitive transcranial magnetic stimulation (rTMS) in treating suicidal ideation in patients with mental illness.

Method: We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Major electronic databases were systematically searched from the time of their inception until July 22, 2021. The primary outcome was the mean change in the scores for suicidal ideation. The secondary outcome was the mean change in depression severity.

Results: Ten randomized controlled trials were eligible with 415 participants in the active treatment group (mean age = 53.78 years; mean proportion of women = 54.5%) and 387 participants in the control group (mean age = 55.52 years; mean proportion of women = 51.78%). rTMS significantly reduced suicidal ideation (k = 10, n = 802, Hedges' g = −0.390, 95% confidence interval [CI] = −0.193 to −0.588, p <.001) and severity of depressive symptoms (k = 9, n = 761, Hedges' g = −0.698, 95% CI = −1.023 to −0.372, p < 0.001) in patients with major mental disorders. In the subgroup analysis, rTMS reduced suicidal ideation among patients with non-treatment-resistant depression (non-TRD) (−0.208) but not in those with TRD. rTMS as combination therapy had a larger effect than did monotherapy (−0.500 vs. −0.210). Suicidal ideation significantly reduced in patients receiving more than ten treatment sessions (-0.255). Importantly, the rTMS group showed favorable tolerability without major adverse events.

Conclusion: The study showed that rTMS was effective and well-tolerated in reducing suicidal ideation and depression severity in patients with major mental disorders.

Keywords: suicidal ideation, repetitive transcranial magnetic stimulation, depression, borderline personality, bipolar disorder

INTRODUCTION

Suicidal behavior is a significant health problem worldwide, accounting for 1.3% of all deaths. More than 700,000 people die by suicide annually. A systematic review of 44 studies from 2000 to 2017 showed that an average of 80% of patients reached out to primary health care in the year prior to suicide (1). Treatments for suicidal patients include psychotherapy, social support intervention, electroconvulsive therapy, and pharmacotherapy using antidepressants, lithium, and clozapine (2). However, owing to the complexity of suicide and associated risk factors, it is difficult to suggest clear treatment guidelines (3).

Mood disorders constitute one-half to two-thirds of all completed suicides (4). A meta-analysis showed that approximately 90% of suicide cases involved a psychiatric disorder, of which approximately 43.2% had some of the affective disorders and 25.7% had issues with substance use (5–7). Among patients with affective disorders, approximately 30%−40% and 50% patients had major depressive disorder (MDD) and bipolar disorder (BD), respectively (8, 9). However, a prospective study showed that BD did not independently influence the risk of suicidal behavior (10). Another study showed that patients with pure major depressive episodes or mixed states in BD had higher risk of suicidal behavior presentation than those with mania, hypomania, and euthymic periods (11). Hence, treatment of depressive episodes in patients with unipolar and bipolar disorder is important for the prevention of suicide attempts.

The effect of psychopharmacology on suicidal outcomes remains unclear because of the heterogeneity of strategies and outcome measures as well as the absence of good standards for evidence level in the literature (2). Another systemic review reported that ketamine and lithium reduced the rate of suicide compared with placebo (12). However, a recent observational study reported that the use of psychotropic medication, including antidepressants and lithium, was not associated with a decrease in suicidal ideation and suicide reattempts (13). Therefore, it is vital to develop more effective and alternative strategies to prevent suicide (2).

Transcranial magnetic stimulation (TMS) is a United States Food and Drug Administration-approved non-invasive brain stimulation technique for treatment-resistant depression (TRD) (14–16). It is also used to treat several psychiatric disorders, such as BD (17), schizophrenia (18), obsessive-compulsive disorder (15, 19), and borderline personality disorder (BPD) (20), all of which led to a higher risk of death from suicide (21). A recent systematic review showed that TMS may be an effective, safe, and well-tolerated technique for treating suicidal behavior, especially in patients with concurrent depression treated with antidepressants (22). Another systematic review of 20 studies, including both randomized controlled trials (RCTs) and open-label trials, found high-frequency ($\geq$ 10 Hz) repetitive TMS over the left dorsolateral pre-frontal cortex to be an adjunct to antidepressants, which significantly reduced suicidal behavior in patients with TRD (23). However, no quantitative outcomes were reported in the meta-analysis method. The results should be cautiously interpreted because of the considerable risk of bias in qualitative studies.

Aside from the above gaps in the literature, no meta-analysis has been performed to estimate the effect of rTMS on suicide-related outcomes. Although some evidence has shown that rTMS is effective in reducing psychiatric symptoms in several mental disorders, the efficacy of rTMS in reducing suicidality remains uncertain. This study aimed to demonstrate the efficacy and safety of rTMS in the treatment of suicidal behavior in major mental disorders. We also compared the effect of rTMS in reducing suicide risk among patients with different psychiatric diagnoses.

METHODS

Database Searches

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (24) (**Supplementary Tables S1A,B**). PubMed, Medline, Embase, and Cochrane Library databases were systematically searched from the date of their inception until July 22, 2021 (**Supplementary Table S2**). The search terms included *brain modulation, rTMS, repetitive transcranial magnetic stimulation, TBS, theta burst stimulation, suicide, suicidality, suicide attempt, and suicide ideation.* Medical subject headings, free text terms, and variations were applied, and Boolean operators (OR, AND) were used to combine the searches. The reference lists of the included articles and recent reviews were also searched to identify additional references. This review was registered in the Prospective Register of Systematic Reviews (PROSPERO, CRD42022269282). Ethical approval was not sought for this study, as it included an analysis of secondary data.

Eligibility Criteria and Study Selection

The following eligibility criteria were applied: (1) peer-reviewed original articles on clinical trials investigating the effects of rTMS treatment for reducing suicidality; (2) RCTs only; and (3) patients with suicidal ideation without restriction to specific psychiatric disorders. We excluded case series, observational studies, open-label trials, conference abstracts, and trials without a placebo arm (**Supplementary Table S3**). If there were overlapping data in the studies, only the study with complete data was included in the analyses. Two authors (CS Chu and GW Chen) independently assessed the inclusion/exclusion criteria and selected the studies. Any discrepancies in article retrieval were discussed between the two authors. In the absence of consensus between the two reviewers, a third reviewer (TW Hsu) made the final decision.

Methodological Quality Assessment

The Jadad score (25) and the Cochrane Risk of Bias version 2 (RoB2) (26) tools were used by the two authors (CS Chu and GW Chen) to assess the methodological quality of the included studies independently and in duplicate. The Jadad score included three categories of study quality: randomization, blindness, and withdrawals and dropouts. The Jadad score ranged from 0 (poor quality) to 5 (high quality). In case of discrepancies, another author (TW Hsu) was consulted to obtain a consensus.

Data Extraction

The two authors (CS Chu and GW Chen) extracted data from the included studies in accordance with a pre-specified data extraction form independently and in duplicate. Any discrepancies were resolved by a third investigator (TW Hsu). The extracted data included basic characteristics of the participants (mean age and percentage of women), stimulation protocol (stimulation site, pulses per session, total sessions, frequency, and power), combined treatment (antidepressant and other usual treatment), and study quality measured by the Jadad scoring system.

Primary and Secondary Outcomes

We defined the primary outcome as the mean change in the scores of suicidal ideation between baseline and the end of the last rTMS session, which had been recorded using a validated scale, such as the Beck Scale of Suicidal Ideation (27), suicide item of the Hamilton Rating Scale for Depression (17 items or 24 items) (28), Self-rating Idea of Suicide Scale, Columbia Suicide Severity Rating Scale (29), or suicidal behavior item of Clinical Global Impression Scale for BPD (30).

We defined secondary outcome as the response rate of depression, which was defined as more than 50% reduction of the depressive symptom score from baseline to the end of the last rTMS session. We defined secondary outcome as the response rate of depression, which was defined as more than 50% reduction of the depressive symptom score from baseline to the end of the last rTMS session. We chose improvement of depression as secondary outcome because patients with suicidal ideation are highly comorbid with depression. We want to know if the efficacy of rTMS on suicidal ideation is related to patients' depression. Therefore, we further investigated whether the effect of rTMS on suicidal ideation is independent from depression change by exploring the association between the improvement of depressive severity and reduction of suicidal ideation. We extracted data on the levels of depression based on the most used scales in the included studies. The Hamilton depression rating scale (28) is the most frequently used scale to assess depression severity, followed by the Montgomery-Åsberg Depression Rating Scale (31) or Beck Depression Inventory (BDI) (32). The secondary outcome was the response rate, which was defined as more than 50% reduction of the depressive symptom score from baseline to the end of the last rTMS session.

Meta-Analysis Procedure

Due to the anticipated heterogeneity across studies, a random-effects meta-analysis was conducted (33). We calculated the Hedges' g statistic as the estimate of the within-group effect size and 95% confidence intervals (CI) for changes from pre-treatment to post-treatment and between-group (intervention group vs. control group) effect size for the primary outcome and mean change in depressive symptoms score. When different scales were used between studies, standardized mean differences between treatment groups were calculated for each trial and used to derive the total estimate of treatment effect on the outcomes. The standardized mean differences offer a summary statistic in meta-analysis when the studies assess the same outcome but with different scales (34). We used the standard error or *t*-value to estimate those without a standard deviation. For interpretation of effect sizes, we followed the rule of classifying <0.2 as very small, 0.2–0.5 as small, 0.5–0.8 as moderate, and >0.8 as large. Odds ratios and 95% CIs were calculated for dichotomous data. All meta-analytic procedures were performed using the Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, NJ). The threshold for statistical significance was set at a two-tailed P-value < 0.05.

Heterogeneity, Publication Bias, Sensitivity Analysis, Meta-Regression Analyses, and Subgroup Analysis

The Cochran's Q test and I^2 metric were used to assess heterogeneity. Egger's regression test and funnel plot inspection were used to assess publication bias. Meta-regression analyses were conducted with unrestricted maximum likelihood random effects when data on each potential moderator were used in at least five different studies (35). The mean age, percentage of women, and Jadad scores were considered as variables for the meta-regression analyses. We performed sensitivity testing with the one study removal test to investigate potential confounders by any one of the outliers in the included studies (36). A subgroup meta-analysis was performed when at least three sets of data were available. We conducted a subgroup analysis to explore the potential difference when comparison was done based on the characteristics of the participants who may require special attention. We performed subgroup analyses for different diagnoses (TRD vs. non-TRD) and treatment protocol (rTMS monotherapy vs. rTMS combination therapy; <10 sessions vs. $\geq$ 10 sessions; rTMS vs. intermittent theta-burst stimulation (iTBS); left dorsolateral pre-frontal cortex (DLPFC) vs. not left DLPFC). The definitions of TRD were based on antidepressant trials Stage I (37, 38) or II (39), Thase and Rush staging model (40), and Stage III or IV (41) in the antidepressant treatment history form (42). We defined those receiving rTMS monotherapy as those: (1) not allowed to receive concurrent treatment with antidepressants (43), (2) at least 2 weeks free from using psychotropic agents except for the habitual use of benzodiazepines, if necessary (37), and (3) 2 weeks free from using antidepressant, antipsychotic, and mood stabilizers (38).

RESULTS

Studies in the Meta-Analysis

After searching the database, we identified 823 potential articles, from which we excluded 704 articles after title and abstract screening. We excluded 109 studies through full-text assessment for specific reasons (**Supplementary Table S3**). Finally, 10 studies satisfied our criteria (**Table 1**) (37–39, 41, 43–48). A flowchart of the search strategy is presented in **Figure 1**. A total of 802 participants were included with a mean age of 54.62 (SD = 11.46) years and a mean proportion of women of 53.2% (429/802).

All 10 studies were RCTs (37–39, 41, 43–48). For the primary and secondary outcomes, available data for further analysis were

TABLE 1 | The characteristics and demographics of the included studies.

Author (year); Country	Population	Follow up time	Intervention, n Control, n	Age (female, %)	Stimulation protocol (stimulate site, pulses per session, total sessions, frequency and power)	Scales for primary outcome	Site targeting
Desmyter S et al. (38); Belgium	TRD	1 weeks	r-TMS + sham control, 12	44.91 ± 10.8(58.3)	L-DLPFC, 1620 pulses per-session, 20 sessions, 54 triplet bursts within 2s, 100% MT	BSI	Neuro-navigation
George MS et al. (44); USA	Post-traumatic stress disorder	6 months	TAU+ r-TMS, 20 TAU+ sham control, 21	38.7 ± 15(10) 46.1 ± 15.9 (19)	L-DLPFC, 6000 pulses per session, 9 sessions, 10Hz, 120% MT	BSI	N/A
Qin BY et al. (45); China	Elderly patients with depression	4 weeks	Escitalopram + r-TMS, 85 Escitalopram + sham control, 100	70.03 ± 5.97 (67.5) 69.43 ± 5.98 (67.34)	L-DLPFC, 120-2000 pulses per session, 20 sessions, 10Hz, 80%∼110% MT	SIOSS	N/A
Yesavage JA et al. (41); USA	TRD	6 months	TAU+ r-TMS, 81 TAU+ sham control, 83	55.6 ± 12.2(33.33) 54.8 ± 12.6(35)	L-DLPFC, 4000 pulses per session, 20-30 sessions, 10Hz, 120% MT	BSI, CSSRS	N/A
Weissman CR et al., (39); Canada	TRD	6 weeks	r-TMS, 128 Sham control, 61	49.26 ± 13.2(61.7) 47.3 ± 12.5(62.3)	L-DLPFC or bil-DLPFC, 1215-2100 pulses per session, 15 sessions, R: 1Hz/ L: 10 Hz, 100-120% MT	Suicide item of HAMD-17	5-cm rule/ structural MRI
Baeken C et al. (37); Belgium	TRD	1 weeks	r-TMS, 21 Sham control, 24	37 ± 18.5(76.2) 47.5 ± 20.75(70.8)	L-DLPFC, 1620 pulses per session, 20 sessions, 54 triplet bursts within 2s, 110% MT	BSI	Neuro-navigation
Rao V et al. (43); USA	MDD after traumatic brain injury	16 weeks	r-TMS, 17 Sham control, 17	39.8 ± 14.2(61.5) 40.2 ± 14.6(35.3)	R-DLPFC, 1200 pulses per session, 20 sessions, 1Hz, 110% MT	BSI	F4 of the International 10–20 System for Electrode Placement
Dai L et al. (46); China	Elderly depression patients	4 weeks	Escitalopram + r-TMS, 62 Escitalopram + sham control, 62	69.99 ± 8.69(63) 67.15 ± 9.9(60)	L-DLPFC, 800 pulses per session, 20 sessions, 10Hz, 100% MT	SIOSS	N/A
Pan F et al. (46); China	MDD	1 weeks	Escitalopram + r-TMS, 21 Escitalopram + sham control, 21	18.14 ± 3.94(90.5) 21.43 ± 6.79(76.2)	L-DLPFC, 6000 pulses per session, 7 sessions, 10Hz, 100% MT	BSI	Neuro-navigation
Calderon-Moctezuma AR et al. (47); Mexico	Borderline personality disorder	3 weeks	TAU+ r-TMS, 9 TAU+ sham control, 9	24 ± 6.29 (71.4) 28.14 ± 8.31 (57.1)	DMPFC, 1500 pulses per session, 15 sessions, 5Hz, 100% MT	Suicidal behavior item in CGI-BPD	N/A

BSI, Beck scale for suicide ideation; CGI-BPD, Clinical Global Impression Scale for Borderline Personality Disorder; CSSRS, Columbia Suicide Severity Rating Scale; DLPFC, Dorsolateral pre-frontal cortex; DMPFC, dorsomedial pre-frontal cortex; HAMD-17, Hamilton Depression Rating Scale-17; MDD, Major depressive disorder; MT, motor threshold; r-TMS, repetitive transcranial magnetic stimulation; SIOSS, Self-rating Idea of Suicide Scale; TAU, Treatment-As-Usual; TRD, Treatment-resistant depression.

obtained from 10 studies on the reduction of suicidal ideation (37–39, 41, 43–48). Nine studies included patients with current depressive episodes. The most common diagnosis was MDD in six studies (37–39, 41, 43, 46). One of these included patients had a diagnosis of MDD and traumatic brain injury (TBI) (43). Among the six studies that included MDD cases, four had TRD (37–39, 41). The remaining four studies included cases with BPD (47), depressive disorder (45, 48), and unipolar or bipolar disorder combined with post-traumatic stress disorder or traumatic brain injury (44). The RCTs included 415 participants in the active treatment group (mean age = 53.78 years, SD = 11.4; mean proportion of women = 54.5%) and 387 participants in the control group (mean age = 55.52 years, SD = 11.5; mean proportion of women = 51.78%) (37–39, 41, 43–48).

Methodological Quality of the Included Studies

We assessed the quality of the included studies using the Jadad scoring system (25) and the Cochrane Risk of Bias version 2 (RoB2) (26) tools. Across all 10 studies, the average Jadad

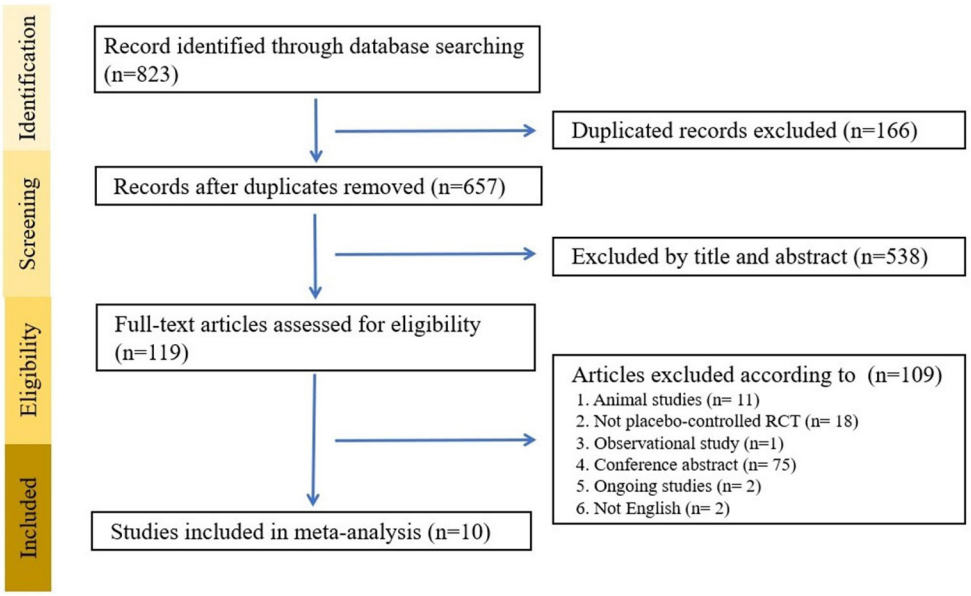

FIGURE 1 | Flow chart of the search strategy.

score was 3 (range: 2–5) (**Supplementary Table S4**). Five of the 10 studies showed a low overall risk of bias according to RoB2 evaluation. The analysis of the remaining five studies revealed some concerns when one or more domains were judged to be at "some concerns" of bias (**Supplementary Table S5**). The included studies revealed 50% (5/10) trials rating as "some concerns" of bias mainly arising from measurement of the outcome.

Handling the Differences in Scales Used to Evaluate the Primary and Secondary Outcome

For the primary outcome, there are five kinds of scales used to evaluate the severity of suicidal ideation. The scales include the Beck Scale for Suicide Ideation, Self-rating Idea of Suicide Scale, Suicidal behavior items of the clinical global impression scale for BPD, Columbia-Suicide Severity Rating Scale, and suicide items in the Hamilton Depression Rating Scale-17. There is no formulation to convert data from one scale to one another. Hence, the standardized mean differences (SMD) between treatment groups were calculated for each trial and used to derive the total estimate of the treatment effect on the outcomes. The SMD is a summary statistic in meta-analysis when the studies assess the same outcome but with different scales (34)." For the secondary outcome, there are four kinds of scales used to evaluate the severity of depression. The scales include the Hamilton Depression Rating Scale-17 (HAMD-17), Hamilton Depression Rating Scale-24 (HAMD-24), BDI-I and BDI-II. We converted BDI-I, BDI-II, and HAMD-24 scores to equivalent HAMD-17 scores based on previous studies (49).

Primary Outcome: Efficacy of RTMS in Reducing Suicidal Ideation

In patients with suicidal ideation, rTMS significantly reduced suicidality (k = 10, n = 802, Hedges' g = −0.390, 95% CI = −0.193 to −0.588, $p < 0.001$) (**Figure 2**). There was no evidence of publication bias (Egger's regression test, $p = 0.117$), but significant heterogeneity was observed (Q value = 22.964, I2 = 56.453, $p = 0.0011$). In the sensitivity analysis, the results remained significant, showing the efficacy of rTMS in reducing suicidal ideation after the one study removal test. Furthermore, after removing the study conducted by Pan et al., no significant heterogeneity was found.

Source of Heterogeneity: Meta-Regression

In the meta-regression analysis, the percentage of females (k=10, slope =-0.994, p =0.004) and baseline BSI score (k=6, slope = −0.03136, $p < 0.016$) emerged as significant moderators. Therefore, rTMS was more efficacious in reducing suicidal ideation in the studies with higher percentage of females and higher baseline suicidal severity than those with lower percentage of females and lower baseline suicidal severity. Age, baseline depression severity, treatment duration, improvement of depression severity (change of equivalent HAMD-17 score), and pulses per session did not contribute to heterogeneity (**Supplementary Table S6A**).

Source of Heterogeneity: Subgroup Analysis

We conducted five subgroup analyses, including TRD compared with non-TRD, rTMS combination therapy compared with rTMS monotherapy, <10 treatment sessions compared with more than

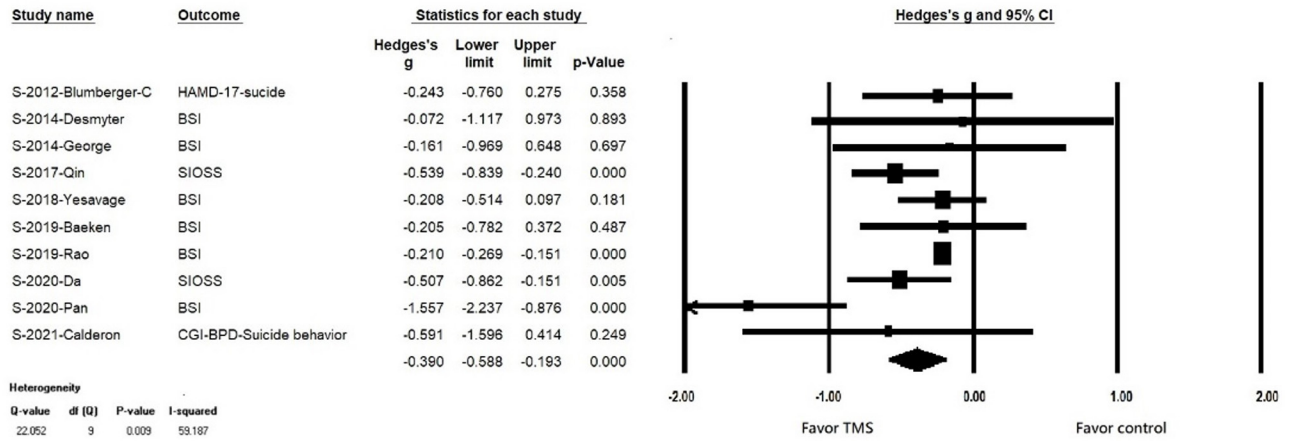

FIGURE 2 | Forest plot of meta-analysis of improvement of suicidal ideation in patients receiving repetitive transcranial magnetic stimulation treatment and in those with control treatment.

10 treatment sessions, target site over left DLPFC compared with non-left DLPFC, and rTMS compared with iTBS (**Table 2**).

We found that rTMS reduced suicidal ideation among patients with non-TRD, but not in the TRD population (TRD, k = 4, n = 410, Hedges' g = −0.208, 95% CI = −0.441 to 0.025, p = 0.081; non-TRD, k = 6, n = 444, Hedges' g = −0.534, 95% CI = −0.856 to −0.213, p = 0.001) (**Figures 3A,B**). Both rTMS monotherapy and rTMS combination therapy significantly reduced suicidal ideation (rTMS combined with usual treatment, k = 7, n = 715, Hedges' g = −0.500, 95% CI = −0.777 to −0.222, $p < 0.001$; rTMS alone, k = 3, n = 87 Hedges' g = −0.210, 95% CI = −0.268 to −0.151, $p < 0.001$) (**Figures 4A,B**). Patients who received rTMS combined with usual treatment had a significantly greater reduction in suicidal ideation than those who received rTMS monotherapy alone (p= 0.005). Patients who underwent more than 10 treatment sessions had a significantly reduced suicidal ideation (10 or more sessions of rTMS, k = 8, n = 719, Hedges' g = −0.255, 95% CI = −0.342 to −0.168, $p < 0.001$); however, we could not perform subgroup analysis in those receiving less than 10 treatment sessions because only two studies were available. Patients who received rTMS showed significant reduction in suicidal ideation (k = 8, n = 797, Hedges'g = −0.427, 95% CI = −0.651 to −0.202, $p < 0.001$) (**Supplementary Figure S1A**); however, we could not perform a subgroup analysis in those receiving iTBS because only two studies were available. Patients who received rTMS over the left DLPFC experienced significantly reduced suicidal ideation (k = 7, n = 613, Hedges'g = −0.47, 95% CI = −0.757 to −0.182, p = 0.001) (**Supplementary Figure S1A**). The other three studies targeted the dorsomedial pre-frontal cortex (DMPFC) (47), right DLPFC (43), and bilateral DLPFC (39) respectively. Therefore, we could not perform a subgroup analysis.

Regarding method of targeting, several different kinds of methods were used, including neuro-navigation (37, 38, 46), 5-cm rule (41), mixed 5-cm rule and neuro-navigation (39), 6-cm rule (44), and the International 10–20 System for Electrode Placement (43, 47). However, the remaining two studies (45, 48) did not mention the method of targeting; therefore, subgroup analysis could not be performed.

Secondary Outcome: The Efficacy of RTMS on Reducing Depressive Symptom Severity

rTMS significantly reduced the severity of depressive symptoms (k = 9, n = 761, Hedges' g = −0.697, 95% CI = −1.023 to −0.371, $p < 0.001$). There was no evidence of publication bias (Egger's regression test, t = 0.399, p = 0.702), but significant heterogeneity was observed (Q value =24.334, I2 = 67.124, p = 0.002). In the sensitivity analysis, the results remained significant, showing the efficacy of rTMS in reducing depressive symptom severity after the one study removal test. Furthermore, after removing the study conducted by Pan et al., no significant heterogeneity was found.

Source of Heterogeneity of Secondary Outcome: Meta-Regression

In the meta-regression analysis, the percentage of women (k=9, slope = −1.226, p= 0.001) and baseline equivalent HAMD-17 score (k=9, slope= −0.109, p= 0.001) emerged as significant moderators. Therefore, rTMS was more efficacious in reducing suicidal ideation in the studies with higher percentage of women and higher baseline equivalent HAMD-17 scores than in the studies with lower percentage of women and lower baseline equivalent HAMD-17 scores. Age, treatment duration, and pulses per-session did not explain the heterogeneity (**Supplementary Table S6B**).

Source of Heterogeneity of Secondary Outcome: Subgroup Analysis

As shown in **Table 2**, we found that rTMS reduced depressive severity among patients with both TRD and non-TRD (TRD, k = 4, n = 410, Hedges' g = −0.289, 95% CI = −0.523 to −0.055, p = 0.015; non-TRD, k = 5, n = 403, Hedges' g =

TABLE 2 | Subgroup analyses of rTMS on suicide ideation reduction and depression symptoms.

	Improvement in suicide ideation scale (Hedges' g, 95% CI)	Improvement in depression scale (Hedges' g, 95% CI)
Diagnoses		
TRD	−0.208 (−0.441 to 0.025) $p = 0.081$, k= 4	– 0.289 (– 0.523 to – 0.055) $p = 0.015$, k= 4
Non-TRD	−0.534 (−0.856 to −0.213) $p = 0.001$, k= 6	−1.054 (−1.432 to −0.677) $p < 0.001$, k= 5
Treatment		
rTMS combination therapy[a]	−0.500 (−0.777 to −0.222) $p < 0.001$, k= 7	−0.685 (−0.853 to −0.517) $p < 0.001$, k= 6
rTMS monotherapy	−0.210 (−0.268 to −0.151) $p < 0.001$, k= 3	−0.271 (−0.775 to 0.234) $p = 0.293$, k= 3
Treatment session		
<10 sessions	k = 2, not applicable	k = 2, not applicable
10 or more treatment sessions	−0.255 (−0.342 to −0.168) $p < 0.001$, $k = 8$	−0.567 (−0.812 to −0.321) $p < 0.001$, $k = 8$
Treatment protocol		
rTMS	−0.427 (−0.651 to −0.202) $p < 0.001$, $k = 8$	−0.799 (−1.179 to −0.419) $p < 0.001$, $k = 7$
iTBS	$k = 2$, not applicable	$k = 2$, not applicable
Target site		
Left DLPFC	−0.47 (−0.757 to −0.182) $p = 0.001$, $k = 7$	−0.73 (−1.132 to −0.328) $p < 0.001$, $k = 6$
Not left DLPFC (including Right DLPFC, DMPFC, and bilateral DLPFC)	each $k = 1$, not applicable	each $k = 1$, not applicable

CI, confidence interval; DLPFC, dorsolateral pre-frontal cortex; DMPFC, dorsomedial prefrontal cortex; Itbs, Intermittent theta burst stimulation; r-TMS, repetitive transcranial magnetic stimulation; TRD, Treatment-resistant depression.

[a]*allowed to combine other usual medication or usual treatment.*

−1.054, 95% CI = −1.432 to −0.677, $p < 0.001$). Patients with non-TRD had a significantly greater reduction in depressive severity than those with TRD after rTMS treatment ($p < 0.001$). Patients receiving rTMS combination therapy had a significantly reduced depressive severity, but not for those receiving rTMS monotherapy (rTMS combination therapy, k = 6, $n = 722$, Hedges' g = −0.685, 95% CI = −0.853 to −0.517, $p < 0.001$; rTMS monotherapy, k = 3, $n = 91$; Hedges' g = −0.271, 95% CI = −0.775 to 0.234, $p = 0.293$). Patients who underwent more than 10 treatment sessions had a significantly reduced depressive severity (10 or more sessions of rTMS, k = 8, $n = 771$, Hedges' g = −0.567, 95% CI = −0.812 to −0.321, $p < 0.001$); however, we could not perform subgroup analysis in those receiving <10 treatment sessions since only two studies were available. Patients who received rTMS had a significantly reduced depressive severity (rTMS, k = 7, $n = 756$, Hedges' g = −0.799, 95% CI = −1.179 to −0.419, $p < 0.001$); however, we could not perform a subgroup analysis in those receiving iTBS because only two studies were available. Patients who received rTMS over the left DLPFC experienced significantly reduced depression severity (k = 6, $n = 572$, Hedges'g = −0.73, 95% CI = −1.132 to −0.328, $p < 0.001$). The remaining three studies targeted the DMPFC (47), right DLPFC (43), and bilateral DLPFC (39). Therefore, we could not perform a subgroup analysis.

Regarding method of targeting, several different kinds of methods were used, including neuro-navigation (37, 38, 46), 5-cm rule (41), mixed 5-cm rule and neuro-navigation (39), and the International 10–20 System for Electrode Placement (43, 47). However, the remaining two studies (45, 48) did not mention the method of targeting; therefore, subgroup analysis could not be performed.

Adverse Effect and Attrition

Most of the included studies reported common adverse effects, such as headaches (39, 41, 43–48) and dizziness (43–45, 47, 48). Other adverse effects such as nausea/vomiting (44, 45, 48), dry mouth (45, 48), eye problems (43, 44), sleep problems (39, 43), constipation (45, 48), and chest tightness (48) have also been reported. The attrition rate ranged from 0% (37, 38) to 55% (44) (**Supplementary Table S7**).

DISCUSSION

The main findings of this meta-analysis are as follows: First, rTMS significantly reduced suicidal ideation and improved depressive symptoms in patients with major psychiatric disorders. Second, rTMS significantly reduced suicidal ideation among patients with non-TRD, but not in those with TRD. Third, both rTMS monotherapy and rTMS combination therapy significantly reduced suicidal ideation, and rTMS combination therapy showed significantly better efficacy than rTMS monotherapy. Fourth, rTMS significantly reduced suicidal

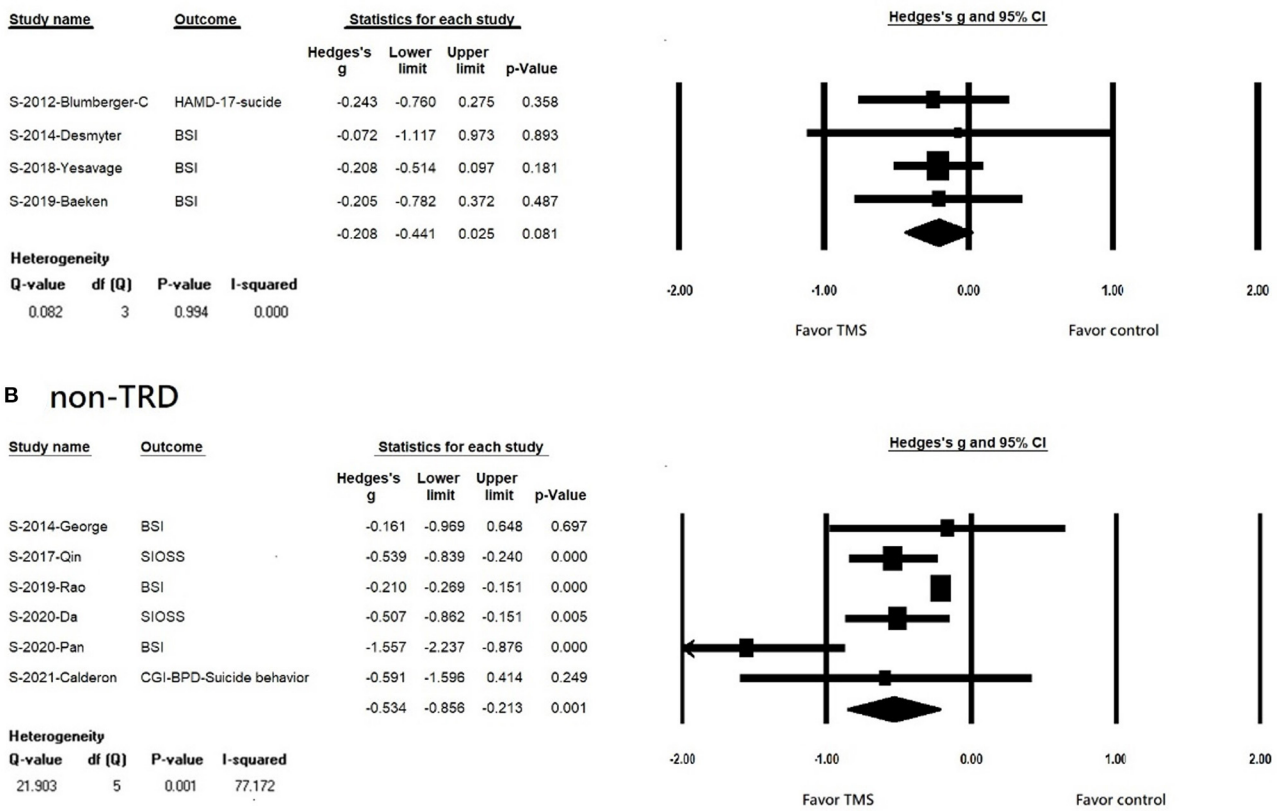

FIGURE 3 | (A) Forest plot of meta-analysis of improvement of suicidal ideation in patients with TRD receiving repetitive transcranial magnetic stimulation treatment and in those with control treatment. **(B)** forest plot of meta-analysis of improvement of suicidal ideation in patients with non-TRD receiving repetitive transcranial magnetic stimulation treatment and in those with control treatment.

ideation among patients receiving more than 10 treatment sessions than those receiving <10 sessions. Fifth, meta-regression analysis showed that rTMS demonstrated greater suicidal ideation reduction among women and those with higher baseline depressive severity. Finally, rTMS was well-tolerated, and most adverse events were minor.

RTMS and Suicidal Ideation

Previous systematic reviews have revealed that rTMS is promising for the reduction of suicide risk (22, 23, 50). The present study found that rTMS reduced both suicidal ideation and depressive symptoms. A previous study demonstrated that a reduction in suicidal risk was mediated by an improvement in depressive severity (51), whereas others did not show this relationship (38). Therefore, it is still unclear whether the impact of rTMS on suicidal ideation reduction was secondary to improvement in depression or mediated by depression. In the present study, meta-regression analysis showed there was no association between the change in the equivalent HAMD-17 score and reduction of suicidal ideation, suggesting the suicidal ideation improvement seems to be independent of depressive severity. However, the number of recruited studies in the present study was relatively small and in most of the studies assessment of suicidal ideation was a secondary outcome measure. More studies are warranted to address this issue.

Regarding meta-regression, we found a significant negative association between outcomes and percentage of women. Studies with a higher percentage of women showed higher likelihood of benefit from rTMS in reducing suicidal ideation. The findings were consistent with that of a previous study that showed an effect of female hormones on the rTMS therapeutic effect. They found that the improvement in the depression score was associated with a higher estradiol/progesterone ratio in premenopausal women (52).

Subgroup Analysis

The study found that rTMS reduced suicidal ideation among those with non-TRD, but not in those with TRD. Theoretically, patients with TRD tended to have more severe depressive symptoms with expected higher suicidal ideation than those with non-TRD. Among the recruited trials, we found that 60.6% of patients in the TRD group and 12.5% of those in the non-TRD

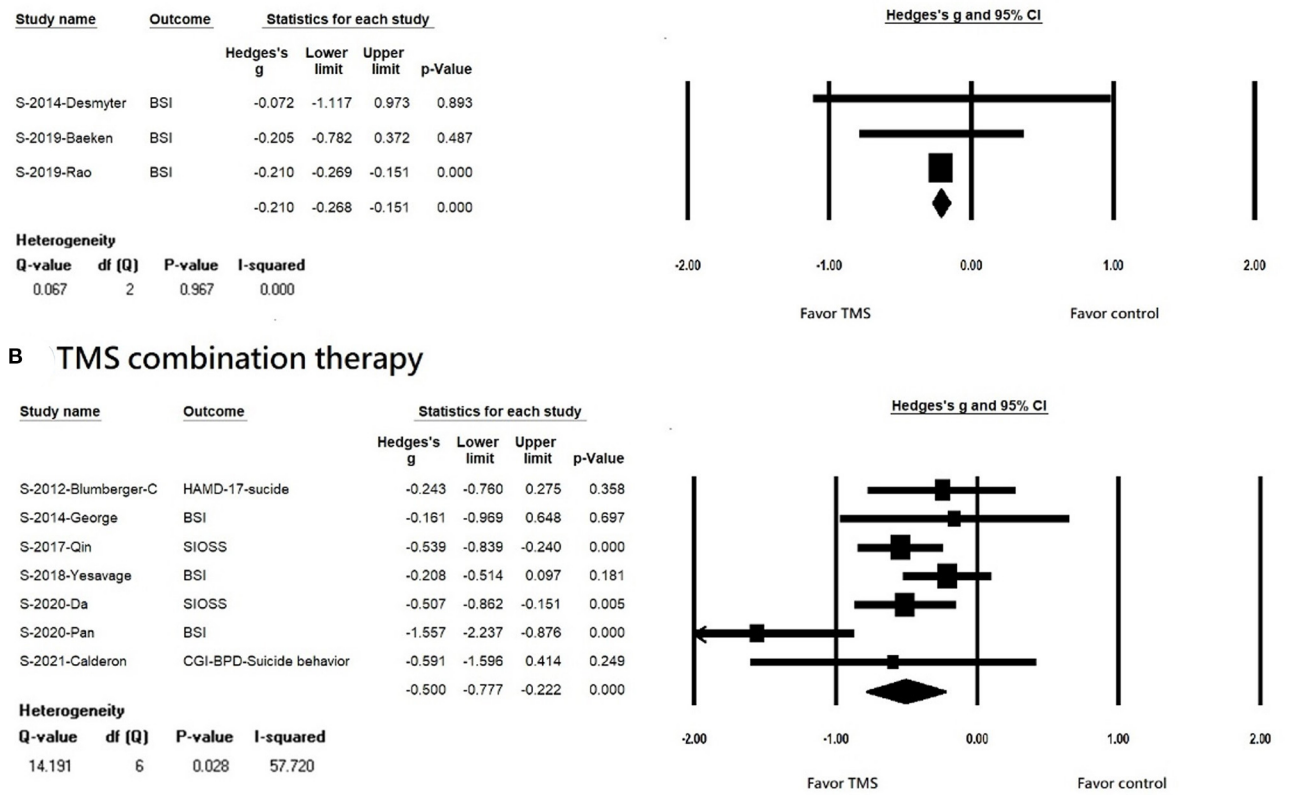

FIGURE 4 | (A) Forest plot of meta-analysis of improvement of suicidal ideation in patients receiving repetitive transcranial magnetic stimulation monotherapy and in those with control treatment. **(B)** forest plot of meta-analysis of improvement of suicidal ideation in patients receiving repetitive transcranial magnetic stimulation combination therapy and in those with control treatment.

group were stratified as severe depression based on the HAMD (53) or BDI (54) scores; therefore, rTMS may contribute to higher suicidal ideation reduction in those with TRD. However, the present meta-analysis study had contradicting results. Some reasons may explain this inconsistency. First, only four RCTs included patients with TRD. Among these, two studies followed up for only 1 week, which is significantly shorter than that for the non-TRD group (mean follow-up of 9 weeks). A recent meta-analysis and systemic review found that more profound depressive symptom improvement was observed in the follow-up assessments several weeks after accelerated rTMS and intermittent theta burst stimulation, suggesting that clinical improvement has delayed onset after brain stimulation (55). This is consistent with our hypothesis that only 1 week of follow-up after rTMS may not be long enough to detect clinical improvement. Second, more than half of the non-TRD studies (60%) conducted once-daily 10-Hz high frequency (HF)-rTMS stimulation over the left DLPFC over 4–6 weeks; however, half of the studies (50%) used an accelerated protocol with intermittent theta burst stimulation. Given the different profiles and mechanisms of action between stimulation protocols, it may contribute to different efficacies or times to reduce suicidal ideation. Third, 75% of the studies recruited patients with TRD who received rTMS monotherapy, but only 16.7% of the studies recruited non-TRD patients who received rTMS monotherapy. Among the six studies on rTMS combination therapy, three concurrently used escitalopram (45, 46, 48) and another three used combined treatments (41, 44, 47). A previous study has shown that antidepressant treatment is associated with a reduction in suicidal ideation and suicide attempts (56). Therefore, rTMS combination therapy may explain the greater reduction in suicidal ideation than rTMS monotherapy.

Another subgroup analysis found that those who underwent more than 10 treatment sessions had greater suicidal ideation reduction than those who underwent <10 sessions. Although early rTMS studies used as few as 5–10 sessions of treatment, more recent studies have demonstrated that at least 20–30 sessions are needed for better treatment efficacy (57). More number of sessions with high number of pulses per session correlated with better efficacy in the treatment of depression (58, 59). A review summarized the effect of rTMS on neurotransmitters, brain blood flow, brain activity, electrophysiological mechanisms, and functional connectivity, which are related to depression and may also be related to suicidal ideation (60). One study showed that brain-derived neurotrophic factor levels gradually increased with treatment

duration. In contrast, inflammatory cytokine levels, such as IL-1b and TNF-a, gradually decreased in patients receiving rTMS treatment (61). Another study found that regional cerebral blood flow significantly increased after 10 sessions of rTMS, but no significant changes were observed during the first rTMS session (62). The evidence indicates that a greater number of sessions are needed to reap the benefit.

RTMS and Depressive Symptoms

It is well-known that rTMS is an effective treatment for patients with depression by reducing depressive symptom severity (63–65). However, patients without a diagnosis of TRD could also experience depressive symptoms and attempt suicide. The present study focused on patients not only with depressive symptoms, but also specifically focusing on suicidal ideation, which is noteworthy. There is no convincing treatment for suicidal ideation except clozapine for psychosis and lithium for mood disorders (2). A previous study showed that antidepressant treatment seemed to be associated with increased suicidality (66). Therefore, it is important to develop effective treatments for these patients. We found that rTMS had a beneficial effect on depressive symptoms among this group of patients. This result emphasizes that it would be reasonable to consider rTMS as a therapy option in patients with treatment-resistant depressive disorder and suicidal ideation in patients with other psychiatric disorders, such as BPD and unipolar or bipolar spectrum disorder. Previous RCTs showed that rTMS lessened the severity of BPD symptoms (47, 67), and a meta-analysis revealed that rTMS appeared to be effective in the treatment of bipolar depression (68). Our study results are consistent with this finding.

Suicide is a complex multifactorial phenomenon wherein several biological abnormalities, in addition to genetic and environmental factors, may play a role. For example, the decreased protein and mRNA expression of brain-derived neurotrophic factor, dysregulation of the hypothalamic-pituitary-adrenal axis, and neuroimmune functions, particularly for pro-inflammatory cytokines, are involved in the neurobiology of suicide (69). The mechanism by which rTMS reduces suicidal ideation remains unclear. One study showed that rTMS may increase brain-derived neurotrophic factor levels and decrease pro-inflammatory cytokine levels in older patients with refractory depression (61). Furthermore, studies have demonstrated that cortisol levels decrease significantly after using a dexamethasone–corticotrophin-releasing hormone test among subjects after HF-rTMS (70, 71). Taken together, rTMS may reduce suicidal ideation by modulating several different inflammatory pathways, as described above.

Strength of the Study

There are several strengths of this study. First, although two previous systemic review studies aimed at discussing the role of rTMS in suicidality (22, 23), both involved qualitative synthesis and not a meta-analysis. The present study conducted a meta-analysis, meta-regression, and subgroup analysis to demonstrate the effect of rTMS on suicidality and explore potential sources of heterogeneity across studies. Second, this study has several advantages over the most recent meta-analysis study (72). We included larger sample sizes (802 vs. 566) and a greater number of eligible studies (10 vs. 8) including three additional RCTs (43, 44, 47) and conducted a meta-regression and a subgroup analysis of TRD vs. non-TRD, which was considered as one of the limitations by Cui et al. (72). Third, the present meta-analysis included high-quality RCTs with sham control, providing robust evidence of the efficacy of rTMS in reducing suicidal ideation.

