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Contents

Monthly Volume 13 Number 9 September 19, 2023

MINIREVIEWS

ORIGINAL ARTICLE

Basic Study

Retrospective Study

Observational Study

Randomized Controlled Trial

World Journal of Psychiatry

Monthly Volume 13 Number 9 September 19, 2023

Contents

ABOUT COVER

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MINIREVIEWS

Past, present, and future of deep transcranial magnetic stimulation: A review in psychiatric and neurological disorders

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Abstract

Deep transcranial magnetic stimulation (DTMS) is a new non-invasive neuromodulation technique based on repetitive transcranial magnetic stimulation technology. The new H-coil has significant advantages in the treatment and mechanism research of psychiatric and neurological disorders. This is due to its deep stimulation site and wide range of action. This paper reviews the clinical progress of DTMS in psychiatric and neurological disorders such as Parkinson's disease, Alzheimer's disease, post-stroke motor dysfunction, aphasia, and other neurological disorders, as well as anxiety, depression, and schizophrenia.

Key Words: Deep transcranial magnetic stimulation; Neurological disorders; Psychiatric disorders; Minireview

Core Tip: Deep transcranial magnetic stimulation as a novel non-invasive neuromodulation technique has been reported to be applied in clinical psychiatric and neurological disorders. The potential clinical efficacy and safety of this technique in each disorder and the mechanisms behind them need to be further summarized and sorted out, and the direction of future development needs to be more clearly defined.

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INTRODUCTION

Transcranial magnetic stimulation (TMS) is a magnetic stimulation technique that acts on the cerebral cortex, using electromagnetic principles to deliver an electric field to the cerebral cortex to alter the action potential of cortical nerve cells, thereby regulating metabolism and neural activity in the brain[1]. Repetitive transcranial magnetic stimulation (rTMS) is another form of TMS, which modulates cortical excitability. At high frequencies (> 5 Hz), cortical excitability increases, whereas at low frequencies (1 Hz), a long-term depression effect is produced and cortical excitability decreases [2]. TMS has been widely used to treat several neurological and psychiatric disorders, such as Parkinson's disease (PD), post-stroke limb movement disorders, and depression, with few adverse events. However, conventional TMS has some limitations[3,4], such as limited and imprecise localization of the stimulation site, which has led to the development of deep TMS (DTMS).

DTMS has the advantages of deeper and wider stimulation, more precise localization, and less damage to the superficial cortex than conventional TMS[5,6]. The depth of stimulation can be controlled by adjusting the intensity of the stimulation or the distance between the skull and the coil element. In recent years, this technique has been used to study and treat a variety of neuropsychiatric and psychiatric disorders and has been approved by the Food and Drug Administration (FDA) for the treatment of refractory depression. There has been an increase in national and international research on the use of DTMS in neurological and psychiatric disorders, but there has not been a systematic review of DTMS in the treatment of neurological and psychiatric disorders to evaluate its specific efficacy. This article presents a comprehensive review of the current state of research on DTMS in neurological disorders, such as PD and AD, and psychiatric disorders, such as schizophrenia (SZ) and depression, to provide a reference for future studies.

DTMS IN PSYCHIATRIC DISORDERS

Treatment-resistant depressive

Major depressive disorder (MDD) is one of the most common and disabling psychiatric disorders, with a prevalence of 5%-15% in the general population[7]. Approximately 30% of patients with MDD who do not respond to two or more trials of first-line antidepressants are considered to have treatment-resistant depression (TRD)[8]. TRD is a debilitating chronic mental illness that is associated with increased morbidity and mortality, reduced quality of life, impaired occupational, social, and offspring development, and increased costs on the healthcare system[9]. Currently, depression is mainly treated with medication, but antidepressants tend to be slow-acting and some of the active ingredients in depressants, such as neuropeptides, can be affected by the blood-brain barrier and cause some adverse effects[10].