Limitations

This study has several limitations. First, the present meta-analysis study included relatively few studies with small sample sizes, which may be underpowered to detect statistical difference. Second, according to the RoB2 analysis, 50% of the studies showed concerns of bias. Thus, caution should be exercised when generalizing the results. Third, the protocol of rTMS was different in different study, including the frequency, total pulses per session, power, sessions per day, etc. Variations in the treatment protocol may also have influenced the results. Hence, we conducted a subgroup analysis and meta-regression analysis to minimize this impact. Unfortunately, not all extracted data could be used to conduct a subgroup analysis. For stimulation site, seven out of the ten studies targeted the L-DLPFC. The other three studies targeted the DMPFC, R-DLPFC, and bilateral DLPFC. Therefore, only the effect of rTMS on reducing suicidal ideation in the target site of L-DLPFC could be analyzed. Fourth, three out of the 10 studies were assigned to rTMS monotherapy group due to restriction of concurrent psychotropic medication use. However, the details of the medication usage were not available. Only one study mentioned the details of how the medication washout before randomized was done and the medication they continued to use, like benzodiazepines (37). Hence, we could not perform examination for medication influence on the effects of rTMS on suicidal ideation. Fifth, most of the eligible studies in the present study considered suicidal assessment as a secondary outcome measure. Not all studies demonstrating the role of rTMS on depression examined the suicidal outcome. Selection bias might be noted. However, no publication bias was found in the present study. Furthermore, we found that there was no association between the change in the equivalent HAMD-17 score and reduction of suicidal ideation via meta-regression, suggesting the possible effect of rTMS on suicidality irrespective of depression severity. Finally, the variable assessment scales used for suicidal ideation and depression across the included studies may limit the comparability and synthesis of studies included in this meta-analysis.

CONCLUSION

The current meta-analysis of 10 studies involving a total of 802 participants with suicidal ideation found that rTMS was effective in reducing suicidal ideation and depression severity. It was well tolerated, and most adverse events were minor. rTMS combined with other therapies may be more effective than monotherapy. Due to the relatively small sample sizes included in the present study, future studies involving a greater number of participants would help in investigating more covariates and conduct further

subgroup analysis to find which stimulation protocol or patient group was more effective in suicide reduction.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

G-WC prepared the manuscript. T-WH and C-SC conceived and designed the study. T-WH, P-YC, and C-CP critically read the manuscript and made important suggestions. P-HC and C-SC, the corresponding authors, take all the responsibility of collecting all the information from the other authors, including the revision of the manuscript and its submission. All authors reviewed the manuscript and had full access to all study data.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.884390/full#supplementary-material

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The Problem and Potential of TMS' Infinite Parameter Space: A Targeted Review and Road Map Forward

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Background: Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive, effective, and FDA-approved brain stimulation method. However, rTMS parameter selection remains largely unexplored, with great potential for optimization. In this review, we highlight key studies underlying next generation rTMS therapies, particularly focusing on: (1) rTMS Parameters, (2) rTMS Target Engagement, (3) rTMS Interactions with Endogenous Brain Activity, and (4) Heritable Predisposition to Brain Stimulation Treatments.

Methods: We performed a targeted review of pre-clinical and clinical rTMS studies.

Results: Current evidence suggests that rTMS pattern, intensity, frequency, train duration, intertrain interval, intersession interval, pulse and session number, pulse width, and pulse shape can alter motor excitability, long term potentiation (LTP)-like facilitation, and clinical antidepressant response. Additionally, an emerging theme is how endogenous brain state impacts rTMS response. Researchers have used resting state functional magnetic resonance imaging (rsfMRI) analyses to identify personalized rTMS targets. Electroencephalography (EEG) may measure endogenous alpha rhythms that preferentially respond to personalized stimulation frequencies, or in closed-loop EEG, may be synchronized with endogenous oscillations and even phase to optimize response. Lastly, neuroimaging and genotyping have identified individual predispositions that may underlie rTMS efficacy.

Conclusions: We envision next generation rTMS will be delivered using optimized stimulation parameters to rsfMRI-determined targets at intensities determined by energy delivered to the cortex, and frequency personalized and synchronized to endogenous alpha-rhythms. Further research is needed to define the dose-response curve of each parameter on plasticity and clinical response at the group level, to determine how these parameters interact, and to ultimately personalize these parameters.

Keywords: repetitive transcranial magnetic stimulation, theta burst stimulation, parameter optimization, resting state fMRI, synchronized rTMS-EEG, synchronized TMS, inverted U-shaped curve, dose-response curve

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive, effective and FDA-approved brain stimulation treatment for treatment resistant depression (TRD) (1), obsessive compulsive disorder (OCD) (2), and smoking cessation (3). While conventional once-daily rTMS elicits remission in ∼30% of TRD patients in a naturalistic setting (4), parameter selection remains largely unexplored, in part due to the infinite combination of possibilities. In this narrative mini-review, we highlight key studies demonstrating the potential impact that parameter selection can have on brain plasticity and clinical response, specifically focusing on: (**1) rTMS Stimulation Parameters** (i.e., Pattern, Intensity, Frequency, Train Duration, Intertrain and Intersession Intervals, Pulse and Session Number, Pulse Width, and Pulse Shape); (**2) rTMS Target Engagement**; (**3) rTMS Interactions with Endogenous Brain Activity**; and (**4) Heritable Predisposition to Brain Stimulation Treatments**. Theme 1 involves rTMS parameters and how they affect the brain; in contrast, Themes 2–4 highlight how underlying brain state affects stimulation efficacy. Understanding and applying optimized rTMS parameters holds enormous potential to improve next generation rTMS therapies across brain disorders, particularly as multiple variables do not simply produce better results with more or higher magnitude stimulation, but rather, appear to follow an inverted U-shaped curve with peak efficacy in the middle (**Figure 1A**).

Parameter Theme 1: How Do RTMS Parameters Impact Brain Activity and Therapeutic Response?

Pulse Pattern

The most notable and widely adopted parameter change to date is pulse pattern. The only FDA-cleared form to date, intermittent theta burst stimulation (iTBS), typically delivers 600 pulses of rTMS in 5 Hz triplet bursts of 50 Hz pulses in sessions that take ∼3 min. These parameters are based on traditional protocols shown to induce long term potentiation (LTP)-like facilitation, and are designed to emulate endogenous hippocampal activity (5) (**Figure 1B**). While iTBS is clearly faster than conventional 10 Hz rTMS protocols, it is unclear whether iTBS has greater, similar, or inferior efficacy compared to 10 Hz with mixed findings to date. In a motor evoked potential (MEP) study in healthy adults, Di Lazzaro et al. (6) found that iTBS increased MEP amplitude significantly more than 5 Hz rTMS. Similarly, Zhao et al. (7) found that iTBS produced significantly greater reductions in negative schizophrenia symptoms than 10, 20 Hz, or sham stimulation. Other studies have found similar results between theta burst and conventional rTMS protocols. In depression, a large non-inferior clinical trial found that iTBS produced nearly identical response rates as conventional 10 Hz rTMS (8). Tsai et al. (9) conducted a randomized controlled trial comparing 5 Hz rTMS and iTBS for post-stroke cognitive impairment, finding that both were effective in treatment certain symptom clusters.

While iTBS is faster to administer and could have superior or similar efficacy to conventional rTMS protocols, other studies have found that conventional rTMS protocols produce superior results, particularly in comorbid post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). Whereas, Philip et al. (10) found that iTBS effectively treated PTSD acutely, and with durable effects assessed out to 1 year post-treatment (11), a retrospective chart review in patients with comorbid PTSD and major depression revealed that 5 Hz stimulation produced superior reductions in PTSD and MDD symptoms than iTBS (12). These data suggest that iTBS may not be the answer in all cases, and may even work through a different cellular mechanism, as 10 Hz rTMS and iTBS produced opposing MEP results in healthy controls when combined with NMDA receptor agonists (13–16).

Train Duration

The most commonly used iTBS protocol is based on the seminal findings by Huang et al. (5), who found that twenty 2 s trains (30 pulses per train) with an 8 s intertrain interval (ITI) produced facilitation for 15 min. It is worth noting that a single 2 s train could produce facilitation for up to 15 s, but a 5 s train caused inhibition at 10 s (7), suggesting that the optimal amount of stimulation is consistent with an inverted U-shaped curve "sweet spot" (**Figure 1A**).

The same principle appears to also apply to traditional rTMS, as Jung et al. (17) found that 1.5 s trains of 10 Hz rTMS produced the canonical excitatory high-frequency effect, while 5 s trains inhibited MEP amplitudes (**Figure 1C**). Interestingly, another group used 8 s trains, also for 20 min at 10 Hz, and observed increased facilitation (18). While increasing the train duration also increases the overall number of pulses, it may hint at a non-inverted U-shaped curve, at least within certain limits. Despite these insightful studies, we still do not know where this theoretical U-curve rises and falls, or where it peaks. Further delineation promises to fine-tune current protocols.

Intertrain Interval

Intertrain interval (ITI) refers to the time between trains of rTMS, and to date, has largely been based on safety considerations (19). Naturalistic clinical data has found no meaningful differences in therapeutic outcomes with ITI ranging from 11 to 26 s (20), suggesting that treatment time could be reduced from the conventional 37.5 to 18 min without meaningful clinical differences. In the motor system, ITI ranging between 3 and 17 s produced inhibitory motor effects from successive single TMS pulses; however, a 1 s ITI, effectively becoming continuous 1 Hz stimulation, lost the suppressive effect (21). In contrast, ITIs of 4, 8, 16, and 32 s produced no difference in motor-evoked potentials of healthy humans using patterned 20 Hz rTMS (**Figure 1D**), although shorter ITI produced a marked disinhibition as measured by short intracortical inhibition (SICI) (22). The meaning of these different findings requires further exploration, but speculatively hints that different protocols may theoretically channel different neuronal populations with their corresponding symptoms or networks.

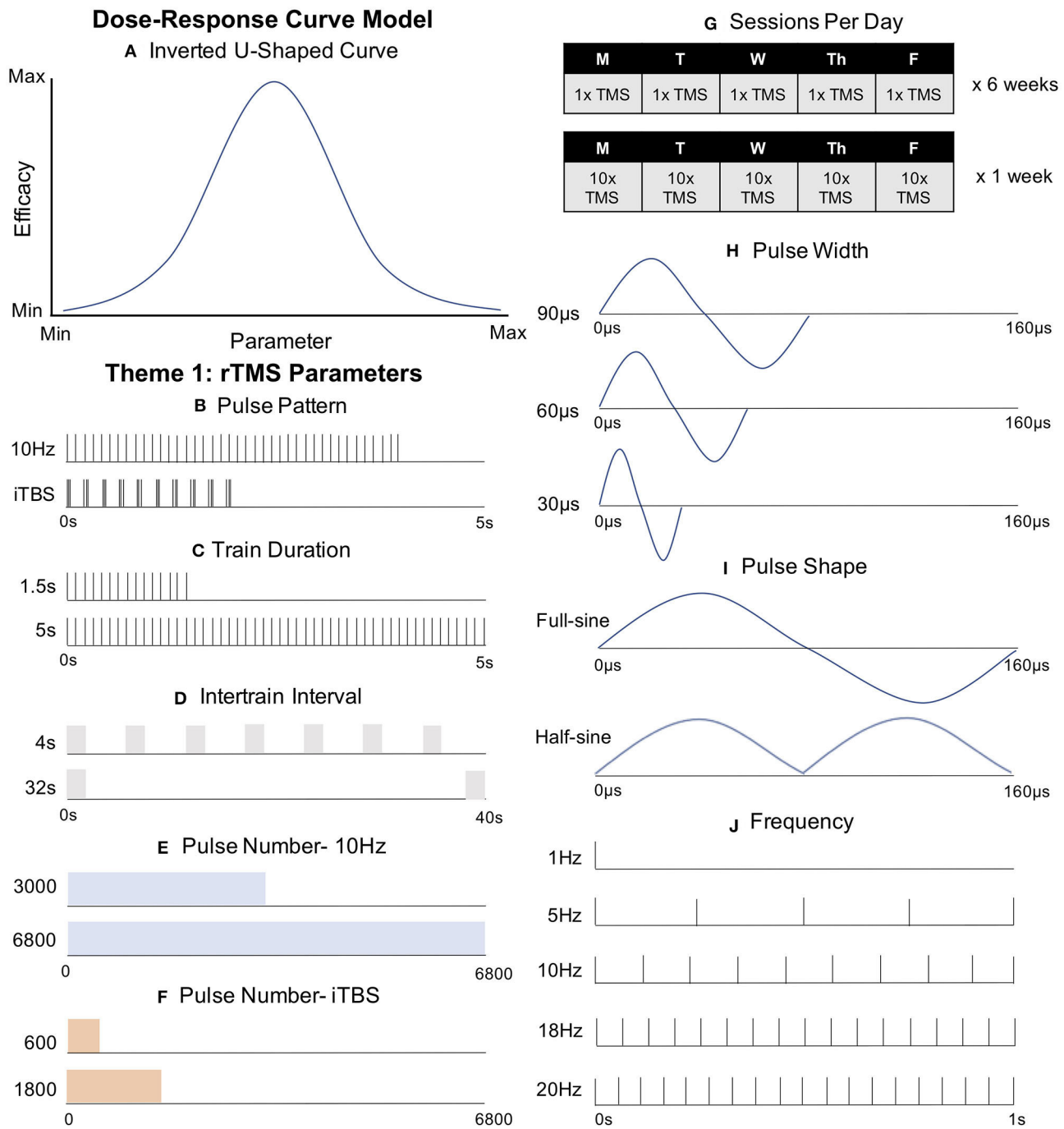

FIGURE 1 | Key rTMS Parameters Guiding the Development of Next Generation rTMS Therapies. **(A)** Dose-Response Curve Model. Some parameters follow an inverted U-shaped curve, with peak efficacy in the middle. **(B)** Pulse Pattern. Intermittent theta burst stimulation (iTBS) has been FDA-cleared as a clinically non-inferior, but more efficient, form of rTMS compared to conventional 10 Hz stimulation. **(C)** Train Duration. Trains of 1.5 s at 10 Hz have produced the canonical excitatory effect while 5 s trains at 10 Hz produced an opposite inhibited effect. **(D)** Intertrain Interval (ITI). Decreased ITI has drastically reduced intracortical inhibition without changing corticospinal excitability or clinical depression outcomes. **(E)** Pulse Number-10 Hz. 6,800 pulses of 10 Hz rTMS did not improve clinical outcomes compared with conventional 3,000 pulse 10 Hz rTMS. **(F)** Pulse Number- iTBS. Doubling pulse number (1,200) produced inhibitory effects, opposing the excitation from the FDA-cleared 600 pulse protocol. **(G)** Sessions Per Day. Relative to conventional rTMS (*top*) "Accelerated rTMS" (applying more than one session per day, *bottom*), may produce a more rapid and effective clinical response. **(H)** Pulse Width. Longer pulse widths may produce more efficient cortical activation. **(I)** Pulse Shape. Full-sine (biphasic) waveforms appear to produce stronger stimulation than single or summated half-sine (monophasic) pulses. **(J)** Frequency. Despite extensive clinical investigation, various stimulation frequencies (including 20, 18, 10, and 5 Hz to the left DLPFC and 1 Hz to the right DLPFC) have not revealed a superior frequency at the group level.

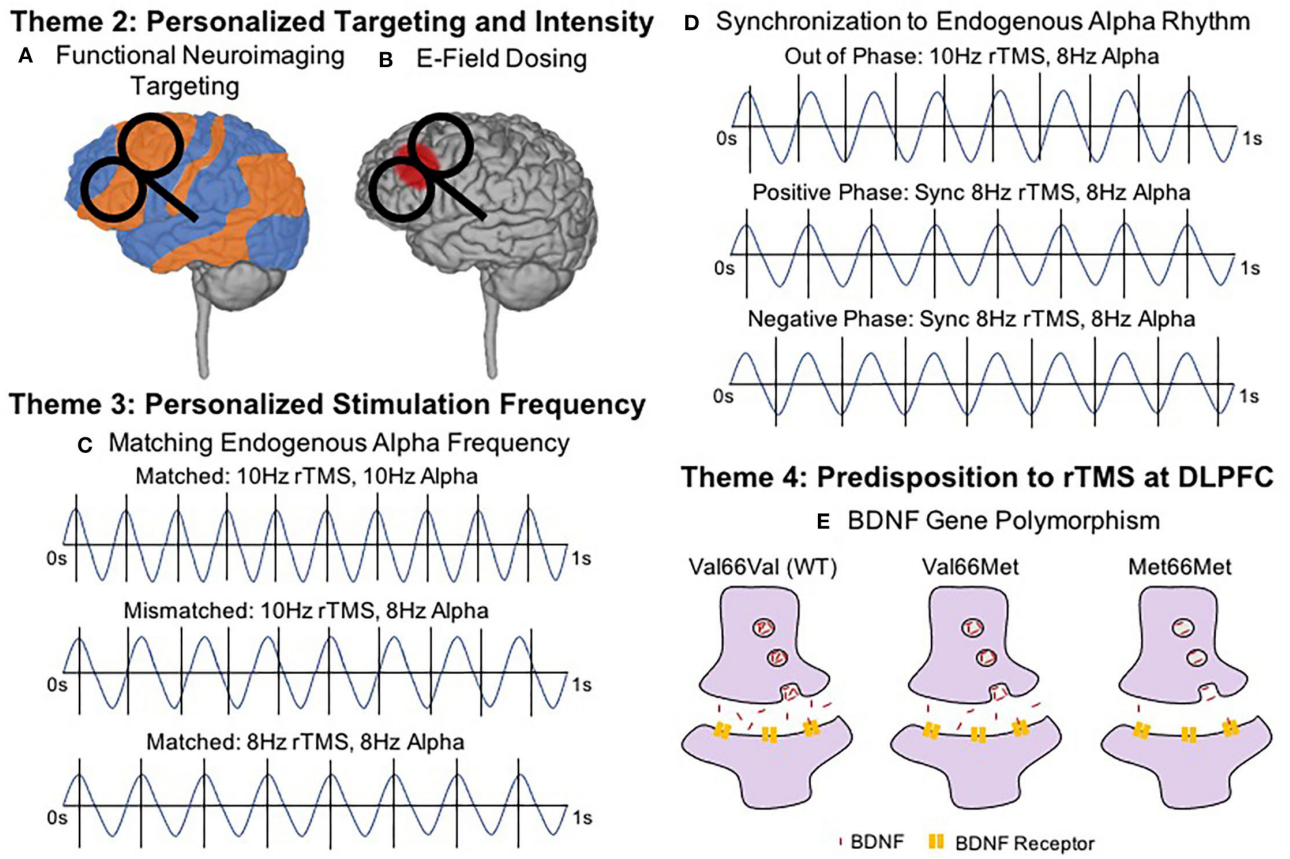

FIGURE 2 | Key Brain States and Predispositions To Consider in Next Generation rTMS Therapies. **(A)** Functional Neuroimaging Targeting (Resting State Functional Connectivity; rsFC Targeting and concurrent TMS-fMRI). Target selection may become personalized based on functional connectivity and/or symptoms. Combining single pulses of TMS and measuring the blood oxygen level dependent (BOLD) signal may further help to individualize stimulation targets and possibly predict treatment course outcomes. **(B)** Electric Field (E-Field) Dosing. Intensity selection may utilize realistic head models and MRI-based E-field dosing to more precisely estimate the stimulation delivered to the target, particularly outside of the motor cortex. **(C)** Matching Endogenous Alpha Frequency. Patients with endogenous alpha rhythms closer to (or at) 10 Hz (top) responded better to 10 Hz rTMS than patients who were mismatched (middle). Most effective rTMS may involve stimulation at the endogenous frequency (bottom). **(D)** Synchronization to Endogenous Alpha Rhythm. Through closed-loop EEG, synchronized delivery of each rTMS train with an individualized endogenous alpha rhythm and aligning the timing of the TMS pulse with a specific phase of the waveform appears to further optimize rTMS effects. Here we show synchronized rTMS-EEG in three phases. *Out of Phase* describes when pulses are delivered without regard to endogenous oscillations (e.g., 10 Hz stimulation delivered for someone with endogenous 8 Hz oscillations). When rTMS is delivered *In Phase*, the pulses can be synchronized with the peak of each oscillation (i.e., *Positive Phase*) or at the trough of each oscillation (i.e., *Negative Phase*). Importantly, synchronizing the endogenous alpha rhythm could occur at any frequency, e.g., 8.5 Hz. **(E)** Predisposition to rTMS—BDNF Gene Polymorphism. Genetic predispositions may influence individual response to rTMS, such as the Val ??Met single nucleotide polymorphism found in the brain derived neurotrophic factor (BDNF) gene which impairs the normal plasticity response to rTMS protocols.

Pulse Number

Pulse number also appears to be consistent with the inverted U dose-response curve with further space for optimization (**Figure 1A**). Huang et al.'s (5) original theta burst findings that 600 pulses produced a more durable response than 300, but that doubling the iTBS pulse number to 1,200 actually produced inhibitory effects instead of the potentiating 600 pulses. More recent studies have produced similarly paradoxical findings that motor iTBS and cTBS at different pulse numbers produce differing facilitatory or inhibitory effects. Notably, Gamboa et al. (23) found that 1,200 iTBS pulses produced inhibitory motor effects, whereas McCalley et al. (24) reported that amongst 600, 1,200, 1,800, and 3,600 pulses of iTBS or cTBS, only 3,600 cTBS pulses produced excitatory motor effects. It is unclear whether these theta burst results in healthy adults over the motor cortex would translate clinically as iTBS is typically applied over multiple treatment sessions, at only 600 pulses per session, and over the prefrontal cortex.

An increasingly popular approach that can be utilized to study the effects of pulse number on brain response combines single pulses of TMS with electroencephalography (EEG) recordings with scalp electrodes, a method known as TMS-EEG (25). Since TMS-EEG directly measures the brain's response to TMS, researchers can assess the cortical effects of TMS outside of the motor system (e.g., in the prefrontal cortex) (26). Utilizing this approach, Desforges et al. (27) used TMS-EEG measured

before and after 600, 1,200, or 1,800 pulses of iTBS over the left prefrontal cortex. The authors found that the number of pulses did not alter the cortical response, but that individual responses to different stimulation parameters varied widely. It is currently unclear how these prefrontal dose-response findings for pulse number might vary between single session studies compared with many sessions over a typical clinical course of TMS. However, there is preliminary evidence that a greater number of pulses could matter clinically. In an open-label trial, Cole et al. (28) showed that 1,800 pulses of iTBS elicited a remission rate of 90.5% (**Figure 1F**). However, due to this study altering other variables, such as session number and total number of sessions, it is difficult to draw definitive conclusions. While this study cannot conclusively tell us that the increased pulse number alone produced this strong antidepressant effect, it at least suggests that this higher pulse number does not appear to block clinical antidepressant efficacy.

Similarly, differing pulse number in conventional rTMS may also produce different effects. Che et al. (29) found that pulse number can cause divergent effects with 10 Hz rTMS, as 1,500 pulses, but not 3,000 pulses, produced analgesic effects. On the other hand, Fitzgerald et al. (30) tested the widely held clinical belief that more pulses per session is more effective, and found that 125 trains (5,625 pulses) vs. 50 (3,000 pulses) produced no differences in an randomized trial with 300 depressed patients. It is worth noting that pulse number has increased steadily from the earlier trials to today's clinical standard of 3,000 pulses (31), broadly suggesting momentum toward applying more pulses per session over time. As safety considerations also inform pulse number, it is important to note that Hadley et al. gave 6,800 pulses per session of open-label 10 Hz TMS to 19 depressed patients with good efficacy and no serious adverse events (32) (**Figure 1E**).

Session Number

TMS clinicians have anecdotally noticed that after a patient has plateaued in clinical improvement, continued treatment sessions could correspond with clinical worsening, again, consistent with the inverted U-shaped dose-response curve (**Figure 1A**). However, among non-responders from one clinical trial, 61% eventually remitted with ongoing twice weekly treatments for up to 16 weeks (33). These data suggest that the number of treatments may be titrated to individual response. One way to personalize session number might be through predictive modeling based on early response (or lack thereof) to rTMS treatment (34). Another intriguing approach used an adaptive algorithm to determine the number of sessions it would take to change the strength of resting state functional connectivity (rsFC) between a cortical parietal target and the hippocampus (35). Using this algorithm, Freedberg et al. (35) found that more than 4 sessions would be needed for 87.5% efficacy at changing rsFC connectivity in the hippocampal-cortical network. However, the exact number of sessions differed in each participant, again pointing to the potential utility of personalizing session number based on response. While repeated fMRI sessions to gauge or predict response could be cost prohibitive, EEG may provide an cheap and feasible alternative to establish desired network engagement, such as recently reported in the first TMS study to show changes in EEG microstates in TMS responders, but not non-responders (36). Researchers have also previously shown that the degree of iTBS-evoked EEG oscillations at baseline can predict iTBS-associated plasticity in the alpha and beta bands (37), providing a further use of EEG to predict rTMS response.

A parallel line of research has not only increased the overall number of sessions but also the number of sessions per day, known as "accelerated" TMS (aTMS). Interest in aTMS is based on two observations: good efficacy and rapid response, such as found in an early open label trial with 27 depressed patients (38). Unfortunately, not all studies agree and the rates of efficacy and response likely depend on the number of sessions per day, which have varied between 2 and 10 thus far. One randomized trial with 98 depression patients showed improved odds of remission with two sessions per day (39), while two other RCTs with 115 and 208 depressed patients showed no difference in remission or response rates, nor did they improve symptoms or speed of response (40, 41). While these trials included 2 or 3 sessions per day, Cole et al. (42) gave 29 depressed patients 10 daily sessions for 5 days, finding that active aTMS produced a 50% symptom reduction compared to just 11% for sham (**Figure 1G**). While this study has justifiably garnered wide attention, we cannot definitively state whether aTMS is solely responsible for this effect given multiple variables changed, including personalized rsFC targeting (see below).

Pulse Width

Altered pulse width may also have biologically meaningful effects. Peterchev et al. (43) varied pulse width between 30, 60, and 90 μs, finding that increased pulse width decreased the motor threshold (MT) by increasing pulse energy (**Figure 1H**). Casula et al. (44) not only found the same negative correlation between pulse width and MT, but also reported that wider pulse widths produced higher local EEG field potentials. In one study, varying pulse widths in 1 Hz rTMS produced divergent effects, pointing to the large impact that pulse widths can have; shorter pulse widths of 40 and 80 μs elicited canonical inhibitory 1 Hz effects while 120 μs pulse width 1 Hz was excitatory, possibly due to differential membrane properties of preferentially activated segment (45). Whether these findings reflect specificity of neuronal activation due to different pulse widths, or are simply a product of increased energy with wider pulse widths as suggested by findings from Shirota et al. (46), remains to be determined. While these findings are in healthy control subjects, perhaps next generation rTMS protocols will utilize wider pulse widths to improve efficacy, which may also produce less discomfort (47). Emerging engineering projects hold promise to make control over these variables more widely accessible (48).

Pulse Shape

Related to pulse width, pulse shape also clearly affects MEPs, but is perhaps the furthest from clinical adaptation (in large part due to most TMS machines not allowing the researcher to alter this parameter). Several principles emerge. First, biphasic (full sinusoidal) produces greater excitation than monophasic (half-sine) (49) and even two summated monophasic waveforms (50).

However, pulse shape is more complicated since biphasic waves (widely used in clinical rTMS) stimulate neurons in both the posterior-anterior (PA) direction and then the anterior-posterior (AP) direction (**Figure 1I**). Each of these directions is thought to activate a distinct group of neurons. Therefore, the biphasic wave may be considered a summated activation of two neuronal populations; PA is activated first and provides the more robust excitatory effect, followed by a delayed and weaker AP activation (49). That different neuronal mechanisms may underlie low-frequency stimulation is suggested by the lack of effect on 1 Hz biphasic rTMS compared to robust inhibition with AP, PA, and rectangular pulse shapes (bidirectional pulse) (51). Taking this concept a step further, Jung et al. (52) applied quadri-pulse (q) TBS (666 Hz quadruplets with 1.5 ms interpulse intervals) and produced opposing motor plasticity effects when applied as single- or double-sine-waves, and as PA and AP directionality is applied. These interactions highlight the complexity of parameter interactions, and the importance of getting it right.

Frequency

rTMS frequency is perhaps the best studied parameter in depression trials, with common protocols including 20, 18, 10, and 5 Hz to the left DLPFC (53–57) as well as 1 Hz to the right DLPFC (**Figure 1J**) (58–60). However, recent evidence suggests that individualized frequency, matched with a patient's endogenous rhythm, may improve clinical outcome (61). Such personalized medicine is the focus of subsequent sections.

Parameter Theme 2: Does Personalized Stimulation Target and Target Engagement Influence Treatment Response?

Functional Neuroimaging for Individualized Targeting

To date, the most common therapeutic target of rTMS for depression has been the left dorsolateral prefrontal cortex (DLPFC). However, the optimal target and method to identify that target within the left DLPFC remains an open discussion. Current standard clinical practice typically identifies the optimal prefrontal stimulation target using a set distance from the motor cortex (i.e., the 5 cm rule) or a probabilistic method of approximating the F3 EEG location (i.e., Beam F3). However, personalizing the rTMS target using resting state functional connectivity (rsFC) analyses may produce more clinically impactful results (**Figure 2A**). Weigand et al. (62) found that treatment response negatively correlated with rsFC strength between the DLPFC and subgenual anterior cingulate cortex (sgACC), two important nodes within the executive network. Several other studies have corroborated these findings (28, 63–66), and thus, it is possible that traditional targeting methods based on scalp measurements or EEG coordinates may be engaging the relevant networks only by chance and only at a group level [see comparisons of common targeting approaches in (64)]. In other words, using rsFC analyses to personalize stimulation target may be fruitful as each individual's optimal rsFC stimulation target often differs from the group averaged target location that may agree with the 5 cm or Beam F3 approaches. Moreover, standard targeting methods ignore the heterogeneity of depression, and emerging evidence supports the feasibility and importance of engaging depression subtypes and even symptoms (67). We can expect that what has been found with rTMS for depression could have relevance across brain disorders.

Another promising tool for identifying individualized rTMS targets involves combining single pulses of TMS and fMRI within the MR scanner environment, a technique called interleaved TMS-fMRI (68–70). By applying single pulses of TMS and recording the resulting blood oxygen level dependent (BOLD) signal, it is possible to directly and causally measure the brain's response to TMS (71). Notably, TMS-fMRI can record how single pulses of TMS affect brain activity, not only at the cortical surface, but also at distal regions of a brain network, such as the sgACC in depression (72, 73). Moreover, baseline TMS-fMRI response may be able to predict clinical outcome. In one study, depressed patients with more negative TMS-fMRI baseline responses in the sgACC corresponded with better symptom improvements (74). Thus, future research and clinical practice might utilize TMS-fMRI to determine optimal stimulation targets for rTMS treatment, or to predict the patients for whom rTMS may be most effective. Alternatively, less expensive and more accessible functional near-infrared spectroscopy (fNIRS), or diffuse optical tomography (DOT) could enable such targeting and even allow real-time visualization of the effects of varied rTMS protocols.

Stimulation Intensity

Even when the correct target is identified, it would produce no clinical benefits if the target were not adequately engaged by stimulation, such as with suboptimal stimulation intensity. In current practice, the stimulation intensity is derived from the motor threshold (MT), which relies on the assumption that cortical excitability in the motor cortex can accurately inform stimulation intensities at other cortical targets such as the prefrontal cortex. However, it remains unclear whether sufficient motor cortex activation equates to adequate prefrontal engagement, or how stimulating at a more optimized intensity might affect response rate. Historically, early TMS researchers in the 1990s proceeded with caution due to safety considerations, first applying rTMS at just 80% MT (75). Incrementally, these early researchers then incrementally increased rTMS intensities to 100% MT and eventually, the now widely adopted 120% MT based on evidence that greater scalp-to-cortex distance in older patients appeared to prevent high response to rTMS therapy at 100% MT intensities (76, 77), but that this could be overcome by individually adjusting for scalp-to-cortex distance (78).

A more recent tool is MRI-based electric field (E-field) modeling, which uses structural MRI-based tissue segmentation and varying tissue conductivities to more accurately estimate the amount of stimulation that reaches the cortex (79–81) and could be used to inform prospective dosing. Since E-field modeling is not dependent on the dubious assumption that motor cortical engagement can accurately estimate how much stimulation reaches prefrontal stimulation targets, E-field dosing could potentially inform higher fidelity, personalized stimulation intensities specifically for the prefrontal cortex or other rTMS targets. Thus, E-field dosing could prove particularly

useful if the dose-response relationship between stimulation intensity and clinical response follows the inverted U-curve model with peak efficacy in the middle (**Figure 1A**). While largely untested, some extant dose-response experiments point to a stimulation intensity sweet spot that neither under- nor over-doses. Notably among these, Chung et al. (82) determined that 75% MT stimulation produced superior DLPFC TMS-evoked EEG potentials, rather than 50 or 100% MT. Similarly, Lee et al. (83) determined that subthreshold iTBS caused greater reductions in depressive symptoms than suprathreshold iTBS, again pointing to an optimal middle stimulation intensity. In retrospective E-field analyses of clinical rTMS for depression and smoking cessation, the prefrontal E-field magnitude from 120% MT stimulation did not linearly correlate with the percentage of symptom change (84, 85), possibly suggesting a non-linear dose-response relationship and perhaps peak efficacy with an optimized middle amount of stimulation. A remaining question is whether there is an optimal E-field dosing intensity, which itself could be prone to interindividual differences due to varied distributions of particular neuron types or different neurotransmitter concentrations between patients. To account for these potential individual differences, Caulfield et al. (86) have proposed to measure the E-field intensity at the MT to first determine an individual neuronal activation threshold by measuring a personalized MT and calculating the required stimulation intensity to replicate this motor E-field over the prefrontal stimulation target (**Figure 2B**). It remains to be seen whether optimized E-field dosing would improve clinical efficacy.

Parameter Theme 3: How Does Endogenous Brain Activity or Brain State Affect RTMS Treatment Response?

Synchronization to Endogenous Brain Activity

Whereas conventional rTMS is applied with the same stimulation frequency across patients, emerging neuroimaging research could inform more personalized stimulation approaches. Leuchter et al. (61) systematically determined the resonant frequency of each subject by analyzing the effect of various rTMS stimulation frequencies (from 3 to 17 Hz) on electroencephalography (EEG)-based power and connectivity metrics. Intriguingly, those individuals with endogenous alpha rhythms closest to 10 Hz had the best treatment outcomes from standard 10 Hz rTMS for depression (87), hinting at the utility of using individualized stimulation frequencies (e.g., 8 Hz rTMS for someone with a strong inherent resonant frequency of 8 Hz) (**Figure 2C**). Similarly, Kundu et al. (88) found that the baseline beta band activity could predicted pulse-by-pulse variations in the TMS-evoked EEG response, again suggesting that endogenous brain activity impacts response to rTMS.

In a related but distinct effort, researchers have begun to study how rTMS pulses interact with brain rhythms in real time (i.e., synchronized TMS-EEG) (**Figure 2D**) (89). Research by Ferreri et al. (90, 91) retrospectively examined the relationship between ongoing EEG recordings and MEP amplitudes recorded concurrent with EEG, finding that there was greater EEG coupling on high MEP trials than low MEP trials. Keil et al. (92) also found that EEG activity impacts MEP response, as higher real-time beta-band EEG coherence with ongoing hand electromyographic (EMG) recordings produced stronger MEP amplitudes in a significant linear relationship. Putting these concepts from single pulse TMS studies together, researchers have begun to test the effects of real-time, closed-loop rTMS-EEG synchronization and whether this causes meaningful neural or behavioral changes compared to unsynchronized rTMS-EEG. These cutting edge synchronized rTMS-EEG experiments have found that personalizing and synchronizing rTMS and iTBS pulse timing to endogenous EEG rhythms in the brain circuit of interest can significantly increase prefrontal EEG response (93) and MEP amplitudes (94) in comparison to unsynchronized conditions.

Increasingly nuanced approaches also consider the importance of EEG phase and whether the rTMS pulse is delivered at the peak (positive phase) or trough (negative phase) of brain rhythms (**Figure 2D**). In particular, Momi et al. (95) have found that phase-locking rTMS pulses to the negative phase of the pulse elicits stronger mu synchrony throughout the sensorimotor network when compared to synchronizing pulses to the positive phase of the EEG signal. In the first application of these synchronized rTMS-EEG approaches in a clinical population, Zrenner et al. (96) demonstrated the feasibility and utility of synchronizing iTBS with alpha oscillations in the prefrontal cortex of MDD patients. These researchers found that alpha-synchronized iTBS caused significantly larger decreases in resting state alpha activity at the left prefrontal target, suggesting that synchronized rTMS-EEG could produce meaningful clinical results if applied over an entire treatment course (96). An ongoing clinical trial (NCT03421808) is attempting to address the therapeutic effects of synchronizing rTMS-EEG for depression over a treatment course.

Lastly, we would be remiss if we did not discuss a prior large scale attempt to synchronize TMS with endogenous alpha rhythm for depression using a technology known as low field synchronized TMS (sTMS) (97). Low field sTMS applies weak magnetic fields using midline rotating magnets that can match the personalized, EEG-determined oscillatory frequency for each depression patient. While the antidepressant effects of sTMS were initially promising (97), the pivotal trial showed no significant differences between active and sham sTMS (98). However, it is important to note that the mechanism of low field sTMS is fundamentally different than patterned rTMS or iTBS, with the maximum magnetic field change over time in low field sTMS ∼1000x lower than conventional rTMS (97). Thus, this emerging concept of matching or synchronizing rTMS or iTBS with endogenous brain oscillations remains a promising area of research.

Brain State

Consistent with principles from fundamental LTP studies, the state of the brain at the time of stimulation may affect treatment outcome. Isserles et al. (99) have demonstrated what we have long assumed, that it matters what our brain is doing during rTMS. They found that reading a script that promoting positive cognitive-emotional activation leads to

greater antidepressant effects than does negative or neutral scripts. A further method of priming the brain for rTMS could be concurrent aerobic exercise, which review articles have proposed could complement the therapeutic effects or rTMS due to aerobic exercise priming synaptic plasticity (100, 101). Surprisingly, these approaches remain untested in large scale clinical trials. Thus, along with personalized cognitive engagement, next generation rTMS may include capitalizing on brain state at the macroscale (i.e., cognitive engagement) and microscale levels (i.e., synchronized with phase of endogenous waveforms).

Parameter Theme 4: Are Some Brains Naturally Receptive vs. Resistant to RTMS?

rsFC States and Genetic Predispositions

Lastly, inherent characteristics may portend individual response to rTMS. In addition to individual baseline differences in rsFC predicting degree of antidepressant rTMS effect, some researchers have identified predispositions that portend the likelihood of rTMS response. Notably, Drysdale et al. (102) identified four distinct rsFC states that relate to different symptom clusters (i.e., dysphoric or anxiosomatic), and found that more anxious patients responded preferentially to dorsomedial (DM) PFC rTMS compared to predominantly dysphoric patients by nearly 4-fold. Perhaps baseline rsFC analyses could predict ideal candidates for rTMS at a given target, with non-ideal candidates provided with alternative therapeutic options.

Genetic predispositions can also influence rTMS response. Cheeran et al. (103) characterized how the heterozygous Val66Met polymorphism, which is associated with lower concentration of brain derived neurotrophic factor (BDNF), has been associated with decreased rTMS plasticity over the motor cortex compared to homozygous Val66Val individuals (103) (**Figure 2E**). Subsequent research has confirmed this seminal finding with the Val66Val genotype associated with the highest TMS motor evoked response (104, 105), Met66Met polymorphism associated with the lowest TMS motor evoked response (106), and BDNF gene predicting up to 59% of between-subject variability of MEP responses (107). These findings in healthy adults over the motor system also hold clinical validity, as the Val66Val genotype is most likely to respond positively to rTMS in stroke (108). Just as genetics are gaining traction as a predictor of pharmacologic response, we may find a useful guide to stimulation type and parameters in our genotypes. For instance, researchers have found that increasing the number of days of motor training can overcome the natural predisposition for Val to Met polymorphism to cause lower cortical responses (109); in a similar vein, perhaps an increased number of rTMS pulses or sessions could overcome individual genetic predilections to respond/not respond to brain stimulation treatments.

DISCUSSION

In this mini-review, we outlined four parameter themes guiding the next generation of rTMS treatments. Implicit in many of these studies is that cortical plasticity (i.e., MEPs) may provide a surrogate for clinical response. Indeed, motor cortex plasticity assessed by MEP response to a 10 Hz protocol reliably predicted whether depressed patients respond to rTMS (18). We envision future rTMS will be delivered to rsFC-determined targets at intensities determined by energy delivered to the cortex, using optimized pulse number, train duration, intertrain intervals, and pulse widths/shapes, with frequency personalized to endogenous alpha-rhythms and even synchronized to coincide with the timing and phase of the endogenous waveforms. Future research is needed to define the "curve" of each parameter on plasticity and clinical response at the group level, to determine how these parameters interact, and to ultimately personalize these parameters. A tiered approach may prove most practical considering the cost-benefit ratio of these complex fMRI and EEG-based techniques, with more advanced and expensive techniques reserved for those not remitting with traditional methods.

AUTHOR CONTRIBUTIONS

KC and JB conceived of the review, wrote the first draft, created the figures, and edited the manuscript. Both authors contributed to the article and approved the submitted version.

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Early Improvement Predicts Clinical Outcomes Similarly in 10 Hz rTMS and iTBS Therapy for Depression

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Background: Prior studies have demonstrated that early treatment response with transcranial magnetic stimulation (TMS) can predict overall response, yet none have directly compared that predictive capacity between intermittent theta-burst stimulation (iTBS) and 10 Hz repetitive transcranial magnetic stimulation (rTMS) for depression. Our study sought to test the hypothesis that early clinical improvement could predict ultimate treatment response in both iTBS and 10 Hz rTMS patient groups and that there would not be significant differences between the modalities.

Methods: We retrospectively evaluated response to treatment in 105 participants with depression that received 10 Hz rTMS ($n = 68$) and iTBS ($n = 37$) to the dorsolateral prefrontal cortex (DLPFC). Percent changes from baseline to treatment 10 (t_{10}), and to final treatment (t_f), were used to calculate confusion matrices including negative predictive value (NPV). Treatment non-response was defined as <50% reduction in PHQ-9 scores according to literature, and population, data-driven non-response was defined as <40% for 10 Hz and <45% for iTBS.

Results: For both modalities, the NPV related to degree of improvement at t_{10}. NPV for 10 Hz was 80%, 63% and 46% at t_{10} in those who failed to improve >20, >10, and >0% respectively; while iTBS NPV rates were 65, 50, and 35%. There were not significant differences between protocols at any t_{10} cut-off assessed, whether research defined 50% improvement as response or data driven kernel density estimates ($p = 0.22$–0.44).

Conclusion: Patients who fail to achieve >20% improvement by t_{10} with both 10 Hz rTMS and iTBS therapies have ∼70% chance of non-response to treatment. With no significant differences between predictive capacities, identifying patients at-risk for non-response affords psychiatrists greater opportunity to adapt treatment strategies.

Keywords: depression, transcranial magnetic stimulation, theta-burst, clinical practice, observational study, prediction

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INTRODUCTION

Major Depressive Disorder (MDD) is a ubiquitous mental health disorder that affects a diverse population across the globe and responds to treatment in a seemingly unpredictable manner. Repetitive transcranial magnetic stimulation (rTMS) exists as an increasingly researched, non-invasive treatment for people with MDD (1). Notwithstanding its demonstrated clinical efficacy,

treatment responses are variable and difficult to predict (2–5). A full 4 to 6-week treatment course is a time and resource-intensive process which can be especially burdensome, especially for the 30–40% of patients destined for non-response (6).

Literature has defined several biomarkers that may help clinicians predict a patient's response to TMS treatment (7, 8); however, the collection and analysis of these markers is often expensive, inaccessible, or time-consuming for patients and providers. Reliable predictors would thus be of immense clinical utility by prioritizing TMS for subjects most likely to respond to optimize clinical outcomes and to potentially avoid ineffective therapies. To address the inaccessibility of biomarker collection and utilization, a meta-analysis of 41 different pharmacotherapy clinical trials demonstrated that early treatment improvement, defined as >20% symptom reduction in the first 2 weeks of treatment, was able to accurately predict treatment response and remission (9).

A seminal study by Feffer et al. adapted analyses of clinical response to treatment at 2 weeks, previously only done for pharmacotherapy or electroconvulsive therapy (10) to rTMS, in order to determine the accuracy of early clinical response in predicting subsequent response to treatment via rTMS (11). In a naturalistic retrospective case series ($N = 101$), they defined distinct subgroups of responders and non-responders based on standard criteria, as well as on population specific data-driven response criteria using kernel density estimates. The study determined that the absence of early clinical improvement by treatment 10 during a course of right sided dorsomedial prefrontal cortex (DMPFC) 10 Hz rTMS or iTBS (intermittent theta burst stimulation) carried a negative predictive value (NPV) of 88% (11).

Subsequent studies examined other potential predictors of treatment response: one demonstrating a NPV of 72.3% when participants had <20% improvement at week two while using final outcomes of extended treatment courses of 10 Hz stimulation at the left dorsolateral prefrontal cortex (DLPFC) (12), and another finding a NPV of roughly 80% for a population receiving 1 Hz rTMS (13). Calculating metrics such as negative predictive value of early treatment response in clinical TMS populations allows clinicians to better prognosticate who will respond to subsequent therapy and aids in the decision making regarding altering or adapting treatment plans to optimize outcomes. As TMS research explores various stimulation frequencies, durations, targets, and targeting methods in the treatment of major depressive disorder, it is imperative to examine the comparative effectiveness of these varying parameters.

Since being cleared by the FDA in 2008, the recognized standard of care for TMS treatments for MDD has been 10 Hz rTMS to the left DLPFC, which delivers 3,000 pulses in over 37.5 min (14). Recently, a study by Blumberger et al. demonstrated that intermittent theta burst stimulation (iTBS), which delivers 600 pulses in just over 3 min, was non-inferior to 10 Hz rTMS in treating major depressive disorder (15), garnering FDA clearance in 2018 for the treatment of MDD. Few studies exist that directly compare these two modalities in their effectiveness at treating depression, and to our knowledge, no studies have examined if any differences exist between 10 Hz rTMS and iTBS in the use of early treatment improvement to predict treatment response.

Taking this into account, in our single-site, naturalistic observation study, we detail the results of a retrospective chart review that used a similar approach to the aforementioned studies to determine the accuracy of predicting final outcomes based on early treatment response in 10 Hz rTMS and iTBS. We also explore if potential differences exist in the predictive capacities between the two modalities. Predicated on prior research, we hypothesized a criterion of at least 20% improvement by treatment 10 would provide the highest negative predictive value for non-response to a full treatment course, as well as hypothesizing that there would not be significant differences between 10 Hz rTMS and iTBS across various improvement criteria.

MATERIALS AND METHODS

Patient Population

This study was conducted using a retrospective chart review of 131 participants that received standard clinical treatment of left DLPFC 10 Hz rTMS or iTBS between December 2016 and February 2020. Inclusion criteria in this study required patients (age $\geq$ 18) to have an existing diagnosis of MDD. Participants in the study were subsequently evaluated by a physician with experience in TMS and were recommended as suitable candidates to receive TMS treatment based on a thorough diagnostic history and physical, medication reconciliation, assessment of other DSM-5 mental health disorders, and review of previous therapy trials. Exclusion criteria included age <18 years old, a prior diagnosis of epilepsy or other seizure disorders, implanted ferromagnetic hardware in the face or skull near TMS targeting sites, or previous treatment with TMS of any kind. Patient consent was obtained prior to treatment. This study was approved the Institutional Review Board at the University of Iowa. **Figure 1** depicts the array of outcomes of the 131 participants who received TMS treatment during the previously described timeframe. We included 105 participants in our final analyses.