Studies have shown that an active state of the left dorsolateral prefrontal cortex (PFC) is associated with depressed mood, and improvement of activity levels in the PFC may reduce depressive symptoms. Although TMS is effective in treating depression after stimulation of the dorsolateral PFC[11], there are limitations to this technique, such as the inability to produce some effect in areas such as deeper cortical and limbic areas, where deeper stimulation may be useful. DTMS is an effective new therapy and the FAD has approved the use of DTMS with H1 coils for the treatment of major depression[12]. So far, great results have been achieved with DTMS in the treatment of TRD. The development of DTMS applied to TRD is shown in Table 1.

Levkovitz *et al*[13] conducted a study to examine the impact of high frequency (20 Hz) repeat DTMS on the PFC in 65 patients with non-medicated depression. The researchers discovered that the use of high stimulus intensity resulted in significant improvements in both Hamilton depression rating scale (HDRS) scores and cognitive performance. Notably, no serious adverse events related to the treatment were observed. This study represents a pioneering exploration of the potential of DTMS in addressing psychiatric and neurological disorders[14]. Levkovitz *et al*[15] conducted a pioneering double-blind controlled randomized multicentre study aimed at validating the safety and efficacy of DTMS for the treatment of MDD. The study enrolled a total of 212 outpatients with MDD who had previously experienced treatment failure with antidepressants. The findings revealed a significant improvement in the HDRS-21 score, with a mean increase of 6.39 points in the DTMS group compared to only 3.28 points in the sham control group. Furthermore, the group that underwent DTMS stimulation demonstrated significantly higher rates of response and remission in comparison to the group that received sham stimulation. Moreover, the therapeutic impact of DTMS persisted throughout the 16-wk maintenance phase, proving to be advantageous for patients who had previously shown no response to alternative treatments[15]. The study findings revealed a remission rate of 60% [95% confidence interval (95%CI): 48%-71%] in the DTMS group, whereas the remission rate for rTMS with conventional figure-of-eight coils was 43% (95%CI: 31%-55%) (Table 1)[16-22]. In a meta-analysis conducted in 2019, it was observed that the DTMS group exhibited a response rate of 47.8%, whereas the sham group demonstrated a response rate of 25.6%. Additionally, the remission rate in the DTMS group was found to be 36.6%, while the sham group exhibited a remission rate of 14.8%. The criteria for response were defined as a 50% or greater improvement from baseline, as determined by the primary depression scale used in the study.

Table 1 Development of deep transcranial magnetic stimulation in treatment-resistant depression

Ref.	Method	Result	Adverse events	Significance
Levkovitz *et al*[13], 2009	20 Hz DTMS stimulates FPC	Significant improvement in HDRS scores	Headaches	This is the first time that TRD has been treated with the new H-coil
McGirr *et al* [14], 2014	20 Hz stimulates DLFPC	Reduction in HAMD-21 scores	Unreported	Five-factor personality assessment may have prognostic value in DTMS for resistant MDD
Levkovitz *et al*[15], 2015	20 Hz DTMS stimulates PFC	HDRS-21 score was improved by 6.39 points	Unreported	It is efficacious and safe in patients not responding to antidepressant medications, and the effect remains stable
Feffer *et al* [16], 2017	18 HZ DTMS stimulation; right abductor pollicis brevis muscle	Depressive symptoms (HDRS-21 total score) decreased significantly	Headaches	The severity of the depressive episode is associated with a positive therapeutic effect of dTMS
Kaster *et al* [17], 2018	18 HZ DTMS stimulates DLPFC and VLPFC	Remission rate was significantly higher with active than sham rTMS (40.0% *vs* 14.8%)	Pain and discomfort from stimulus	High-dose DTMS appears to be safe, well tolerated, and efficacious in the treatment of LLD
Tendler *et al* [18], 2018	10 HZ DTMS combined with SSRIs	The remission rate was 35.3%	Headaches	DTMS can augment formerly ineffective SSRI treatment
Filipčić *et al* [19], 2019	18 HZ DTMS stimulates LDLPFC	The response was significantly better in H1-coil than in 8-coil group (OR = 2.33; 95%CI: 1.04-5.21; P = 0.040)	Unreported	DTMS had better response rate than rTMS
Matsuda *et al* [20], 2020	18 Hz DTMS stimulates LDLPFC	HDRS-21 was more significantly improved	Unreported	DTMS might be effective and safe for office workers with treatment-resistant depression
Bahun *et al* [21], 2022	18 Hz stimulates DLFPC	Cognitive function all showed mild to moderate improvement	Unreported	Can improve MDD symptoms