DLPFC-rTMS and iTBS Technique

From 2016 until iTBS was cleared by the FDA for its indication in treating major depressive disorder in 2018, patients in our study received 10 Hz rTMS. After iTBS approval, the prescribing physician and the participants decided on 10 Hz rTMS vs. iTBS therapy through shared decision-making. Resting motor threshold (RMT) was determined via right-handed thumb twitches in three of five trials while delivering stimulation to the left primary motor cortex via the Magventure MagPro X100 Figure 8 Butterfly Coil with Active Cooling (Magventure, Alpharetta, GA) (16). Technicians trained in TMS delivery then targeted the left DLPFC using either the 5.5 cm rule, or the Beam F3 techniques (16–18). Participants receiving 10 Hz stimulation received 3,000 pulses with 4 s trains and a 26-s intertrain interval at 120% of their RMT over a 37.5-min session (14). This contrasts with patients receiving iTBS that received 600 pulses with 50 Hz

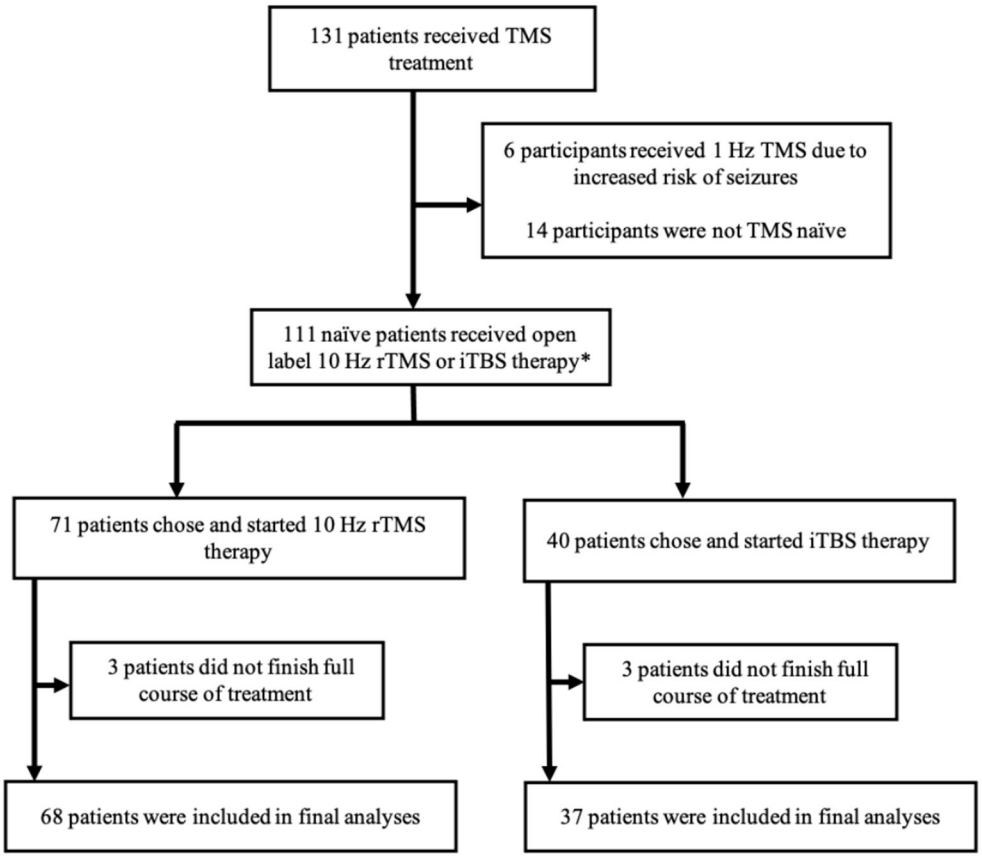

FIGURE 1 | Summary of study participant disposition. A graphical depiction of the various outcomes and participation status of the study participants. TMS, transcranial magnetic stimulation; rTMS, repetitive transcranial magnetic stimulation; iTBS, intermittent theta burst stimulation. *Prior to FDA clearance of iTBS in 2018, participants mainly received 10 Hz rTMS. After the FDA clearance, participants were able to choose between 10 Hz rTMS and iTBS therapy.

triplets patterned into 5 Hz stimulation with 2 s trains and 8 s intertrain intervals, also at 120% the intensity of their RMT in a 3-min treatment session (19, 20). In this study, participants received a varying number of sessions over their treatment course (average of 33) following clinical indication, with stimulation sessions occurring for five consecutive days a week for four to six subsequent weeks.

Clinical Assessments

Every participant in this study completed a baseline clinical assessment via a self-report scale [Patient Health Questionnaire 9 (PHQ-9)] prior to the start of treatment (21, 22). Participants subsequently completed the PHQ-9 at the start of their treatment course (t_1), at the end of each treatment week, treatment 10 (t_{10}), and at the final treatment session (t_f) to track depression symptomatology and improvement over time. The percent changes in PHQ-9 scores at t_{10} and t_f were subsequently used to determine outcome measurements such as negative predictive value to ascertain if early improvement scores could be used to predict future treatment response, as well as if discrepancies between this predictive capacity existed between the two treatment modalities. Secondary outcome measures included using the PHQ-9 t_f percent reductions within kernel density estimates to determine the distribution of response levels, allowing classification of distinct data-driven subgroups of "non-responders" and "responders" for analysis that possibly varied from the classically defined >50% reduction dichotomy to define treatment response.

TABLE 1 | Baseline demographic and clinical characteristics of study participants (105).

	10 Hz rTMS ($n = 68$)	iTBS ($n = 37$)	p-value
Age	53.47 ± 15.7	49.62 ± 17.3	0.251
Women	41 (60.0%)	21 (57.0%)	0.728
Baseline PHQ-9 (range 0–27)	17.8 (4.9)	19.0 (4.4)	0.270
Generalized anxiety disorder	46 (67.7%)	16 (43.2%)	0.178
Post-traumatic stress disorder	13 (19.1%)	5 (13.5%)	0.019*
Benzodiazepines	45 (66.1%)	13 (35.0%)	0.161
Stimulants	14 (20.6%)	11 (29.7%)	0.928

Data in the table are means (SD) or the number of participants in with group (% total). Statistical significance of between-group analyses was assessed with Student's t-test for continuous data and Pearson's chi-square test for categorical data.
*$p < 0.05$.

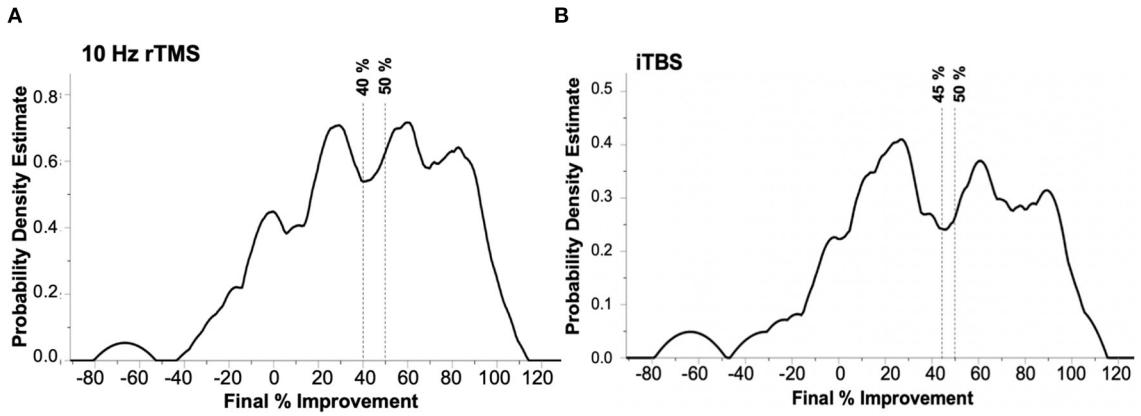

FIGURE 2 | Kernel density estimate (KDE) depicting the modality specific distribution of treatment outcomes as determined by percentage improvement of PHQ-9 scores from baseline to final treatment. **(A)** Kernel density estimates (KDE) with Epanichnikov kernels of participants that received 10 Hz rTMS ($n = 68$) demonstrating a non-normal distribution with distinct sub-group of "non-responders" at 40% compared to the traditional 50% final improvement cut-off. **(B)** KDE of participants receiving iTBS ($n = 37$) with distinct "non-responder" sub-group at 45% compared to traditional 50% final improvement cut-off.

Data-Analysis

Therapy-stratified summary statistics for continuous and categorical measures are represented as means (standard deviations) and counts (percentages), respectively. Tests for differences in measures between therapies utilized Student's *t*-test and Pearson's chi-square test. Using IBM SPSS Statistics (Version 26), we used cutoff criteria of TMS non-response with 0, 10, and 20% improvement thresholds at t_{10} to populate confusion matrices that detailed sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and total accuracy of t_f outcomes. Similar to previous studies that analyzed early treatment response and its predictive capacities in rTMS (11–13), these t_f outcomes were subsequently used to define our patient population as responders or non-responders two ways: first using the classically defined criterion of >50% improvement by the final treatment, and secondly, using kernel density estimates (KDE) with an Epanechnikov kernel.

The KDEs allowed us to use a data-driven approach to determine if there were distinct subgroups of "non-responders" based on our data population. This was considered an important analysis based on prior research demonstrating that patient populations do not respond homogenously, and a data-driven cutoff may better dichotomize populations phenomenologically rather than an arbitrary 50% cutoff. This resulted in the use of more liberal response criteria for both the 10 Hz and iTBS groups, respectively. To directly compare if significant differences of predictive capacity existed between 10 Hz rTMS and iTBS treatment modalities, we measured the NPV across the various improvement thresholds at t_{10}. Comparisons were made using two-sample proportional *z*-tests to examine if significant differences existed between the two modalities across the both the classically defined >50% improvement criterion for a response or the KDE data-driven response criterion. A p-value < 0.05 was considered statistically significant.

RESULTS

Demographics

Of the 105 participants included in the final analyses who received standard clinical left DLPFC stimulation, 68 received 10 Hz rTMS and 37 received iTBS between 2016 and 2020. **Table 1** depicts the baseline demographics of the participant population. They were 58.5% female, mean (SD) age of 52.3 ± 16.3. At baseline, the only significant difference between treatment groups was comorbid post-traumatic stress disorder with 13 (19.1%) participants in the 10 Hz group and five (13.5%) participants in the iTBS group, $p = 0.019$ (**Table 1**). No other differences between the two modalities were found in variables analyzed, including age, sex, baseline PHQ-9 score, use of benzodiazepines, or use of stimulant medications.

Outcomes

Previously reported findings demonstrated that using our dataset there were no statistically significant differences between 10 Hz rTMS and iTBS groups regarding response rates, remission rates, or minimum clinically important difference (MCID) rates (23).

Categorization of Responders and Non-responders

Within the kernel density estimates, similarly to prior studies' methodology (11–13), we used the first major troughs as the cut-off for the unique "non-responder" subgroup. The distribution of participants in the 10 Hz group was trimodal (**Figure 2A**) with a discrete non-responder group of individuals achieving < 40% improvement, and the distribution in the iTBS group was trimodal as well, with a distinct non-responder group achieving < 45% improvement (**Figure 2B**). This allowed us to create a data-driven, t_f response criterion in both the 10 Hz and iTBS groups using these 40 and 45% improvement cut-offs, respectively. Results from the confusion matrices were compared

TABLE 2 | Early improvement confusion matrices determining final treatment predictive capacity differences between 10 Hz rTMS and iTBS.

	10 Hz rTMS ($n = 68$)	iTBS ($n = 37$)	p-value
Classically defined > 50% improvement			
>20% improvement by treatment 10			
Sensitivity	76.7	58.8	0.20
Specificity	73.7	65.0	0.49
PPV	69.7	58.8	0.44
NPV	80.0	65.0	0.22
Total accuracy	75.0	62.2	0.17
>10% improvement by treatment 10			
Sensitivity	68.3	56.5	0.35
Specificity	81.5	71.4	0.46
PPV	84.8	76.5	0.47
NPV	62.9	50.0	0.35
Total accuracy	73.5	62.2	0.23
>0% improvement by treatment 10			
Sensitivity	59.6	53.6	0.61
Specificity	76.2	77.8	0.93
PPV	84.8	88.2	0.74
NPV	45.7	35.0	0.44
Total accuracy	64.7	59.5	0.60
KDE defined improvement (>40% 10 HZ, >45% ITBS)			
>20% improvement by treatment 10			
Sensitivity	83.3	64.7	0.15
Specificity	68.4	65.0	0.79
PPV	67.6	65.1	0.64
NPV	83.9	68.4	0.20
Total accuracy	75.0	64.9	0.27
>10% improvement by treatment 10			
Sensitivity	75.6	60.9	0.22
Specificity	77.8	71.4	0.65
PPV	83.8	77.8	0.59
NPV	67.7	52.6	0.29
Total accuracy	76.5	64.9	0.20
>0% improvement by treatment 10			
Sensitivity	66.0	57.1	0.45
Specificity	71.4	77.8	0.72
PPV	83.8	88.9	0.61
NPV	48.4	36.8	0.42
Total accuracy	67.6	62.2	0.57

Using PHQ-9 score percent changes at treatment 10 and the final treatment, confusion matrices were calculated for 10 Hz rTMS and iTBS across an array of improvement criteria. Classically defined improvement in scores is >50% from baseline. Kernel density estimate calculations were used to determine data-driven non-responder populations to create more stringent and improvement criteria, which was determined to be >40% for 10 Hz rTMS and >45% for iTBS. rTMS, repetitive transcranial magnetic stimulation; iTBS, intermittent theta burst stimulation; PPV, positive predictive value; NPV, negative predictive value; KDE, kernel density estimate.

to those achieved with the standard non-response criterion of <50% improvement as a secondary outcome for completeness.

Negative Predictive Value Analyses

Using the classically defined >50% response criterion for response, we first determined the NPV at three t_{10} cut-offs (0, 10, and 20%) of improvement at t_{10} for 10 Hz and iTBS using confusion matrices, and next used proportional z-tests to determine if there was a significant difference between the two modalities as detailed in **Table 2**. For participants who failed to reach >20% improvement at t_{10}, the NPVs for 10 Hz rTMS and iTBS were 80.0 and 65.0%, respectively: $p = 0.22$. When the improvement criterion was decreased to >10% improvement the NPV for 10 Hz and iTBS decreased to 62.9 and 50.0%: $p = 0.35$. Lastly, at >0% improvement the NPV for 10 Hz and iTBS decreased further to 45.7 and 35.0%: $p = 0.44$.

Subsequently, using the KDE data-driven, population defined criteria for response for 10 Hz rTMS at >40 and >45% iTBS, using the same parameters, we determined the NPV at three cut-offs (0, 10, and 20%) of improvement at t_{10} for 10 Hz and iTBS using confusion matrices, and subsequently used proportional z-tests to determine if there was a significant difference between the two modalities. At >20% improvement at t_{10}, the NPV for 10 Hz rTMS and iTBS were 83.9 and 68.4%, respectively: $p = 0.20$. Then at >10% improvement the NPV for 10 Hz and iTBS decreased to 67.7 and 52.6%: $p = 0.28$. Lastly, at >0% improvement the NPV for 10 Hz and iTBS decreased further to 48.4 and 36.8%: $p = 0.44$.

DISCUSSION

The results from our naturalistic observational study suggest that early improvement can be useful for prognosticating who will respond to treatment and suggest similar patterns exist for both 10 Hz rTMS and iTBS targeting the left DLPFC. These findings held true when comparing the two modalities across an array of early improvement criteria (0, 10, and 20%) at treatment 10, and they were unaffected by choice of conventional (>50%) vs. data-driven (>40–45% by kernel density estimates) metrics of response categorization. Our data demonstrated that as the early treatment improvement criterion increased, so did the NPVs of both 10 Hz rTMS and iTBS, while maintaining no significant differences between the two modalities.

Moreover, despite no identified significant differences, it is evident that 10 Hz rTMS stimulation had a clear trend of higher NPVs and was more reliable at predicting response at each improvement criterion, as well as when comparing classically defined final response criteria vs. data-driven response criteria. Although it is unclear as to why this discrepancy exists, possible explanations include a smaller sample size in the iTBS group, which could contribute to an increased artifact of variability in response to treatment. Additionally, it is possible that with reduced patient-technician contact time and reduced time spent in the potentially therapeutic environment of the clinic, that the iTBS group may have a more variable response to treatment. It is worth noting that in an accepted study using the same dataset, that no significant differences were found in the time in which patients responded to treatment or overall response rates between 10 Hz rTMS and iTBS on a variety of clinical outcomes (23).

Further corroborating existing literature that demonstrates a lack of differences in the clinical utility of 10 Hz rTMS and iTBS (15, 23), our current study did not find any significant differences between the two treatments in the predictive capabilities of

early treatment improvement on final treatment response. Regarding the precision of the predictive capabilities, our data was comparable with previous studies in that a 20% improvement cut-off by treatment 10 achieved the best NPV as a predictor of rTMS treatment response. One study showed a NPV of 72.3% when participants failed to reach 20% improvement at week two while using final outcomes of extended treatment courses of 10 Hz stimulation at the left DLPFC (12), and another which had ∼80% NPV when using 1 Hz at the left DMPFC (13). Notably, our study focused on NPV as we felt this was the most important clinical information for rTMS practitioners to consider 10 treatments into an rTMS course.

Strengths

Early treatment response has been demonstrated to be an effective clinical outcome prognosticator (24). Nonetheless, it is important to compare its clinical usefulness to biomarkers and their ability to predict treatment response. Interestingly, a study found that when examining potential predictive biomarkers such serum and plasma BDNF increases at week 1, as well as EEG markers, and comparing them to a 20% improvement criterion on MADRS scores at week two of SSRI treatment, clinical predictors were superior (25). This study found that the 2-week improvement evaluation had a 92% NPV, whereas the serologic studies had a NPV of 57%, and the EEG markers had a NPV of 72%–this further highlights the utility of early treatment response and negative predictive values in a clinical setting.

In general, our study found that non-response to iTBS or 10 Hz treatment for major depressive disorder can be predicted with ∼70% accuracy in patients exhibiting at least 20% improvement after 10 sessions. Our results will help inform future clinical trials designed to investigate what parameter changes may increase response rates at t_{10}. In addition, although ∼70% accuracy may not be robust enough to create stringent treatment parameters for psychiatrists across the map, this data may help guide treatment decisions by identifying patients at risk for treatment non-response at the 2-week time point so therapeutic adjustments can be made to enhance treatment response. Some potential adaptations to existing treatment paradigms could include removing plasticity-impeding agents like benzodiazepines (26), accelerating TMS treatments with additional pulses (27), reducing stimulus intervals (28), increasing frequency (29), switching to bilateral stimulation (30), or other similar considerations.

Limitations

Despite the benefit of naturalistic, observational study designs allowing a greater generalizability of results to other "real-world" populations, there are several limitations that impede interpretation of our results. One such limitation was that although patients received standard clinical TMS treatment, the non-randomized nature creates opportunities for several uncontrolled variables, such as comorbid psychiatric conditions or psychotropic medications to influence TMS response. This blurs our ability to comment on early treatment improvement to TMS treatment in isolation. In light of the lack of more stringent patient stratification, several studies exist that have already examined the efficacy of rTMS in the treatment of depression when evaluated against sham groups (3, 14, 31–33). Furthermore, to address these potential limiting factors, we advocate for additional multi-site trials to create larger participant pools so that subsequent studies may have the statistical power to control for some of the above confounders and further evaluate predictive capabilities of early treatment response in TMS. Another limitation worth noting is that studies using conditional-probability metrics such as negative predictive value have been previously critiqued for the use of seemingly inconsistent improvement thresholds (e.g., 0, 10, 20%) (34), which could create difficulties in comparing predictive capabilities in subsequent studies.

CONCLUSION

To conclude, our naturalistic observational study, one of the first to directly compare the predictive capacity of early treatment improvement on ultimate treatment response between 10 Hz rTMS and iTBS, contributes to the growing consensus that there are no significant differences between the two modalities in the treatment outcomes for major depressive disorder. As the collection and analysis of biomarkers continues to remain expensive, time consuming, and inaccessible for many, studies like this further support the utility of easily attainable clinical predictors of treatment response in depression. TMS therapy often entails daily treatments for up to 6 weeks and beyond, requiring patients to take time off work or find transportation. The ability to forecast early in a treatment course a possible non-response to therapy will help both clinicians and patients decide if a parameter adjustment, or switch of therapy modalities entirely, may be warranted to maximize patient outcomes. Lastly, as iTBS sessions can be completed often ∼30 min faster than 10 Hz rTMS, the lack of significant differences in prognostication of treatment response between the two modalities, as suggested here, may encourage future clinicians to increase preferential utilization of iTBS over 10 Hz rTMS to reduce the time burden on patients without sacrificing effectiveness.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Iowa Institutional Review Board. The patients/participants provided their written informed consent to participate in this study. A waiver of consent was obtained for some subjects from the IRB if only clinical observational data was utilized.

AUTHOR CONTRIBUTIONS

NS: conceptualization, methodology, investigation, formal analysis, and writing-original draft. BP: methodology, data curation, resources, investigation, and reviewing and editing.

PT: investigation, data curation, formal analysis, and reviewing and editing. NT: conceptualization, methodology, investigation, resources, supervision, reviewing and editing, and project administration. All authors contributed to the article and approved the submitted version.

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Baseline Clinical and Neuroimaging Biomarkers of Treatment Response to High-Frequency rTMS Over the Left DLPFC for Resistant Depression

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Background: Repetitive transcranial magnetic stimulation (rTMS) has proven to be an efficient treatment option for patients with treatment-resistant depression (TRD). However, the success rate of this method is still low, and the treatment outcome is unpredictable. The objective of this study was to explore clinical and structural neuroimaging factors as potential biomarkers of the efficacy of high-frequency (HF) rTMS (20 Hz) over the left dorso-lateral pre-frontal cortex (DLPFC).

Methods: We analyzed the records of 131 patients with mood disorders who were treated with rTMS and were assessed at baseline at the end of the stimulation and at 1 month after the end of the treatment. The response is defined as a 50% decrease in the MADRS score between the first and the last assessment. Each of these patients underwent a T1 MRI scan of the brain, which was subsequently segmented with FreeSurfer. Whole-brain analyses [Query, Design, Estimate, Contrast (QDEC)] were conducted and corrected for multiple comparisons. Additionally, the responder status was also analyzed using binomial multivariate regression models. The explored variables were clinical and anatomical features of the rTMS target obtained from T1 MRI: target-scalp distance, DLPFC gray matter thickness, and various cortical measures of interest previously studied.

Results: The results of a binomial multivariate regression model indicated that depression type ($p = 0.025$), gender ($p = 0.010$), and the severity of depression ($p = 0.027$) were found to be associated with response to rTMS. Additionally, the resistance stage showed a significant trend ($p = 0.055$). Whole-brain analyses on volume revealed that the average volume of the left part of the superior frontal and the caudal middle frontal regions is associated with the response status. Other MRI-based measures are not significantly associated with response to rTMS in our population.

Conclusion: In this study, we investigated the clinical and neuroimaging biomarkers associated with responsiveness to high-frequency rTMS over the left DLPFC in a large sample of patients with TRD. Women, patients with bipolar depressive disorder (BDD), and patients who are less resistant to HF rTMS respond better. Responders present a lower volume of the left part of the superior frontal gyrus and the caudal middle frontal gyrus. These findings support further investigation into the use of clinical variables and structural MRI as possible biomarkers of rTMS treatment response.

Keywords: rTMS (repetitive transcranial magnetic stimulation), major depression (MDD), bipolar disorder, structural MRI (sMRI), DLPFC (dorsolateral prefrontal cortex), high-frequency, response

INTRODUCTION

Mood disorder [major depressive disorder (MDD) and bipolar disorder (BD)] is a heterogeneous and complex psychiatric condition. It is a major public health issue, ranking as the leading cause of disability worldwide, and the burden of mood disorders continues to grow despite the availability of validated interventions (1). MDD and BD both exhibit similar severe depressive symptoms (major depression, MD) (2).

The primary approaches to deal with MD include pharmacotherapy and psychotherapy. Although these approaches are effective, they still leave a significant proportion of patients with incomplete remission (3). This frequently results in TRD, which is associated with significant morbidity and high suicide risk (4).

As a result, several alternative treatments have been developed to target TRD, one of which is repetitive transcranial magnetic stimulation (rTMS) (5, 6). TMS is a non-invasive brain stimulation procedure that applies repeated magnetic pulses over the scalp to generate an electrical current in the cortex, provoking electrophysiological effects that modify the neural excitability in the target area and correlated brain networks (7). Safe profile (particularly the lack of systemic side effects associated with pharmacotherapy) and improved focality are some of its advantages over other neuromodulation techniques, such as electroconvulsive therapy (ECT).

Over 150 randomized controlled trials (RCTs) in unipolar and bipolar depression have been carried out, and their efficacy has been confirmed in multiple meta-analyses (8, 9). Moreover, real-world data have also confirmed the effectiveness of rTMS for major depressive disorder in clinical practice (10), with the most recent literature indicating response rates of 40–50% and remission rates of 25–30% (11).

The rTMS is effective in major depressive disorder but presents a high interindividual heterogeneity of clinical effectiveness (12). Moreover, this technique is costly in the real world and requires significant financial and time commitment from the patient and the practitioner. These elements highlight the pressing need for clinical and biological markers to predict treatment outcomes.

Clinical factors associated with rTMS response are divided into three main categories (13): patient-related factors (e.g., age, gender, and treatment resistance); illness-related factors (e.g., bipolar depression, duration and severity of depression, therapeutic resistance, previous response to rTMS or ECT), and TMS procedure-related factors (e.g., TMS intensity, number of pulses per session, and number of sessions) (14). Despite the extensive literature, data remain heterogeneous and contradictory with the need to be pursued.

Recent studies suggest that neuroimaging markers may achieve higher predictive accuracy than clinical or demographic variables [for review, see (15)]. Earlier studies showed promising results using methods derived from resting-state functional MRI or diffusion-weighted MRI (16). However, these biomarkers involve complex imaging protocols with few patients and a very specific patient selection. These imaging methods are rarely available in clinical settings, need specialized data processing, and are costly. Therefore, as suggested by Baeken et al., (17), simpler biomarkers like cortical thickness measures, as derived from anatomical MRI data, could be more feasible in current clinical practice. Indeed, to date, two studies have explored cortical thickness before stimulation as a predictor of rTMS response in patients with MDD (17, 18).

We conducted a retrospective naturalistic study to evaluate whether clinical factors or cerebral cortex thickness and volume may be a potential biomarker of rTMS treatment response in drug-resistant patients with depression of a large dataset from patients that received rTMS for the treatment of depression in a real-world clinical setting of a tertiary referral hospital.

MATERIALS AND METHODS

Between September 2014 and February 2018, we revised and analyzed the records of 131 patients with mood disorders who received rTMS treatment in the Neurostimulation Department of Henri Laborit Psychiatric Hospital. Each patient was treated only one time with rTMS. Non-opposition to the use of the participants' research data was obtained retrospectively. All patients provided informed written consent, and the study was registered at the Health Data Hub platform (F20210128152411).

Patients and Assessment

Patients treated with rTMS in our department met the criteria for major depressive disorder or bipolar disorder as defined by DSM-IV-TR. The diagnosis was made using the Mini International Interview for Neuropsychiatric Disorders (19) by an experienced psychiatrist. All patients had to be in a current

major depressive episode with a MADRS score higher than 20. The exclusion criteria included a DSM-IV-TR Axis I of psychotic disorder, a DSM-IV-TR diagnosis of alcohol or substance dependence, significant current active medical problem, and known neurological disease or a contraindication to rTMS (e.g., history of seizure disorder, presence of a pacemaker or metal somewhere in the head other than in the teeth) or MRI scanning (aneurysm clips, stents, or metal anywhere in the body).

Treatment resistance was defined as non-responsiveness to at least two courses of antidepressant medications for at least 6 weeks [Stage II, of Thase and Rush's definition (20)], as determined by their primary treating clinician and patient judgment of medication effectiveness. No medications changes were allowed in the 3 weeks before the beginning of the rTMS treatment or during the rTMS treatment itself.

The inclusion criteria for the retrospective analysis were as follows: rTMS-naïve (only the patient's first treatment with rTMS was considered), primary diagnosis of a depressive disorder (including bipolar disorder, currently depressive episode, major depressive disorder, and recurrent depressive disorder), a complete documented MADRS at the beginning (baseline), at the end of rTMS treatment (Day 14), and 1 month after (Day 45) the end of the rTMS course, and absence of a serious somatic illness. Both in- and out-patients were included.

Trained psychiatrists completed clinical assessments. All assessments included MADRS and BDI. Patients were assessed at baseline, post rTMS treatment (after 2 weeks of treatment, D14), and at one-month follow-up (45 days after baseline, D45). The primary outcome measure was the total MADRS score. The responder status was defined as a 50 % decrease in the MADRS score.

Treatment

Before the treatment period, each patient underwent an anatomical T1-weighted magnetic resonance imaging to set up the neuronavigation system (Syneika One; Syneika). The left DLPFC is detected by the Syneika neuronavigation system, which uses T1 imaging and the Talairach atlas to define the optimal target. The following acquisition parameters were used: Axial 3D T1 MPRAGE: TR, TE, TI = (2,000, 2.54, 900) ms; slice thickness 0.799 mm, Nex 1. The coil was positioned to target the left DLPFC. All patients had their motor cortex excitability evaluated at baseline and weekly using the Resting Motor Threshold (RMT). For 2 weeks, 10 rTMS sessions were delivered one time daily, five days a week. The rTMS treatment was administered with the MagPro® X100 with an option stimulator (MagVenture, Inc) using the Figure 8 coil.

Stimulation parameters were as follows: stimulation intensity was 110% of resting RMT, the stimulation frequency was 20 Hz, the train duration was 2 s, the inter-train interval was 10 s, the number of trains per session was 80, and the total number of pulses per session was 3,200. The stimulation lasted approximately a quarter of an hour (16 min) (21, 22). The rTMS protocol is based on the French guidelines. The variables for frequency and train duration were based on the study of Machii et al. (21), for the inter-train interval on the study of Chen et al. (22), and for the number of pulses on the study of Naihaus et al. (23). The number of sessions was determined by the previous trial with a frequency of 20 Hz (24, 25).

Anatomical Measures

The DICOM MRI images were converted to the Nifti format with a 1 mm isometric spacing and were used as input to FreeSurfer 6 software to compute the segmentation of white matter and cortical regions defined in the Desikan–Killiany atlas (26). This was accomplished by running brain pictures through the "recon-all" pipeline, which consists of skull-stripping, segmentation of gray and white matter voxels, tessellation, inflation, and registration to a brain template. In the previously mentioned atlas, the left-DLPFC will be defined as the union of the superior frontal and the caudal and the rostral middle frontal gyri. These three structures were then truncated at Talairach coordinates, at $y = 26$ [similar to Ehrlich et al. (27)] to filter out the pre-motor areas and at $x = -15$ to get rid of the medial regions. Cortical volume and thickness were then extracted for each subject within this region using the *mris_anatomical_stats* command. Other parameters will be studied, as they have previously been highlighted for their link with clinical response (28): left and right hippocampus volumes, left and right amygdala volumes, and left and right ACC, which are obtained by adding the volumes of caudal and rostral anterior cingulate as defined in the Desikan-Killiany atlas. The volumes of the hippocampus and the amygdala were obtained using the *asegstats2table* command, while the volumes of rostral-ACC and caudal-ACC were obtained using the *aparcstats2table* command. All volumes are divided by the estimated total intracranial volume (eT as computed by FreeSurfer.

After registering all patient segmentations to an average space, a whole-brain analysis was performed using the FreeSurfer tool QDEC ("Query, Design, Estimate, Contrast"). The null hypothesis states that the two groups' intercepts are not significantly different, which is equivalent to checking whether the average measure at a given vertex differs significantly between responders and non-responders. These results were then corrected for multiple observations using a Montecarlo null-Z simulation with a significance threshold of at least 0.05. Results that did not pass corrections were not considered. Following the literature, the analysis was carried out for the measures of thicknesses and volumes on the left and right hemispheres with a smoothing kernel of 15 mm (17, 18). We added the clinical variables as nuisance factors if their p-value in the univariate tests was inferior to 0.2. However, age and gender were added as nuisance factors regardless.

RTMS Targeted Anatomical Features

The coordinates of the individual stimulation targets for all subjects were extracted. pheres with a radius of 2 mm were created for each stimulation target using the SPM add-on MarsBar (29) and overlaid on an average brain using BrainNet Viewer (30) (**Figure 1A**). A sphere with a 10 mm radius was defined as the mean position target (red dot) of all subjects' coordinates. The mean sphere of interest will be used to extract anatomical features of TMS. To provide additional information, each subject's individual target coordinates were

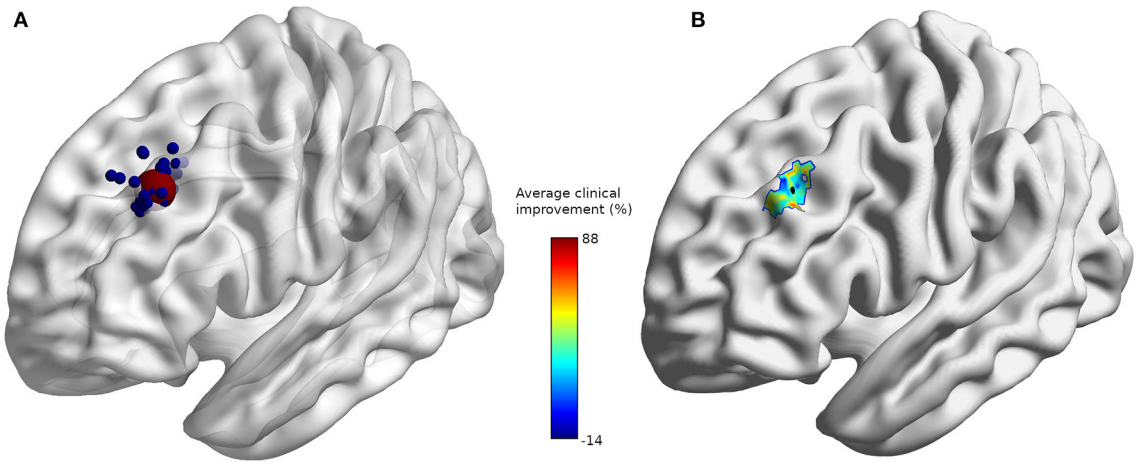

FIGURE 1 | (A) Individual stimulation sites (blue) and average stimulation site (red). **(B)** Average clinical improvement (%) with average stimulation site (black) at coordinates [−32, 32, 38].

weighted according to their clinical improvement, and the mean improvement field was displayed on an average brain (**Figure 1B**) (29). The minimum brain-scalp distance between the target and the scalp was computed using the freely available ScalpGM tool (31)[1], which relies on the SPM toolbox (spm12)[2] ScalpGM performs segmentation, computes minimal scalp distance for each gray matter voxel, and then warps the distance maps to a common space (MNI) for comparison. We used the mean radius sphere to extract scalp distance for all subjects. ScalpGM maps were thresholded at 1 mm (we assume that any value below 1 mm could not possibly be picked up since it would be inferior to the original image spacing and was therefore discarded as an artifact). To preserve the original image range, the interpolation type was set to the nearest neighbors. The cortical distance was defined as the minimal distance exceeding a threshold of 1 mm in the limits of the mean sphere.

Statistical Analysis

We used jamovi software (The jamovi project (2021). jamovi (Version 2.2.3.0). Retrieved from[3]) to conduct univariate statistical tests. The responder status was analyzed using binomial multivariate regression models. First, using clinical variables (gender, age, type of depression, resistance stage, baseline MADRS score, duration of illness, and current episode). Second, rTMS target anatomical features (target minimal distance and gray matter thickness at target) were added. Finally, the specific volumes of interest, such as left and right hippocampal volumes, left and right amygdala volumes, left and right ACC volumes, and left and right insula, that were previously highlighted for their link with clinical response were added The clinical covariates were included in the whole-brain analysis using the same method as the one used for the nuisance factors (univariate model $p < 0.2$; gender and age always included). Statistical significance is set at $p < 0.05$; a $p < 0.1$ will be considered a noteworthy trend. Additionally, robust binomial multivariate regressions were performed to mitigate the impact of the non-normality of the data. The implementation used is the *glmrob* function implemented in the *robustbase* R package (32). The results presented will be of the non-robust multivariate binomial model.

[1]https://github.com/nickjdavis/ScalpGM
[2]https://www.fil.ion.ucl.ac.uk/spm/software/spm12/
[3]https://www.jamovi.org

RESULTS

All patients in our study population were taking antidepressants and/or thymoregulators, with 3.2% on lithium and 22.1% on anti-epileptic drugs prescribed for thymoregulatory purposes (clonazepam, lamotrigine, oxcarbazepine, and valpromide), with the exception of pregabalin, which was prescribed as an anxiolytic. The majority of patients were treated with one or more antidepressants: 40% were on SSRIs, 27.4% on SNRIs, 24.2% on tricyclic antidepressants, 5.3% on tetracyclic antidepressants, 3.2 % on MonoAmine Oxidase Inhibitors (MAOI), and 8.4 % were prescribed other types of antidepressants. Benzodiazepines or related drugs were prescribed for a majority of patients (80%) and antipsychotics for approximately half of the patients (53.7%).

Of the 131 patients, 20 refused to participate in the study. The final assessment of the MADRS score was missing for 16 patients. For one patient, the MADRS assessment on day 14 was missing. For 94 patients with neither of these variables missing, the evolution between day MADRS0 and MADRS14, as well as the evolution of MADRS0 and MADRS45, was computed and found to be moderately correlated (Pearson's r, $r = 0.475$, $p < 0.001$). As a result, we decided to exclude from the following analyses any patient whose final assessment was missing. We, therefore, included 95 patients. Some clinical factors, such as depression type ($p = 0.034$), sex ($p = 0.022$), and Thase and Rush resistance

TABLE 1 | Clinical factors and univariate tests.

Variable	N	NR	R	Test statistic	*p*-value
Age	95 (NR = 57; R = 38)	52.12 ± 11.59	51.45 ± 10.75	U = 1,038.50**	0.738
Duration of the episode	94(NR = 57; R = 37)	38.76 ± 46.12	38.08 ± 57.83	U = 1,009.00**	0.728
Duration of illness	91 (NR = 56; R = 35)	184.39 ± 151.00	225.16 ± 148.85	U = 794.00**	0.130
Baseline Beck score	91 (NR = 56; R = 35)	20.11 ± 6.32	19.09 ± 0.66	U = 908.00**	0.559
Baseline MADRS score	95 (NR=57; R = 38)	28.91 ± 5.39	27.50 ± 5.63	U = 899.00**	0.162
Resistance stage	95 (NR = 57; R = 38)	2.65 ± 0.94	2.32 ± 0.66	U = 847.00**	0.053
Motor Threshold	95 (NR = 57; R=38)	51.11 ± 9.07	53.29 ± 9.35	U = 965.50**	0.374
Depression type: Bipolar	95 (NR = 57; R = 38)	10/57	14/38	X^2 (1) = 4.50*	0.034
Gender: F	95 (NR = 57; R = 38)	27/57	27/38	X^2 (1) = 5.21*	0.022
SSRIs	95 (NR = 57; R = 38)	22/57	16/38	X^2 (1) = 0.117*	0.732
SNRIs	95 (NR = 57; R = 38)	16/57	10/38	X^2 (1) = 0.0353*	0.851
Tricyclic antidepressants	95 (NR = 57; R = 38)	13/57	10/38	X^2 (1) = 0.153*	0.696
Tetracyclic antidepressants	95 (NR = 57; R = 38)	3/57	2/38	X^2 (1) = 0.000***	1.000
MAOIs	95 (NR = 57; R = 38)	3/57	0/38	X^2 (1) = 0.702***	0.402
Other	95 (NR = 57; R = 38)	4/57	4/38	X^2 (1) = 0.0512*	0.821
Benzodiazepine	95 (NR = 57; R = 38)	45/57	31/38	X^2 (1) = 0.0987*	0.753
Anti-epileptics	95 (NR = 57; R=38)	12/57	9/38	X^2 (1) = 0.0917*	0.762
Anti-psychotics	95 (NR = 57; R = 38)	33/57	18/38	X^2 (1) = 1.0160*	0.313
Lithium	95 (NR = 57; R = 38)	1/57	2/38	X^2 (1) = 0.129***	0.719

*Pearson's X^2; **Mann–Whitney U; ***Continuity-corrected X^2. NR, Non-Responders on Day 45; R, Responders on Day 45.*

TABLE 2 | Differences in clinical factors and MADRS scores between patients with unipolar disorder and bipolar disorder.

Variable	*N*	Unipolar	Bipolar	Test statistic	*p*-value
Age	95 (Unipolar = 71; Bipolar = 24)	52.32 ± 11.08	50.46 ± 11.72	U = 783**	0.557
Gender: F	95 (Unipolar = 71; Bipolar = 24)	40/71	14/10	X^2 (1) = 0.0291*	0.865
Benzodiazepine	95 (Unipolar = 71; Bipolar = 24)	56/71	20/24	X^2 (1) = 0.0314***	0.859
Baseline MADRS score	95 (Unipolar = 71; Bipolar = 24)	28.80 ± 5.61	27.00 ±5.03	U = 678**	0.136
Day 14 MADRS score	95 (Unipolar = 71; Bipolar = 24)	20.73 ± 9.21	13.50 ± 8.74	U = 477**	0.001
Day 45 MADRS score	95 (Unipolar = 71; Bipolar = 24)	19.75 ± 9.01	13.13 ± 8.78	U = 510**	0.003
Day 14 Responder	95 (Unipolar = 71; Bipolar = 24)	20/71	13/24	X^2 (1) = 5.35*	0.021
Day 45 Responder	95 (Unipolar = 71; Bipolar = 24)	24/71	14/24	X^2 (1) = 4.50*	0.034

*Pearson's X^2; **Mann–Whitney U; ***Continuity-corrected X^2.

stage ($p = 0.053$), play an important role (**Table 1**). **Table 2** highlights the differences between unipolar and bipolar patients.

If the duration of illness or current episodes was missing from subsequent analyses, it was replaced by the mean of the entire population. Five additional patients were excluded due to a failed parcellation or a faulty MRI acquisition, resulting in a sample size of 90 subjects for the analyses relying on MRI data.

None of the patients participating in the study reported having seizures or shifting between hypomanic/manic states. Patients did not complain about local pain or dizziness after stimulation. Moreover, none of the patients discontinued treatment due to adverse effects.

Whole-Brain Analysis

Whole-brain analysis based on the volume difference between responders and non-responders (comparing the intercepts of the two groups) revealed a decreased volume for the responder's group in the superior-frontal and caudal middle frontal regions of the left hemisphere (**Figure 2**). This result passed the Monte-Carlo null-Z cluster correction up to a threshold of 0.005 (Z-score of 2.3). The same observation could not be reproduced in the opposite hemisphere. No significant difference was observed in cortical thickness between the responder and non-responder groups, even at a more relaxed correction threshold of 0.05 (Z-score of 1.3).

Region of Interest Analyses

Gender, type of depression, and resistance stage all appear to play a role in the binomial model containing the DLPFC measures (**Table 3**), consistent with the results of the univariate tests conducted previously. The baseline MADRS score seems to be significant as well ($p = 0.027$). Imagery-based measures, such as

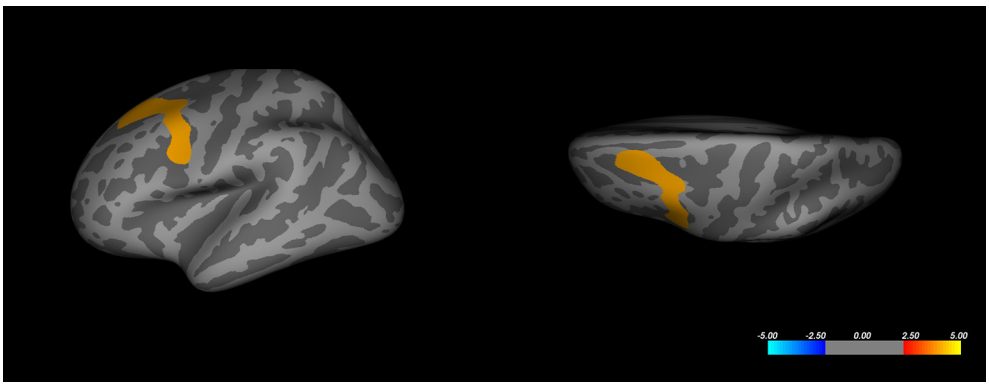

FIGURE 2 | Whole-brain analysis corrected cluster on left hemisphere cortical volume. Color represents significance as a Z-score. Corrected maximal significance Z = 4.000 is at Talairach coordinates [−30.8, 9.3, 53.6] (FreeSurfer annotation: caudal-middle frontal).

TABLE 3 | Multivariate binomial regression coefficients of DLPFC measures and clinical factors.

Predictor	Estimate	SE	Z	*p*	Odds ratio
Intercept	0.440149	4.531280	0.097136	0.923	1.550
Gender: M – F	−1.454878	0.565119	−2.574462	0.010	0.230
Depression type: Unipolar – Bipolar	−1.380683	0.616408	−2.239885	0.025	0.250
Age	0.023513	0.026489	0.887671	0.375	1.020
Resistance stage	−0.690661	0.359458	−1.921395	0.055	0.500
Duration of illness	0.000000	0.001897	0.000030	1.000	1.000
Baseline MADRS score	−0.117649	0.053201	−2.211380	0.027	0.890
DLPFC average thickness	2.361551	1.467189	1.609575	0.107	10.610
Minimal brain-scalp distance	−0.053008	0.037102	−1.428713	0.153	0.950

Deviance = 97.095; R^2 [Nagelerke's] = 0.31697; $\chi^2 = 24.047$; df = 8; p = 0.002; accuracy = 0.7; specificity = 0.74074; sensitivity = 0.63889; AUC = 0.78601.

the left DLPFC thickness and the minimal scalp distance to the cortical target, did not appear to be significant (both $p > 0.1$).

The second model (**Table 4**) does not appear to demonstrate the significance of any of the volumes considered (all $p > 0.1$). Gender, type of depression, stage of resistance, and severity of depression represented by the baseline MADRS score retain their significance. Clinical factors appear to have the greatest influence on predicting individual treatment responses in both models, owing to the low variation of the model fit and predictive measures.

The results of the robust analyses did not appear to change drastically. The robust model for literature volumes showed a decrease in the significance of depression type (from significant to $p < 0.1$) and in the resistance stage ($p < 0.1$ to insignificant). On the model containing the DLPFC measures, no such changes were observed.

DISCUSSION

In this retrospective and naturalistic study, we aimed to identify clinical and neuroimaging factors associated with the efficacy of rTMS evaluated 1 month after the beginning of treatment in 95 patients with drug-resistant depression who were treated with high-frequency rTMS (20 Hz) over the left DLPFC.

The response rate at 1 month after rTMS treatment in our study is 40%. This is consistent with previous studies reporting a 40–50% response rate to rTMS treatment in MDD (33, 34) and BDD (35–37).

Our analysis of clinical variables (type of depression, illness severity evaluated by MADRS and Beck, resistance stage, associated treatment, gender, and resting state) demonstrated that the type of depression, gender, and resistance stage are associated variables with response to rTMS.

First, we found that bipolar depression responds better to HF rTMS over the left DLPFC. To our knowledge, no naturalistic study to date has highlighted bipolar illness as a factor in better response to rTMS or has established a correlation between the type of depression and the clinical effect of rTMS (12, 38). Treating bipolar depression is clinically challenging as antidepressants can worsen the outcome for this category of patients, which is why rTMS has been suggested as a treatment option for bipolar depression (39). Patients with bipolar depression were enrolled in studies focused primarily on unipolar major depression or in dedicated sham-controlled studies examining the efficacy of rTMS in bipolar depression. Three meta-analyses and quantitative syntheses have been conducted to date (9, 40, 41). According to Nguyen et al., active-rTMS is associated with a higher response rate than sham-rTMS

TABLE 4 | Multivariate binomial regression coefficients of literature volumes and clinical factors.

Predictor	Estimate	SE	Z	p	Odds ratio
Intercept	6.787604	4.589525	1.478934	0.139	886.786
Gender: M – F	−1.625463	0.628189	−2.587536	0.010	0.197
Depression type: Unipolar – Bipolar	−1.470419	0.682712	−2.153790	0.031	0.230
Age	0.004934	0.029839	0.165357	0.869	1.005
Resistance_stage	−0.764139	0.381127	−2.004945	0.045	0.466
Duration_of_illness	−3.3961*e*−4	0.001926	−0.176332	0.860	1.000
MADRS_J0	−0.119086	0.057000	−2.089244	0.037	0.888
Left_Amygdala	21.738405	35.078504	0.619707	0.535	2,759,700,000.000
Right_Amygdala	4.182690	31.611853	0.132314	0.895	65.542
Left_Hippocampus	4.585550	18.287139	0.250753	0.802	98.057
Right_Hippocampus	−11.560154	18.888773	−0.612012	0.541	0.000
lh_insula_volume	−6.102632	7.858057	−0.776608	0.437	0.002
rh_insula_volume	0.229891	7.950897	0.028914	0.977	1.258
lh_ACC_volume	7.054542	7.553866	0.933898	0.350	1158.106
rh_ACC_volume	6.737072	6.511928	1.034574	0.301	843.089
DLPFC_volume	−2.444911	2.623072	−0.932079	0.35	0.087

Deviance = 96.831; R^2 [Nagelerke's] = 0.3200; $\chi^2 = 24.311$; df = 15; p = 0.06; accuracy = 0.74444; specificity = 0.81481; sensitivity = 0.63889; AUC = 0.78704.

in bipolar depression, but subgroup analyses testing differences based on stimulation target and site revealed no significant differences. However, when analyzed separately, HF over the left DLPFC stimulation was associated with a statistically significant greater response than sham treatment. In contrast, bilateral stimulation and low-frequency rTMS over the right DLPFC were not.

We identified the effectiveness of rTMS in bipolar depression in our study. This result differs from that of Yang et al. (42). In fact, in their naturalistic study with an adequately large cohort of participants, they suggest that patients with BD are less likely to achieve clinical response with high-frequency L-DLPFC rTMS than those with unipolar depression (10 Hz). The antidepressant response to rTMS might vary with stimulation frequency. In our study, we used 20 Hz stimulation in seven sham-controlled studies (43–49) in patients with mixed depression and one naturalistic study in patients with BDD (50). Apart from the same frequency of stimulation, there is still significant methodological heterogeneity between studies, including trial duration, stimulation intensity, and several pulses per session, which makes it difficult to compare different findings. Therefore, the stimulation parameters used in our study could account for the improved response in patients with BDD. This difference in response to treatment could be explained by differences in the clinical expression of bipolar and unipolar depressive episodes (51) and indeed by the potential differences in the neurophysiological mechanisms that cause them.

Second, in our study, patients with a high treatment resistance stage respond less to rTMS. The refractoriness of depressive episodes appears to be one of the best-supported predictors of rTMS response. Many studies have suggested that a higher degree of medication resistance may be tied to worse rTMS outcomes in depression (13). Most findings from rTMS response predictor studies suggest that a lower degree of drug resistance is one of the more robust predictors of superior outcomes for rTMS therapy using standard stimulation parameters and targeting methods. While definitive prospective studies are still needed, the existing literature appears to support the use of standard rTMS therapy relatively early during the treatment, prior to the occurrence of numerous medication treatment failures.

Third, we found that women respond better to rTMS than men do. The association between female gender and response to treatment is debatable. A recent meta-analysis, which included 54 sham-controlled trials between 1997 and 2013, revealed that gender might be a positive predictor of response, as studies showing good antidepressant response to rTMS had more female patients (52). In fact, in our study, women (56.8 %) outnumber men (43.2 %). In a second meta-analysis, the same authors show that the antidepressant effect of specifically HF rTMS was higher in RCTs with a greater proportion of female patients (53). They suggested that women's profiles, rather than their sex, might have influenced their response to treatment.

Other clinical and demographic variables, such as age, associated treatment, and resting motor threshold, had no effect on treatment response in our study. The link between treatment response and these variables is debated in the literature. Some studies revealed that younger patients respond better to rTMS (54, 55), whereas other studies found no correlation between age and response (56). Regarding associated treatment, there is growing evidence that concomitant use of medication can impair the clinical effectiveness of rTMS, especially for benzodiazepines (57). However, the impact of concomitant medication on rTMS effectiveness is still debatable (58, 59). Finally, we did not find a link between baseline RMT and response. The correlation between clinical efficiency and stimulation intensity is not precisely known (60, 61). Some studies suggest a dose efficiency correlation. Another hypothesis assumes a more complex and non-linear correlation.

We also investigated the relationship between structural neuroimaging variables (whole-brain analysis, thickness of the left DLPFC and ACC, volumes described in the literature, and distance between scalp and cortical target) and response to rTMS. Neuroanatomical predictors may be particularly useful for brain stimulation interventions, which directly modify the activity within neural circuits, contrary to indirect reorganization caused by psychological or pharmacological interventions.

We initially performed an exploratory analysis of thickness and volume across the brain, in addition to the main cortex-wide analysis that was unconstrained by a priori hypotheses. We also performed ROI analyses to further evaluate the *a priori* hypotheses and then explored specifically the link between the left DLPFC and rostral ACC thickness at baseline and treatment response.

We did not find a statistically significant link between cortical thickness and treatment response. The link between cortical thickness and the responses to ECT (62), tDCS (63), and rTMS (17, 18) has been reported before. Boes et al. (18) describe that cortical thickness in the left rostral anterior cingulate cortex region correlates with rTMS treatment response in 48 TRD patients treated with HF (10 Hz) rTMS over the left DLPFC baseline. In fact, patients with thinner cortex before treatment tended to have the most clinical improvement. Baeken et al. (17) recently suggested that baseline cortical thickness in the right caudal part of the anterior cingulate cortex was significantly correlated with direct clinical responses in the subgroup that received active aiTBS (21 patients) over the left DLPFC during the first stimulation week, but no correlation was found with delayed response. In this study, we did not confirm the results of these two preceding studies. In Boes and Baeken study's, no accurate correction for multiple comparison testing was performed, increasing the risk of type I error. This can partly explain why we did not find the same results. Different stimulation parameters and the number of patients are also potential explanations for this discrepancy. Moreover, increased cortical thickness after rTMS treatment has been described in longitudinal studies (18, 64).

Response to rTMS was also evaluated in terms of the cortex-scalp distance. According to Lee et al. (65), the non-invasive brain stimulation scalp-to-cortex distance has been reported to critically influence the focality and strength of the electric field induced by rTMS. Our result indicated that there is no difference inefficacy related to this distance. Kozel et al. (66) discovered that these distances do not directly correlate with antidepressant clinical response in 29 depressed patients, but a correlation was established between the motor threshold measurement and the distance from the cortex to the skull under the TMS coil. In our study, the scalp-motor cortex distance was not possible because the stimulation point was not recorded during each session. Moreover, the lack of statistical correlation between response and distance in our study could have been influenced by the position of the stimulation coil. This could be in part due to the fact that the exact targeting zone for every session is unknown. One could also question the validity of the chosen region of interest (10 mm radius sphere around the average theoretical cortical target.

Gray matter volume (GMV) at baseline has been previously described as a predictor of treatment response in mood disorders. We first performed a whole-brain mapping without an *a priori* hypothesis for a specific brain volume. Interestingly, when taking into account depression type, gender, age, resistance stage, duration of illness and episode, and baseline MADRS score, this whole-brain analysis associated with clinical factors in a regression model shows that the average volume of the left part of the superior frontal gyrus and the caudal middle frontal gyrus was associated with the status of the response, where responders present a lower gray matter volume. The same result could not be reproduced in the right hemisphere.

The superior frontal gyrus and the middle frontal gyrus are usually defined as a part of the DLPFC (67). The superior frontal gyrus contributes to higher cognitive functions (68). It is part of the "hate circuit," which is involved the pathogenesis of depression symptoms, risk and action responses, attention, reward, and emotion (69). The middle frontal gyrus is critical for higher-order executive functions related to stress perception and appraisal, including attention, working memory, planning, executive cognition, and emotion regulation (70–72), and may confer vulnerability to depression. The GMV deficits of the frontal cortex have been reported in several studies on MDD. Abe et al. (16) found that patients with MDD might have GMV deficits in frontal-temporal-limbic regions, which also included the middle frontal gyrus. Leung et al. (73) found that attention biases toward negative stimuli are associated with a reduced gray-matter concentration in the right superior frontal gyrus. Lai et al. (74) found a GMV increase in the frontal lobe after treatment with aripiprazole in patients with depression and deficits in the superior and medial frontal gyrus for patients with MDD at baseline status. Moreover, Lai et al. (74) compared structural differences between patients who were able to achieve remission and those who responded poorly to antidepressants. The remitting MDD patients showed a bilaterally smaller superior frontal gyrus volume. Yuan et al. (75) found that geriatric patients with depression in remission from their first episode of depression had reduced GMV in the right superior frontal gyrus in comparison with well-matched healthy controls. Although the nature of the involvement of the superior frontal gyrus and the caudal middle frontal gyrus in mood disorders remains a matter of debate, in our study, a greater volume in the left part of the superior and the caudal middle frontal gyrus was observed in non-responder patients. The association of this region with response to rTMS was not previously described in structural MRI studies that investigated response factors.

No statistically significant differences in baseline structural volumes were found between treatment responders and non-responders. Few studies have investigated the association between GMV and treatment response in MDD. Treatment response was evaluated for cognitive behavioral therapy (CBT) (76), antidepressant (77), ECT (78, 79), and rTMS (80). The study found a link between clinical response and the volumes of the left and right hippocampus, the left and right amygdala, the left and right ACC, and the left and right insula (28). In our study, none of these regions were found to be associated with response to rTMS.

Despite the strengths of this study (larger number of patients than already described in the literature, correction for multiple comparison testing with independent logistic regression models, naturalistic design), several limitations must be considered. First, all of the patients included in this study were under medication; prior exposure to medication is a strong confounding factor as it may affect the brain structure. In fact, Hoexter et al. (81) found that the thickness of the orbitofrontal cortex in patients with OCD can serve as a predictive biomarker of treatment response, exclusively in treatment-naive patients. Second, our investigation does not have a placebo-controlled group, which means that any predictive biomarker of treatment response could be confounded by the placebo effect. Third, our patients have multiple comorbidities, which may have confounded our results. Finally, MRI was performed only at baseline. In the future, recording structural MRI data at multiple time points to retrieve information about structural changes after rTMS is recommended.

There remains significant interest in understanding how to optimize the application of rTMS for each patient in order to achieve greater remission rates and provide more efficient symptom relief. The use of structural MRI is an essential tool to achieve this objective. Besides, this type of imaging is easy to perform, and collaborations between several centers can be envisioned to allow for the acquisition of a sufficient volume of imaging and clinical data in the future to establish solid correlations. Moreover, it would be interesting to characterize the structural covariance networks (SCN) to better understand the response to rTMS. SCN analyses aim to identify network patterns of common influences and characterizations within the brain across the population rather than differences in the structure of isolated brain regions in individuals (82). In addition, MDD is associated with deregulation of neural networks rather than a disruption of individual brain regions in isolation (80). Recently, preliminary evidence suggested that gray matter could be used to distinguish rTMS responders and non-responders, particularly in the fronto-parietal network (83, 84).

CONCLUSION

In conclusion, we investigated the clinical and neuroimaging biomarker associated with the response to high-frequency rTMS over the left DLPFC in a large sample of patients with TRD depression. Women, patients with BDD, and patients who are less resistant were found to respond better to HF rTMS. Responders present a lower volume of the left part of the superior frontal and the caudal middle frontal gyri. The thickness of the DLPFC and ACC, the volumes of the amygdala, hippocampus, ACC, insula, DLPFC, and the distance from the scalp to the target were not associated with the clinical response. Our results reinforce the need to identify accurate and reliable clinical and neuroimaging biomarkers of treatment response. This biomarker that can be translated into clinical practice holds promise for the advancement of precision medicine. Our findings may serve as a guide to future studies with larger datasets to investigate specific neuroimaging biomarkers (the distance between scalp and target and specific volume) and clinical biomarkers (sociodemographic and clinical characteristics), with the ultimate aim of defining a multimodal biomarker profile that predicts rTMS treatment response.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

GH-G, IW, DD, and NJ conducted the patient assessments. RG provided MRI images of the patients. GH-G, NL, and TL and performed analyses. The manuscript was written by GH-G and TL and all authors revised and proofread the manuscript.

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Accelerated Intermittent Theta Burst Stimulation in Smoking Cessation: Placebo Effects Equal to Active Stimulation When Using Advanced Placebo Coil Technology

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Smoking is currently one of the main public health problems. Smoking cessation is known to be difficult for most smokers because of nicotine dependence. Repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex (DLPFC) has been shown to be effective in the reduction of nicotine craving and cigarette consumption. Here, we evaluated the efficacy of accelerated intermittent theta burst stimulation (aiTBS; four sessions per day for 5 consecutive days) over the left DLPFC in smoking cessation, and we investigated whether the exposure to smoking-related cues compared to neutral cues during transcranial magnetic stimulation (TMS) impacts treatment outcome. A double-blind, randomized, controlled study was conducted in which 89 participants (60 males and 29 females; age 45.62 ± 13.42 years) were randomly divided into three groups: the first group received active aiTBS stimulation while watching neutral videos, the second group received active aiTBS stimulation while watching smoking-related videos and the last group received sham stimulation while watching smoking-related videos. Our results suggest that aiTBS is a tolerable treatment. All treatment groups equally reduced cigarette consumption, nicotine dependence, craving and perceived stress. The effect on nicotine dependence, general craving and perceived stress lasted for at least 1 week after the end of treatment. Active aiTBS over the left DLPFC, combined with smoking related cues, is as effective as active aiTBS combined with neutral cues as well as placebo aiTBS in smoking cessation. These findings extend the results of previous studies indicating that TMS therapy is associated with considerably large placebo effects and that these placebo effects may be further increased when using advanced placebo coil technology.

Clinical Trial Registration: www.clinicaltrials.gov, identifier NCT05271175.

Keywords: smoking cessation, intermittent theta burst stimulation (iTBS), repetitive transcranial magnetic stimulation, provocative smoking cues, placebo effect

INTRODUCTION

Cigarette smoking is one of the foremost causes of preventable disease and premature death (1–5). According to the World Health Organization (WHO), in 2020, 22.3% of the global population used tobacco (6). Nicotine is a highly addictive chemical compound (7) in tobacco and is released directly in the mesolimbic dopamine pathways where reward processing takes place (8). In 2014, 68% of US adult smokers wanted to quit smoking and in 2017, 55.1% of US adult smokers had made an attempt to quit smoking (9–11). However, only a small percentage of adult smokers (7.4%) actually achieved to quit smoking (11). To support smokers in smoking cessation, behavioral, psychological and pharmacological interventions as well as nicotine replacement therapy are some of the most used interventions (12) with medium to low success rates (12, 13). Recently, there has been growing interest in new, alternative, and effective treatments for smoking cessation.

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation therapy (14, 15) that delivers magnetic pulses to a brain region, inducing an electric current that can depolarize neurons and induce action potentials (14). Repetitive (r)TMS protocols have been found to have lasting effects on excitability that can either be (generally) inhibitory (1 Hz) or excitatory (10 Hz) in nature by engaging synaptic plasticity mechanisms, such as long-term potentiation (LTP) and long-term depression (LTD) (16). Theta Burst Stimulation (TBS) is a more recent TMS protocol that delivers a comparable number of pulses in a very short time (17, 18). Two different patterns of TBS were developed: intermittent TBS (iTBS) and continuous TBS (cTBS) which generally increases and decreases cortical excitability, respectively (17).

The dorsolateral prefrontal cortex (DLPFC) is a frontal brain region that plays a crucial role in meso-cortico-limbic and serotonergic systems (19) and is involved in executive functions such as inhibitory control, as well as emotion regulation and decision making; processes modified by substance use and dependence (19–21). Mesolimbic dopamine reward circuits and frontoparietal networks are associated with craving and are activated by addictive drugs (22). Exposure to cigarette-related cues has been associated with activation in the DLPFC (23, 24). Smoking related cues provoke activation of these brain circuits of smokers (24, 25). The combination of rTMS with smoking related cues has been found to be more effective compared to the combination of rTMS alone (26).

Several lines of evidence support the efficacy of high frequency (HF)-rTMS over the left DLPFC in the reduction of nicotine craving and cigarette consumption (21, 24, 27) and cue-induced smoking craving (28). A recently published double blind RCT showed that HF-rTMS (20 Hz) over the left DLPFC for 10 daily sessions is effective in reducing cigarette consumption, craving, dependence as well as in improving anxiety and depressing symptoms (29). According to a recent systematic review, multiple target HF-rTMS may be effective in smoking cessation (21). Accelerated TMS (aTMS), is used increasingly in research and clinical practice and has been shown to be as effective as a standard TMS procedure (30–32). Recently, an accelerated, high-dose, iTBS protocol has shown promising results in patients with treatment resistant depression (33).

A growing body of research highlights the importance of determining the efficacy of TMS in neuropsychiatric disorders using randomized controlled trials (RCT) with placebo-controlled groups. Placebo effects in TMS are a very common phenomenon (34–37) and can have a big influence on the results of a study (38). Several studies indicated that the placebo effect may be a component of the therapeutic response to rTMS in neuropsychiatric disorders like major depressive disorder, and stroke rehabilitation (35, 37).

Considering current knowledge of the efficacy of iTBS in substance use disorders, we investigated in a double-blind randomized control trial efficacy of four iTBS sessions per day during five consecutive days over the left DLPFC in smoking cessation, using the Cool-B65 Active/Placebo (A/P) coil, an advanced coil that is designed to support true "double blinded" clinical trials. Moreover, we wanted to investigate whether the exposure to smoking-related cues during the rTMS treatment, compared to neutral cues impacts cigarette craving. We hypothesized that 20 sessions of accelerated theta burst simulation over the left DLPFC while exposed to smoking-related cues, would reduce cigarette consumption and cigarette cravings, accompanied by reduced stress and motivation to quit smoking to a greater extent than active stimulation combined with neutral cues and sham stimulation with smoking-cues.

MATERIALS AND METHODS

Participants

One hundred fifty-nine cigarettes smokers, who wanted to quit smoking, were recruited *via* internet advertisements and printed flyers in the period of April 2019 to December 2020 in Cyprus. Potential participants were screened in a short telephone interview where a total of 104 participants were eligible to participate. Inclusion criteria were the following: (a) aged 18–70, (b) native or fluent Greek speaker. Exclusion criteria were the following: (a) mental objects or implants in the brain, skull or near head (e.g., pacemakers, metal plates), (b) past or current of diagnosis of neurological or psychiatric disorder, (c) use of psychiatric medication, (d) past or current drug or alcohol abuse, other than nicotine, (e) use of IQOS ("I Quit Original Smoking") or electronic cigarettes (e-cigarettes). A total of 89 participants were included in the final analysis (60 males and 29 females; age 45.62 $\pm$ 13.42 years), excluding dropouts ($n = 15$). The minimum number of participants required was determined by an a priori power analysis where at least a sample size of 100 participants was suggested. [*Measures that suggested this sample size were determined by the mixed model, a small to medium effect size (0.4), at an alpha level of probability of 0.05]. The experiment was carried out in the Cyprus rTMS Center in Larnaca, Cyprus. This study was approved by the Cyprus National Bioethics Committee and written informed consent was obtained from all participants (ΕΕΒΚ/ΕΠ/2019/08).

TABLE 1 | Demographic and smoking-related characteristics of ($N = 89$) participants.

Characteristics	TMS&N group $n = 29$	TMS&S group $n = 30$	Sham group $n = 30$	*p*-Values
Demographic				
Age (year)	46.52 ±13.05	42.93 ± 14.42	47.43 ± 12.72	0.395[a]
Gender (M/F)	22/7	20/10	18/12	0.427[b]
Education (year)	14.07 ± 3.95	14.43 ± 30.77	13.60 ± 3.27	0.681[a]
Occupation*				0.167[b]
Private employee	13 (14.61%)	19 (21.35%)	22 (24.72%)	
Public employee	7 (7.87%)	4 (4.49%)	1 (1.12%)	
Self-employed/Freelancer	5 (5.62%)	1 (1.12%)	4 (4.49%)	
Unemployed	2 (2.25%)	1 (1.12%)	0 (0%)	
Retired	2 (2.25%)	4 (4.49%)	3 (3.37%)	
Student	0 (0%)	1 (1.12%)	0 (0%)	
Smoking-related				
Cigarettes per day	27.55 ± 15.37	26.83 ± 12.86	30.00 ± 13.38	0.654[a]
Types of cigarettes*				0.184 [b]
Normal	16 (17.98%)	25 (28.09%)	24 (26.97%)	
Hand-rolled	10 (11.24%)	5 (5.62%)	5 (5.62%)	
Cigarillos	1 (1.12%)	0 (0%)	0 (0%)	
Mixed	2 (2.25%)	0 (0%)	1 (1.12%)	
Years of smoking	23.18 ± 9.82	23.13 ± 13.58	28.73 ± 12.21	0.125[a]
If ever quitted*				0.899[b]
No	9 (10.11%)	10 (11.24%)	11 (12.36%)	
Yes	20 (22.5%)	20 (22.5%)	19 (21.3%)	
How many times quitted	0.90 ± 0.77	1.00 ± 1.11	1.20 ± 1.56	0.614[a]

Data are means ± standard deviation.
**n (%).*
[a]One-way ANOVA.
[b]Pearson chi-square test.
TMS, transcranial magnetic stimulation.

Experimental Design

A multi-arm parallel group, double-blind, randomized, controlled study was conducted in which participants were randomly divided into three groups: the first group received active iTBS stimulation while watching neutral videos (TMS&N group), the second group received active iTBS stimulation while watching smoking-related videos (TMS&S group) and the last group received sham stimulation while watching smoking-related videos (Sham group). The Latin square design was used for the randomization. Both participants and the investigator who applied the rTMS and administered the self-reported measurements to the participants were blinded to the treatment condition. A second investigator was not blinded to the procedures to be able to set-up the appropriate stimuli. Four iTBS sessions (active or sham) were administrated every day, with 30 min break between them over a 5-day period. Both active iTBS stimulation and sham stimulation were applied over the left DLPFC.

RTMS Procedure

Stimulation was performed using a MagPro X100 (MagVenture, Farum, Denmark) and a figure-of-eight coil (Coil Cool-B65 A/P) for both active and sham stimulation. The Cool-B65 Active/Placebo (A/P) coil is designed to support true "double blinded" clinical trials as it can produce active and placebo stimulation by flipping the coil and can mimic a tapping sensation during placebo condition (39) (see The MagVenture Cool-B65 Active/Placebo (A/P) Coil in **Supplementary Material 1** for additional information).

Before the first session, the resting Motor Threshold (rMT) was determined by placing the coil over the left primary motor cortex (40) (see Resting Motor Threshold (rMT) in **Supplementary Material 2** for additional information). Stimulation was performed at 100% of rMT. Two experimenters were in the treatment room with the participant. The TMS operator (blinded experimenter) avoided watching the video while it was playing to remain blinded to the procedure and was only looking into the patients' direction. The videos were played by the second researcher.

In both active and sham conditions, an accelerated iTBS (aiTBS) treatment (four sessions with 30 min break between them) was administered daily for a 5-day period over the left DLPFC. Beam_F3 Locator software was used to locate the left DLPFC (41) (see Beam_F3 Locator Software in **Supplementary Material 3** for additional information). The stimulation coil was placed at a 45° angle of the midline. iTBS was

TABLE 2 | Overview of data collection time points.

Measurements	Time points
Primary measures	
Self-reported cigarette consumption	i Baseline ii AfterDay1 iii AfterDay2 iv AfterDay3 v AfterDay4
Carbon monoxide (CO)-evaluated nicotine consumption	Prior to each rTMS session
Fagerström test for nicotine dependence (FTND)	i Baseline ii End of the treatment iii 1 week follow up
The Visual Analog Scale (VAS)	Prior to and post each rTMS session
Tobacco Craving Questionnaire–Short Form (TCQ-SF)	i Baseline ii End of treatment iii 1 week follow up
Secondary measures	
Perceived Stress Scale-4 (PSS-4)	i Baseline ii End of the treatment iii 1 week follow up
Motivation to quit smoking	i Baseline ii End of the treatment iii 1 week follow up
Adverse events	After each treatment day

administrated at 5 Hz and each session included 20 trains with 8 s inter train interval (10 pulses per train at 50 Hz). A total number of 600 pulses was given per session.

Data Collection and Measurements

Demographic information as well as smoking-habits profile information were collected (**Table 1**). Participants were asked to report the number of cigarettes usually smoked during a day as well as the type of cigarettes, years of smoking and whether they ever quit smoking and if yes, how many times, to record smoking habits (**Table 1**).

Smoking-Related and Neutral Video Cues

During the rTMS treatment, participants were instructed to pay attention to videos that were presented on a monitor (Height: 20 cm; Width: 35 cm) placed opposite the treatment chair. Two different forms of videos were used (smoking related videos e.g., a person smoking cigarette in a restaurant and neutral videos e.g., a man cleaning his shoes) in order to elicit craving at the time of stimulation. Each video was presented for approximately 3 min during the stimulation.

Primary Measures

Cigarette consumption: (a) Self-reported nicotine consumption: Participants had to daily record the number of cigarettes smoked from the completion of the four sessions until their next treatment visit. Participants were asked not to smoke during the breaks of the four daily rTMS sessions; (b) Carbon monoxide (CO)- evaluated nicotine consumption: CO levels were measured using the piCO Smokerlyzer breath carbon monoxide meter device

Nicotine dependence: Fagerström test for Nicotine Dependence (FTND) (42) is a short, self-report measure that assesses nicotine dependence. It contains six questions, and the total score is calculated as a sum of these six questions. The total scores of the questionnaire vary from 0 to 10, with lower scores indicating lower dependence on nicotine. This scale has been used previously in Cypriot samples and has been translated into Greek, showing good internal consistency (43, 44).

Craving: (a) Momentary Craving: The Visual Analog Scale (VAS) is a psychometric measurement instrument that measures symptom severity on a continuous scale (45). We used the VAS to assess smoking craving by asking participants to respond to the question "How much do you want to smoke right now?", on a scale from 0 "no craving" to 100 "most craving ever experienced"; (b) General Craving: Tobacco Craving Questionnaire–Short Form (TCQ-SF) (46) is a self-report measure that assesses tobacco craving in four dimensions: emotionality, craving in anticipation of relief from withdrawal or negative mood; expectancy, craving in anticipation of positive outcomes from smoking; compulsivity, craving in anticipation of an inability to control tobacco use; and purposefulness, craving coupled with intention and planning to smoke. Each factor scale contains three items. TCQ-SF items were rated on a Likert scale of 1 (strongly disagree) to 7 (strongly agree). Total scores vary from 12 to 84, by summing the 12 items and the scores for each factor scale vary from 3 to 21 by summing the three items in each factor scale. A high score indicates high tobacco craving. We translated the TCQ-SF into Greek using the forward and backward-translation procedure (Cronbach's $\alpha = 0.90$, see Cronbach's alpha in **Supplementary Material 4** for additional information).

Secondary Measures

Perceived Stress: Perceived Stress Scale-4 (PSS-4) (47) is a self-report measure that is used to assess psychological stress. The original PSS comprises 14 items (PSS-14) with two (negative and positive) subscales. We here used the shorter version with four items (PSS-4) that were rated on a Likert scale, ranging from 0 to 4, with those on the positive subscale scored in reverse and the total score was calculated as a sum of these items. The scores vary from 0 to 16, with a higher score indicating higher perceived stress.

Motivation to quit smoking: Participants were asked to estimate how motivated they were to quit smoking from 0 to 100%.

Adverse events: Participants were asked to daily report the adverse events they may have had experienced.

(For the time points of each measurement, see **Table 2**).

Data Analysis

SPSS software version 27.0 was used for the statistical analysis of the data (IBM corporation, Endicott, New York). We calculated the mean score of the 8 VAS scores and 4 CO scores of each day. A one-way ANOVA and Pearson chi-square test were used to test for differences in baseline demographic

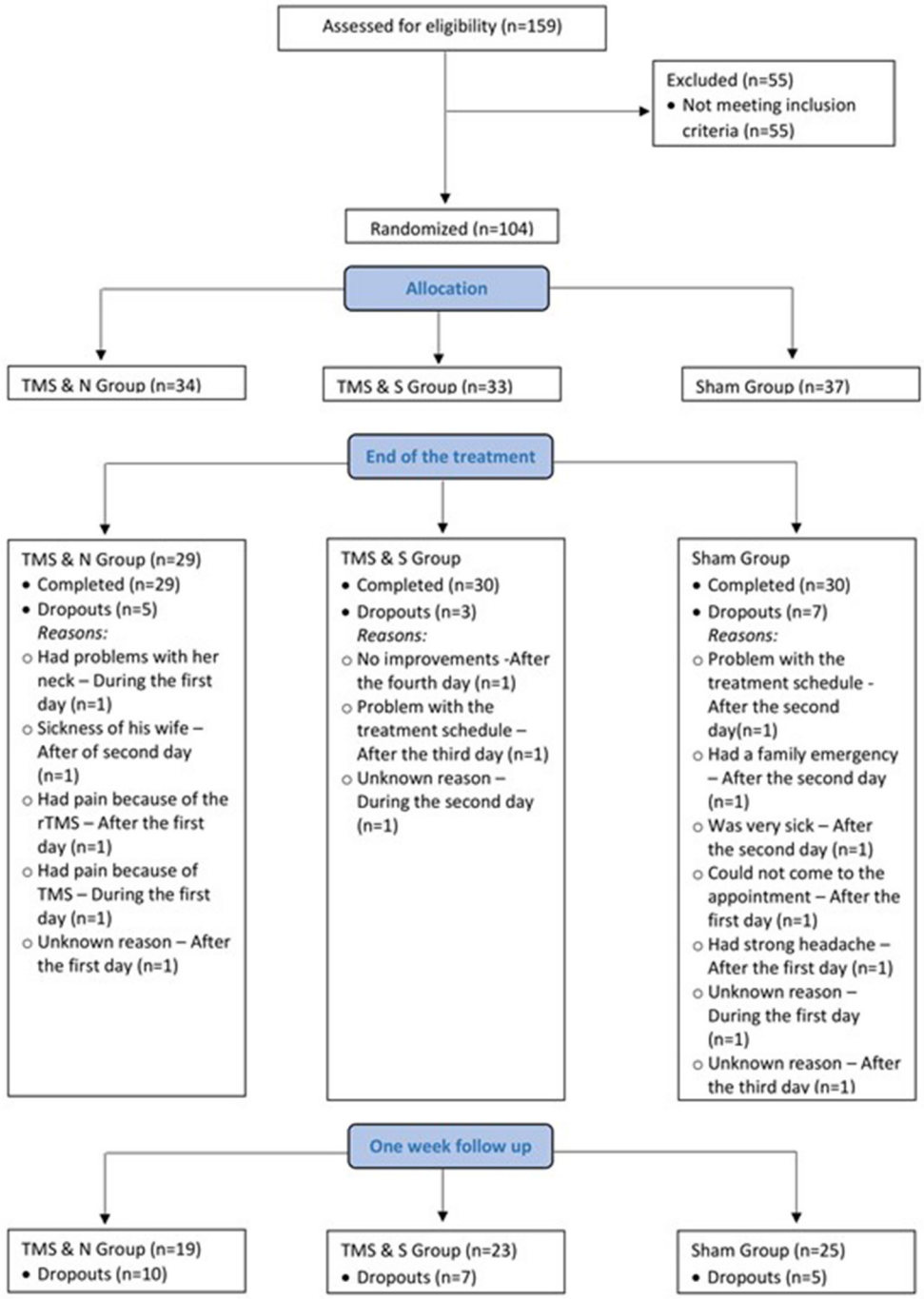

FIGURE 1 | Flow chart of the selection procedure.

and smoking-related variables and rMT scores between the three groups. Mixed factorial ANOVAs were conducted to investigate the effect of both the within factor (Time) and the between factor (Group: TMS-N group, TMS-S group, Sham group). The dependent variables used for each model were: cigarette consumption, nicotine dependence, craving and perceived stress. Greenhouse–Geisser and Huynd-Feldt degree of freedom corrections were applied to correct for the non-sphericity the data. *Post hoc* comparisons using paired-samples *t*-test were used to evaluate the significance of mean change in cigarette consumption, nicotine dependence, craving and perceived stress at different timepoints. Non-parametric tests were used as the variable *Motivation to quit smoking* was not normally distributed at all time-point assessments.

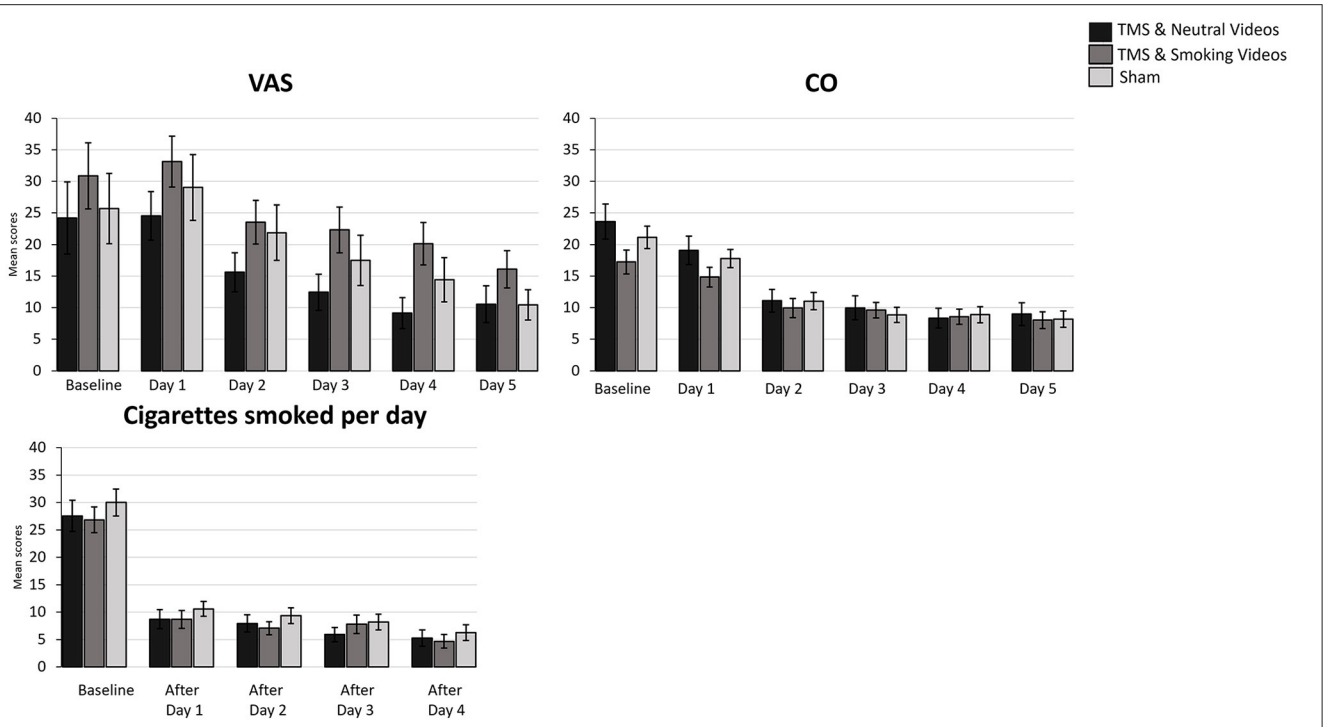

FIGURE 2 | Bar graphs showing difference in mean scores of VAS, CO, Cigarettes smoked per day over time. Data are presented as mean ± SEM.

TABLE 3 | Results of paired sample *t*-test for the number of cigarettes smoked per day.

	Mean change	SD	*t*-Value	*p*-Value
Pair 1: Baseline vs. AfterDay1	−19.13	11.89	14.731	**<0.0001**
Pair 2: Baseline vs. AfterDay2	−20.48	11.73	16.188	**<0.0001**
Pair 3: Baseline vs. AfterDay3	−21.20	12.83	14.962	**<0.0001**
Pair 4: Baseline AfterDay4	−22.93	12.89	16.208	**<0.0001**
Pair 5: AfterDay1 vs. AfterDay2	−1.14	5.35	1.940	0.056
Pair 6: AfterDay1 vs. 1 AfterDay3	−2.13	7.44	2.597	0.011
Pair 7: AfterDay1 vs. AfterDay4	−3.82	6.85	5.051	**<0.0001**
Pair 8: AfterDay2 vs. AfterDay3	−1.09	4.90	2.006	0.048
Pair 9: AfterDay2 vs. AfterDay4	−2.84	5.09	5.050	**<0.0001**
Pair 10: AfterDay3 vs. AfterDay4	−1.74	4.64	3.363	**0.001**

Paired sample t-test; p < 0.05. Significant after Bonferroni correction in bold.

Non-parametric Wilcoxon signed-rank tests were conducted to evaluate the significance of mean change in *Motivation to quit smoking* scores at different time points for each Group separately and non-parametric Kruskal–Wallis *H* tests were conducted to compare the mean scores of motivation to quit of the three Groups at different timepoints. Pearson chi-square test was used to test for differences in adverse events between the active TMS and sham TMS. Finally, a Pearson correlation analysis was applied to correlate a subjective measure (self-reported) with an objective measure (CO) of nicotine consumption. A significance level was set at $\alpha = 0.05$ for all analyses.

RESULTS

Baseline Characteristics

Eight-nine participants completed the entire treatment program (60 males and 29 females; age 45.62 ± 13.42 years; see Enrollment in **Supplementary Material** for enrollment information and **Figure 1** for study recruitment flow diagram). Participant demographics and smoking-related variables are listed in **Table 1**. Analysis showed that the three groups did not differ significantly in demographic or smoking-related characteristics (all $p > 0.05$).

Primary Outcomes

Self-Reported Nicotine Consumption

A 5 (Time: Baseline, AfterDay1, AfterDay2, After Day3, AfterDay4) × 3 (Group: TMS&N group, TMS&S group, Sham group) mixed factorial ANOVA was conducted for the analysis of the number of cigarettes smoked per day. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(9) = 167.688$, $p = 0.00$, therefore degrees of freedom were corrected using Greenhouse-Geisser of sphericity ($\varepsilon = 0.470$). There was a statistically significant main effect of Time, $F(1.879,142.840) = 166.548$, $p < 0.0001$, $\eta p^2 = 0.687$, suggesting a significant decrease in the number of cigarettes smoked per day over time. However, there was no significant effect of Type of Group, $F(2,76) = 0.363$, $p = 0.697$, $\eta p^2 = 0.009$ (**Figure 2**, see **Supplementary Table 1** for means and standard deviations). The interaction effect between Time and Group was not statistically significant, $F(3.759,142.840) = 0.414$, $p = 0.787$, $\eta p^2 = 0.011$. *Post hoc* comparisons using paired-samples *t*-test

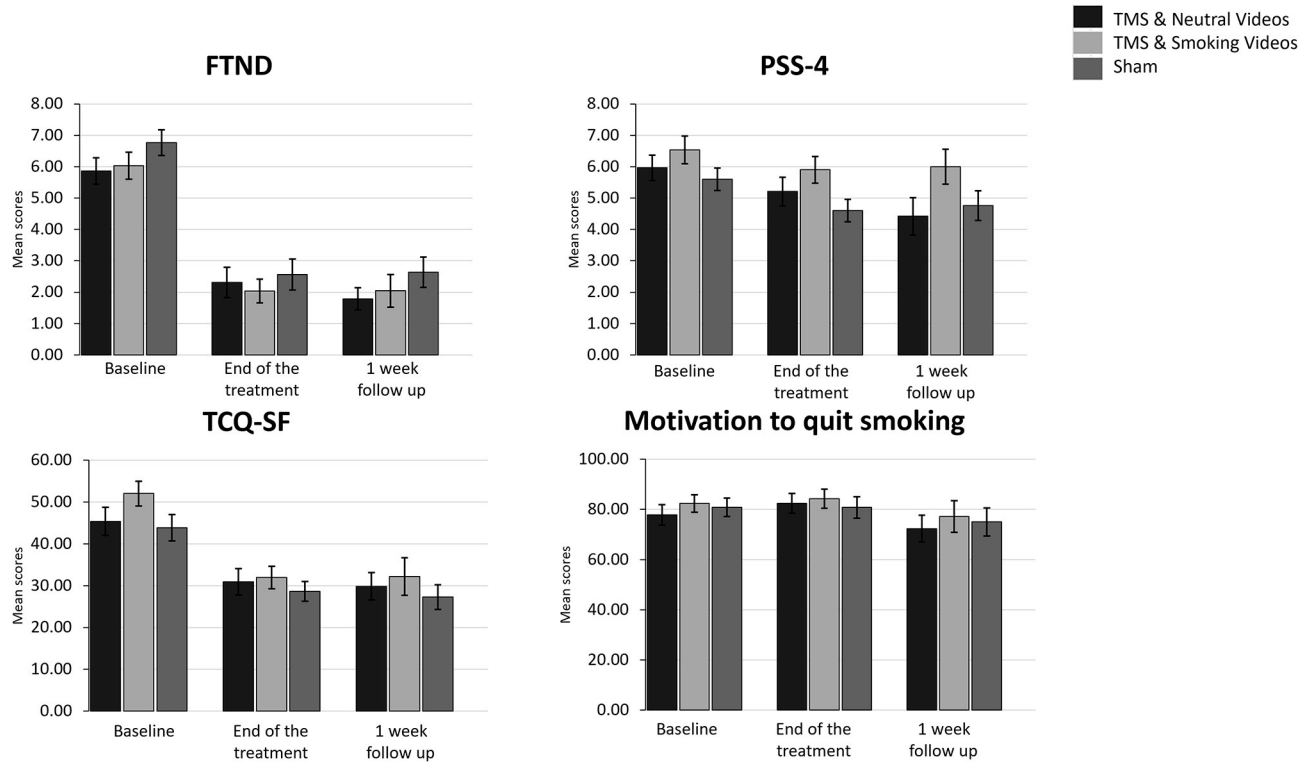

FIGURE 3 | Bar graphs showing difference in mean scores of FTND, PSS-4, TCQ-SF and Motivation to quit smoking over time. Data are presented as mean ± SEM.

were used to evaluate the significance of mean change in the number of cigarettes smoked per day at different time points (**Table 3**). Results indicate that mean scores were statistically significantly lower over time in all the comparisons, except of the pair AfterDay1 vs. AfterDay2, where no statistically significantly changes were found.

CO-evaluated Nicotine Consumption

A 6 (Time: Baseline, Day1, Day2, Day3, Day4, Day5) × 3 (Group: TMS&N group, TMS&S group, Sham group) mixed factorial ANOVA was conducted for the analysis of CO scores. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(14) = 340.631$, $p = 0.00$, therefore degrees of freedom were corrected using Greenhouse-Geisser of sphericity ($\varepsilon = 0.368$). The interaction effect between Time and Group was not statistically significant, $F(3.678,154.484) = 1.964$, $p = 0.109$, $\eta p^2 = 0.045$. There was a statistically significant main effect of Time, $F(1.839,154.484) = 82.421$, $p < 0.0001$, $\eta p^2 = 0.495$, suggesting a significant decrease in CO scores over time. However, there was no significant effect of Group, $F(2,84) = 0.589$, $p = 0.557$, $\eta p^2 = 0.014$ (**Figure 2**, see **Supplementary Table 1** for means and standard deviations).

Nicotine Dependence

A 3 (Time: Baseline, End of treatment, 1 week follow up) × 3 (Group: TMS&N group, TMS&S group, Sham group) mixed factorial ANOVA was conducted as measured by the FTND. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(2) = 11.064$, $p = 0.004$, therefore degrees of freedom were corrected using Huynh-Feldt of sphericity ($\varepsilon = 0.911$). The interaction effect between Time and Group was not statistically significant, $F(3.642,116.549) = 0.095$, $p = 0.978$, $\eta p^2 = 0.003$. There was a statistically significant main effect of Time, $F(1.821,116.549) = 119.672$, $p < 0.0001$, $\eta p^2 = 0.652$, suggesting a significant decrease in nicotine dependence over time. However, there was no significant effect of Group, $F(2,64) = 1.784$, $p = 0.176$, $\eta p^2 = 0.053$ (**Figure 3**, see **Supplementary Table 1** for means and standard deviations). *Post-hoc* paired sample *t*-tests were used to evaluate the significance of mean change in FTND scores at different time points (**Table 4**). Results indicate that mean scores were statistically significantly lower at the End of treatment and at 1 month follow up compared to the baseline, however, no statistically significantly changes were found between the scores at the End of treatment compared to the scores at 1 week follow up.

Momentary Craving

A 6 (Time: Baseline, Day 1, Day 2, Day3, Day 4, Day 5) × 3 (Group: TMS&N group, TMS&S group, Sham group) mixed factorial ANOVA was conducted for the analysis of VAS scores. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(14) = 160.748$, $p = 0.00$, therefore degrees of freedom were corrected using Greenhouse-Geisser of sphericity ($\varepsilon = 0.539$). The interaction effect between

TABLE 4 | Results of paired sample *t*-test for the three self-reported measures.