DLFPC: Dorsolateral prefrontal cortex; HDRS-21: Hamilton Depression Rating Scale-21; DTMS: Deep transcranial magnetic stimulation; HAMD-21: 21-item Hamilton Depression Rating Scale; VLPFC: Ventrolateral prefrontal cortex; MDD: Major depressive disorder.

Remission, on the other hand, was defined as a HDRS-17 score of 7 or less, or a HDRS-24 score of 10 or less. Based on these findings, it can be concluded that DTMS is a safe and effective intervention for patients suffering from TRD. Studies combining DTMS and antidepressant medications seemed to show greater therapeutic effects[23].

From the above studies, it is clear that DTMS is an effective treatment for MDD and is well tolerated by patients without major adverse events, and may be a good option for patients who are antidepressant-resistant or ineffective.

Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is a common and disabling psychiatric disorder characterised by the presence of intrusive thoughts and repetitive behaviors[24], with a lifetime prevalence of 2% to 23%[25]. It is characterised by early onset, which places a heavy burden on patients and their families. Currently, only 40% to 60% of patients can improve certain symptoms with treatment[26]. Studies have shown that the cortico-striatal-thalamic-cortical circuit is dysfunctional in patients with OCD[27], including the orbitofrontal cortex, anterior cingulate cortex (ACC), cingulate cortex, and ventral striatum[28]. A meta-analysis published in 2023 suggested that the average treatment response rate (percentage reduction in total Y-BOCS score) across studies was 39.5% for rTMS and 8.8% for sham conditions. rTMS showed a moderate therapeutic effect (g = 0.65) on OCD symptom severity and a threefold increased likelihood of treatment response (relative risk = 3.15) compared with sham conditions. Greater improvements in comorbid depression severity were associated with greater treatment effects of rTMS on OCD symptom severity. In addition, longer rTMS sessions and fewer total sessions predicted greater clinical improvement[29].

The development of DTMS applied to OCD is shown in Table 2. DTMS was first applied in 2015, when Modirrousta *et al*[30] found that 1-Hz frequency DTMS applied to Brodmann areas 24 and 32 improved OCD symptoms and Yale-Brown-Obsessive-Compulsive Scale (Y-BOCS) scores. In 2018, Carmi *et al*[27] noted a significant increase in Y-BOCS scores with high-frequency (20 Hz) deep magnetic stimulation and the ability to safely and effectively reduce OCD symptoms. They then conducted a prospective multicentre, randomized, double-blind, placebo-controlled trial[31], the results of which showed that patients treated with DTMS had a more significant reduction in OCD symptom scale scores, with an efficacy rate of 38.1%. At the 1-mo follow-up, the efficacy rate increased in both the treatment and sham-stimulation groups, to 45.2% in the treatment group and 17.8% in the sham-stimulation group. In 2018, the United States FDA approved DTMS with the "H7 coil" for the treatment of OCD, potentially for patients for whom medication and psychological interventions have not been effective. Based on previous studies, the response of patients with OCD to DTMS treatment was determined by whether the total score on the Y-BOCS decreased by 30% or more from baseline[32]. We summarised the available studies and found that the remission rate of OCD treated with DTMS was 29.22%-53.90% [31,33,34].