	Mean change	SD	*t*-Value	*p*-Value
FTND				
Pair 1: Baseline vs. End of treatment	−3.92	2.570	14.379	**<0.0001**
Pair 2: Baseline vs. 1 week follow up	−3.82	2.57	12.170	**<0.0001**
Pair 3: End of treatment vs. 1 week follow up	0.12	1.79	**–0.5**44	0.588
TCQ-SF				
Pair 1: Baseline vs. End of treatment	−16.59	19.60	7.988	**<0.0001**
Pair 2: Baseline vs. 1 week follow up	−15.13	20.56	6.026	**0.010**
Pair 3: End of treatment vs. 1 week follow up	1.72	14.09	**–0.9**97	0.323
PSS-4				
Pair 1: Baseline vs. End of treatment	**–0.7**9	1.95	3.861	**<0.0001**
Pair 2: Baseline vs. 1 week follow up	−1.07	2.47	3.561	**0.001**
Pair 3: End of treatment vs. 1 week follow up	**–0.1**8	2.24	0.654	0.516

Paired sample t-test; p < 0.05. Significant after Bonferroni correction in bold.

Time and Group was not statistically significant, $F(5.389,231.740) = 0.400$, $p = 0.861$, $\eta p^2 = 0.009$. There was a statistically significant main effect of Time, $F(2.695,231.740) = 25.667$, $p < 0.0001$, $\eta p^2 = 0.230$, suggesting a significant decrease in VAS scores over time. However, there was no significant effect of Group, $F(2,86) = 1.511$, $p = 0.226$, $\eta p^2 = 0.034$ (**Figure 2**, see **Supplementary Table 1** for means and standard deviations).

General Craving

A 3 (Time: Baseline, End of treatment, 1 week follow up) × 3 (Group: TMS&N group, TMS&S group, Sham group) mixed factorial ANOVA was conducted as measured by the TCQ-SF. Mauchly's test indicated that the assumption of sphericity had been violated in both situations, $\chi^2(2) = 11.572$, $p = 0.003$, therefore degrees of freedom were corrected using Huynh-Feldt of sphericity ($\varepsilon = 0.905$). The interaction effect between Time and Group was not statistically significant, $F(3.620,115.845) = 1.320$, $p = 0.269$, $\eta p^2 = 0.040$. There was a statistically significant main effect of Time, $F(1.810,115.845) = 32.881$, $p < 0.0001$, $\eta p^2 = 0.339$, suggesting a difference in tobacco craving over time. However, there was no significant effect of Group, $F(2,64) = 2.289$, $p = 0.110$, $\eta p^2 = 0.067$ (**Figure 3**, see **Supplementary Table 1** for means and standard deviations). *Post-hoc* paired sample *t*-tests were used to evaluate the significance of mean change in TCQ-SF scores at different time points (**Table 4**). Results indicate that mean scores were statistically significantly lower at the End of treatment and at 1 month follow up compared to the baseline, however, no statistically significantly changes were found between the scores at the End of treatment compared to the scores at 1 week follow up.

Secondary Outcomes

Perceived Stress

A 3 (Time: Baseline, End of treatment, 1 week follow up) × 3 (Group: TMS&N group, TMS&S group, Sham group) mixed factorial ANOVA was conducted as measured by PSS-4. The interaction effect between Time and Group was not statistically significant, $F(4,128) = 1.132$, $p = 0.344$, $\eta p^2 = 0.034$. There was a statistically significant main effect of Time, $F(2,128) = 9.398$, $p < 0.0001$, $\eta p^2 = 0.128$, suggesting a significant decrease in perceived stress over time. However, there was no significant effect of Group, $F(2,64) = 1.415$, $p = 0.250$, $\eta p^2 = 0.042$ (**Figure 3**, see **Supplementary Table 1** for means and standard deviations). *Post-hoc* paired sample *t*-tests were used to evaluate the significance of mean change in PSS-4 scores at different time points (**Table 4**). Results indicate that mean scores were statistically significantly lower at the End of treatment and at 1 month follow up compared to the baseline, however, no statistically significantly changes were found between the scores at the End of treatment compared to the scores at 1 week follow up.

Motivation to Quit Smoking

Wilcoxon signed-rank tests yielded no statistically significantly changes, expect of the pair End of treatment vs. 1 week follow up of the TMS& N Group ($Z = -2.392$, $p = 0.017$) where scores at 1 week follow up (Mean = 72.37, SD = 23.41) were statistically significantly lower compared to the scores at the End of treatment (Mean = 82.41, SD = 20.59). Also, Kruskal–Wallis *H* tests showed that there were no statistically significant differences in Motivation scores between the different Groups in the baseline, $\chi^2(2) = 0.646$, $p = 0.724$, at the End of treatment, $\chi^2(2) = 0.202$, $p = 0.904$ and at the 1 week follow up, $\chi^2(2) = 0.810$, $p = 0.667$ (**Figure 3**, see **Supplementary Table 1** for means and standard deviations).

Adverse Events

Eleven participants (37.93%) of the TMS-N Group, five participants (16.67%) of the TMS&S group and seven participants (23.33%) of the Sham group reported mild adverse events. There were no statistically significant differences between Active and Sham TMS in terms of adverse events as determined by Pearson chi-square test ($p = 0.574$). The most frequent adverse events were mild headache and sleepiness

TABLE 5 | Adverse events of ($N = 23$) participants, *n* (%).

Adverse events	Active TMS	Sham TMS	Total
Mild headache	6 (26.1%)	1 (4.3%)	7 (30.4%)
Sleepiness	3 (13%)	2 (8.7%)	5 (21.7%)
Insomnia	1 (4.3%)	1 (4.3%)	2 (8.7%)
Tension	1 (4.3%)	1 (4.3%)	2 (8.7%)
Nausea	0 (0%)	1 (4.3%)	1 (4.3%)
Numbness on stimulation site	1 (4.3%)	0 (0%)	1 (4.3%)
Lightheadedness	1 (4.3%)	0 (0%)	1 (4.3%)
Coughiness	1 (4.3%)	0 (0%)	1 (4.3%)
Numbness on stimulation site & Forgetfulness	0 (0%)	1 (4.3%)	1 (4.3%)
Numbness on stimulation site & Sleepiness	1 (4.3%)	0 (0%)	1 (4.3%)
Mild headache & Sleepiness	1 (4.3%)	0 (0%)	1 (4.3%)
Total adverse events	**16 (69.6%)**	**7 (30.4%)**	**23 (100%)**

TMS, transcranial magnetic stimulation.

(**Table 5**). No severe adverse events such as seizure or mania have been reported in the study.

Correlations Between Self-Reported and CO-measured Nicotine Consumption

A Pearson correlation analysis was applied to correlate self-reported and CO-measured nicotine consumption. Results showed a significant positive correlation between the two variables in all timepoints (see **Supplementary Table 2**).

DISCUSSION

The current study investigated the efficacy of a rapid accelerated iTBS therapy (four sessions per day for five consecutive days) combined with smoking related cues in smoking cessation. We hypothesized that an active TMS group that is exposed to smoking related videos during stimulation (TMS&S group) shows more improvement with regard to reducing their cigarette consumption and smoking craving compared to the group that receives sham stimulation while watching smoking-related videos (sham group), and to the group receiving active TMS while watching neutral videos (TMS&N group).

In contrast to these expectations, we however found that all conditions, including sham stimulation, were equally effective in reducing cigarette consumption, CO levels, smoking craving and nicotine dependence. Contrary to our expectations and to what is reported in the literature, active TMS combined with smoking related cues was not more effective than active TMS combined with neutral cues, not sham stimulation.

Most interestingly was the fact that our TMS intervention was highly effective in facilitating smoking cessation. Our participants in the active TMS conditions showed 80.7 and 82.59% decrease in cigarette consumption in TMS &N Group and TMS&S group respectively, and 56.38 and 47.59% reduction in nicotine craving in TMS &N Group and TMS&S group respectively. The number of cigarettes smoked per day was statistically significantly lower over time, from the baseline to the End of treatment of the fifth day. These results are consistent with previous TMS trials, which show that rTMS can significantly reduce cigarette consumption and nicotine craving (21, 24, 26). Surprisingly, our advanced placebo coil technology condition specifically designed to support true "double blinded" clinical trials showed to be equally effective in treating smoking cessation. Our participants in Sham group showed 79.1% decrease in cigarette consumption and 59.34% reduction in nicotine craving. A similar reduction in cigarette consumption was found in a recent RCT, where the reduction in the active group was 76.19% (27), although, contrary to our findings, a much smaller reduction in cigarette consumption was found in the sham group (35.29%). Similarly, participants in all conditions showed huge reductions in CO scores (TMS&N group: 62.01%, TMS&S group: 53.42%, Sham group: 61.29%).

We were thus able to show, that, especially when using such an advanced double blind placebo stimulation technology, the placebo effect of TMS in clinical context can be considerably large and even equal to the effect achieved with active TMS stimulation. Placebo effects in TMS are known to be playing a certain role on the clinical results obtained with TMS and have been documented before (35–38). There are several factors that contribute to the enhancement of placebo effect in rTMS studies (38, 48). A systematic review and meta-analysis by Razza et al. (37) evaluated the efficacy of rTMS for depression using data from a sham group of 61 RCTs, concluding that placebo effect sizes in depression trials are rather large ($g = 0.8$). Previous studies also demonstrated that placebo effects may be a component of the therapeutic response to rTMS (35, 37). The placebo effect was also shown to be larger in more intense TMS protocols [HF rTMS (48)] and especially accelerated protocols (49).

We therefore support that several specific factors not directly associated with rTMS treatment have contributed to the enhanced placebo effect found in the present study. First, our participants were highly motivated to quit smoking. Our data clearly indicate that already at day 1 and 2 during the treatment cycle, a strong effect of both, active and placebo TMS, was revealed. The timeline of these effects indicate that this is likely driven more by the motivation and expectation of our participants rather than by actually induced neuroplastic changes. Second, we used an intensive and state-of-the art TMS design, applying accelerated TMS with multiple sessions per day using theta burst stimulation sequences. It has been shown before that placebo effects scale with the intensity and complexity of the used TMS technology (48, 49). Finally, we used an advanced placebo coil technology capable of creating a true double blind clinical trial and an undistinguishable experience for each participant whether or not to be in a placebo or active stimulation condition. Unlike previous TMS studies, we did not use a simple coil tilting procedure (50), or a standard sham coil (51) to achieve our placebo condition. Instead, we used a novel and advanced placebo coil technology capable of mimicking not only the visual and auditory experience of active TMS, but also the somatosensory skin sensation using a low intensity current stimulator built into the A/P coils and a pair of surface electrodes

placed just below the hairline on the scalp of each participant. These factors likely contributed to the fact that we do find our accelerated TMS intervention to be highly effective in reducing cigarette consumption and smoking craving, but not significantly more effective than placebo. The actual effect of our active rTMS had to show statistically to be on top of the highly effective placebo condition, which turned out to be not the case in our trial due to the factors mentioned above.

Additionally, our results demonstrated a statistically significant difference in perceived stress over time. However, due to the absence of a significant effects of the Group and the interaction effect between Time and Group, these results are inconclusive regarding the efficacy of active TMS in reducing perceived stress. Nevertheless, previous findings have shown that left DLPFC is a principal target of noninvasive brain stimulation techniques in regulating stress-related cognitive processes (52). It was reported in the literature that perceived stress may be a barrier to smoking cessation (53), and thus further investigation on the association of perceived stress and smoking cessation during rTMS treatment is required.

The follow up assessment proved that these positive effect in nicotine dependence and perceived stress, as measured by FTND, TCQ-SF and PSS-4, lasts at least 1 week after the End of treatment. The findings of this study have to be seen in light of some limitations. Firstly, we did not measure self-reported cigarette consumption after the fifth day of treatment and during the 1-week follow up. Another potential limitation is the absence of a fourth group receiving sham stimulation while watching neutral videos. Finally, we did not use any formal assessment of blinding efficacy.

Although future RCTs are necessary to validate these conclusions, the present study highlights the importance of placebo effects and the role of specific placebo coil technologies in evaluating the efficacy of TMS in any psychiatric and psychological contexts. This could be used to further improve the administration of TMS based interventions, both for designing better placebo conditions in clinical trials, as well as for utilizing TMS placebo for enhancing coping and other psychological strategies of patients during rTMS treatment (48).

CONCLUSION

Our findings show that active aiTBS combined with smoking related cues, is as effective as active aiTBS combined with neutral cues as well as placebo aiTBS in smoking cessation. These findings extend the results of previous studies indicating that rTMS therapy is associated with considerably large placebo effects and that these placebo effects may be further increased when using advanced placebo coil technology. These beneficial effects in reducing cigarette consumption and craving for smoking in this and previous studies are likely a combination between the active rTMS effect and the placebo TMS effect. Future RCTs using advanced placebo coil technology are needed to confirm these results. Finally, future studies should emphasize on how to minimize placebo effect on TMS treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Cyprus National Bioethics Committee (ΕΕΒΚ/ΕΠ/2019/08). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GM: conceptualization, methodology, formal analysis, data curation, writing—original draft, and project administration. PM: formal analysis, data curation, and writing—original draft. LP: formal analysis, data curation, and writing—review and editing. AS: conceptualization, methodology, participant recruitment, data collection, formal analysis, data curation, and writing—review and editing. TS: supervision and writing—review and editing. ATS: conceptualization, supervision, and writing—review and editing, and project administration. All authors agree with the contents of the manuscript and were fully involved in the study and preparation of the manuscript and have read the final version of the manuscript and have approved the submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.892075/full#supplementary-material

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Efficacy of Repetitive Transcranial Magnetic Stimulation in Patients With Methamphetamine Use Disorder: A Systematic Review and Meta-Analysis of Double-Blind Randomized Controlled Trials

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Background: Repetitive transcranial magnetic stimulation (rTMS) has demonstrated therapeutic potential for treating patients with methamphetamine use disorder (MUD). However, the most effective target and stimulation frequency of rTMS for treating MUD remains unclear. This meta-analysis explored the effect of rTMS on MUD.

Methods: In this study, PubMed, Cochrane Systematic Reviews, and the Cochrane Collaboration Central Register of Controlled Clinical Trials were searched electronically for double-blind randomized controlled trials that used rTMS for treating MUD. We used published trials to investigate the efficacy of rTMS in MUD up to March 5, 2022, and pooled studies using a random-effect model to compare rTMS treatment effects. Patients who were diagnosed with MUD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders were recruited. Clinical craving scores between baseline and after rTMS were compared using the standardized mean difference (SMD) with 95% confidence intervals (CIs). The heterogeneity of the included trials was evaluated through a visual inspection of funnel plots and the I^2 statistic.

Results: We identified seven trials with 462 participants with MUD that met the inclusion criteria. All the studies evaluated craving scores, with rTMS demonstrating a more significant effect than the sham treatment on reducing craving scores (SMD = 0.983, CI = 0.620–1.345, $p \leq 0.001$). A subgroup meta-analysis revealed that intermittent theta-burst stimulation (iTBS) had a greater positive effect than 10-Hz rTMS. A metaregression revealed that the SMDs increased with the increase in baseline

craving scores, whereas they decreased with the increase in the proportion of men and duration of abstinence.

Conclusion: The meta-analysis suggests that rTMS may be associated with treatment effect on craving symptoms in patients with MUD. iTBS may have a greater positive effect on craving reduction than 10-z rTMS.

Keywords: repetitive transcranial magnetic stimulation (rTMS), methamphetamine, craving, theta-burst stimulation, substance use disorder

INTRODUCTION

Methamphetamine is a synthetic drug in Germany in 1887 and used widely during WWII by the Nazi and Japanese armies. Methamphetamine is medically used for the treatment of attention deficit hyperactive disorder and obesity (1). Methamphetamine is marketed as Desoxyn and Adderall in United States and other countries. Initially, students and young workers abuse methamphetamine because it could improve their performance by last their study and working time. However, methamphetamine is a highly addictive substance due to the tolerance of methamphetamine developing fast.

Methamphetamine initially improves a person's awareness, focus, and physical performance, providing a feeling of euphoria. Additionally, its use leads to psychotic symptoms, such as anxiety, agitation, paranoia, and hallucinations. However, somatic symptoms are frequently experienced, such as seizures, chest pains, sweating, shortness of breath, palpitations, and high blood pressure.

The long-term use of methamphetamine usually results in a high dose because tolerance to the drug develops relatively rapidly. It may also trigger serious outcomes, such as arrhythmia and cerebral hemorrhage. The habitual use of methamphetamine often causes weight loss, poor cognitive functioning, persistent psychotic symptoms (e.g., persecutory delusions and hallucinations), and decreased sleep (2, 3).

The highest prevalence of methamphetamine abuse has been recorded in Asia, particularly in East and Southeast Asia, and this abuse is becoming a considerable socioeconomic burden worldwide according to the World Drug Report 2016 published by the United Nations Office on Drugs and Crime (UNODC). The UNODC estimates that 35.65 million people or 0.8% of the world's population aged 15–64 was using methamphetamine in 2014.

People who abuse methamphetamine via different routes such as mouth ingestion, nose inhalation, or intravenous injection in different area of the world (4). Methamphetamine enter bloodstream rapidly after traverses the blood–brain barrier directly, entering the brain parenchyma because it is lipophilic. The drug mainly influences the reuptake of monoamine neurotransmitters such as dopamine, norepinephrine, and serotonin (1), increasing dopamine levels in the cytoplasm and neuromuscular junction. The abundance of dopamine provides the feeling of euphoria, explaining why chronic methamphetamine users feel unwell during withdrawal when their dopamine levels are low; hence, they feel the need for an increasing amount of stimulation (5).

Non-invasive brain stimulation including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have been widely applied to different neurological and psychiatric conditions. It is considered to have therapeutic effects because of the neuromodulation produced by a change in unidentified mechanisms in the human brain that might include cortical excitability, neurotransmitter release, signaling pathways, and gene expression (6–10). Initially, rTMS was determined to have an antidepressant effect by inhibiting the dorsolateral prefrontal cortex (DLPFC). However, craving related to addiction is suspected to be correlated with the "brain reward circuit" through the dopamine pathway in the brain. Furthermore, inhibitory control is exerted by the DLPFC over the reward circuit through the mesofrontolimbic connections (11, 12). Studies have suggested that rTMS stimulates the DLPFC to reduce drug cravings through two processes. First, the DLPFC interacts with the ventral tegmental area, which is correlated with the reward system through an increase in dopamine. Second, stimulation of the DLPFC stimulates glutamate, inducing increased dopamine excretion and reducing cravings (13, 14). These findings support the use of rTMS for substance use disorders, although negative findings on alcohol and cocaine use disorder have also been revealed (15, 16). Therefore, in this study, we focused on methamphetamine use disorder (MUD), which is a central nervous system stimulant addiction similar to cocaine addiction. Studies on rTMS in relation to MUD have revealed that this treatment significantly reduces cravings and relapse (17–20). Theta-burst stimulation (TBS) is a novel TMS protocol in which short bursts of high-frequency (50 Hz) stimulation are repeated at 5 Hz (200-ms intervals). Both intermittent TBS (iTBS) and continuous TBS (cTBS) can rapidly induce synaptic plasticity (21). Pilot studies have reported the effects of TBS on patients with MUD (19, 22). However, the most effective frequency for both conventional rTMS and iTBS remains unclear. Because findings related to this promising anticraving intervention are varied, a meta-analysis of all studies on rTMS and MUD is warranted.

MATERIALS AND METHODS

Search Strategy and Study Selection

In this study, two well-trained authors (C-HC and M-FL) independently performed a systematic literature search from the study's inception until March 5, 2022. The search terms were (methamphetamine OR methylamphetamine) AND

(repetitive transcranial magnetic stimulation OR rTMS OR brain stimulation OR theta-burst) (23–25). We searched the PubMed, Cochrane Collaboration Central Register of Controlled Clinical Trials, and Cochrane Systematic Reviews databases for studies on rTMS for MUD. The included trials and related review articles were reviewed manually to acquire pertinent references. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed (26) (**Figure 1**).

Eligibility Criteria

Studies were included if they (a) had participants with MUD, (b) were double-blind randomized placebo-controlled trials (DBRCTs), and (c) used rTMS as a monotherapy or adjunctive treatment. Articles were excluded if they (1) were not related to human clinical trials, (2) were review or comment papers, (3) did not include rTMS, (4) did not include a DBRCT, (5) were based on animal studies, (6) involved a duplicate dataset, (7) were a protocol, or (8) did not focus on patients with MUD.

Data Extraction

The two authors independently extracted data of interest following the PRISMA guidelines. They examined all the retrieved articles and recorded information relating to the first author, year of publication, number of participants, sex ratios, mean age, baseline craving scores, brain target, frequency, number of sessions, onset age, duration of abstinence, duration of methamphetamine use, and methamphetamine dose per day (**Table 1**).

Methodological Quality Appraisal

In this study, Jadad scoring (27) was used to assess the methodological quality of the randomized controlled trials (RCTs) in the enrolled studies. Jadad scores evaluate the methodology quality of RCTs based on the following three aspects: (a) randomization (two points), (b) blinding (two points), and (c) an account of all patients (one point). Potential Jadad scores range from 0 to 5, with a higher score indicating higher methodological quality. Between-reviewer discrepancies were solved through discussions under the supervision of the corresponding author.

Outcome Measures

We aimed to evaluate the rTMS effect on craving in participants with MUD. In this study, the reduced craving scores for rTMS and sham treatment were compared.

Data Synthesis and Analysis

We used the standardized mean difference (SMD), which expresses changes in craving scores, in each selected meta-analysis to calculate the SMD. Positive values indicated that the craving scores improved after rTMS or sham therapy. We used a random-effects model to pool the individual SMDs. We used I^2 tests to evaluate between-trial heterogeneity, and values $> 50\%$ were considered to indicate considerable heterogeneity. Two-tailed p values of < 0.05 were considered statistically significant. We used a sensitivity test with a "one study removal" test to evaluate the effect on the results of removing each individual study and reanalyzing the overall effect on the remaining studies.

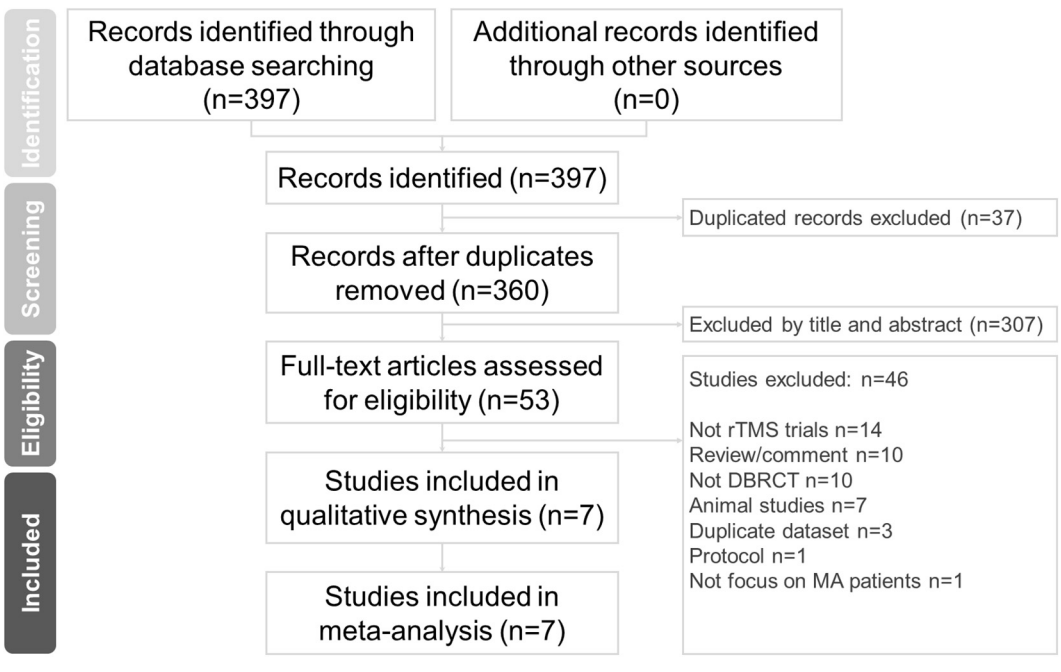

FIGURE 1 | PRISMA flow diagram for the identification of included studies. Database: PubMed (n = 312), Cochrane Central Register of Controlled Trials (n = 85), Cochrane Database of Systematic Reviews (n = 0). Keyword: (methamphetamine OR methylamphetamine) AND (repetitive transcranial magnetic stimulation OR rTMS OR brain stimulation OR theta-burst). Date: date available to Mar 2022. DBRCT, double-blind randomized placebo-controlled trial; MA, methamphetamine; rTMS, repetitive transcranial magnetic stimulation.

TABLE 1 | Summary of the characteristics of the studies included in the meta-analysis.

Study (first author, year)	*N*	Gender (%male)	Mean age (years)	Baseline mean craving scores	Brain target	Frequency	Sessions	Onset age	Abstinence (months)	Duration of MA use (months)	MA (g/d)
Su et al. (20)	30	100.00	32.35 (5.03)	30.6 (31.54)	Left DLPFC	10 Hz	5	25.90 (5.21)	2.90 (1.63)	50.57 (37.02)	0.49 (0.33)
Liang et al. (28)	50	100.00	33.30 (9.80)	NA	Left DLPFC	10 Hz	10	NA	0.25 (0.14)	61.20 (37.85)	0.50 (0.30)
Su et al. (19)	126	84.10	31.66 (6.31)	46.52 (30.71)	Left DLPFC	iTBS	20	23.90 (6.79)	3.12 (1.66)	67.56 (41.40)	0.66 (0.43)
Yuan et al. (30)	73	100.00	38.49 (7.69)	22.63 (25.10)	Left DLPFC	1 Hz	10	NA	9.27 (4.61)	NA	NA
Chen et al. (17)	74	NA	34.89 (4.97)	45.18 (26.55)	Left DLPFC vmPFC	iTBS*	10	27.49 (5.64)	NA	73.56 (43.50)	NA
Su et al. (29)	60	63.20	32.62 (6.71)	29.72 (26.89)	Left DLPFC	iTBS	20	24.15 (7.48)	3.80 (1.24)	76.26 (44.34)	0.57 (0.34)
Chen et al. (22)	49	63.00	30.08 (5.54)	57.68 (30.80)	Left DLPFC	iTBS	20	23.54 (6.17)	2.79 (1.41)	60.00 (41.83)	NA

*DLPFC, dorsolateral prefrontal cortex; iTBS, intermittent theta-burst stimulation; NA, not available; vmPFC, ventromedial prefrontal cortex. *Four-arm trial (Group A: iTBS targeting the left DLPFC; Group B: cTBS targeting the left vmPFC; Group C: a combination of the Group A and B treatment protocols; Group D: sham TBS).*

In addition, we evaluated potential publication bias with funnel plots and an Egger's test. The meta-analysis was performed using Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ, United States).

RESULTS

Characteristics of Included Studies

The seven included studies had enrolled a total of 462 patients with MUD (mean age = 33.44 ± 2.57 years, men = 84.44%). The average number of participants was 78.10 ± 31.67 (range: 20–65), and the average number of treatment sessions was 14.76 ± 5.47 (range: 5–20). The mean baseline craving scores were 39.30 ± 10.87. The mean age of onset was 24.86 ± 1.52 years, and the mean duration of methamphetamine use was 66.96 ± 7.28 months. Six trials (19, 20, 22, 28–30) were two-arm trials with a sham-controlled design, and one (17) was a four-arm trial (Group A: iTBS targeting the left DLPFC; Group B: cTBS targeting the left vmPFC; Group C: a combination of the Group A and B treatment protocols; Group D: sham TBS). A schematic of the search process is presented in **Figure 1** and **Table 1** summarizes the study characteristics.

OVERALL REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION EFFECT ON CRAVING ANALYSES

Meta-Analyses of Repetitive Transcranial Magnetic Stimulation Effect

Among the seven trials (17, 19, 20, 22, 28–30), all reported the effect on craving. The positive SMD results indicated the improvement of clinical symptoms after the treatment with add-on rTMS. rTMS showed a more significant effect than the sham treatment on reducing craving scores in participants with methamphetamine use disorder (SMD = 0.983, CI = 0.620–1.345, $P \leq 0.001$; **Figure 2A**).

Subgroup Analyses of Repetitive Transcranial Magnetic Stimulation Frequency

Four trials (17, 19, 22, 29) that used iTBS had significant ESs: 1.217 (95% CI: 0.953–1.481, $P < 0.001$), whereas two trials used 10 Hz showed significant ESs: 0.877 (95% CI: 00.412–1.342, $P < 0.001$; **Figure 2B**).

Subgroup Analyses of Brain Target

Six studies (19, 20, 22, 28–30) targeted at left DLPFC showed significant ESs: 0.956 (95% CI: 0.535–1.378, $P < 0.001$; **Figure 2C**).

Meta-Regression Analyses of Overall Clinical Symptoms

We noted that the increased effect of rTMS on reducing craving scores was significantly correlated with the baseline craving

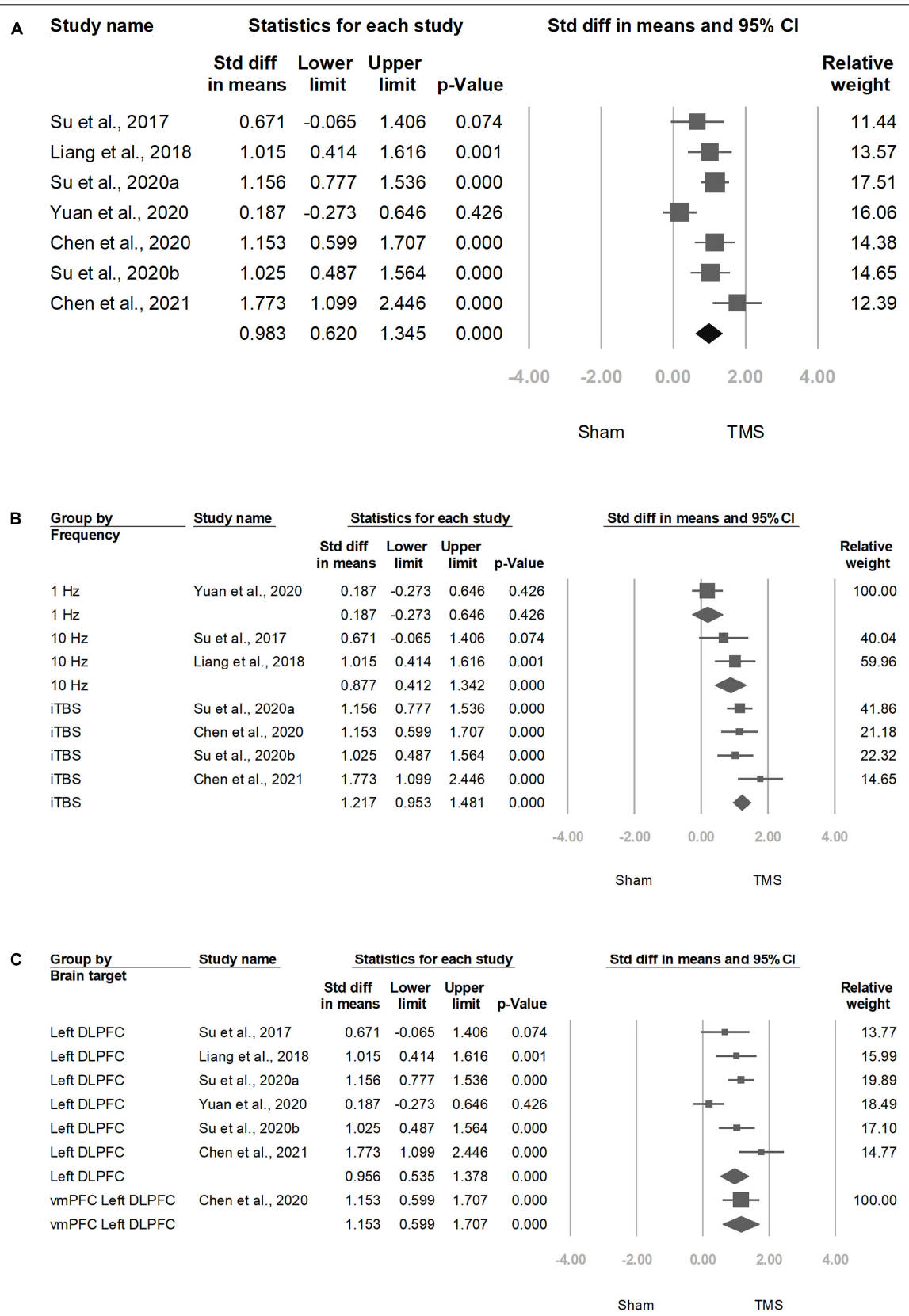

FIGURE 2 | Meta-analyses of **(A)** overall standardized mean difference, **(B)** group by frequency, and **(C)** group by brain target.

scores, whereas a decreased effect of rTMS on craving scores was correlated with the proportion of men and duration of abstinence (**Figure 3**).

Heterogeneity and Publication Bias

Significant heterogeneity was observed within the seven studies (Q = 18.641, df = 6, I^2 = 67.814%, P = 0.005). Egger's test revealed no significant publication bias regarding the overall SMD (P = 0.6959). The funnel plots for the SMD of overall clinical symptoms are shown in **Figure 4**.

Sensitivity Analysis

In the meta-analysis of the rTMS effect on reducing craving scores, the conclusion remained significant when removing any single study.

DISCUSSION

To the best of our knowledge, this is the first meta-analysis focusing on the efficacy of rTMS in patients with MUD. We revealed that (1) rTMS had a significant positive effect on craving score reduction in participants with MUD compared with a sham treatment (SMD = 0.983, CI = 0.620–1.345, $p < 0.001$), (2) studies targeting the left DLPFC revealed significant positive effects, (3) TBS had a greater positive effect than 10-Hz rTMS, and (4) the ES increased with the baseline craving scores and decreased with the proportion of male participants and duration of abstinence.

Our findings are consistent with those of three meta-analyses (23–25). We included seven DBRCTs in our study, whereas other studies had four (25), five (24) and six (23). Zhang et al. included 26 trials, with four (20, 28, 31, 32) focusing on MUD. The ESs of these four trials ranged from a Hedges' g of −0.398 to −1.611. Ma et al. included 12 trials, with five (20, 28, 31–33) focusing on rTMS and MUD. The mixed-effect subgroup analysis suggested that the treatment for methamphetamine addiction was positive (N = 10, Hedges' g = 1.541, CI = [0.735, 2.347], z = 3.749, $p < 0.001$). Gay et al. included 34 trials, with six (19, 20, 28, 30, 31, 33) focusing on MUD. The subgroup analysis using a random-effects model demonstrated a significant positive effect on reducing methamphetamine cravings (SMD = −0.57, CI = −0.96 to −0.18, z = 2.83, p = 0.005). These meta-analyses reveal the effect of rTMS

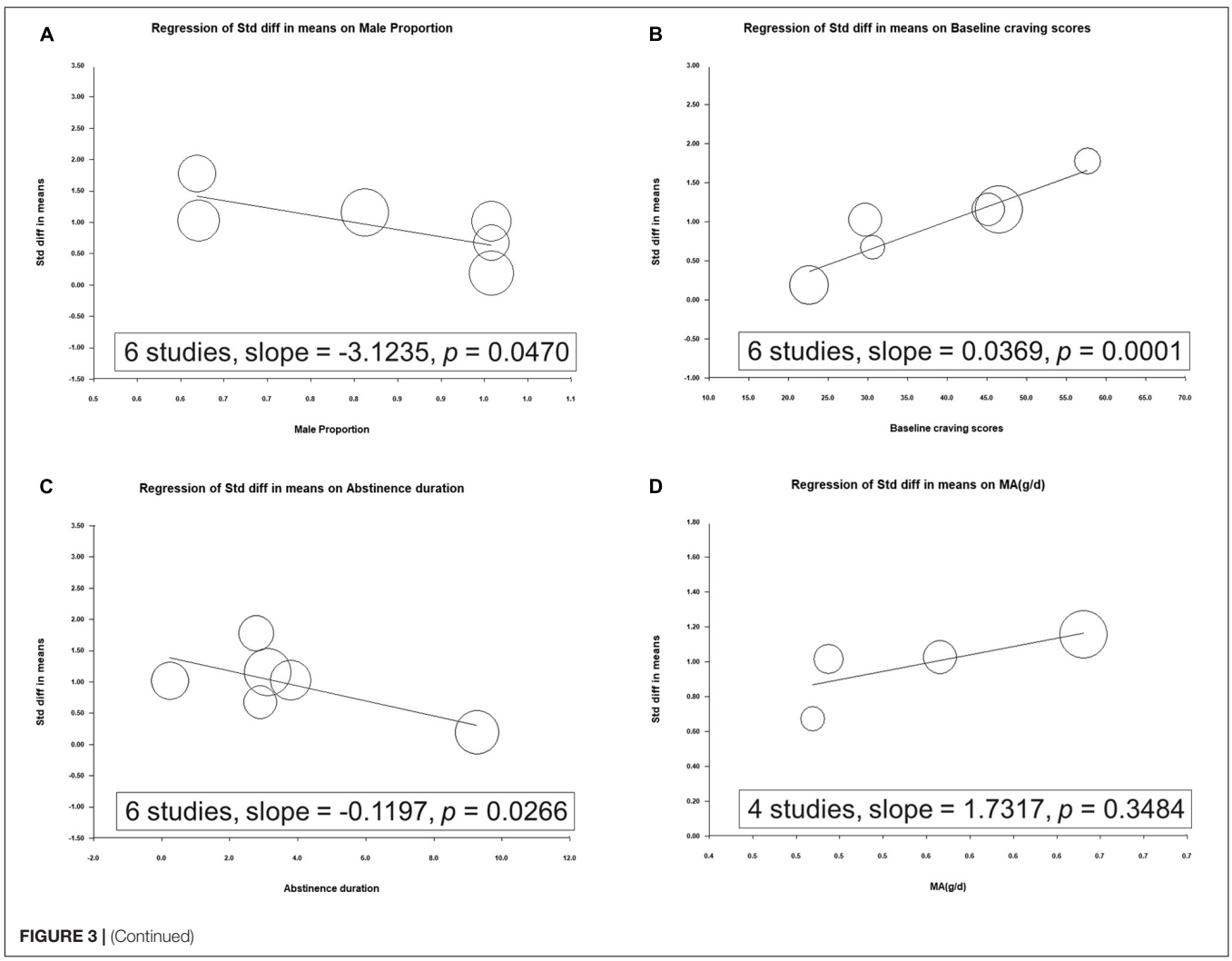

FIGURE 3 | (Continued)

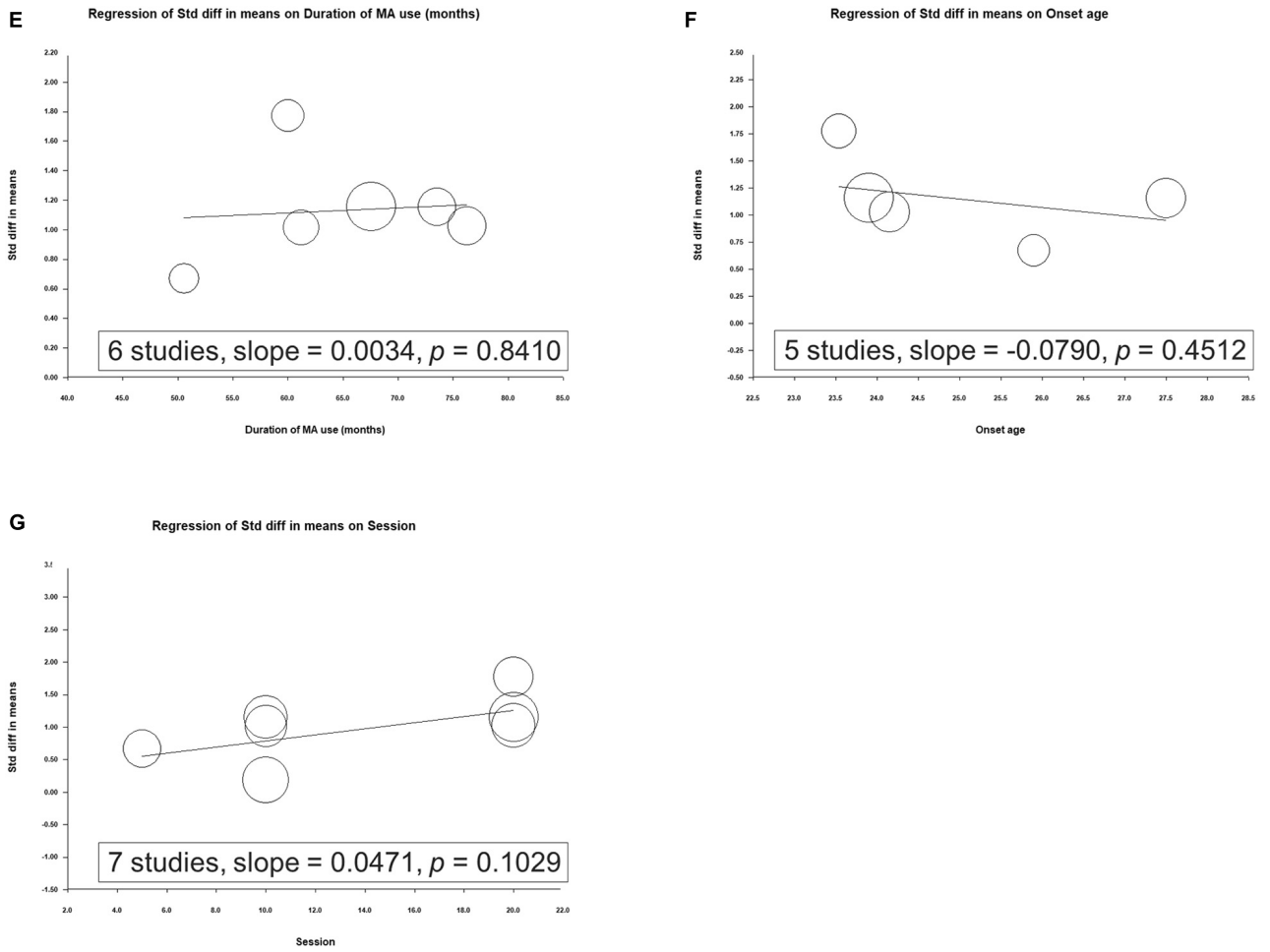

FIGURE 3 | Metaregression of the effects of repetitive transcranial magnetic stimulation on craving in relation to **(A)** proportion of men, **(B)** baseline craving scores, **(C)** duration of abstinence, **(D)** mean methamphetamine use per day, **(E)** duration of methamphetamine use, **(F)** onset age, and **(G)** number of sessions.

on methamphetamine cravings. In our study, the overall effect on craving was SMD = 0.983, CI = 0.620–1.345, $p < 0.001$. The differences in effect results might be explained by design of the included trials and ES methodology.

Moreover, in our study, high-frequency rTMS, including 10-Hz rTMS and TBS, had a significant effect on craving reduction, whereas low-frequency rTMS did not (**Figure 2B**). Our findings are consistent with other meta-analyses on substance use disorders. A systematic meta-analysis of non-invasive brain stimulation on stimulant-craving users of cocaine, amphetamine, and methamphetamine reported that in studies using high-frequency rTMS ($N = 7$), the craving level decreased (Hedges' $g = 1.671$, CI = [0.669, 2.673], $z = 3.269$, $p = 0.001$), but in low-frequency rTMS studies, it did not ($N = 4$, Hedges' $g = 0.962$, CI = [−1.137, 3.061], $z = 0.898$, $p = 0.369$) (24). Another meta-analysis of the effect of rTMS on craving in patients with substance dependence reported that in studies using excitatory rTMS over the left DLPFC ($N = 13$), the craving level decreased (Hedges' $g = -0.624$, CI = [−0.894, −0.354], $z = -4.531$, $p < 0.0001$) (25). A single-blind sham-controlled crossover study enrolled 10 non-treatment-seeking methamphetamine-dependent users and discovered that low-frequency (1 Hz) rTMS of the left DLPFC transiently increased cue-induced craving for methamphetamine (1-Hz rTMS group: 17.86 ± 1.46 vs. sham group: 24.85 ± 1.57, $p = 0.001$) (31). Another study enrolled 50 male methamphetamine users and randomly assigned them to five groups (10 Hz left P3, 10 Hz L-DLPFC, 10 Hz R-DLPFC, 1 Hz L-DLPFC, 1 Hz R-DLPFC), revealing that on either the left or right side, both high-frequency and low-frequency rTMS were effective at decreasing the cue-induced cravings (32). However, this study lacked a sham control and was not double blinded.

We further evaluated different levels of high frequency. Two articles (20, 28) included in our meta-analysis investigated the effects of 10-Hz rTMS, whereas four studies (17, 19, 22, 29) investigated TBS. We noted that iTBS treatment was more effective than the 10-Hz treatment ($N = 4$, SMD = 1.217, $p < 0.001$ and $N = 2$, SMD = 0.877, $p < 0.001$, respectively). We aimed to clarify why patients receiving TBS experienced greater benefits than those receiving conventional 10-Hz rTMS. A network meta-analysis of the acute treatment of major depression enrolled

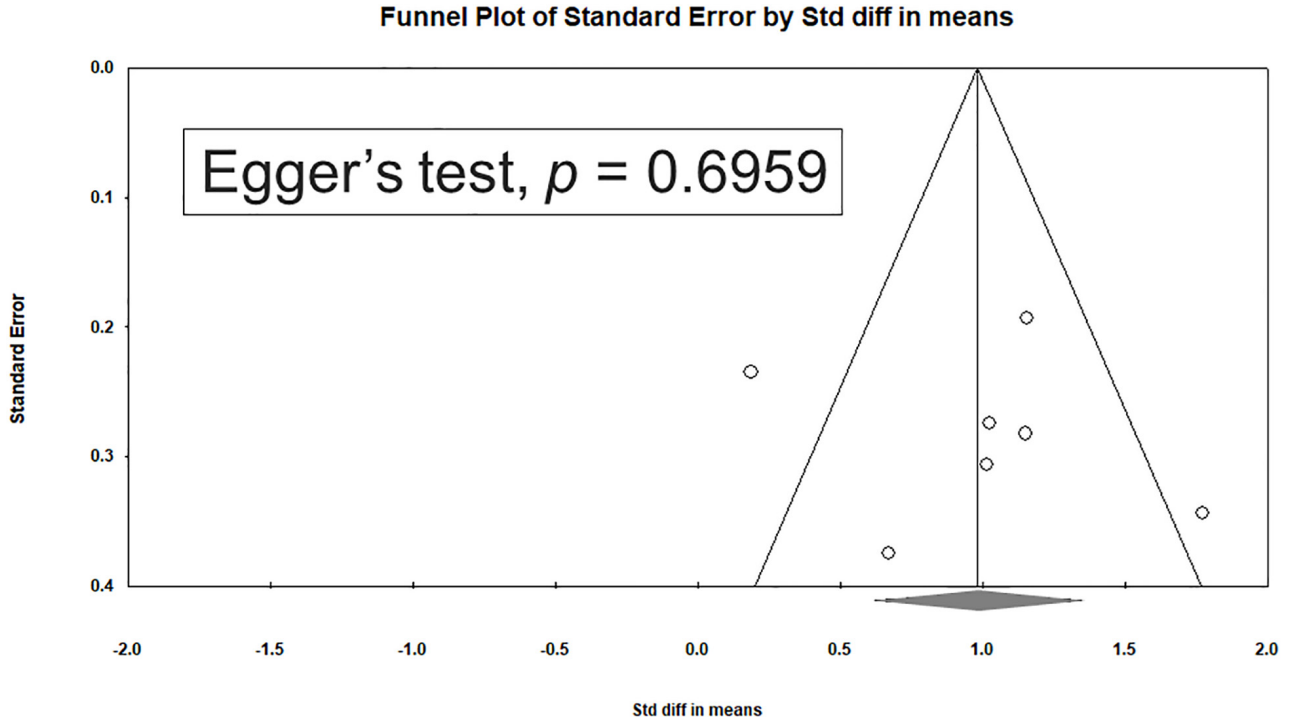

FIGURE 4 | Funnel plots for the standardized mean differences of craving.

81 studies. Their results indicated that TBS is more effective than high-frequency rTMS in terms of remission (TBS: odds ratio [OR] = 3.37, 95% CI = 0.52–22.05; high-frequency rTMS: OR = 2.73, 95% CI = 1.78–4.20) (34). A randomized multicenter non-inferiority clinical trial evaluated the effectiveness of theta-burst versus high-frequency rTMS in patients with depression (35). They randomly allocated 205 participants to 10-Hz rTMS treatment and 209 to iTBS treatment. After 4–6 weeks of treatment, Hamilton rating scale for depression (17-item version) scores improved from 23.5 (SD 4.4) to 13.4 (7.8) in the 10-Hz rTMS group and from 23.6 (4.3) to 13.4 (7.9) in the iTBS group (adjusted difference = 0.103 [corrected], 95% CI = −1.16, p = 0.0011), indicating the non-inferiority of iTBS. Notably, these studies focused on depression rather than MUD. Further studies are warranted to evaluate the difference between TBS and high-frequency rTMS in patients with MUD.

We further evaluated the effect of each modulator on craving reduction. Through a metaregression analysis, we identified trials with a higher proportion of men demonstrating lower SMDs for the effects of rTMS on craving (**Figure 2A**). Previous studies have observed potential sex-related differences in rTMS-induced cortical plasticity. Inghilleri et al. observed that the motor-evoked potential (MEP) size increased progressively during women's menstrual cycle, suggesting that rTMS may induce increased MEP in women in the late stage of the menstrual cycle (36). This is consistent with the results of other studies, highlighting the excitatory neuronal effect associated with estradiol and inhibition associated with progesterone (37, 38). A meta-analysis of rTMS used to treat patients with major depression observed that women may have a greater response to rTMS treatment than men (39). However, whether rTMS treatment yields a comparable sex-related difference in methamphetamine abuse populations remains undetermined. Further well-designed studies with larger samples are required to evaluate sex-related differences in relation to treatment and brain function.

In the metaregression analysis, we revealed that the increased effect of rTMS on craving scores was significantly correlated with baseline craving scores, whereas a decrease in the effect of rTMS on craving scores was correlated with the duration of abstinence (**Figures 3B,C**). Studies have noted that methamphetamine withdrawal may cause long-term effects, including dry mouth, paranoia, itching, sleeplessness, psychosis, and depressive symptoms (40). Craving is associated with withdrawal discomfort during abstinence (41, 42); thus, in the early stages of withdrawal, rTMS may have a greater effect on craving scores. Further studies should evaluate the different stages of abstinence after discontinuing methamphetamine use.

Strengths and Implication

Our study has several strengths compared with the three other meta-analyses (23–25). First, we included seven trials, whereas other studies included four, five, and six (23–25). Second, we conducted a subgroup analysis on conventional rTMS and TBS, revealing that TBS had a higher positive effect on cravings than 10-Hz rTMS. Third, we used a metaregression to analyze the relationship between ES and key factors. In addition to rTMS, non-invasive brain stimulation like tDCS have shown promising effect in substance use disorder (10). A randomized

and sham-controlled trial including 60 male patients showed that the combination of Matrix Model psychotherapy and tDCS may improve cognition and craving in MUD (9). Further trials are suggested to evaluate the treatment effect of rTMS and tDCS in patients with MUD.

Limitations

Our study also has some limitations. First, the numbers of included trials and patients were small. Second, the duration of most trials was less than 36 weeks, and the long-term positive effect of rTMS treatment on craving remains uncertain. Third, not all trials used the same protocols to evaluate craving and rTMS treatment. Fourth, we did not consider trials without a double-blind design or unpublished studies. Five, comprehensive genetic or psychosocial factors that are potential confounders of treatment outcomes were not evaluated in this study. Further trials with larger sample sizes and including comprehensive variables may be warranted.

CONCLUSION

This meta-analysis revealed that rTMS has a significantly positive effect on patients with MUD and a positive effect on craving reduction. In addition, iTBS has a greater positive effect on craving reduction than 10-*z* rTMS, and the effect correlated with an increased proportion of women. Further trials with larger sample sizes are suggested to evaluate these findings and explore the role of rTMS in patients with MUD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

C-HC and M-FL drafted the initial manuscript. C-YL and W-HL provided suggestions and reviewed the manuscript. S-JC critically reviewed the draft of manuscript, and approved the final submitted version manuscript. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Transcranial Direct Current Stimulation on the Left Superior Temporal Sulcus Improves Social Cognition in Schizophrenia: An Open-Label Study

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Background: Patients with schizophrenia show impairments of social cognition, which cause poor real-world functional outcomes. Transcranial direct current stimulation (tDCS) delivered to frontal brain areas has been shown to partially alleviate disturbances of social cognition. In this study, we aimed to determine whether multisession tDCS targeting the superior temporal sulcus (STS), a brain region closely related to social cognition, would improve social cognitive performance in patients with schizophrenia.

Methods: This was an open-label, single-arm trial to investigate the benefits and safety of multisession tDCS over the left STS. Fifteen patients received tDCS (2 mA × 20 min) two times per day for 5 consecutive days. Anodal and cathodal electrodes were placed over the left STS and right supraorbital regions, respectively. Assessments with the Social Cognition Screening Questionnaire (SCSQ), the Hinting Task (HT), the Brief Assessment of Cognition in Schizophrenia (BACS), and the Positive and Negative Syndrome Scale (PANSS) were conducted at baseline and 1 month after the final stimulation.

Results: Significant improvements were found on theory of mind, as measured using the SCSQ ($d = 0.53$) and the HT ($d = 0.49$). These changes on social cognition were not correlated with those of neurocognition, as measured using the BACS or psychotic symptoms, as measured using the PANSS. There were no adverse events of serious/moderate levels attributable to tDCS.

Conclusion: These results suggest that administration of multisession tDCS with anode stimulation targeting the left STS provides a novel strategy to improve functional outcomes in patients with schizophrenia.

Ethics Statement: The National Center of Neurology and Psychiatry Clinical Research Review Board (CRB3180006) approved this study.

Trial Registration: This study was registered within the Japan Registry of Clinical Trials (jRCTs032180026).

Keywords: neuromodulation, transcranial direct current stimulation (tDCS), schizophrenia, social cognition, superior temporal sulcus

INTRODUCTION

Schizophrenia is one of the most common psychiatric diseases affecting 0.7% of the world population (1). People who develop schizophrenia experience positive (e.g., hallucinations, delusions) and negative (e.g., including apathy, anhedonia, and social withdrawal) symptoms, as well as cognitive impairments, which mostly persist throughout life, if not treated properly (2). During this process, social function often deteriorates (2, 3), causing an unemployment rate of 70% in chronic patients (4).

Cognitive dysfunction is one of the core symptoms of schizophrenia and presents from the early to chronic phases of the illness (3, 5). Impairments of cognitive functions, including neurocognition, social cognition, and metacognition, may be present before the onset of psychosis, become pronounced in the first episode, and continue throughout the entire course of the illness (3). With regard to the treatment of schizophrenia, antipsychotic drugs are used, e.g., to ameliorate positive symptoms, while cognitive dysfunctions are mostly resistant.

Among several types of cognitive function, neurocognition, including learning memory, working memory, executive function, verbal fluency, and attention/information processing, is impaired in schizophrenia (5). Similarly, social cognition, i.e., mental operations underlying social behavior, is also affected (6, 7). It includes emotion recognition, theory of mind (ToM), social perception, and attributional bias (8), whose neural basis may be partially different from that of neurocognition (9). Improvements in social cognition may be directly related to improvements of social functioning (e.g., employment) and the link between neurocognition and social functioning may be mediated by social cognitive functioning (10). Specifically, disturbances of social cognition, including ToM, have been shown to worsen the ability to perform well in occupation and interpersonal relationships in patients with schizophrenia (7, 8, 10). Therefore, the development of therapeutics for impaired social cognition has been intensively pursued in the field of psychiatry (3).

To overcome social cognitive disturbances of schizophrenia, psychosocial (e.g., cognitive rehabilitation) (11) and pharmacological (e.g., second-generation antipsychotic drugs) (12) approaches have been attempted with limited success. As an alternative approach, some types of neuromodulations, particularly non-invasive brain stimulation, e.g., transcranial direct current stimulation (tDCS), have been drawing attention (13). tDCS modulates neural activities in the brain by delivering low-amplitude (usually no more than 2 mA) electrical currents over a short period (generally no more than 30 min) between electrodes, i.e., anode and cathode (14). In a meta-analysis (15), the ability of tDCS on the prefrontal cortex, e.g., the dorsolateral prefrontal cortex (DLPFC), to improve working memory has been shown in patients with schizophrenia (Hedges' $g = 0.49$). Likewise, it is speculated that tDCS may partially alleviate social cognition impairments that are resistant to antipsychotic drugs (16).

Potential benefits of tDCS for social cognition have been tested in patients with schizophrenia with limited success (13). In a systematic review (13), we reported that anode stimulation on frontal brain areas shows minimal effects on social cognition in these patients. In that report, three articles on tDCS met the inclusion criteria (see **Table 1**). All the studies adopted 2-mA current with 20-min duration of stimulation. Three studies used single-session online protocols, while one used a two-session online protocol. For outcome measures of social cognition, the following tests have been used: the Awareness of Social Inference Test for ToM, the Bell Lysaker Emotion Recognition Task, and the Mayer–Salovey–Caruso Emotional Intelligence Test for emotion recognition. Social perception was evaluated in one study (19), which used the Profile of Non-verbal Sensitivity (PONS).

The above studies used 4 patterns of tDCS montage, with the anode/cathode placement on F3/Fp2 (18), Fp1/Fp2 (19), between P6 and CP6/left bicep (17), or AFz/opposite side of the skull, 1 cm below Iz (17) based on the International 10–20 electroencephalography system (**Table 1**). Frontal brain areas have been adopted for the placement of the anode electrode (17–19), but these studies observed minimal effects on ToM (17) and emotion recognition (18, 19). One study placed anodal electrodes on the right temporoparietal junction (rTPJ), which did not produce positive findings (17). Overall, anodal stimulation of the frontal brain areas or rTPJ has been associated with the lack of benefits for social cognition, suggesting the need to search for effective stimulation sites (13, 20).

To identify the optimal conditions to maximize the benefits of tDCS, it is important to be aware that the neural bases of social cognition and neurocognition are partly different (9, 20). Most studies reporting positive results on neurocognitive function have used the DLPFC for anodal stimulation (15). As noted above, three studies have been conducted to determine the effect of tDCS targeting frontal cortical areas on social cognitive disturbances of schizophrenia (see **Table 1**) (13, 17–19). Among them, only one study reported facilitative effects of tDCS on emotion recognition with the Fp1 as the anodal site (19). Unlike the case for neurocognition, the neural network for social cognition may include the orbitofrontal cortex, medial prefrontal cortex (mPFC), superior temporal sulcus (STS), and amygdala; functional connectivity of these brain regions is attenuated in schizophrenia (20–22). Accordingly, impaired connectivity between these brain regions is associated with poor social cognitive functioning (6, 9). Especially, the ventral and orbital parts of the mPFC have extensive and reciprocal

TABLE 1 | Transcranial direct current stimulation and social cognition impairments in schizophrenia [adapted from Yamada et al. (13)].

Study	Diagnosis	Sample size (active/sham)	Montage (anode/cathode)	Intensity (mA)	Duration (min)	No. of sessions	Evaluation	Outcomes	Results
Klein et al. (17)	Schizophrenia	36/36	Between P6 and CP6/Left bicep	2	20	1	Online	ER40, BLERT, TASIT	No significant effect
		33/33	AFz/Opposite side of the skull, 1 cm below Iz	2	20	1	Online	ER40, BLERT, TASIT	Limited effects in theory of mind
Rassovsky et al. (18)	Schizophrenia	37/37	F3/Fp2	2	20	2	Online	MSCEIT, TASIT, EIT, EAT	No significant effect
Rassovsky et al. (19)	Schizophrenia	12/12	Fp1/Fp2	2	20	1	Online	MSCEIT, TASIT, PONS, FEIT	Significant effects in emotion recognition

tDCS, transcranial direct current stimulation; ER40, Emotion Recognition-40; BLERT, Bell Lysaker Emotion Recognition Task; TASIT, The Awareness of Social Inference Test; MSCEIT, Mayer–Salovey–Caruso Emotional Intelligence Test; EIT, Emotion Identification Test; EAT, Empathic Accuracy Task; PONS, Profile of Non-verbal Sensitivity; FEIT, Facial Emotion Identification Test. Each study used the same parameters among active and sham groups. "Limited effects in theory of mind" meant that the exploratory analysis suggested an improvement only in one sub-domain of theory of mind. "Significant effects in emotion recognition" meant that stimulation enhanced the ability to identify facial emotion based on photographs or videos.

TABLE 2 | Neural basis of social cognition [Yamada et al. (20)].

Domains of social cognition	Corresponding brain regions
Theory of mind (ToM)	Superior temporal sulcus, Medial prefrontal cortex, Middle temporal gyrus, etc.
Attributional bias	Orbitofrontal cortex, Superior temporal sulcus, Insular cortex, Striatum, Amygdala, etc.
Emotion recognition	Amygdala, Medial prefrontal cortex, Inferior occipital gyrus, Superior temporal sulcus, etc.

connections with the limbic system, including the amygdala and surrounding prefrontal regions. Impaired functional connectivity has been indicated for these brain areas in patients with schizophrenia (22).

Among these brain regions, the STS is considered to play a pivotal role in multiple domains of social cognition (**Table 2**) (20). Furthermore, as tDCS provides electrical currents via the skull, surface areas of the brain, such as STS, provide a feasible target for anodal stimulation. In fact, reduced gray matter volume in the STS was reported to be correlated with severity of social cognitive impairments in patients with schizophrenia (23). On the other hand, stimulation of other brain sites governing social cognition, i.e., the orbitofrontal cortex and mPFC, has been found ineffective (**Table 1**). Therefore, it was hypothesized that stimulation of the STS would be advantageous for enhancing social cognition.

These considerations prompted us to determine whether stimulation of skull surface above the STS, e.g., T3 or T4 (mid-temporal), would ameliorate social cognition disturbances in patients with schizophrenia. Since there is little information on the safety of anodal stimulation on temporal brain areas, unlike the case for frontal cortical regions, e.g., F3 (frontal) or Fp1 (front polar), which has been the main target for tDCS (24), this study also investigated the presence/absence of adverse events related to this stimulation method. This constituted a rationale for adopting the present study design, which we have reported elsewhere (20). To the best of our knowledge, this is the first attempt to determine whether tDCS delivered to the skull surface for the STS would enhance social cognitive functioning in patients with schizophrenia.

MATERIALS AND METHODS

Trial Design

This was a single-center trial at the National Center of Neurology and Psychiatry, Tokyo, Japan. An open-label, single-arm study was conducted on 15 participants with a diagnosis of schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5). We selected an open-label, single-arm design because there was no precedent for tDCS over the left STS and one of the major focuses of this study was to verify the tolerability and safety of tDCS over the STS. This study design was in accordance with the 2013 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement (20, 25), and was registered within the Japan Registry of Clinical Trials (Trial ID: jRCTs032180026).

Participants

Outpatients treated at National Center Hospital, National Center of Neurology and Psychiatry were enrolled. Participants were recruited by referrals from treating psychiatrists. After providing a written informed consent, subjects were screened by a treating psychiatrist to establish whether they met the eligibility criteria.

Inclusion and Exclusion Criteria

Participants met the following inclusion criteria (20):

(1) Diagnosis of schizophrenia in the DSM-5 made by well-trained and experienced clinicians with extensive clinical research experience in the National Center of Neurology and Psychiatry.

(2) Aged between 20 and 70 years.

(3) Being able to understand the objectives and content of this study and provide consent to participate in it [the ability

to consent to participate in this study is considered insufficient, when patients' intelligence quotient (IQ) is <70 or they present with acute psychiatric symptoms].

(4) Having the Social Cognition Screening Questionnaire (SCSQ) scores of <34 points.

Patients with any of the following conditions were excluded from this study:

(1) Present or past history of severe organic lesions in the brain, dementia, or epilepsy.

(2) With alcohol or substance use disorder that was present within 12 months from screening.

(3) Contraindicated against electroconvulsive therapy or tDCS, e.g., severe cardiovascular diseases, such as myocardial infarction, or aneurysms at high risk of rupture.

(4) Were treated with tDCS or other neuromodulations within the past 2 months (we asked whether participants had any history of tDCS or other neuromodulations).

(5) Deemed inappropriate to participate judged by the principal investigator, e.g., when participants' psychiatric symptoms were unstable.

The dose of psychotropic drugs was not changed during this study period. Furthermore, the type and dosage of psychotropic medications were not changed from 8 weeks prior to the baseline assessment.

Sample Size Calculation

Sample sizes ($n = 15$) were calculated by assuming an estimated mean difference of the UCSD Performance-based Skills Assessment (UPSA-B) scores from baseline to follow-up of 10.6, with a SD of 15.5 (26). In these assumptions, the power of the primary analysis was 0.8, so approximately $n = 13$ was estimated (one-sample Student's t-test). Therefore, it was decided to include a total of 15 samples, taking into account the dropouts from the study (20).

Intervention

Direct current was transmitted through 35 cm^2 saline-soaked sponge electrodes and the intervention was performed by a 1 × 1 transcranial direct current low-intensity stimulator (Model 1300 A; Soterix Medical Incorporation, New York, USA). The tDCS montage placed the anode in the left STS and the cathode in the contralateral supraorbital region, which corresponded to the T3 (mid-temporal) and FP2 (front polar) regions, respectively. We applied 10 sessions of direct current of 2 mA for 20 min in 5 consecutive days (twice per day, with an interval of 30 min). tDCS was administered by trained psychiatrists or researchers who did not evaluate any outcome measures.

Outcomes

Patients received psychological and clinical assessments, including the screening evaluation, after being briefed on the purpose of this study and agreeing to participate in it. Clinical data were collected at baseline and 1 month after the final stimulus (see **Table 3**).

Social Cognition

The primary outcome was scores on the SCSQ (27), which included test of ToM and attributional style. The task comprised 10 short vignettes presenting an interaction between a fictional character and the study participant. Each vignette was read aloud by the tester. The tester then had the subject respond "Yes" or "No" to three questions about the vignette, addressing ToM and attributional style (full score was 40; higher scores indicated better performance).

To evaluate ToM more accurately, we also used the Hinting Task (28). In the Hinting Task, subjects were required to infer real intentions behind indirect speech. The task comprised 10 short passages presenting an interaction between two characters ending with one of the characters uttering a hint. Each passage was read aloud by the tester. The subject was then asked what the character really meant when he/she uttered the hint. If the subject failed to give the correct response, an even more obvious hint was added to the story and the subject was asked again. A correct response was, therefore, scored as 2 or 1, depending on when the response was given (full score was 20; higher scores indicated better performance).

To evaluate emotion recognition, we used the Facial Emotion Selection Test (FEST) (29). The FEST measured the ability to infer emotions from the facial expressions of others. Participants viewed 21 photographs and answered which emotion (joy, sadness, anger, fear, surprise, disgust, or no emotion) it corresponded to. Performance was indexed as the total number of correct answers (full score was 21; higher scores indicated better performance).

Neurocognition

The Brief Assessment of Cognition in Schizophrenia (BACS) was used to evaluate cognitive domains that were impaired in patients with schizophrenia, including verbal memory (list learning task), working memory (digit sequencing task), motor speed (token motor task), verbal fluency (verbal fluency task), attention/speed of information processing (symbol coding task), and executive function (Tower of London task). Each of the six measures was standardized by creating z-scores, whereby the mean scores of the healthy participants were set to zero and their SDs were set to one. The higher scores represented better cognition. To provide a standard metric for combining test scores into domains and comparing performance over time, the Brief Assessment of Cognition in Schizophrenia (BACS) scores were converted to z-scores, which showed performance relative to healthy people (30). The premorbid IQ was also estimated using the Japanese Adult Reading Test (JART) (31).

Psychotic Symptoms

Psychotic symptoms were evaluated by the Positive and Negative Syndrome Scale (PANSS) (32), which consisted of positive syndrome, negative syndrome, and general psychopathology subscales (with scores ranging from 7 to 49, from 7 to 49, and from 16 to 112, respectively). The higher scores indicate the more severe psychotic symptoms.

TABLE 3 | Study schedule [Yamada et al. (20)].

		Study period			
	Baseline	**Intervention**			**Follow-up**
Time point	Within 2 weeks before the start of intervention	Day 1	Days 2–4	Day 5	1 Month after the end of the last stimulation
Enrollment					
Eligibility screen	X				
Informed consent	X				
Sociodemographic characteristics	X				
Intervention					
tDCS (twice/day)		X	X	X	
Assessments					
SCSQ	X				X
Hinting task	X				X
FEST	X				X
BACS	X				X
PANSS	X				X
JART	X				
Adverse events	X	X	X	X	X
Prescribed drugs	X	X	X	X	X

tDCS, transcranial direct current stimulation; SCSQ, Social Cognition Screening Questionnaire; FEST, Facial Emotion Selection Test; BACS, Brief Assessment of Cognition in Schizophrenia; PANSS, Positive and Negative Syndrome Scale; JART, Japanese Adult Reading Test. The timepoint of follow-up evaluation was allowed to be up to 7 days off.

Adverse Events

Adverse events were defined as unwanted experiences seen during tDCS. Serious adverse events were defined as requiring inpatient treatment. Moderate adverse events were defined as requiring therapeutic intervention, and mild adverse events as requiring no therapeutic intervention. The treating physician recorded the symptoms, date of onset, severity, treatment given, and association with study interventions. If symptoms were already present at baseline and did not worsen during tDCS intervention, they were not treated as adverse events. An experienced psychiatrist checked the presence and extent of adverse events and their association with tDCS before and after each session and assessed safety at all the visits during the intervention by a set of questionnaires. Specifically, 13 adverse event items, including headache, neck pain, scalp pain, itching, tingling, burning, scalp redness, sleepiness, fatigue, and nausea, were assessed. The presence/absence, severity (very mild, mild, moderate, or severe), and probable association with the tDCS (no association, little association, possible, probable, or certain) were evaluated for these events. We followed-up any unresolved adverse events after trial completion.

Data Collection and Management

The assessments were conducted at baseline and 1 month after the end of the last stimulation (**Table 3**). All evaluations were conducted by experienced psychologists. All the data were recorded to the Electronic Data Capture system (HOPE eACReSS; Fujitsu, Tokyo, Japan), which is a secure system designed for storage of personal and patient data. The data were sent to independent data managers to assess whether the data were collected properly, focusing on the status of consent acquisition, eligibility of participants, evaluation items, and confirmation of dropout/terminated cases. These data managers also oversaw and reviewed the progress of the trial. The Efficacy and Safety Assessment Committee, whose members were independent of the study and came from the National Center of Neurology and Psychiatry, checked and assessed whether the trial was conducted safely and properly, and also decided whether to stop the trial, if any severe adverse events or protocol violations occurred. In addition, an on-site data monitor conducted monitoring to ensure the trial was performed properly, data were properly recorded, and data reliability was ensured. If we conducted any necessary protocol modifications, we reported them to the Clinical Research Review Board and to the Ministry of Health, Labor and Welfare for registration in the Japan Registry of Clinical Trials website (https://jrct.niph.go.jp).

Statistical Analysis

Normality was considered for baseline and change values of demographic (i.e., age, gender, and duration of disease) and clinical outcome (i.e., SCSQ, Hinting Task, FEST, BACS, and PANSS) parameters. Since the sample size of this study is relatively small, we checked distribution of each variable by examining histograms to see, if there is any trend to doubt the normality of collected data.

For evaluating efficacy variables, the Student's paired *t*-test was used for the clinical outcomes and their effect sizes were calculated as standardized mean difference (Cohen's d). Correlations between baseline values and change of scores on clinical outcomes were evaluated by single regression analysis. Safety data were collected by a common questionnaire and were not subjected to statistical analysis. Statistical analysis was

TABLE 4 | Clinical characteristics of patients ($n = 15$).

Variables	Mean (SD) or *n*
Inpatient/outpatient	0/15
Male/female	7/8
Age (year)	40.1 (11.8)
Married/unmarried	3/12
Living alone/living with family	5/10
Employed/unemployed	3/12
Duration of education (year)	13.6 (1.8)
Premorbid IQ	102.1 (11.0)
Duration of present illness (year)	12.6 (10.2)
Number of past hospitalizations	3.0 (3.1)
Chlorpromazine equivalent dose of antipsychotics (mg/day)	727.9 (323.1) [min. 300, max. 1,400]
Diazepam equivalent dose of benzodiazepines (mg/day)	14.2 (14.6) [min. 0, max. 40]
Imipramine equivalent dose of antidepressants (mg/day)	21.2 (59.2) [min. 0, max. 225]

SD, standard deviation; IQ, Intelligence Quotient. Equivalent doses of chlorpromazine, diazepam, and imipramine were calculated (33).

conducted using STATA version 15, created by Stata Corporation in Texas, USA.

RESULTS

Participants

Fifteen outpatients were enrolled and completed this study without any dropout. Baseline characteristics of patients are shown in **Table 4**. No medication was changed during this study period and cognitive rehabilitation was not performed for the participants.

Effect of tDCS on Cognition

Significant improvements were found on the SCSQ, and the Hinting Task scores. Improvements of the SCSQ and the Hinting Task were associated with medium effect sizes. On the other hand, no significant change was found on FEST or BACS scores (**Table 5**).

Psychotic Symptoms

Improvement was found on the PANSS general psychopathology subscale scores with a small effect size. On the other hand, no significant improvement was found for positive syndrome and negative syndrome subscale scores (**Table 5**).

Correlations Between Psychotic Symptoms and Cognitive Data

No correlations were found between the PANSS positive syndrome, negative syndrome, and general psychopathology scores at baseline and changes in scores on the SCSQ ($r = -0.154$, $p = 0.366$; $r = -0.040$, $p = 0.803$; $r = -0.083$, $p = 0.453$, respectively), the Hinting Task ($r = -0.108$, $p = 0.355$; $r = 0.121$, $p = 0.262$; $r = 0.029$, $p = 0.704$, respectively), and the FEST ($r = -0.099$, $p = 0.124$; $r = 0.001$, $p = 0.986$; $r = 0.077$, $p = 0.059$, respectively). Likewise, changes in the PANSS positive syndrome, negative syndrome, or general psychopathology scores were not correlated significantly with changes in scores on the SCSQ ($r = -0.086$, $p = 0.701$; $r = -0.265$, $p = 0.307$; $r = -0.403$, $p = 0.157$, respectively), Hinting Task ($r = 0.373$, $p = 0.245$; $r = -0.083$, $p = 0.831$; $r = 0.040$, $p = 0.926$, respectively), or FEST ($r = 0.567$, $p = 0.318$; $r = -0.014$, $p = 0.984$; $r = -1.028$, $p = 0.159$, respectively).

Adverse Events

Some mild or moderate adverse events were recorded, e.g., itching (60%), sleepiness (46.7%), and tingling (20%). However, two cases with adverse events of the "Moderate" severity turned out not requiring specific medical treatments, and should have been reported as "Mild". On the other hand, serious adverse events were not observed (**Table 6**).

DISCUSSION

To the best of our knowledge, this study is the first to suggest the ability of multisession tDCS delivered to the left STS to improve social cognition, especially ToM, in patients with schizophrenia. These effects of tDCS were not associated with changes on neurocognition or psychosis.

So far, three studies have been conducted to examine the ability of tDCS to improve social cognitive disturbances of schizophrenia (see **Table 1**) (13, 17–19). Among them, only one study reported facilitative effects of stimulation on the left prefrontal cortex on emotion recognition (19). However, there has been little evidence that tDCS, with anodes on frontal brain regions, improves ToM, a core domain of social cognition, suggesting the need for alternative regimens. It should be noted that the current study is an open-label trial, whereas the previous study with a large sample size (17–19) used randomized controlled designs. Further trials with a more rigorous design are essential to confirm the efficacy of tDCS delivered to the STS for ameliorating social cognitive disturbances of schizophrenia.

The neural circuit underlying social cognition involves the left STS, corresponding to T3 (mid-temporal). Accordingly, it was hypothesized that anodal tDCS targeting this brain region would be effective in alleviating social cognitive disturbances in patients with schizophrenia (**Table 2**) (13, 20, 34). As expected, anodal stimulation of the left STS was found to improve performance on the SCSQ and the Hinting Task, tests of social cognition, especially ToM, with medium effect sizes. The lack of correlation between changes on the SCSQ or the Hinting Task scores and severity of psychotic symptoms at baseline or its change suggests that the change of ToM performance is not secondary to amelioration of psychotic symptoms.

To effectively enhance specific domains of symptoms/cognitive function, neural circuits underlying them should be considered. So far, most studies with positive results on neurocognitive function used the DLPFC for anodal stimulation (15). By contrast, stimulation of the same brain region mostly failed to produce benefits for social cognition, e.g., ToM (17, 18). The negative results in previous studies may have been due to the difference in neural circuits governing respective cognitive functions (neurocognition *vs.* social cognition) (9, 20, 22). As neural substrates for social cognition include the orbitofrontal

TABLE 5 | Outcome measures at baseline and 1 month after the tDCS.

	Baseline, mean (SD) [range]	Follow-up, mean (SD) [range]	*t*-value (degree of freedom) or *z*-Value	*p*-value	Effect size
SCSQ					
Total	29.93 (4.49) [20.33–33.66]	32.17 (3.91) [26.00–38.00]	$t = -2.356$ (14)	**0.034**	***d* = 0.53**
Hinting task					
Total	15.33 (3.51) [8.00–20.00]	16.93 (3.03) [11.00–20.00]	$t = -2.449$ (14)	**0.028**	***d* = 0.49**
FEST					
Total	13.20 (2.51) [8.00–17.00]	13.46 (2.85) [8.00–17.00]	$t = -0.718$ (14)	0.484	$d = 0.10$
BACS (*z*-score)					
Composite score	−1.85 (1.41) [−4.14–0.67]	−1.79 (1.33) [−4.46–0.55]	$z = -0.469$	0.646	$d = 0.04$
PANSS					
Positive syndrome	16.20 (6.01) [8.00–27.00]	15.60 (6.34) [8.00–31.00]	$t = 0.788$ (14)	0.444	$d = 0.10$
Negative syndrome	19.33 (6.47) [11.00–31.00]	17.93 (6.29) [8.00–28.00]	$t = 1.567$ (14)	0.139	$d = 0.22$
General psychopathology	37.53 (9.28) [25.00–54.00]	33.46 (9.20) [21.00–52.00]	$t = 4.077$ (14)	**0.001**	***d* = 0.44**

tDCS, transcranial direct current stimulation; SD, standard deviation; SCSQ, Social Cognition Screening Questionnaire; FEST, Facial Emotion Selection Test; BACS, Brief Assessment of Cognition in Schizophrenia; PANSS, Positive and Negative Syndrome Scale. Values reaching statistical significance are bolded.

TABLE 6 | Adverse events related to tDCS reported by patients.

Adverse Events	*N* (%)	Severity of adverse events (*N*)	Intensity of association (*N*)
Headache	1 (6.6%)	Moderate (1)	Possible (1)
Neck pain	2 (13.3%)	Very mild (1), Mild (1)	Little association (2)
Scalp pain	0 (0%)	–	–
Tingling	3 (20%)	Very mild (2), Mild (1)	Little association (1), Possible (2)
Itching	9 (60%)	Very mild (8), Mild (1)	Little association (1), Possible (8)
Burning sensation	0 (0%)	–	–
Skin redness	0 (0%)	–	–
Sleepiness	7 (46.7%)	Very mild (6), Mild (1)	No association (1), Little association (3), Possible (3)
Trouble concentrating	0 (0%)	–	–
Tiredness	1 (6.6%)	Very mild (1)	Little association (1)
Dizziness	1 (6.6%)	Moderate (1)	Possible (1)
Nausea	1 (6.6%)	Very mild (1)	Little association (1)
Others	0 (0%)	–	–

N, number; tDCS, transcranial direct current stimulation. Severity of adverse events was rated on a scale of 4, i.e., very mild, mild, moderate, or severe. Intensity of association was rated on a scale of 5, i.e., no association, little association, possible, probable, or certain. These cases with severity of "Moderate" turned out not requiring medical treatments.

cortex, mPFC, STS, and amygdala (20, 21), we chose the left STS for anodal stimulation. As expected, tDCS delivered to the skull for this brain area was found to improve ToM (measured by the Hinting Task and the SCSQ), but not neurocognition (measured by the BACS). These results suggest that the left STS may provide an optimal stimulation site for alleviating social cognitive impairments of schizophrenia.

Findings of this study indicate multisession tDCS may be advantageous for producing later improvement of social cognition in patients with schizophrenia. The effect sizes of tDCS for this benefit were about 0.5 SD) (**Table 5**), which is considered clinically meaningful (7). By contrast, its immediate effects after 1–2 sessions tDCS have been reported not to improve social cognitive disturbances (**Table 1**) (13, 17–19). As social cognition is considered to be directly linked to real-world social functioning (3, 10), multisession tDCS, rather than single-session tDCS, may provide benefits for functional recovery in patients with schizophrenia. Further investigations to elucidate the time course of the effect of multisession tDCS are warranted.

Improvements of cognitive symptoms by multisession tDCS may be mediated through several mechanisms, including long-term potentiation (LTP), continuous enhancement of signal transduction between neurons, and related neural events (14, 34, 35). Specifically, LTP has been shown to enhance the synthesis of various proteins, e.g., neurotransmitter synthases, receptors, ion channels, and intracellular signal proteins, thus facilitating the efficiency of neurotransmissions in cortical circuits (14, 34, 35). Moreover, improvement in cognitive function becomes more apparent a few weeks after administration of tDCS (36), suggesting that tDCS may induce LTP.

As this was the first trial using tDCS to the STS, an open-label, single-arm study design was adopted to ensure safety (20). Although some mild adverse events were observed, serious or moderate adverse events were absent. These findings suggest that the method of tDCS, used here, would be safe and feasible.

The facilitative effect of tDCS on social cognition in patients with schizophrenia may provide some clinical implications. First, the effect sizes obtained in this study are no less than those of cognitive rehabilitation that requires a greater constraint of time for patients and medical staffs (11). Second, effect sizes of tDCS on social cognition, reported here, are also greater than those of pharmacotherapy (37–39), while tDCS is only associated with local insults in most cases, unlike the case for medications that penetrate into the whole body. Therefore, tDCS may be useful in patients who cannot receive other modalities of treatment due to time constraints or intolerance caused by systemic side effects.

LIMITATIONS

The lack of blinding associated with this study design might have produced practice (repeated measure) effect in some measures used. Second, the small sample size may raise caution in concluding that these results represent effects in the population. Third, the lack of randomization, controlled group, and blinding might have produced placebo effects. A randomized controlled trial is currently considered to confirm the benefit of tDCS targeting the left STS for social cognition in schizophrenia and other psychiatric conditions.

CONCLUSION

In conclusion, the results of this study suggest that tDCS delivered to the left STS may produce potential benefits for some domains of social cognition, especially ToM, in patients with schizophrenia. These observations provide a novel therapeutic strategy to improve functional outcomes for these patients.

DATA AVAILABILITY STATEMENT

The raw data belonged to the present study cannot be made publicly available, because the disclosure of personal data was not included in the research protocol.

ETHICS STATEMENT

The protocol for this study was reviewed and approved by National Center of Neurology and Psychiatry Clinical Research Review Board (CRB3180006). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YujY developed the original concept for the trial, established the protocol, and wrote the initial version of the manuscript. YujY and TS designed the trial. YumY advised the statistical analysis, while KS advised the outcome measures. AS and YujY administered tDCS. TI, NH, and TS recruited participants. HO managed the data. TS organized the team for this study. All the other authors have reviewed and commented on the subsequent draft, and agreed to the published version of the manuscript.

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P300 Modulation *via* Transcranial Alternating Current Stimulation in Adult Attention-Deficit/Hyperactivity Disorder: A Crossover Study

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Objective: A repeated finding regarding event-related potentials (ERPs) is that patients with ADHD show a reduced P300 amplitude. This raises the question of whether the attention of ADHD patients can be increased by stabilizing the P300. Assuming that the P300 is generated by event-related oscillations (EROs) in the low frequency range (0–8 Hz), one approach to increase the P300 could be to stimulate the patient's P300 underlying ERO by means of transcranial alternating current stimulation (tACS). The aim of this follow-up study was to investigate this hypothesized mechanism of action in adult ADHD patients.

Materials and Methods: Undergoing a crossover design, 20 adult ADHD patients (10 female) received an actual stimulation *via* tACS on one day and a sham stimulation on another day. Before and after each intervention, EEG characteristics (P300 amplitudes, low frequency power) and attention performances (d2 attention test, visual oddball task (VOT)) were recorded.

Results: Electrophysiological analyses revealed no evidence for an enhanced P300 amplitude or low frequency power increase after actual stimulation compared to sham stimulation. Instead, a significant effect was found for a stronger N700 amplitude increase after actual stimulation compared to sham stimulation. Consistent with the P300 null results, none of the examined neuropsychological performance measures indicated a tACS-induced improvement in attentional ability.

Conclusion: Contrary to a previous study using tACS to modulate the P300 in adult ADHD patients, the current study yields no evidence that tACS can increase the P300 amplitude in adult ADHD patients and that such P300 enhancement can directly improve neuropsychological parameters of attention.

Keywords: P300, attention deficit/hyperactivity disorder, ADHD, transcranial alternating current stimulation, tACS, therapy

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common developmental disorder that persists into adulthood, and is associated with core symptoms of inattention, hyperactivity, and impulsivity (1). With an estimated global lifetime prevalence of 2.58% (2), ADHD causes not only severe individual suffering such as difficulties in academic career (3, 4), occupational burdens (5–11) and difficulties in social interactions and relationships (12–19), but also a high burden for society and economy. Considering not only direct diagnostic and treatment costs, but also secondary follow-up costs (e.g., productivity losses due to inability to work or early retirement, justice system costs), the global total annual costs of ADHD are estimated to be at least 831 million [for a systematic review, see (20)]. Therefore, the treatment of ADHD is not only important to reduce individual suffering, but also to avert economic damage.

So far, ADHD is primarily treated by psychostimulants, cognitive behavioral therapy, or a combination of both (21). Although stimulant medication is thereby usually considered as first-choice treatment (22–24), it often leads to undesirable side effects such as sleep disturbances (25), decreased appetite and weight decrease (26) or cardiovascular effects (27). Moreover, in a significant subgroup of ADHD patients, psychostimulants have no, or no sufficient treatment effect (28–30). Also, some patients develop tolerances to psychostimulants (31) and often interrupt or discontinue their medication (32), particularly due to adverse events (33). Consequently, the development of further, effective ADHD therapy approaches with fewer side effects is urgently required.

One explanatory factor for individual differences in response to psychostimulants may be the high pathophysiological heterogeneity within the ADHD population [for a critical discussion, see (34)]. Various combinations of environmental and genetic factors, for instance, lead to diverse neuropsychological impairments and thus to different ADHD symptom profiles (35). Consequently, great research effort is currently being undertaken to identify ADHD biomarkers that are of predictive value for ADHD treatments and could guide practitioners in deciding which treatment options hold most promise in each individual case [for a systematic review, see (36)]. Similarly, there is hope that the discovery of reliable biomarkers helps to develop new treatment approaches that directly target the pathomechanisms revealed by the biomarkers and are not merely symptom-driven.

One such biomarker that might prove useful as a target site in ADHD treatment is the P300 component in electroencephalographic event-related potentials (ERPs) (37). The P300 is a positive voltage deflection around 300 ms after a target stimulus over centro-parietal regions and associated with attentional allocation and stimulus processing (38, 39). Reliable elicitation of the P300 can be achieved, for example, by oddball paradigms, in which subjects are required to respond to infrequent target stimuli and to ignore frequent distractor stimuli (40). Probing such oddball paradigms in ADHD, several studies have found a reduced P300 amplitude (41–48) and prolonged latency (44, 49–53) in adult ADHD patients compared to typically developed individuals. In addition, several research groups report increased P300 amplitudes along with attention improvements after administration of ADHD medication (54–57) or mindfulness-based cognitive behavior therapy (MBT) (58). Hence, the P300 appears to be a reasonable target site for the exploration and development of further therapeutic methods.

If the P300 is abnormally altered in ADHD patients but normalizes after psychostimulant administration or MBT, the question arises whether an attention improvement is also achievable by a direct modulation of the P300, e.g., by applying transcranial alternating current stimulation (tACS). tACS is a non-invasive technique in which the brain is stimulated *via* an alternating current of a beforehand determined frequency. As certain can be considered that tACS can modulate endogenous brain oscillations and, more importantly, cognitive processing [for review, see (59)]. Regarding attentional processing, for instance, an improved accuracy in conjunction search after alpha tACS (i.e., a stimulation frequency around 8 to 12 Hz) (60) and an improved voluntary top-down attention after gamma tACS (i.e., a stimulation frequency >30 Hz) (61) has been reported.

During tACS, the presumed mechanism of action is mainly attributed to the entrainment of intrinsic brain oscillations to the external stimulation signal (59, 62, 63). Entraining oscillations is observed to be most efficient when the frequency of the applied current is close to the intrinsic brain frequency (64). The administered current alters internal neuronal excitability by causing changes in the resting potential (65). Whether neuronal excitability is thereby enhanced or weakened, and consequently increases or decreases the probability of neural firing, is determined either by depolarization or hyperpolarization (66). Taken together, when tACS is applied, the external sinusoidal force and the internal neural firing patterns are synchronized. Moreover, tACS is thought to induce changes in synaptic plasticity (67–69). Whether the synaptic activity between neurons is intensified or attenuated is thereby determined by the timing of the neurons' input and output activity (pre- and post-synaptic events). TACS can affect this spike probability of neurons and it is believed that these synaptic changes persist after cessation of stimulation, leading to increased power at the chosen stimulation frequency (70–72). This phenomenon is called spike-timing-dependent plasticity [for further details, see e.g., (73)].

Whether tACS can also modulate ERPs is less validated. While the few existing empirical studies on this issue (74–78) yielded mixed results, at least from a theoretical perspective such modulability appears expectable, given that ERPs can be regarded as event-related oscillations (ERO) (79). The P300 component at issue here, for instance, has been closely linked with an ERO in the delta (0–4 Hz) to theta (4–8 Hz) range (80–84). Therefore, at least theoretically, tACS appears to offer a promising therapeutic approach to modulate not only oscillations but also ERPs in ADHD patients.

Despite this high potential tACS may have for the treatment of ADHD, the use of tACS in ADHD has so far little been studied. In fact, consistent with the findings of a recent review of neurostimulation in ADHD (85) that found 30 studies, but none of which applied tACS, our own literature search only yielded one study recently published Dallmer-Zerbe et al. (75) and another study recently published by Farokhzadi et al. (86).

In the study by Farokhzadi et al. (86), treatment with 10 Hz alpha tACS was compared to psychostimulant treatment in 62 ADHD children. Over the course of 8 weeks, one group received alpha tACS thrice a week for 10–15 min at pre-frontal electrode sides, while another group received psychostimulant treatment over the same course of time. The reported result is that tACS was more effective than psychostimulant treatment in improving attention and impulsivity, as assessed by the "integrated visual and auditory test." Although promising, one methodological problem with this result is that it is only based on behavioral, but not on neurophysiological investigations (i.p. an investigation of the EEG alpha spectrum). Therefore, it cannot be ruled out that the group differences found are due to some other mechanisms (e.g., more social devotion during the tACS than psychostimulant intervention) rather than being due to the assumed electrostimulative mechanism of action.

In the study by Dallmer-Zerbe et al. (75), in turn, 18 adult ADHD patients either underwent tACS or placebo stimulation for approximately 20 min. TACS was thereby applied at the participant's individual ERO, and the presentation of the target stimuli was timed in such a way that the participant's induced P300 always coincided with the positive voltage peaks of the ongoing tACS. Results showed a significant enhancement of the P300 amplitude in the stimulation group and a tACS-induced decrease in omission errors (75). Also this study had, however, some methodological flaws. In particular, the implemented oddball task turned out to be too easy, so that hardly any errors were committed. Moreover, a between-subjects design was used with only 8 patients per group. Hence, the study might have been underpowered.

Therefore, the aim of the current study was to replicate overall study findings by the previous study by Dallmer-Zerbe et al. (75), and consequently to investigate to what extent tACS can modulate the target P300, the low frequency range, and neuropsychological test performances in adult ADHD patients. To this end, we carried out a crossover study with two separate measurement days in which our 20 adult ADHD patients received a placebo stimulation (sham) in one case and an actual tACS in the other, while conducting an optimized visual oddball task (VOT). Using a mobile EEG system, individual stimulation parameters were determined and individually adjusted on site, using a time-frequency decomposition of the P300. We revised several aspects of the former study by Dallmer-Zerbe et al. (75) like, for example, we used a crossover study design instead of between-subjects design or adjusted the VOT to increase task difficulty (a detailed list comparing both experiments can be found in the **Supplementary Table 1**).

MATERIALS AND METHODS

Participants

A total of 22 ADHD patients (11 female, M_{age} = 28.55, SD = 8.77, age range: 19–48) volunteered in this study, out of which 20 underwent the entire experiment. All participants were recruited *via* the specialized outpatient clinic for adult ADHD of the Clinic for Psychiatry and Psychotherapy of the University Hospital Bonn. Participants were either personally invited to the study during medical consultations or contacted *via* a study applicant pool in which they had previously registered. A brief telephone screening was then conducted with each study prospect, and if there were no reasons for exclusion, the patient was allowed to participate in the study. Written informed consent was obtained from all participants and they all received an expense allowance of 30 € for their participation. Moreover, the study was approved by the medical ethics committee of the University of Bonn (protocol number: 357–19) and pre-registered at the German Clinical Trials Register (Trial-ID: DRKS00020828).[1]

Study Design and General Procedure

The study was carried out on three measurement days and as a crossover study with two interventions. The two interventions compared "actual stimulation" and "sham stimulation." On Day 1, a comprehensive clinical examination was performed, during which the ADHD diagnosis was validated, and the patient's mental state was evaluated. On Days 2 and 3 in turn, the actual experiment took place, with one of the two conditions being run on each measurement day. While fifty percent of the participants underwent the actual stimulation first on Day 2 and the sham stimulation on Day 3, the remaining fifty percent underwent the sham stimulation first on Day 2 and the actual stimulation on Day 3.

Eligibility Assessment and Clinical Characterization

All participants were already diagnosed with ADHD or were in the process of diagnosis at our specialized outpatient clinic for adult ADHD. To confirm the ADHD diagnoses and further characterize their individual ADHD symptom profiles, all participants underwent the structured clinical "Interview of Integrated Diagnosis of ADHD in Adulthood" [IDA-R; (87)]. Moreover, to clarify potential comorbidities and exclusion criteria, the German version of the "diagnostic short interview for mental disorders" [Mini-Dips-OA; (88)] was carried out. Likewise, participants filled in four further self-rating questionnaires:

- *Demographic questionnaire*: A lab-internal, self-designed questionnaire that gathered some biographical data (birth, gender, education, family status) relevant for the study.
- *ADHD Self-Report-Scale* [*ADHS-SB*; (89)]: The ADHS-SB is a 22-item questionnaire that surveys key symptoms of ADHD and allows to derive three domain-specific scores (inattention, hyperactivity, impulsivity) and one overall ADHD score.
- *Depression-anxiety-stress-scales* [*DASS-21*; (90)]: A short 21-item questionnaire that assesses indications of depression, anxiety, and stress. For each symptom area, a separate score from 0 (no burden at all) to 21 (maximum burden) may be calculated.
- *WHO quality of life scale questionnaire–short version* [*WHOQOL-Bref*; (91)]: A 26-item questionnaire assessing quality of life in the past 4 weeks in four main domains

[1] https://www.drks.de/

(physical health, psychological health, social relationships, and environment). To be eligible for the study, participants needed to be right-handed [according to the Edinburgh Handedness Inventory; (92)], to be between 18 and 50 years old, and to have corrected-to-normal or normal vision. In addition, any of the following exclusion criteria had to be absent: Presence of a severe comorbid affective disorder (mild to moderate was included), any psychosis or substance dependence, current use of any psychotropic medication other than ADHD medication, presence of a serious neurological disorder (especially epilepsy), presence of a dermatological disorder of the head, or pregnancy.

Experimental Procedure

Except for the stimulation method applied (actual stimulation vs. sham stimulation) and a short familiarization with the VOT at the first experimental session, the experimental procedure on Day 2 and 3 was identical (cf. **Figure 1**). Whether participants first received the actual or sham stimulation was counterbalanced across all participants. While participants knew that on one session, they would receive a placebo stimulation and on the other session an actual stimulation, they were kept uninformed about the order of stimulation procedures. On both days of measurement, ADHD medication had to be discontinued 24 h beforehand. For both measurement days, the experiment took place in the Virtual Reality laboratory of the University Hospital of Bonn and the experimental procedure was as follows: First, to record their momentary attention level, participants performed the d2 attention test (d2; cf. section "d2 Attention Test"). Next, the participants were prepared for the actual stimulation or sham stimulation and concomitant EEG measurement. In both experimental sessions, the preparation procedure was thereby identical. After that, the actual experiment started, which consisted of three experimental blocks: a *pre-intervention block*, an *intervention block*, and a *post-intervention block*. The three experimental blocks were each separated by 5- to 10-min breaks (depending on the duration of the online EEG analysis). EEG was recorded throughout blocks and a VOT (cf. section "Visual Oddball Task") had to be performed in each of the three blocks. The only difference between the three blocks was that during the intervention block, actual stimulation or sham stimulation was applied. To customize the electrical stimulation, the participants' individual frequency of ERO and P300 peak latency was determined (cf. section "Online Analysis") in the first short break immediately before the intervention block. As soon as the stimulation parameters were determined, the intervention block with either actual stimulation or sham stimulation started (for details, see section "Synchronization Between Stimulus Presentation and Transcranial Alternating Current Stimulation"). From here on, the experimenter could no longer be blinded to intervention since the stimulator had to be operated manually according to either the sham stimulation or actual stimulation. After the intervention block and a further short break, the last post-intervention block started. Finally, after finishing all three experimental blocks, participants again completed the d2 and filled in a questionnaire assessing adverse effects of tACS (93). In total, the experimental procedure took approximately 2.5 to 3 h, including preparation time for attaching tACS and EEG electrodes.

d2 Attention Test

As stated, the d2 (94) was applied before and after the three experimental blocks to compare the participant's individual attention and concentration performances before and after intervention. In accordance with the test manual, the d2 was thereby administered as a paper-pencil test. That is, participants had to cross out target symbols (letter "d" with two strokes) between distracting non-target stimuli (letter "d" with one, three, or four strokes and letter "p" with one, two, three, or four strokes) through 14 consecutive lines of 47 characters each. They were instructed to cross out as many target symbols as possible within a time limit of 20 s per line. Between these 20 s phases, there was no pause, so that the total test time was less than 5 min. To evaluate d2 test performances, the following performance metrics were calculated: the total number of characters processed (as a measure of processing speed), the d2 concentration performance (i.e., the number of correctly identified characters minus all conducted errors), commission errors (i.e., deleted non-target characters), and omission errors (i.e., missed target characters).

Visual Oddball Task

In all three blocks, the VOT was conducted for about 20 min. Participants sat on a chair 70 cm away from a computer screen on which the oddball task was presented. Stimuli were displayed *via* NBS Presentation (Version 21.0 build 06.06.19, Neurobehavioral Systems Inc., Albany, CA, United States) and logged together with keyboard inputs *via* Lab Streaming Layer (LSL)[2].

On the center of a gray computer screen, 2° to the left or right tilted gabor stimuli ($\sim$ 4 cm $\times$ 4 cm) were iteratively displayed, each with a duration of 500 ms. In total, 400 gabor stimuli were presented, out of which 300 (75%) represented standard stimuli and 100 (25%) target stimuli. Whether the left-tilted or right-tilted gabor stimuli represented the standard stimuli, and thus were presented thrice as often, was counterbalanced across all subjects. That is, in 50% of participants, the left-rotated gabor stimuli represented the frequent standard stimuli throughout measurement days, while in the remaining 50%, they represented the infrequent target stimuli. The ISI between the gabor stimuli was jittered between 1,000 and 2,500 ms. During the intervention block, the target stimulus onset was adjusted so that the peak of the individual mean P300 amplitude coincided with the positive peak of the tACS signal (details below). The participants' task was to press a key with their left index finger upon each left-rotated stimulus and a key with their right index finger upon each right-rotated stimulus. Thereby, they were requested to execute their keyboard presses as quickly as possible and as accurately as possible and to fixate onto a fixation circle displayed on the computer screen throughout the task. For assessing VOT performances, four main parameters of interest were extracted for each participant: omission error rate (i.e., the percentage of non-target button responses to target stimuli), commission

[2]https://github.com/sccn/labstreaminglayer

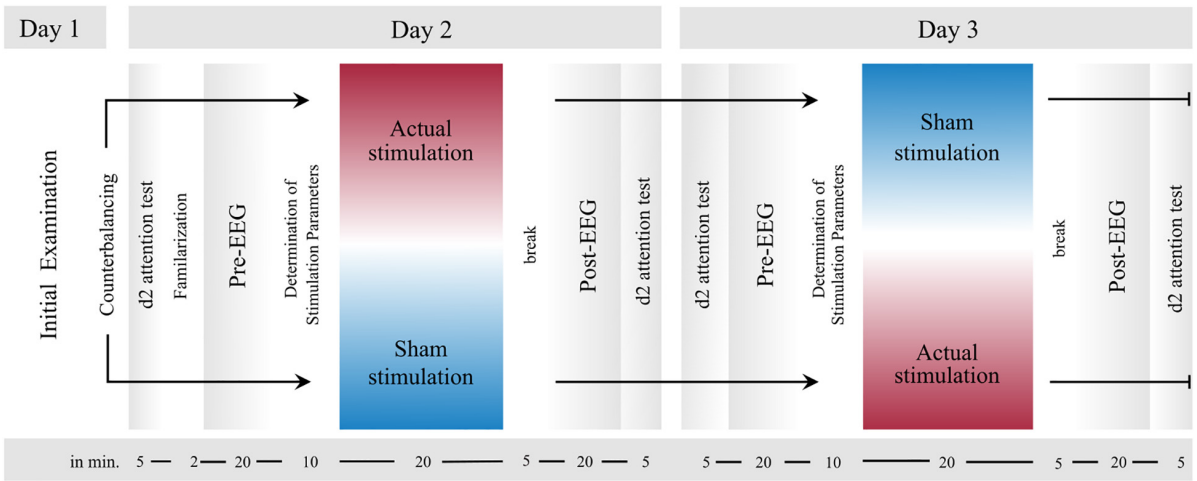

FIGURE 1 | Experimental Design. After an initial examination (Day 1), the two experimental sessions (Day 2 and Day 3) proceeded in the same order, except for a brief familiarization with the visual oddball task (VOT, cf. section "Visual Oddball Task") in the first experimental session. First, the d2 attention test was performed before all electrodes were attached to the participants' head. Next, the first block (pre-intervention) started, in which participants accomplished the VOT. Immediately thereafter, there was a short break, during which the tACS parameters were computed from the EEG data of the first block. As soon as these parameters were collected, the second block (intervention) started, during which actual stimulation or sham stimulation was applied. Finally, the third block (post-intervention) started after a short break. During all three blocks EEG was measured. Last, the d2 was conducted again.

error rate (i.e., the percentage of target button responses to standard stimuli), d-Prime [i.e., a sensitivity measure, calculated by d' = z(Hit Rate)–z(False alarm rate)] and mean reaction time (RT, mean reaction time of the correct target responses). While the omission error rate is considered as a measure of inattention, the commission error rate is thought to reflect impulsivity (95).

Electrical Brain Stimulation and Electrode Montage

Electrical stimulation was only administered during the intervention block using a battery-operated stimulator system (DC-stimulator plus, Neuroconn, Ilmenau, Germany). In total, four 7 cm × 3.5 cm rubber electrodes were placed on the participant's head, whereby two of them were placed above C1/C2 and the other two above C5/C6 (for orientation of the electrodes, see **Supplementary Figure 1**). The electrode montage was selected based on a simulated finite-element model of current flow. More specifically, using the ROAST Toolbox (96) and the MNI standard brain as template, different electrode montages were simulated in respect to their predicted intracranial electrical field in parietal and temporal regions (i.e., the region, where the P300 is most prominent) (97). The selected electrode montage thereby offered the best compromise between the requirement to generate a high intracranial current flow in the target region and the requirement to avoid blocking any EEG electrodes relevant for the EEG analyses. A graphical illustration of the conducted electrode montage simulation may be found in the **Supplementary Figure 1**. The four tACS electrodes were applied using conductive paste (Ten20 conductive paste, Weaver and Co, Aurora, CO, United States), and for all participants, impedances were kept below 10 kΩ .

For the actual stimulation condition, tACS was applied for about 20 min, with an intensity of 1 mA (peak-to-peak). The previously conducted electric field simulation with an injected current of 1 mA peak-to-peak per electrode pair yielded to an electric field strength of ∼ 0.1 V/m (**Supplementary Figure 1**). Previous studies showed [c.f. e.g., (98)] that similar electric field strengths in the target area produced aftereffects. The stimulation frequency was individually adjusted for each participant and reflected the participants' individual frequency peak between 1 and 8 Hz during target trials (details below). To minimize discomfort, the stimulation was faded in and out for about 10 s. For the sham stimulation, in turn, tACS was again faded in for about 10 s, but then only lasted for another 10 s, before it was again faded out for 10 s. Hence, in total, the "tACS" during the sham stimulation conditions only lasted for 30 s including fade-in and fade-out phases and served the purpose of realistically mimicking the phenomenological experience of actual stimulation. This procedure is one of the commonly used placebo stimulation techniques [e.g., (99)]. To identify potential differences in the perception of both conditions, at the end of each session participants were asked whether they received actual or sham stimulation, and whether they perceived any tACS side effects (93).

Synchronization Between Stimulus Presentation and Transcranial Alternating Current Stimulation

To always coincide each participant's individual target P300 during the intervention block with a positive voltage peak of the running tACS, a similar synchronization approach was used as in the previous study (75) (cf. **Figure 2A**). As the internal oscillation is believed to synchronize with the external tACS

force and to thereby enhance its power, in-phase tACS (internal oscillation frequency matches with external force) is reported to synchronize EROs, while anti-phase tACS (internal oscillation frequency does not match with external force) is reported to desynchronize EROs [for a discussion, see (100)]. That is, the presentation of the next stimulus was paused by a waiting period until a pulse of the stimulator signaled that the tACS waveform was at a certain position that its next positive peak would coincide with the next P300 peak triggered by the stimulus (cf. **Figure 2**). During this wait period, a fixation point was shown. Technically, this was realized by transmitting the pulse from the stimulator to NBS Presentation at the beginning of each new sinusoidal wave (i.e., upon each zero crossing in the sinusoidal's ascending flank). Based on this, it was possible to define when the next positive tACS peak would occur and thereby adapt the delay for showing the stimuli (cf. **Figure 2B**). This calculation thereby considered both, the fixed P300 latency and individual stimulation frequency, which were already determined during the VOT pre-intervention block (cf. see section "Online Analysis").

Electroencephalography Recording and Analysis

Electroencephalography (EEG) was acquired *via* a wireless EEG system (Smarting®, mBrainTrain®, Belgrade, Serbia) from 22 Ag/AgCl sintered ring electrodes (Fp1, Fp2, AFz, F3, Fz, F4, T7, C3, Cz, C4, T8, CPz, P7, P3, Pz, P4, P8, POz, O1, O2, M1, M2 according to the international 10/20 system). FPz served as ground (DRL) and FCz as reference electrode (CMS). The amplifier was attached to the EEG cap (Easycap, Herrsching, Germany) and communicated wirelessly with the recording computer *via* Bluetooth. Keeping all impedances below 15 kΩ, the EEG was digitized at 500 Hz (one data set was unintentionally recorded at 250 Hz) and with a 24-bit step-size resolution *via* (LSL). The marker stream originating from NBS Presentation was thereby also acquired *via* LSL, such that the EEG recording files entailed all event information of the conducted VOTs. Data analysis was performed using Matlab 2021b (The MathWorks Inc., Natick, MA, United States) and eeglab 2021.0 (101).

Online Analysis

For the on-site EEG analysis during the experiment, the participant's EEG data from the pre-intervention block was filtered with a 40 Hz low-pass filter and a 0.1 Hz high pass filter, and then detrended. Next, before the computation of an independent-component-analysis (ICA) the continuous EEG data was epoched into 2 s time windows. After that, a fast ICA was computed using pop_runica (ica type "fastica") on the epoched EEG data and its components were visually inspected. ICA components reflecting obvious artifacts (e.g., horizontal or vertical eye movements, heartbeats, muscle activity or electrode artifacts) were identified, backprojected to the filtered continuous EEG data, and then rejected. Next, for the calculation of the P300 peak latency, the ICA-corrected continuous EEG data was first epoched from −2 to + 5 s relative to each target stimulus, and then baseline-corrected beginning from −2 s until target onset. Remaining non-stereotypic artifacts were removed by built-in EEGLAB functions (kurtosis thresholding and joint probability test with ± 3-SD single-channel and global-channel thresholds). Then, the participant's P300 latency was derived by averaging all epochs for electrode Pz and identifying the maximum P300 amplitude peak between 250 and 450 ms after target stimulus onset.

The participant's most dominant event-related oscillation during the P300 time window, in turn, was determined by a frequency analysis. First, using Matlab's pspectrum function, the power spectrum at electrode Pz was calculated for each epoch and then all derived power spectra were averaged to obtain one mean power spectrum. The obtained frequency resolution was 0.1 Hz and the obtained time resolution 0.124 ms. Next, the highest frequency power within the time frame of ± 200 ms around the previously determined P300 latency and within the frequency range of 1 and 8 Hz was determined and used as the individual stimulation frequency.

Pre-processing and Data Cleaning

For the EEG offline analyses, the EEG datasets from the pre-intervention and post-intervention block were first merged, down-sampled to 250 Hz, temporally filtered between 0.5 and 40 Hz, and detrended.

In three datasets, noisy EEG channels (max. 3) were identified and replaced *via* spherical interpolation using the pop_interp function. For one dataset, a 1.1 s long highly artifactual data segment was removed. Next, for the computation of an ICA, the continuous EEG data was segmented in 2 s time windows and non-stereotypic artifacts were removed using built-in EEGLAB functions (joint probability test, ± 2-SD single-channel and global-channel thresholds). After that, an ICA ("extended" version) was computed and components reflecting horizontal or vertical eye movements, heartbeat, muscle activity or electrode artifacts, were visually identified, backprojected to the continuous EEG data and then rejected. Hence, at the end of this cleaning process, continuous EEG data sets were obtained that were already filtered between 0.5 and 40 Hz and cleaned from stereotypic artifacts by means of the conducted ICA.

Event-Related Potentials Analyses

Event-related potentials analyses focused on differences in the target P300 between interventions (actual stimulation vs. sham stimulation) and blocks (pre-intervention vs. post-intervention block). To this end, the merged and ICA-corrected continuous EEG datasets for each intervention were first rereferenced to the common average, low-pass filtered below 6 Hz (to exclude alpha activity), epoched from −0.5 to 1.5 s relative to each target stimuli, and then cut into two separate subsets: One subset containing the epochs of the pre-intervention block before actual stimulation or sham stimulation, another subset containing the epochs of the post-intervention block after actual stimulation or sham stimulation. Next, the same following pre-processing and analysis steps were performed on each subset: First, a baseline correction was applied on each epoch by subtracting the mean voltage of the −0.5 s epoch prior to stimulus onset from all data points. Second, within each epoch, channels that exceeded a differential average amplitude of 150 μV were marked for rejection. Channels that were marked as bad on more than

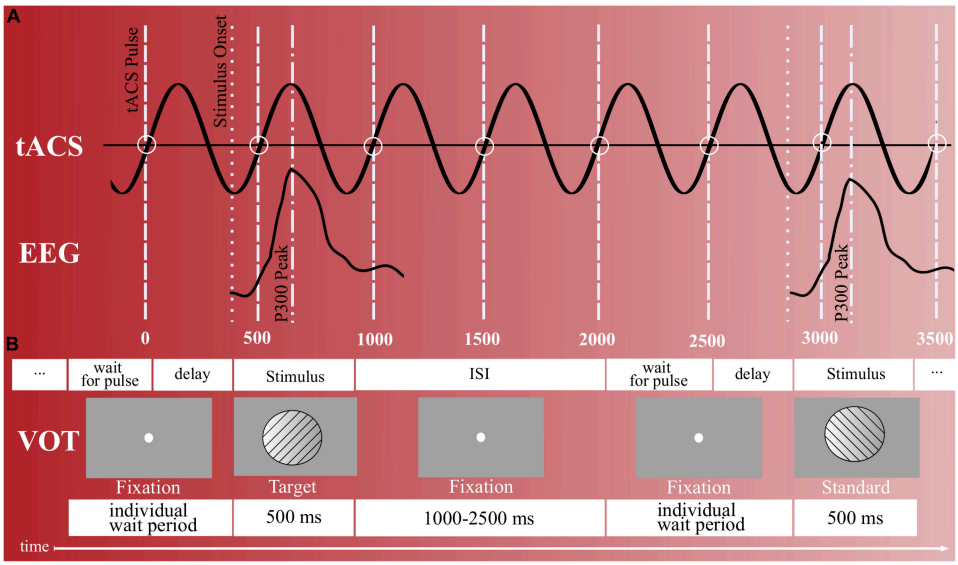

FIGURE 2 | Stimulus presentation and timing. **(A)** Synchronization between target trials and tACS peaks during the intervention block (actual stimulation). To coincide the participant's elicited P300s with the tACS's positive voltage peaks, NBS presentation waited for a pulse of the stimulator (wait for pulse). In addition, an individual delay existed that delayed until the tACS waveform was at the specific position so that its next positive peak would coincide with the next P300 peak triggered by a target stimulus. **(B)** Visual oddball task with right- and left-tilted gabor stimuli. Upon each left-rotated stimulus, participants were to respond with a left-hand button press and upon each right-rotated stimulus with a right-hand button press. In total, 400 gabor stimuli were presented, out of which 25% represented target stimuli and 75% standard stimuli. ISI = inter stimulus interval.

15% of all epochs were excluded. Epochs having more than 10 bad channels were excluded, while epochs with less than 10 bad channels were included. The bad-channel data was replaced with spherical interpolation of the neighboring channel values [TBT, (102)]. Third, the ERP of the respecting condition was calculated by taking the average across epochs. Finally, for the statistical analyses, for each dataset, the mean P300 amplitude was calculated for electrode Pz within the time range from + 200 to + 550 ms. In addition, the maximum P300 peak between 250 and 550 ms was extracted for each dataset. The same processing procedure was implemented for inspecting the standard P300.

Frequency Analysis

The frequency analyses focused on spectral differences in the delta to theta range between interventions and blocks. To this end, the ICA-corrected continuous EEG datasets for each condition were again rereferenced to the common average, epoched from −0.5 to + 1.6 s relative to each target stimulus, and then cut into two subsets for pre- and post-block measurements. Next, the identical following pre-processing and analysis steps were performed on each subset: First, a baseline correction was applied from −0.5 to 0 s, before the same non-stereotypic artifact removal was implemented as described for the P300 analysis. Next, a continuous wavelet transformation (CWT) was conducted on each retained epoch for channel Pz. The frequency range obtained reached from 0.25 to 6 Hz in 47 steps on a log scale and the time resolution amounted to 0.004 ms. After that, the derived power spectra were logarithmized and a mean power spectrum was derived by averaging across all derived power spectra. Finally, for the statistical analyses, the mean delta and theta (0.5–5.5 Hz) power of the respecting subset (condition) was derived by taking the average power across all frequency bins falling into the respecting frequency range and time range between 250 and 550 ms.

Statistical Analyses

Two participants had to be excluded after the first diagnostic appointment, one because of meeting the exclusion criteria and another one due to health problems. Additionally, out of the 20 participants who completed the entire experiment, one participant had to be excluded from the analyses due to incorrect task execution. Hence, 19 participants remained for further analyses from which the following outcome variables were extracted: Omission error rate, commission error rate, mean RT and reaction time variabilities (RTV) for the VOT analyses; processing speed, omission errors, commission errors and concentration performance for the d2; target P300 mean amplitudes for the ERP analyses; and low frequency power values for the wavelet analysis.

For each main dependent variable, a two-way repeated measures ANOVA with the two within-factors "Block" (pre-intervention vs. post-intervention) and "Intervention" (actual stimulation vs. sham stimulation) was conducted. For specifying ANOVA effect sizes, partial eta squared (η_p^2) was used, where $\eta_p^2 = 0.01$ indicates a small effect, $\eta_p^2 = 0.06$ a medium effect, and $\eta_p^2 = 0.14$ a large effect (103). For indicating effect sizes of *t*-tests, on the other hand, Cohen's d was used, where $d = 0.20$ indicates a small effect, $d = 0.50$ a medium effect, and $d = 0.80$ a large effect (103). The α-level was set to 0.05.

In addition, to identify potential associations between the different outcome parameters, exploratory Pearson correlation analyses between each possible variable pair were conducted on the absolute change (difference from pre-to-post) across both intervention types. Correlation analyses were tested for significance and Bonferroni-Holm correction was applied to correct for multiple comparisons. All statistical analyses were carried out using Matlab (The MathWorks Inc., Natick, MA, United States, Version 2021b).

RESULTS

Sample Characteristics

Sociodemographic and clinical characteristics of the finally analyzed sample are reported in **Table 1**. 57.89% of participants were diagnosed with the combined ADHD type, 5.26% with the predominantly hyperactive-impulsive subtype and 36.84% with the predominantly inattentive ADHD subtype. The most common current comorbidities found were anxiety disorders (36.84%) and affective disorders (21.05%). According to the DASS-21 (90), participants revealed, on average, only mild scores for depression (M = 10.26; SD = 3.48), anxiety (M = 9.11; SD = 2.45) and stress (M = 12.53; SD = 5.65). On average, participants were 27.95 years (SD = 8.57) and most participants had a higher education entrance qualification (78,95%). After each experimental session, participants were asked to judge if they were actually stimulated with tACS or if they received the sham stimulation. 47,37% of the sample correctly judged that they received actual stimulation at the actual stimulation session, while 52,63% thought they were actually stimulated at the sham stimulation session. Since it was a 50% chance to correctly identify the actual stimulation, participants seemed to be blinded.

Visual Oddball Task

Results of the VOT analyses are shown in **Figure 3**. Regarding omission error rate (**Figure 3A**), the ANOVA revealed a significant main effect of "Block" [$F_{(1,18)}$ = 20.13, $p < 0.001$, η_p^2 = 0.53], but no main effect of "Intervention" [$F_{(1,18)}$ = 0.08, p = 0.781, η_p^2 = 0.00] and no interaction effect [$F_{(1,18)}$ = 0.16, p = 0.693, η_p^2 = 0.01]. The block effect consisted of more omission errors being committed during the post-intervention (M = 26.63; SD = 17.49) than pre-intervention (M = 17.55; SD = 13.01) block.

Regarding d-Prime (**Figure 3C**), the ANOVA revealed a significant main effect of "Block" [$F_{(1,18)}$ = 17.85, $p < 0.001$, η_p^2 = 0.50], but no main effect of "Intervention" [$F_{(1,18)}$ = 0.47, p = 0.501, η_p^2 = 0.03] and no interaction effect [$F_{(1,18)}$ = 0.32, p = 0.576, η_p^2 = 0.02]. The "Block" effect consisted of a smaller d-Prime sensitivity score during the post-intervention (M = 1.88; SD = 0.94) than pre-intervention (M = 2.25; SD = 0.87) block.

For commission error rate (**Figure 3B**), RT (**Figure 3C**) and reaction time variability (**Figure 3D**), the ANOVA yielded neither a main effect of "Block" or "Intervention," nor an interaction effect (detailed ANOVA tables are shown in the **Supplementary Table 2**).

d2 Task

Overall performances of the d2 task are depicted in **Figure 4**. Two datasets had to be excluded due to complications in the execution of the task. For processing speed and concentration performance, there were 2 outliers (>3 SD), and for errors of omission and commission, there was 1 outlier (>3 SD), so that a total of only 16 and 17 datasets, respectively, were included in the respective statistical analyses.

For all d2 performance parameter, the ANOVA revealed a significant block effect. Regarding processing speed (**Figure 4A**), the effect of "Block" revealed higher processing speed during the post-intervention block (M = 570.19; SD = 60.48) as compared to the pre-intervention block (M = 538.06; SD = 59.66). For concentration performances (**Figure 4B**) the "Block" effect consisted of a higher concentration performance during the post-intervention (M = 235.97; SD = 36.44) than pre-intervention (M = 216.75; SD = 34.61) block. For omission errors (**Figure 4C**) results revealed that less target stimuli were missed during the post-intervention (M = 10.03; SD = 6.91) than pre-intervention (M = 14.71; SD = 8.31) block. Results for commission errors (**Figure 4D**) yielded that more stimuli were wrongly identified as a target during the post-intervention (M = 3.85; SD = 3.08) than pre-intervention (M = 2.44; SD = 1.69) block.

There was neither a significant effect for "Intervention," nor an interaction effect for all four d2 performance parameter (detailed ANOVA tables are shown in the **Supplementary Table 3**).

Analyses of Event-Related Potentials

Planned Analysis of the Event-Related Potential P300

The topographies and waveforms of the examined ERPs are depicted in **Figure 5**. Consistent with the literature, extracted ERPs showed the typical waveform and topography of a P300 during an oddball task [for review see e.g., Polich (38)], with a maximum peak at around 250 to 550 ms over centro-parietal electrodes. Moreover, also in agreement with the literature (104, 105), the P300 mean amplitude across conditions turned out to be significantly [$t(18) = -4.25$, $p \leq 0.001$]) higher for target ERPs than standard ERPs (cf. **Figure 5A**).

Regarding experimental conditions, the ANOVA on target P300 mean amplitudes revealed a trend for the main effect "Block" [$F_{(1,18)}$ = 3.40, p = 0.082, η_p^2 = 0.16] but neither an effect of "Condition" [$F_{(1,18)}$ = 0.27, p = 0.609, η_p^2 = 0.01], nor an interaction [$F_{(1,18)}$ = 0.03, p = 0.870, η_p^2 = 0.00]. The trend for "Block" consisted of an amplitude decrease during the post-intervention (M = 2.72; SD = 1.30) compared to the pre-intervention (M = 3.00; SD = 1.48) block. Individual mean amplitude plots are included in the **Supplementary Figure 2**. The ANOVA for maximum P300 peak amplitude revealed no significant effects (cf. **Supplementary Table 4**).

Exploratory Analysis of a Late Event-Related Potential

On visual inspection of the ERP waveforms, there appears to be a difference in a late negative ERP component that peaks around 800 ms after target onset (cf. **Figure 5B**). Therefore, to examine whether this difference is not merely descriptive, we performed

an exploratory ERP analysis using the same analysis procedure and the same preprocessed datasets than before, but with a time window of interest slightly shifted backward (700 to 1000 ms). The ANOVA on this late ERP mean amplitudes revealed no main effect of "Intervention" [$F_{(18,1)} = 0.24$, $p = 0.240$, $\eta_p^2 = 0.08$], but a trend for "Block" [$F_{(1,18)} = 4.03$, $p = 0.060$, $\eta_p^2 = 0.18$] that consisted of higher ERP mean amplitudes during the post-intervention ($M = 0.69$; $SD = 1.29$) than pre-intervention ($M = 0.16$; $SD = 1.48$) block. Moreover, the ANOVA revealed a significant interaction [$F_{(1,18)} = 6.56$, $p = 0.020$, $\eta_p^2 = 0.27$]. Following up this effect, paired *t*-tests revealed that the late ERP mean amplitudes significantly increased from pre-intervention ($M = -0.09$; $SD = 1.14$) to post-intervention ($M = 0.71$; $SD = 1.31$) under actual stimulation [$t(18) = -2.70$, $p = 0.015$], but not under sham stimulation [$t(18) = -0.98$, $p = 0.339$].

Frequency Analyses

Time-frequency power spectra of the wavelet analyses are depicted in **Figure 6**. In line with previous research (74, 75), our wavelet analysis revealed strongest activity in the P300 time window for the ERO in the delta to theta (0–8 Hz) frequency spectrum. The ANOVA on the

TABLE 1 | Sociodemographic and clinical sample characteristics.

Total sample (*n*):		19*	
Female [*n* (%)]:		10 (52.63)	
Age [*M* (*SD*)]:		27.95 (8.57)	
Interview data:			
IDA-R			Maximum reachable scores:
ADHD presentations [*n* (%)]			
Combined type		11 (57.89)	
Predominantly hyperactive-impulsive type		1 (5.26)	
Predominantly inattentive type		7 (36.84)	
ADHD scores [*M* (*SD*)]			
Total		36.42 (9.14)	54
Inattention		21.58 (3.04)	27
Hyperactivity		7.32 (5.08)	15
Impulsivity		7.53 (3.99)	12
Mini-DIPS			
n (%)	Current diagnosis	Previous diagnosis	
Affective disorder	4 (21.05)	5 (26.32)	
Anxiety disorder	7 (36.84)	1 (5.26)	
Post-traumatic stress disorder	0	2 (10.53)	
Obsessive-compulsive disorder	3 (15.79)	0	
Sleep disorder	3 (15.79)	1 (5.26)	
Impulsivity Screening	1 (5.26)	4 (21.05)	
Questionnaire data: *M* (*SD*)			
ADHS-SB			Maximum reachable scores:
Total		23.53 (11.78)	54
Inattention		12.95 (5.52)	27
Hyperactivity		5.79 (4.95)	15
Impulsivity		4.79 (3.44)	12
WHOQOL			Maximum reachable scores:
Total		70.97 (10.46)	100
Physical health		73.12 (10.67)	100
Psychological health		63.16 (15.67)	100
Social relationships		69.30 (16.45)	100
Environment		78.29 (12.61)	100
DASS-21			Maximum reachable scores:
Total		10.63 (3.41)	21
Depression		10.26 (3.48)	21
Anxiety		9.11 (2.45)	21
Stress		12.53 (5.65)	21

*ADHS-SB, ADHD self-assessment scale; DASS, depression-anxiety-stress-scales; IDA-R, integrated diagnosis of ADHD in adulthood; Mini-DIPS, diagnostic short interview for mental disorders; WHOQOL, world health Organization quality of life questionnaire. *Out of 20 participants who completed the entire experiment, one participant had to be excluded from the analyses due to incorrect task execution. Hence, 19 participants remained for analyses.*

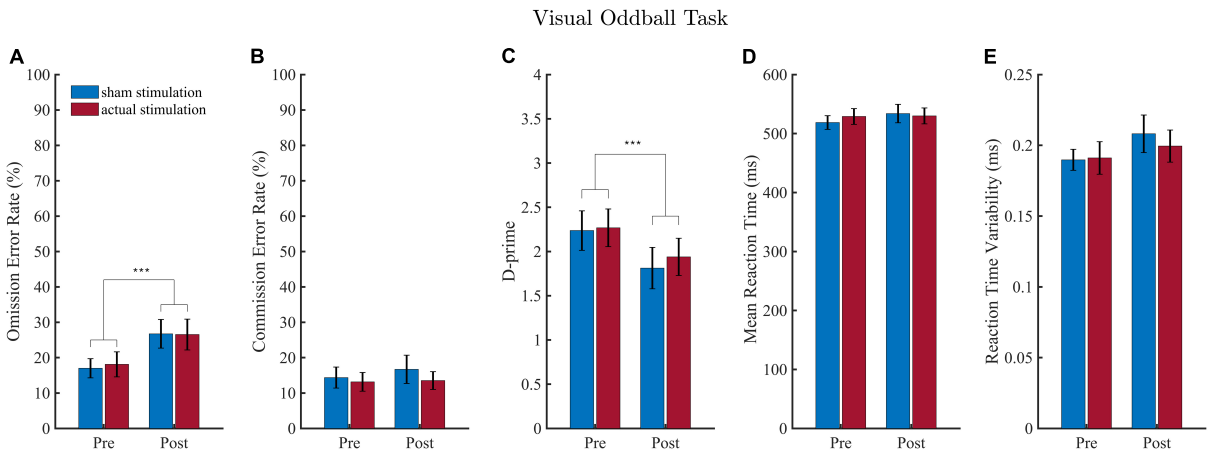

FIGURE 3 | Results of the visual oddball task (VOT). Error rates are depicted in **(A,B)** and the sensitivity measure D-prime in **(C)**. Results of the mean reaction time (RT) and reaction time variability (RTV) are illustrated in **(D,E)**. Values depict means and SEMs for the sham stimulation (blue bars) and actual stimulation (red bars) before and after actual or sham stimulation. ***$p < 0.001$.

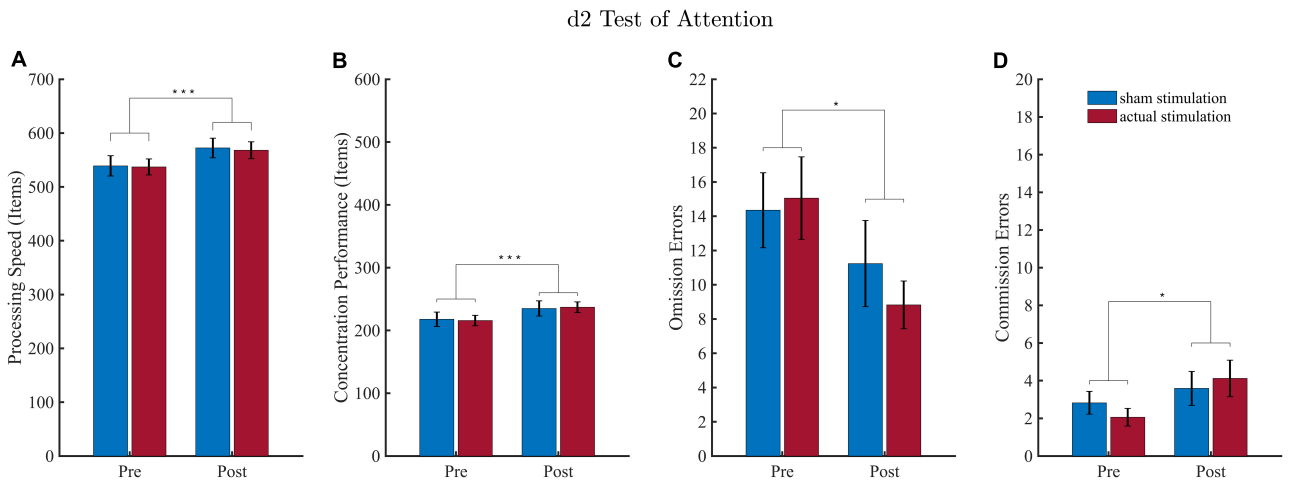

FIGURE 4 | Results of the d2 attention test (d2). Values depict means and SEMs for the sham stimulation (blue bars) and actual stimulation (red bars) before and after intervention. **(A)** Processing speed depicts the total number of characters processed on average for each condition. **(B)** Concentration performance depicts the number of correctly identified characters minus all conducted errors averaged for each condition. **(C,D)** Number of omission and commission errors averaged for each condition. *$p < 0.05$, ***$p < 0.001$.

ERO power values revealed a significant main effect of "Block" [$F_{(1,18)} = 8.26$, $p = 0.010$, $\eta_p^2 = 0.31$], but no main effect of "Intervention" [$F_{(1,18)} = 0.01$, $p = 0.934$, $\eta_p^2 = 0.00$] and no significant interaction [$F_{(1,18)} = 0.21$, $p = 0.653$, $\eta_p^2 = 0.01$]. The "Block" effect consisted of less activity in the ERO band during the post-intervention ($M = 0.58$; $SD = 0.30$) than pre-intervention ($M = 0.63$; $SD = 0.31$) block. Topography plots are shown in the **Supplementary Figure 3**.

Explorative Correlation Analyses

Results of the correlation analysis are shown in **Table 2**. There was a significant positive correlation between the late ERP mean amplitude and VOT RT [$r(18) = 0.70$, Bonferroni-Holm adjusted $p = 0.045$] as well as between the VOT omission error rate and the d prime scores [$r(18) = -0.89$, Bonferroni-Holm adjusted $p < 0.001$]). In addition, there was a significant positive correlation between maximum and mean P300 amplitude [$r(18) = 0.70$, Bonferroni-Holm adjusted $p < 0.05$]. All remaining correlations did not remain significant after Bonferroni-Holm adjustment.

DISCUSSION

In this study, we aimed to increase the P300 amplitude in ADHD patients *via* tACS and to demonstrate an attentional improvement induced by this P300 elevation.

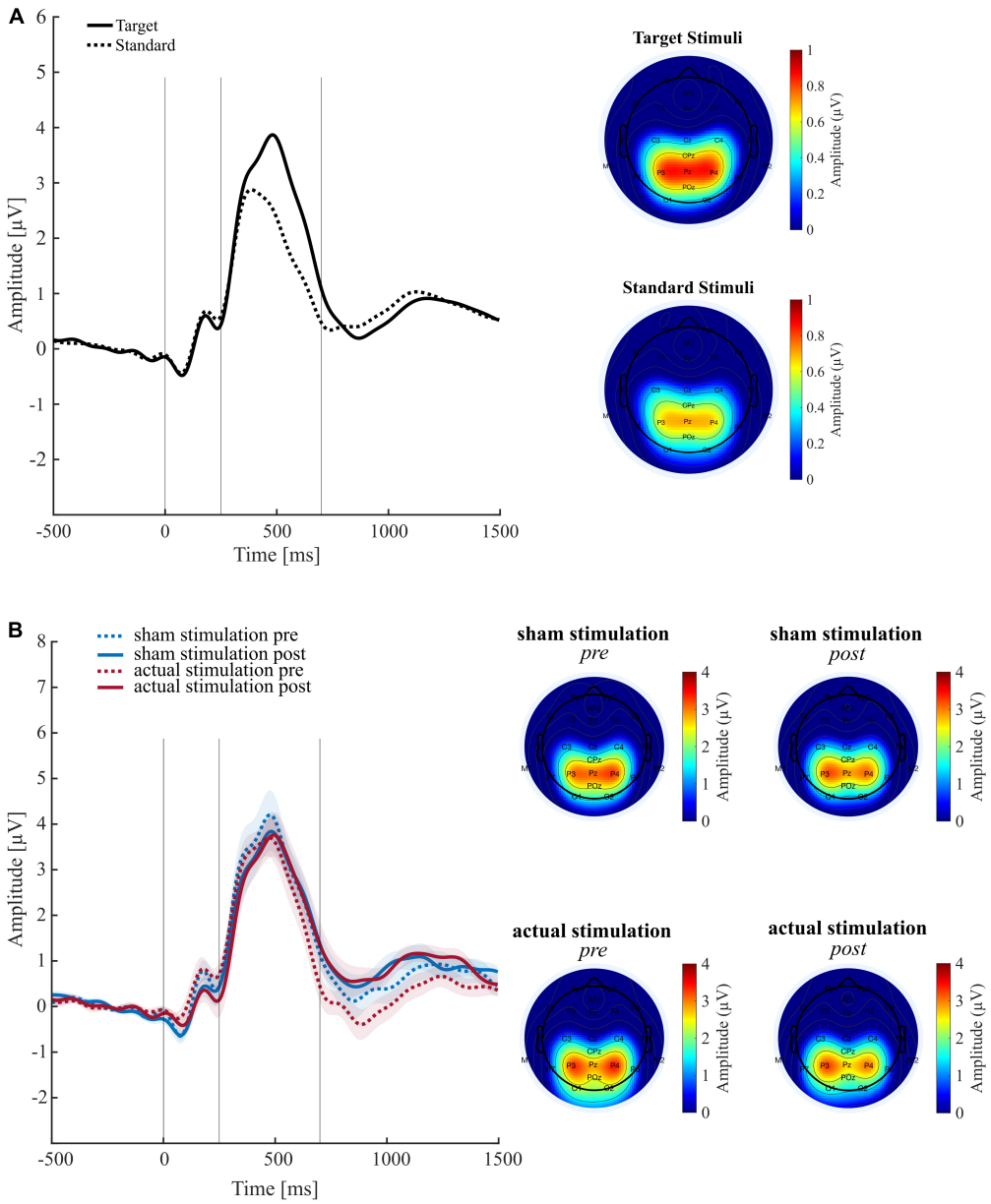

FIGURE 5 | Results of the event related potential (ERP) analyses. **(A)** Grand average ERP waveforms (left panel) and associated topographies (right panel) across all conditions for target and standard stimuli. **(B)** Target P300 ERPs (left panel) and associated topographies (right panel) for each main experimental condition. Shaded curves reflect the standard error of the mean. Time windows for statistical analysis are depicted in the entire 250–550 ms time window.

Specifically, our hypotheses were (1) that by applying tACS at the participant's individual ERO, it would be possible to enhance the P300 amplitude in ADHD patients, and (2), that this induced P300 elevation would lead to immediate improvements in neuropsychological attention measures. To test our hypotheses, we subjected our ADHD patients to both, an actual stimulation, and a sham stimulation, and evaluated their EEG characteristics (P300 amplitudes, low frequency power) and attention performances (d2 attention test, VOT) before and after the two interventions.

No Evidence for a Stimulation-Induced P300 Increase

Contrary to our expectations, we were not able to demonstrate a stronger increase in P300 amplitude under actual stimulation than sham stimulation. Instead, we only found some indication for a tACS-induced amplitude increase in a late ERP component (discussion below). Hence, limited to our analyses and in contrast to the previous study with ADHD patients (75), but in line with another study conducted in healthy participants (74), we currently cannot provide evidence that our methodological

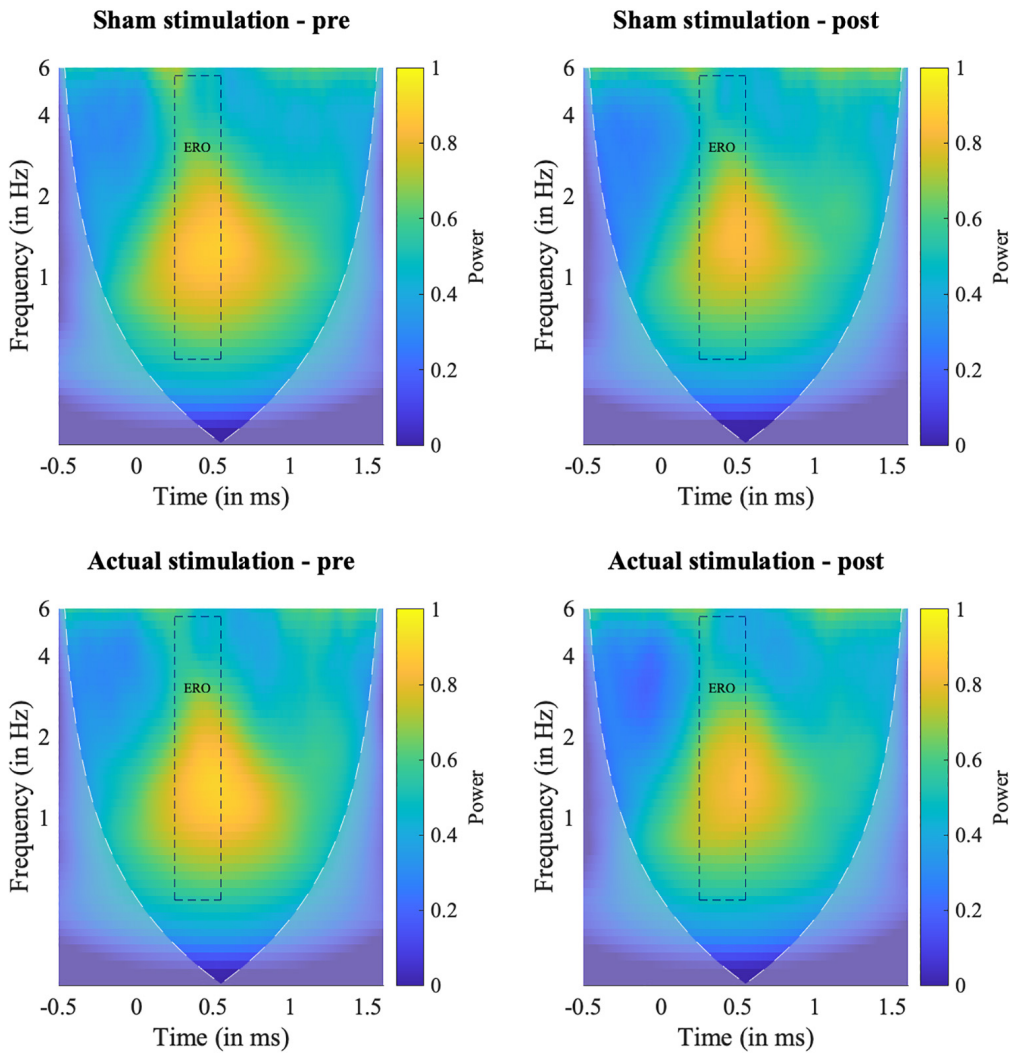

FIGURE 6 | Results of the frequency analyses. Time-Frequency spectra of the wavelet analyses for target hits for the ERO between 0 and 6 Hz at electrode Pz (Grand average). Squares indicate the temporal (0.25–0.5 s) and spectral (0.5–5.5 Hz) region of interest used for the statistical evaluation. Shaded areas outline the area where the calculated wavelet power might be distorted due to edge artifacts.

approach of aligning the participant's generated P300 peaks with positive deflections of the tACS signal is able to amplify the P300.

Why we did not succeed in increasing the participants' P300 through our tACS application cannot be conclusively determined, but some possible reasons can be suggested. First, it should be noted that the effect of tACS may vary due to individual differences in the neuroanatomy, which result in varying electric fields inside the brain (98). Therefore, one explanation might be that despite our careful simulation attempts to find the right electrode montage, we failed to stimulate the correct target region by assuming an inaccurate P300 source location. In the future, it should therefore be considered whether individualized electrode assemblies can be employed, with the help of which individual neuroanatomical peculiarities can be better accounted for.

Likewise, inter- and intraindividual variability in brain activity may have influenced the success of brain stimulation, for example, by an unfavorable brain state during stimulation (106). If this has been the case, a closed loop system that measures brain activity during stimulation *via* EEG and adjusts the applied stimulation accordingly, could potentially provide mitigation here. However, research studies targeting closed loop systems aiming to adapt fluctuating stimulation parameters to momentary brain activity are currently rare and require further investigation (107–110).

TABLE 2 | Results of correlations analyses.

	P300 mean amplitude	P300 maximum amplitude	Late ERP mean amplitude	Low frequency Power	VOT omission error rate	VOT commission error rate	VOT dprime	VOT RT	VOT RTV	d2 omission errors	d2 commission errors
Pre-to-Post											
P300 mean amplitude		0.70*	0.13	0.14	0.19	−0.28	−0.15	−0.04	−0.17	0.07	−0.21
P300 max. amplitude			0.36	0.39	0.14	−0.20	−0.14	−0.06	−0.37	0.07	−0.13
Late ERP mean amplitude				0.23	0.20	−0.14	−0.18	0.69*	0.14	0.31	0.01
Low frequency Power					0.17	0.25	−0.37	0.09	0.14	0.23	0.02
VOT omission error rate						0.35	−0.89***	0.33	0.29	−0.12	0.23
VOT comission error rate							−0.56	0.02	0.36	−0.13	−0.23
VOT dprime								−0.34	−0.39	0.12	0.07
VOT RT									0.63	0.07	−0.02
VOT RTV										0.06	−0.24
d2 omission errors											−0.12
d2 commission errors											

*Pearson correlations (r) between the absolute change (i.e., the difference from pre to post intervention) for all main behavioral and neurophysiological measures across intervention conditions. Correlations including d2 outcome parameter are calculated with 16, while all others with 19 datasets. *$p < 0.05$, ***$p < 0.001$. Bonferroni-Holm correction was applied to correct for multiple comparisons. RT, reaction time; RTV, reaction time variability; VOT, visual oddball task.*

Moreover, we find that not only the participant's P300, but also their event-related low frequency power (0–6 Hz) remained unaffected by our two stimulation interventions. Hence, the reason for failing to increase the P300 could be that the participant's ERO, which is assumed to be causative of the P300 (80, 81, 83, 84), could not sufficiently be increased. Thus, the question arises why the participant's ERO has not been changed by tACS. One finding to consider here is that brain oscillations only seem to be increasable by tACS if their power is rather low before stimulation (111, 112). Hence, one possible reason might be that the EROs of our adult ADHD sample were already elevated before the tACS intervention, and therefore could not be further increased. This would be in line with some evidence for an elevated delta and theta power in adult ADHD (113–118), although other studies did not find this effect (119–121). If an elevated delta to theta power in ADHD patients would explain our null finding, the question, however, arises why this effect did not also show up in the previous ADHD study by Dallmer-Zerbe et al. (75) and why the low-frequency power even decreased from pre- to post.

Another reason why we might have failed to enhance the participant's ERO might be some mismatch between the externally applied tACS frequency and actual ERO. Time constraints during experimental sessions with patients demand a quick EEG data analysis, which may have prevented us from being sufficiently accurate in identifying the participant's exact ERO. If the external stimulation frequency matches the endogenous frequency, already low stimulation intensities lead to entrainment. However, the larger the variance between internal and external frequency is, the stronger the force of tACS must be to entrain these oscillation (122).

Finally, evaluations of an experiment by Wischnewski et al. (76, 123) indicate that frontal theta tACS (and perhaps this effect also applies to our tACS electrode montage) may induce a P300 drop at least in healthy participants. That is, contrary to their intention of enhancing the participant's P300 by theta tACS, the participant's P300 decreased by this intervention. Surprisingly, however, this P300 decrease (76) does not seem to have been caused by modulating the participant's internal theta power, since it was not affected by the application of tACS (123). One possible implication of this is that there is another indirect mechanism by which an externally applied theta tACS may reduce the P300 amplitude, and perhaps a similar mechanism may potentially also have occurred in our experiment, but further research is required to explore underlying mechanisms.

Preliminary Evidence for a Stimulation-Induced Late Component Increase

While we found no evidence for a tACS-induced P300 increase, we interestingly found a significant ($p = 0.020$) interaction effect for a late negative ERP component (700–1,000 ms), in that this ERP component was significantly increased after actual stimulation [$t(18) = -2.70$, $p = 0.015$], but not after sham stimulation [$t(18) = -0.98$, $p = 0.339$]. Hence, at least on this ERP component, tACS seems to have had some effect. While

we do not yet have a sound neurophysiological explanation on how tACS affected this ERP component, this possible effect clearly warrants further investigation for several reasons. First, previous studies found a relationship between the amplitude of the late negative ERP component N700 and the amount of attention allocated to stimuli (124–126). And second, there is evidence that the N700 amplitude is correlated with a dopamine transporter allele (127) which is considered as a risk factor for ADHD. Consequently, a targeted modulation of this component *via* tACS could also be interesting for the treatment of ADHD.

No Indication for a Stimulation-Induced Improvement of Attention

In line with the P300 null findings were also the neuropsychological outcomes in our study. For both, the VOT and d2 attention task, none of the assessed performance measures indicated any "Block" × "Intervention" interaction. Altogether, these results suggest that the application of tACS had little to no influence on the measured neuropsychological performance of our participants. This is, however, not surprising, given that the anticipated P300 amplification was already inefficient.

Successful Optimization of Our Visual Oddball Task

To enhance omission and commission errors, we changed the VOT used in the previous study (75). In particular, we changed the used stimuli, reduced the time period of stimulus presentation and, in addition, the response behavior. Our results suggest that this adaptation of the VOT has been successful in elevating the level of difficulty. In contrast to the previous study with almost no commission errors and a low omission error rate, we now encountered higher omission error rates (M_{pre} = 17.55%, SD_{pre} = 13.01% and M_{post} = 26.63%, SD_{post} = 17.49%) and commission rates (M_{pre} = 13.76%, SD_{pre} = 9.55% and M_{post} = 15.11%, SD_{post} = 11.64%), while still observing a plausible P300 ERP (40). For future follow-up studies on the same topic, we therefore propose to use our improved VOT variant instead of our original one.

Marginal Associations Between Main Experimental Parameters

Most of the major correlation parameters were non-significant. However, there was one significant positive correlation between late ERP mean amplitude and VOT RT [$r(18) = 0.70$, Bonferroni-Holm adjusted $p = 0.045$]. While preliminary, this finding might suggest that the amplitude change of the late ERP component could be influenced by the participant's RT during the VOT. Therefore, the modulation of this late ERP component could be a future target site to be investigated to influence responsiveness in ADHD individuals.

Limitations and Future Directions

One limitation of our study is that the experimental design is rather time critical and grounds on the presupposition that the participant's P300 latency remains stable across trials. If this requirement is violated too strongly, there is a risk that the tACS peaks do not sufficiently coincide with the P300 peaks, and thus the P300 cannot sufficiently be elevated. For the future, this problem could perhaps be attenuated by using an oddball task that induces a particularly low P300 latency variability, choosing a less time-critical target site instead of the P300 (e.g., an oscillation instead of an ERP component), or by implementing a closed loop system that may recognize P300 latency changes over time and may adapt the stimulation frequency accordingly.

In comparison to the study of Dallmer-Zerbe et al. (75), we changed various aspects in our present study. For example, we chose another study design (crossover design instead of between design), we used other electrodes for the application of tACS (rubber electrodes instead of EEG ring electrodes) and programmed a different visual oddball task with different stimuli and reaction patterns (for further details and differences cf. **Supplementary Table 1**). Therefore, it is not possible to directly compare both studies. However, with our experimental procedure, the application of tACS did not enhance low frequency power or the P300 amplitude, which challenges to some extent the robustness of the found effect in the previous study.

One aspect that needs further investigation is to find the optimal P300 time window to be extracted for the online analyses. A limitation of our online analyses was our rather narrowly chosen P300 time frame of 250 to 450 ms, since in four datasets the averaged ERP peaked maximally beyond our chosen P300 time frame. Therefore, for those four participants, the P300 latency, which is used for adjusting the stimulus presentation during the VOT, was not accurate enough. On the other hand, selecting a larger P300 time frame might have led to maximum peaks that fall below (e.g., <200) or exceed (e.g., >600) the usual P300 time window. Hence, future studies might expand the P300 time frame to 250–600 ms targeting ADHD patients.

Another caveat is that our study did not allow for full experimenter blinding, given that the neurostimulator had to be manually adjusted. Hence, an experimenter bias cannot fully be precluded. Therefore, for future studies, it would be helpful to control the neurostimulator automatically instead of manually entering the stimulation parameter.

Another limitation of our study is that our sample size is, unfortunately, not large enough to also allow for ADHD subtype analyses. Such an analysis would have been very interesting, though, because it could be that not all ADHD patients, but at least a certain ADHD subtype or subgroup of ADHD patients (e.g., the predominantly hyperactive/impulsive subtype) benefit from our tACS application. In addition, a sub analysis of patients with certain comorbidities may also have been interesting to look at, since our sample included, for example, ADHD patients with comorbid mild to moderate affective disorders or anxiety disorders. Similarly, the sample we collected may not have been large enough to detect even small tACS-induced changes. In this case, however, the question arises whether these undetected effects are clinically relevant.

Although ERP data give valuable insights into cognitive processing of ADHD patients, it is important to bear in mind that it is still unclear whether the P300 amplitude decrease in ADHD (41–48) is a cause, consequence, or compensatory process. Although first explanation attempts have been put forward (128), further studies are clearly necessary to shed more light on this unresolved question.

Moreover, a question that remains unanswered in our study is the question of possible tACS long-term effects. In particular, our study cannot exclude the possibility that the tACS effects we expected do not occur immediately, but perhaps not until after several sessions. For example, in the study Farokhzadi et al. (86), where alpha-tACS achieved higher reductions in inattention and impulsivity than Ritalin, the effect was measured after 24 sessions. Therefore, it would be interesting to compare various tACS conditions over more than one session. In this respect, it is also conceivable to vary the stimulation frequencies or electrode montages.

In addition, it should be considered that the application of tACS is accompanied by a large artifact in EEG data. It is a major challenge to recover artifact-free brain signals during tACS because it hinders direct insights into electrophysiological processing during stimulation. So far, current computational approaches still fail to obtain artifact-free data (129–132). In the future, however, it would be interesting to analyze EEG data during actual stimulation to lighten the current black box.

CONCLUSION

In conclusion, our study cannot provide further evidence that tACS can increase the P300 amplitude in ADHD patients and that by such P300 amplification an immediate improvement of neuropsychological attention parameters can be achieved. However, we found a possible effect of our tACS stimulation on a late ERP component and a positive correlation between this component and the participants' VOT RTs that both warrant further investigation. Moreover, our chosen setup included many actuation parameters (e.g., stimulation intensity, electrode mounting, waveform type) that could have been set differently. Therefore, there are still many alternative parameter settings for the application of tACS that can be tested and that may potentially yield more promising results.

DATA AVAILABILITY STATEMENT

The anonymized raw data supporting the conclusions of the article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the University of Bonn. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KK and CB designed the experiment under the supervision of NB, AP, and CH. CB conducted the tACS electrode simulations. KK collected and analyzed the data under the supervision of NB and CH, and intervision with CB. KK and NB wrote major parts of the manuscript. BA and HR recruited ADHD patients. AW, BS, CB, AP, SL, HR, BA, and CH contributed to reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.928145/full#supplementary-material

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Home-based transcranial direct current stimulation in dual active treatments for symptoms of depression and anxiety: A case series

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Transcranial direct current stimulation (tDCS) is a potential treatment strategy across some psychiatric conditions. However, there is high heterogeneity in tDCS efficacy as a stand-alone treatment. To increase its therapeutic potential, researchers have begun to explore the efficacy of combining tDCS with psychological and pharmacological interventions. The current case series details the effect of 6–10 weeks of self-administered tDCS paired with a behavioral therapy smartphone app (Flow™), on depressive and anxiety symptoms, in seven patients (26–51 years old; four female) presenting distinctive psychiatric disorders (major depression, dysthymia, illness anxiety disorder, obsessive-compulsive disorder, and anxiety disorders). tDCS protocol consisted of an acute phase of daily 30 min sessions, across 10 workdays (2 weeks Monday-to-Friday; Protocol 1) or 15 workdays (3 weeks Monday-to-Friday; Protocol 2). A maintenance phase followed, with twice-weekly sessions for 4 or 3 weeks, corresponding to 18 or 21 sessions in total (Protocol 1 or 2, respectively). The Flow tDCS device uses a 2 mA current intensity, targeting the bilateral dorsolateral prefrontal cortex. The Flow app offers virtually guided behavioral therapy courses to be completed during stimulation. We assessed depressive symptoms using MADRS-S and BDI-II, anxious symptoms using STAI-Trait, acceptability using ACCEPT-tDCS, and side effects using the Adverse Effects Questionnaire, at baseline and week 6 of treatment. Six patients underwent simultaneous cognitive-behavioral psychotherapy and two were on antidepressants and benzodiazepines. According to the Reliable Change Index (RCI), for depressive symptoms, we found clinically reliable improvement in five patients using MADRS-S (out of seven; RCI: −1.45, 80% CI; RCI: −2.17 to −4.82, 95% CI; percentage change: 37.9–66.7%) and in four patients using BDI-II (out of five; RCI: −3.61 to −6.70, 95% CI; percentage change: 57.1–100%). For anxiety symptoms, clinically reliable improvement was observed in five patients (out of six; RCI: −1.79, 90% CI; RCI: −2.55 to −8.64, 95% CI; percentage change: 12.3–46.4%). Stimulation was well-tolerated and accepted, with mild tingling sensation and scalp

discomfort being the most common side effects. This case series highlights the applicability, acceptability, and promising results when combining home-based tDCS with psychotherapy and pharmacotherapy to manage depression and anxiety symptoms in clinical practice.

KEYWORDS

tDCS, home-based, Flow, anxiety, depression, case series

Introduction

Anxiety and mood disorders are amongst the most widespread psychiatric diseases, with a lifetime prevalence of 28.8 and 20.8%, respectively (1). Several pharmacological and psychological approaches are currently available. However, a high number of patients are classified as partial, non-responders or do not experience long-term clinical benefits (2, 3).

Transcranial direct current stimulation (tDCS) is an alternative and complementary therapeutic option, particularly promising due to its low cost, potential cost-effectiveness, easy application, and safe and tolerable profile (4, 5). As a non-invasive and non-pharmacological technique, tDCS applies a weak direct current through scalp electrodes (anode and cathode), modifying neuronal excitability and cortical activity according to stimulation parameters (6, 7). Stand-alone tDCS has already shown therapeutic efficacy in patients diagnosed with major depressive disorder (MDD) and anxiety (5, 7–9), being superior to sham in what concerns clinical response; however, its results are still highly heterogeneous (4, 10). In MDD, the hypoactive anode is usually positioned over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the right DLPFC or the right supraorbital or frontotemporal area (7).

To improve the therapeutic efficacy of tDCS and psychological interventions, researchers have been exploring the combination of both approaches. Using the Flow solution (a home-based tDCS and app-based psychological intervention; Flow Neuroscience™, Malmö, Sweden; https://flowneuroscience.com/), Borrione et al. (11) found that four out of five patients with MDD responded substantially to the treatment, suggesting a synergistic/additive effect. Furthermore, promising effects have been reported for comorbid generalized anxiety disorder and MDD (12). However, a recent review highlights that the current setup of dual active treatments combining tDCS with psychological interventions may not achieve increased efficacy in MDD as compared to stand-alone interventions, possibly due to a lack of a full-factorial design (i.e., control psychological intervention), small sample sizes, high variability in study characteristics (e.g., number of sessions, type of psychological intervention), and individual patient characteristics (e.g., brain state at time of stimulation) (10). Additionally, recent studies failed to find the superior efficacy of concurrent tDCS and CBT (13) or concurrent tDCS and other psychosocial interventions (14) when compared with stand-alone treatments, warranting further evidence to the field.

Here, we build on current literature and present the effects of Flow™ combined with psychotherapy and medication on depression and anxiety symptoms, in seven patients presenting MDD, illness anxiety disorder, obsessive-compulsive disorder (OCD), and anxiety disorders. Flow™ offers the possibility of a dual active treatment (tDCS and an app offering evidence-based behavioral therapy sessions), while being a patient-friendly device with no physical restraints. It further provides psychoeducational materials and enables long-distance supervision, through its web-based clinicians dashboard which differentiates Flow™ from other home-based solutions.

Methods

Participants

This case series reports retrospective data from seven patients attending a private healthcare clinic for treatment of depressive symptoms, with and without comorbid anxiety or obsessive-compulsive symptoms, between August 2020 and March 2022. Patients provided written informed consent for participation in the intervention protocol and for their individual clinical information to be used.

Patients were diagnosed with MDD and/or other comorbidities by a psychiatrist and/or trained licensed psychologist at baseline and reassessed at week 6 and at the end of treatment following a semi-structured interview based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria (15). The self-report version of the Montgomery-Åsberg Depression Rating Scale (MADRS) (16) was further applied as the primary outcome to assess clinical severity across treatment.

The Flow program was introduced to patients who presented mild to moderate depressive symptoms, were resistant to initiate or augment medication, or who showed a preference for non-pharmacological treatments. Following treatment admission, patients started Flow sessions (cf. Supplementary Figure 1) and completed the following questionnaires to assess clinical status and improvement: the self-reported Montgomery-Åsberg

Depression Rating Scale (MADRS-S) (17), the Beck Depression Inventory-II (BDI-II) (18, 19), and the State-Trait Anxiety Inventory (STAI) (20, 21). tDCS acceptability was assessed using the ACCEPT-tDCS (22).

Questionnaires were administered at baseline and at the end of weeks 3 and 6 of treatment. MADRS-S was requested at the 1-month follow-up. Patients reported side effects weekly using the Portuguese translation of the Thair et al. questionnaire (23). Side-effect management strategies are reported in section "Adverse Effects Results" of supplementary material. Clinical progress monitoring was performed in-person and remotely using Zoom [Zoom Video Communications, Inc., 2020 (Computer software)], according to individual preference. At the end of week 6, patients were re-assessed and the treatment proceeded according to the patient's choice and clinical recommendation (i.e., to continue in psychotherapy and/or pharmacology as stand-alone treatments when the patient was responding positively to treatment as per self-reports and clinical interview, to start maintenance treatment [when symptoms' remission was achieved (MADRS-S $\leq$12)], or to repeat the Flow program (when clinical response was ongoing but symptoms remission not achieved). The Flow Program schedule can be found in Table 1.

Clinically significant change was calculated based on percentage change and the Reliable Change Index (RCI). RCI (24) was assessed using the formula $(Xpost–Xpre)/\sqrt{2}\,(SD*\sqrt{1–\alpha})^2$, where Xpost is the result post-intervention, Xpre the result at baseline and SD the standard deviation and α the reliability from the corresponding psychometric publications. We adopted the indexes and confidence intervals (CI) by Wise (25) as indicative of clinically significant change: RCI $\geq |1.96|$, 95% CI; RCI $\geq |1.64|$, 90% CI; RCI $\geq |1.28|$, 80% CI.

Patients included four women and three men (26–51 years), of which two were diagnosed with comorbid MDD and anxiety disorder, one with OCD, one with anxiety disorder, two with dysthymia and one with illness anxiety disorder. All patients presented depressive symptomatology at intake. Four patients started cognitive-behavioral therapy (CBT) prior to Flow and maintained concomitantly. Five patients were medication-free and two were on medication at the start of the program. The latter were in stable dose for at least 4 weeks prior to treatment (cf. Supplementary Table 1). Two patients initiated CBT at the same time as Flow.

Case 1

Patient 1 was a 41-year-old married woman, with a high education level and stable employment. She presented a history of recurrent major depressive episodes, concomitant to an unspecified anxiety disorder. During her second pregnancy, patient 1 developed moderate MDD (peripartum onset). At intake (6 years after her second pregnancy), she exhibited depressed mood, sadness, irritability, decreased sleep and appetite, and anxiety symptoms (increased physiological activity). No suicidal ideation or suicide attempts were reported. The patient had no history of drug or alcohol abuse and no family history of mental illness. She had sought professional help before for the presenting symptoms and had previously completed one psychotherapy course. Prior to treatment, the patient was medication-free. The patient completed Protocol 1 (18 tDCS sessions).

Case 2

Patient 2 was a 22-year-old unmarried young man. At intake, he was a university student and a professional football athlete. He reported having alopecia for several years and resolved Guillain-Barre syndrome in the past months. He had a history of major depressive episodes, initiating in his childhood. Presenting complaints included persistent depressive symptoms, comorbid with anxiety disorders [specific phobia (heights) and agoraphobia], with a significant impact on his academic and athletic performance. The patient had no history of drug or alcohol abuse and no previous psychiatric admissions but reports a suspected family history of MDD (father). This was the second time the patient sought professional help for the presenting symptoms which were addressed with psychotherapy and pharmacotherapy (sertraline 50 mg). This time the patient's treatment of choice was FLOW. Patient 2 initiated Flow at the same time as psychotherapy and completed Protocol 1 (17 tDCS sessions).

Case 3

Patient 3 was a 31-year-old unmarried man with stable employment and a high education level. He presented to the clinic with prior long-term cannabis use associated with withdrawal syndrome with mild depressive symptoms and social anxiety disorder (performance only). No substance use in the present and no psychiatric family history or prior psychiatric events were reported. Symptoms onset occurred at the start of the COVID-19 pandemic. The patient reported no prior attempts of psychotherapy or pharmacotherapy. Patient 3 initiated Flow simultaneously to CBT, having completed 25 sessions (Protocol 2, with maintenance phase).

Case 4

Patient 4 was a 37-year-old single woman with a high education level and unstable employment. She presented comorbid depressive and anxious symptoms at intake (depressed mood, irritability, feelings of worthlessness and guilt, reduced attention, muscular tension), emerging during adolescence. She was previously diagnosed with persistent depressive disorder (dysthymia) and medicated with Vortioxetine, without improvement. Afterward, she

TABLE 1 Flow program treatment schedule.

Timepoint	Screening session	Day 1 of week 1	Day 1 of week 2	Day 1 of week 3	Day 1 of week 4	Day 1 of week 5	Day 5 of week 6	Follow-up (1 month)
Clinical assessment	X							X
Eligibility screening (and monitoring)	X	X	X	X	X	X	X	
Informed consent	X							
MADRS interview	X						X	
ACCEPT-tDCS		X		X			X	
STAI-Y2		X		X			X	
BDI-II		X		X			X	
MADRS-S*		X	X	X	X	X	X	X
Adverse effects questionnaire		X	X	X	X	X	X	
Patient feedback		X	X	X	X	X	X	X

MADRS, Montgomery-Åsberg depression rating scale; ACCEPT-tDCS, transcranial direct current stimulation acceptability in the treatment of anxiety disorders questionnaire; STAI-Y2, subscale trait-anxiety of the state-trait anxiety inventory (form Y); BDI-II, beck depression inventory-II; MADRS-S, self-report version of the MADRS; *Completed using the Flow depression app.

initiated Bupropion (150 mg), Quetiapine (25 mg), and Bromazepam (1.5 mg in SOS). The patient reported no history of drug or alcohol consumption. Also, she reported no prior psychotherapeutic treatments. Psychiatric family history included an aunt diagnosed with MDD and her grandmother with suspected MDD. Patient 4 was diagnosed with dyslexia early at school age but never benefited from any formal support. The patient initiated Flow concomitantly to CBT (24 tDCS sessions; Protocol 2, with maintenance phase).

Case 5

Patient 5 was a 27-year-old unmarried woman. At intake, she was a university student with simultaneous stable employment. She presented depressive symptoms (diminished ability to think and indecisiveness, lack of energy) associated with episodes of binge eating and was diagnosed with dysthymia. No previous resolution attempts were reported. Although no family history of mental illness was observed, the patient highlighted psychosocial impairments, namely family conflict and difficulty in establishing boundaries. Patient 5 completed two consecutive acute cycles of Flow treatment simultaneously with psychotherapy (Protocol 2, 39 tDCS sessions; reasons detailed below).

Case 6

Patient 6 was a 27-year-old unmarried woman, in her last doctoral years. She presented an illness anxiety disorder, emerging in early childhood (4 years old) and currently comorbid with depressive symptomatology (loss of appetite, loss of interest). Symptoms were associated with avoidance behaviors related to fear of contamination. Although not diagnosed, a family history of illness anxiety disorder was suspected (father). This was the first time the patient sought professional help. No relevant medical background was reported, except a weakened immune system with recurrent candidiasis. Patient 6 completed two independent cycles of Flow (Protocol 1, 18 tDCS sessions each), at two distinctive episodes 3 months apart, simultaneously with CBT. During the second cycle, patient 6 also initiated pharmacotherapy.

Case 7

Patient 7 was a 51-year-old married man with an intermediate level of education and stable employment, diagnosed with OCD. At intake, he was in psychotherapy and medicated with Sertraline (100 mg), Clomipramine (75 and 25 mg), and Clonazepam (0.5 mg), in another clinic. The patient was referred for Flow as a complementary treatment to manage severe depressive symptoms causing significant distress. Patient 7 completed 18 tDCS sessions (Protocol 1).

Intervention

Flow (Flow Neuroscience AB, Sweden) combines self-administrated tDCS with a smartphone app (Flow Depression) for behavioral therapy, aiming to activate neural networks and implement healthy habits and contribute to the reduction of depressive symptoms. Flow app is combined with a certified tDCS medical device approved for home-use MDD treatment in adult patients (>18 years old) in the United Kingdom and the European Union. The one-size-fits-all wireless and portable tDCS headset targets the prefrontal cortex (the anode electrode over the left and the cathode electrode over the right dorsolateral prefrontal cortex; cf., Supplementary Figures 2, 3), as evidenced by electric field modeling (26). The device uses a current

intensity of 2 mA, administered through two spheric electrodes of 22.9 cm^2 size (current density = 0.09 mA/cm^2) for 30 min.

After clinical studies evidence showing the beneficial effect of 15 consecutive sessions in depression (27, 28), Flow updated the number of sessions during the acute treatment, transitioning from Protocol 1 (acute treatment phase for 2 weeks) to Protocol 2 (acute treatment phase for 3 weeks). The protocols consisted of an acute phase of daily sessions, five sessions per week during the first 2 weeks (Protocol 1) or the first 3 weeks (Protocol 2), followed by a maintenance phase of twice-weekly sessions for 4 or 3 weeks, respectively (18 or 21 sessions in total, for a total of 6 weeks). According to the manufacturers, the maintenance phase can be extended up to week 10.

Patients were introduced to Flow and trained by a clinical psychologist certified in tDCS. Weekly appointments with the psychologist allowed to monitor clinical progression, discuss treatment adherence, answer patients' questions, and collect self-reported adverse effects.

The app offers automated virtually guided behavioral therapy sessions developed by licensed clinical psychologists. The different courses focus on behavioral activation, sleep hygiene, mindfulness-based meditation, physical exercise, and nutrition. Sessions can be completed during the 30 min stimulation, and are not mandatory. Upon patient's approval, a dashboard for clinicians is currently available to monitor clinical progression and adherence.

To initiate Flow, eligibility criteria were verified across time. Exclusion criteria were followed according to recommendations in the field (6) (cf. Supplementary Table 1) and assessed using the Exclusion Criteria Questionnaire for tDCS (23).

Clinical findings/results

Depression and anxiety symptoms

MADRS-S, BDI-II, and STAI-Y2 scores from baseline to week 6 of treatment are shown in Figure 1. Percentage change scores and Reliable Change Index (RCI) are reported in Table 2. At the end of week 6, five patients showed clinical improvement for depressive symptoms using MADRS-S (percentage change: 37.9–66.7%; RCI: −1.45, 80% CI; RCI: −2.17 to −4.82, 95% CI) and four using BDI-II (percentage change: 57.1–100%; RCI: −3.61 to −6.70, 95% CI). Five patients presented significant improvement in anxiety symptoms (STAI-Y2 percentage change: 12.3–46.4%; RCI: −1.79, 90% CI; RCI: −2.55 to −8.64, 95% CI). One patient (Patient 1) did not respond to treatment. Patients that presented significant clinical improvements combined Flow with CBT and/or psychopharmaceuticals.

According to clinical decisions and patients' preferences, patients 3 and 4 were recommended for eight additional tDCS sessions after the maintenance phase (until week 10) to consolidate clinical response. However, both completed only four sessions across 4 weeks. During the maintenance phase, we registered a significant improvement between weeks 6–10 in anxiety symptoms for patient 3 (STAI-Y2 percentage change: −30%) and depression symptoms for patient 4 (MADRS-S percentage change: −60.87%; cf. Supplementary Table 2).

Patients 5 and 6 initiated two cycles. Patient 6 started the second cycle 3 months after the first treatment due to the re-emergence of depression symptoms. This second course had a significant impact on depression and anxiety symptoms with decreased percentage changes between 41.6 and 57.9% (cf. Table 2). Patient 5 initiated the second cycle after 5 weeks of reduced adhesion to treatment. The second course was significantly associated with symptom improvement at 6 weeks as assessed by MADRS-S (percentage change: −50%; RCI: −2.17, 95% CI), but not as assessed by BDI-II and STAI-Y2 (cf. Table 2).

Across patients, improvement of depression and anxiety symptoms was maintained at 1-month follow-up (cf. Supplementary Table 3). Having completed Flow treatments, six patients (except patient 1) maintained weekly to once-a-month psychotherapy. Two patients initiated Escitalopram (10 mg): patient 6 during the second cycle as her anxiety symptoms became the primary concern, associated with ritual behaviors, and patient 1 after the lack of response to the Flow program. Patients 4 and 7 maintained their antidepressants and benzodiazepines.

Intervention adherence and compliance

Patients' adherence and acceptability were overall high (76.2–100%; cf. ACCEPT-tDCS scores in Supplementary Table 2). Patients 3 and 4 reported personal challenges that negatively influenced the treatment process which led to 50% missed tDCS sessions during the maintenance phase. Considering the minimal improvement presented by these patients, missed sessions were not compensated. Patient 5 did not comply with the prescribed treatment and dropped out after the first 3 weeks of Flow. Data regarding adherence to the app was available for three patients through the clinician's dashboard. Only one patient completed the courses proposed by the app consistently (cf. Supplementary Table 2). Finally, follow-up assessments at 1 month for three patients are not available.

tDCS was well-tolerated, without severe side effects (cf. Supplementary Table 4). Our observed side effects are in line with the tDCS literature, and no unexpected events were reported. The most common adverse effects were scalp irritation, tingling, itching, and burning sensation. Patient 4 reported high levels of back and neck pain, attributed to the seated position while completing tDCS sessions and to muscles' tension (an anxiety symptom reported by this patient) and not a direct effect

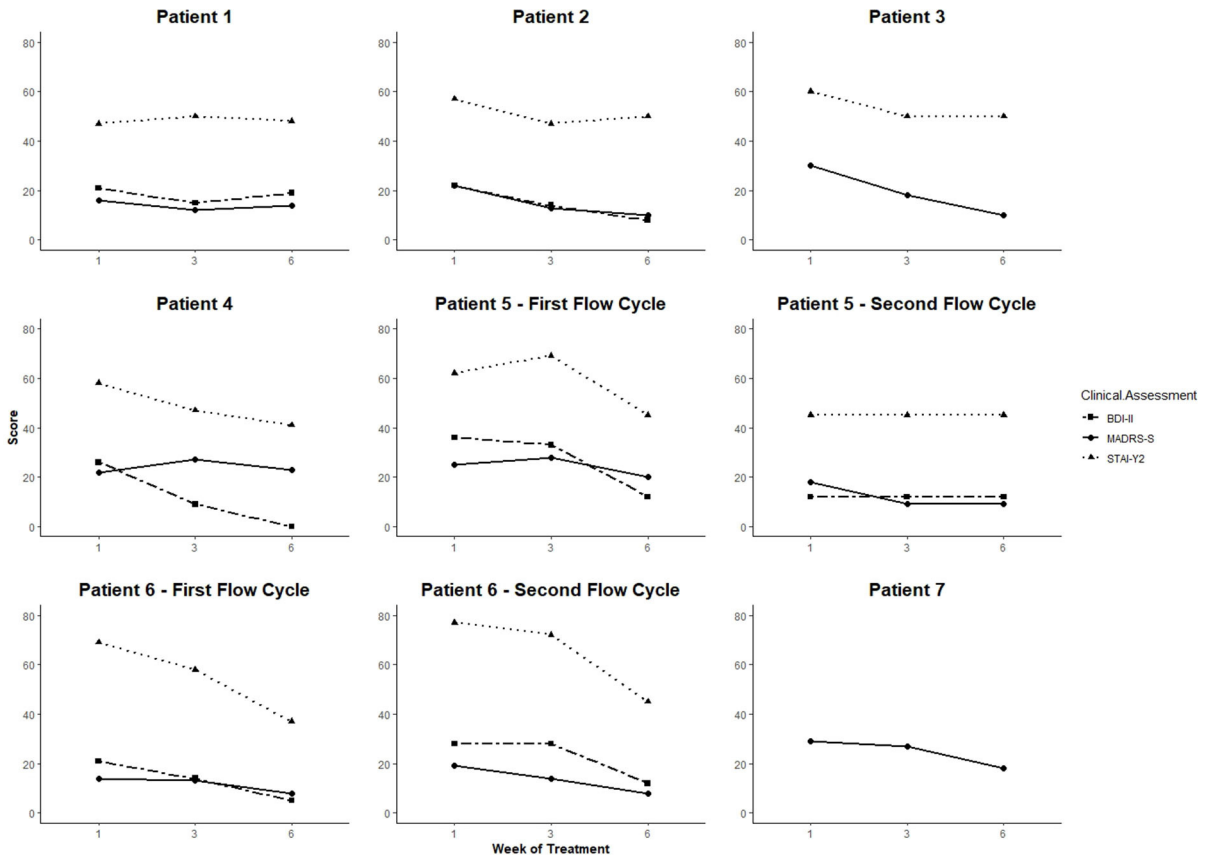

FIGURE 1
MADRS-S, BDI-II, and STAI-Y2 results by patient across the Flow treatment. X-axis shows measuring time points, y-axis shows scores. MADRS-S results were not available for patient 7. MADRS interview performed by the clinician is depicted as a proxy value.

of stimulation. No patient interrupted the tDCS treatment due to the side effects.

Discussion

This case series explored the effect of the Flow Program combined with psychotherapy and/or pharmacotherapy in seven patients affected by depressive and anxious disorders. Overall, we found mood and anxiety improvement after treatment, except for one MDD patient who was not undergoing simultaneous psychotherapy or pharmacotherapy. tDCS efficacy is promising in dysphoric and psychomotor retardation symptoms of depression but not in vegetative/somatic symptoms (29). Patient 1's non-response to tDCS may be associated with her somatic depression related to dysfunction of the autonomic nervous system, and not the prefrontal cortex (30).

Our findings are in line with previous case series (11) and may be explained by synergistic effects on neuroplasticity of combining tDCS and individually tailored psychotherapy (10). Both tDCS and psychological interventions have the potential to restore basic and higher-order psychological mechanisms (31). Specifically, tDCS can be used to facilitate learning of cognitive control and emotional and behavioral regulation, targeting adaptive processes and restoring brain functioning in the prefrontal cortex (10, 31, 32). Consequently, patients' benefit from psychotherapy increases, as it requires higher-order cognitive processes frequently impaired in depressed and anxious patients (31). In our case series, patient 2 was not benefiting from CBT prior to Flow. After 6 weeks of Flow, he manifested significant improvement in both depressive and anxious symptomatology, which was maintained at the 1-month follow-up.

Although the results of dual active treatments of tDCS with antidepressants are conflicting [e.g., lower depression scores and higher response rates (33) vs reduced antidepressant effect of tDCS when combined with benzodiazepines (34, 35)], warranting new clinical studies to unveil treatment parameters, the potential benefit of tDCS combined with

TABLE 2 Clinical findings before and after 6 weeks of treatment.

Patient	Diagnosis	MADRS-S				STAI-Y2				BDI-II				Flow protocol	Total tDCS sessions	Dual active treatment
		Baseline	Week 6	Percentage change	RCI	Baseline	Week 6	Percentage change	RCI	Baseline	Week 6	Percentage change	RCI			
1st FLOW cycle																
Patient 1	MDD and unspecified AD	16	14	−12.5%	−0.48	47	48	2.1%	0.27	21	19	−9.5%	−0.52	1	18	Flow stand-alone
Patient 2	MDD and Agoraphobia + Specific Phobia	22	10	−54.5%	−2.89***	57	50	−12.3%	−1.79**	22	8	−63.6%	−3.61***	1	17	Flow and CBT
Patient 3	Social AD (performance)	30	10	−66.7%	−4.82***	60	50	−16.7%	−2.55***	27	N/A	N/A	N/A	2	25	Flow and CBT
Patient 4	Dysthymia	22	23	4.5%	0.24	58	41	−29.3%	−4.59***	26	0	−100%	−6.70***	2	24	Flow, CBT and antidepressant/ benzodiazepine (bupropion 150 mg; quetiapine 25 mg; bromazepam 1.5 mg in SOS)
Patient 5	Dysthymia	25	20	−20%	−1.20	62	45	−27.4%	−4.59***	36	12	−66.7%	−6.18***	2	23	Flow and CBT
Patient 6	Illness AD	14	8	−42.9%	−1.45*	69	37	−46.4%	−8.64***	21	5	−76.2%	−4.12***	1	18	Flow and CBT
Patient 7 [a]	OCD	29	18	−37.9%	−2.65***	40	N/A	N/A	N/A	33	N/A	N/A	N/A	1	18	Flow, CBT and antidepressant/ benzodiazepine (sertraline 100 mg, clomipramine 75 mg and 25 mg; clonazepam 0,5 mg)
2nd FLOW cycle																
Patient 5	Dysthymia	18	9	−50%	−2.17***	45	45	0%	0	12	12	0%	0	2	16	Flow and CBT
Patient 6	Illness AD	19	8	−57.9%	−2.65***	77	45	−41.6%	−8.64***	28	12	−57.1%	−4.12***	1	18	Flow, CBT and antidepressant at week 4 (Escitalopram 10 mg)

MADRS-S, self-report version of the Montgomery-Åsberg depression rating scale; STAI-Y2, subscale trait-anxiety of the state-trait anxiety inventory (form Y); BDI-II, beck depression inventory-II; Baseline, Pre-Treatment; Percentage Change, ((Week 6–Baseline)/Baseline)*100; RCI, reliable change index (improvement from Baseline to week 6; difference between week 6 and Baseline divided by the standard error of the difference for the test); MDD, major depressive disorder; AD, anxiety disorder; CBT, cognitive-behavioral therapy; N/A, not available; OCD, obsessive-compulsive disorder.

[a] MADRS-S results were not available for patient 7 (missing value). Accordingly, we used the MADRS interview administered by the clinician as a proxy value.

RCI significance levels: ***RCI ≥ |1.96|, 95% CI; **RCI ≥ |1.64|, 90% CI; *RCI ≥ |1.28|, 80% CI.

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antidepressants was preliminarily observed in our patients 4 and 7, with a reduction of depression and anxiety scores. Moreover, our findings seem to contrast with the literature reporting the lack of effect of tDCS combined with psychotherapy (33) which might be due to differences in stimulation parameters. The observed improvements during the maintenance phase are also in accordance with dosage-dependent tDCS effects and the need for short intervals in the post-acute treatment of depression (36–38), suggesting that longer treatment courses may lead to optimal results (5). Finally, our study highlights home-based tDCS safety profile.

Dual active treatments seem to improve in parallel depressive symptoms and trait-anxiety (although to a lesser extent) across patients. This is supported by the neural commonalities between depression and anxiety described by Maggioni et al. (39) that suggested that clinical similarities between MDD and anxiety could be attributed to shared alterations in prefrontal regions, associated with emotional processing and regulation. Consequently, targeting the prefrontal cortex with tDCS concurrently with other treatments may result in greater cognitive and emotional regulation and subsequent reduced depressive and anxiety symptoms (12).

Brain-derived neurotrophic factor (BDNF) is a key regulator of neuronal growth and survival, contributing to neural function and plasticity (40). It has frequently been proposed that BDNF lower expression has a role in the pathophysiology of MDD (41). Although with inconsistent results, it has emerged as an important mechanism associated with antidepressant clinical response (41). Also, longer-lasting tDCS-elicited changes in synaptic plasticity may involve BDNF-mediated mechanisms (42). Studies on the relationship between tDCS effects and elevated BDNF levels after treatment in depressed patients have shown conflicting results thus far with BDNF plasma levels not increasing following tDCS (43). This suggests that whereas BDNF levels might not be impacted by tDCS treatments, pre-treatment BDNF levels can be a predictor of treatment response. In fact, a similar effect was seen with psychotherapy by the study from Bruijniks et al. (44) which observed that higher levels of BDNF at baseline were related to lower post-treatment depression although only in patients with high working memory.

For patients 4 and 5, improvement in depression scores for MADRS-S and BDI-II were incongruent. Although BDI-II and MADRS-S are self-assessment depression screening measures, with sufficient agreement between them, they are also different in several aspects. Compared with the Beck Depression Inventory (BDI-I), MADRS-S has been found to be less influenced by maladaptive personality traits and more focused on core depressive symptoms and states. Consequently, MADRS-S has been recommended to discriminate state depressiveness in mild depression and coexisting personality traits (45). Additionally, the two measures report distinctive time windows (the past 3 days vs the past 2 weeks) and use distinctive response systems (fixed sentences vs fixed sentences interleaved with open scores) leading to different reports of the phenomenological processes.

An increased interest in home-based tDCS solutions has been growing as it removes the disadvantages of in-person visits (46, 47). Our results show not only its promising early antidepressant effects but also the high rates of treatment adherence, potentiated by comprehensive training and remote supervision (37). Such findings further drive our recommendation of tDCS as an alternative treatment for patients who cannot or do not wish to take medication (e.g., pregnant women) (30), broadening treatment decisions while increasing patients' self-management of their mental health.

To support patients in the management of their own treatment and adverse effects, a thorough informational stage concerning what is expected during treatment is needed. This stage offers patients the perception of control and adds to their perception of self-efficacy managing their mental health. Additionally, a close access by the patient to the health professional is critical. In the current case series, we describe a set of case studies where patients were instructed to reach out to their health professional by WhatsApp (text or phone call) at any time during the first week in case of adverse effects or to answer any question concerning the treatment. From there, patients were able to discuss side effects and worries during the weekly sessions. Of interest, our experience shows that although available, most patients do not request daily support to manage treatment delivery nor side effects in the first week. However, from their feedback, patients feel well-supported with this option as well as welcome open discussions about their experience during the weekly sessions.

This case series offers a report of real-context dual active treatments that include home-based tDCS. This study has several limitations worth considering. It lacks strategies to control bias and follow-up assessments were not available for all patients, compromising a better overview of the long-term impact of the treatment. Additionally, most patients have a high-education level and possibly a high cognitive reserve and learning capacity, which might be positive bias to the effects of the dual active treatment. Patients also presented heterogeneous symptoms and treatment protocols (i.e., variable concomitant adjunct pharmacotherapy and psychotherapy). Clinical outcomes were based on self-reported measures, which in a clinical sample with cognitive deficit/biases warrants consideration. Finally, difference in the mode of tDCS administration may be an additional source of variability. Further randomized trials using home-based tDCS are needed to establish its efficacy as a stand-alone or part of dual active treatments.

Patient perspective

Patients' perspectives collected through an anonymous online survey showed that both the Flow Depression App, tDCS sessions, and weekly appointments with the clinician assisted in symptom reduction. The most positive aspects of treatment were the almost immediate effects felt and maintained across time; the equipment portability and ease of use; and the app providing tools for everyday life challenges. One patient highlighted that the combination of different treatment strategies has led to an optimized result. Tingling sensation and discomfort during stimulation were the only negative experiences reported in this survey. However, only 3 of the 7 patients replied to the survey, which may reflect a positive bias and absence of negative feedback in the patient's perspective. Considering the reduced/absent therapeutic response in some of the cases and the adverse side effects experienced, we cannot discount the existence of unreported negative experiences in the case series. For example, in patient 1, the acceptability of tDCS reduced from week 1 to week 6, while for others there is a positive slope on treatment acceptability across the treatment protocol (cf. Supplementary Table 2).

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MS, RG, VM, and AG-Á: conceptualization, formal analysis, investigation, and writing-original draft preparation. MS, RG, and AG-Á: methodology. MS and AG-Á: validation. RG, VM, and AG-Á: writing-review and editing. MS: visualization. AG-Á: supervision. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

Author(s) MS and VM were employed by Neuroncircuit. AG-A had non-financial support from Soterix and commercial interests with Flow Neuroscience tDCS equipment during the study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.947435/full#supplementary-material

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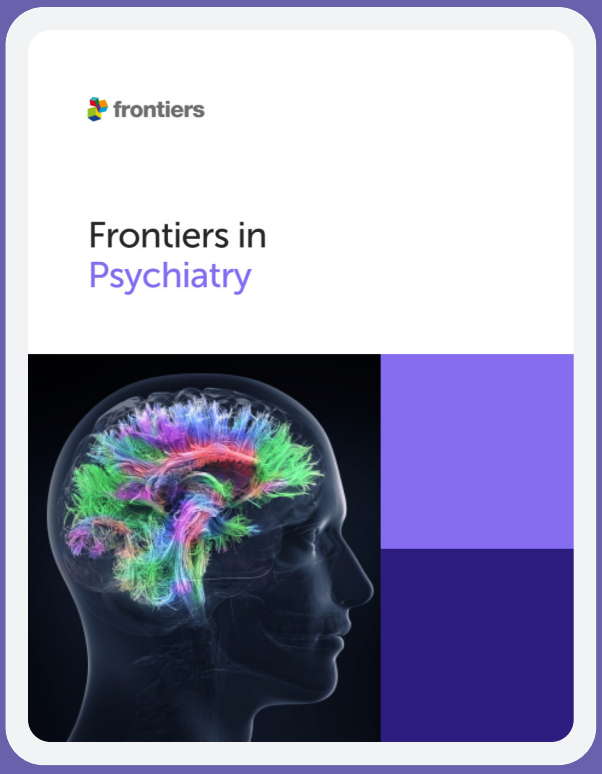

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