Table 2 Development of deep transcranial magnetic stimulation in obsessive-compulsive disorder

Ref.	Method	Result	Adverse events	Significance
Modirrousta *et al* [30], 2015	1 Hz DTMS stimulates PFC	Improvement in Y-BOCS	Electric shocking sensation	Low frequency deep rTMS was effective in OCD symptom reduction
Carmi *et al*[27], 2018	20 Hz or 1 Hz DTMS stimulates mPFC and ACC	Improvement in Y-BOCS	Slight headache	DTMS has the ability to directly modify ACC activity
Carmi *et al*[31], 2019	20 Hz DTMS stimulates mPFC and ACC	Improvement in Y-BOCS	Slight headache	High-frequency DTMS in special region can significantly improve OCD symptoms
Ikawa *et al*[33], 2022	20 Hz DTMS stimulates mPFC and ACC	Improvement in Y-BOCS	Slight headache	DTMS treatment of OCD had a favorable therapeutic effect
Ikawa *et al*[33], 2022	20 Hz DTMS stimulates mPFC and ACC	Improvement in Y-BOCS	Electric shocking sensation	DTMS was found to be a safe and effective intervention for OCD symptoms in adolescents

Y-BOCS: Yale-Brown obsessive compulsive scale; mPFC: Medial prefrontal cortex; ACC: Anterior cingulate cortex; DTMS: Deep transcranial magnetic stimulation; PFC: Prefrontal cortex; OCD: Obsessive-compulsive disorder.

Although DTMS is effective in improving OCD symptoms and Y-BOCS scores, the biological basis for the efficacy of DTMS is not yet clear, and more randomised, double-blind, placebo-controlled trials (using dummy coils, at different parameter frequencies) and larger-sample clinical trials are needed to explore this further.

Schizophrenia

SZ, a chronic illness of unknown etiology, is a psychiatric disorder that affects 1% of the world's population[35,36] and may be associated with genetic and environmental risk factors. SZ is often associated with severe impairments in emotions, thinking, and behaviour. A common symptom in people with SZ is hallucinations, which can cause mental debilitation in schizophrenics. Although antipsychotic medications are effective for this symptom, they are still less effective in about 25% of patients. Some studies have shown that hallucinations are associated with increased activity in areas such as the temporal cortex and prefrontal cortex[37], so inhibitory DTMS could be considered to reduce abnormal activity in these areas.

The development of DTMS in SZ is shown in Table 3. DTMS treatment may improve positive symptoms. Rosenberg *et al*[38] conducted an open-label study in which the investigators treated eight patients with SZ diagnosed with persistent hallucinations (hallucinations that had persisted for an average of 11 years) with low-frequency DTMS using an H1 coil, using the Auditory Hallucinations Rating Scale (AHRS) and the Positive Symptom Rating Scale (SAPS) to assess the patients. Five of the patients' AHRS scores decreased by 34.5% and the SAPS score improved by 23.1%. Three patients were subsequently treated with 20 sessions of DTMS, resulting in a 27.8% improvement in AHRS and a 13.75% improvement in SAPS at the end of treatment, and these improvements were maintained over the subsequent 1-mo follow-up period[38]. They then conducted a double-blind study in 2012, in which a total of ten patients completed the treatment and both groups showed an increase in phantom hearing scores, but the difference between the treatment and sham stimulation groups was not statistically significant on either scale[39]. Negative symptoms and cognitive deficits are central to SZ, but current treatments for this condition are underdeveloped. Levkovitz *et al*[40] used DTMS to stimulate the prefrontal cortex of 15 patients with SZ in 2011, and the results obtained 2 wk after treatment showed improvements in both negative symptoms and cognitive function. Some previous studies have suggested that the temporal and parietal cortices are central parts of the language system, that verbal hallucinations may be related to abnormal activity in these regions, and that it may be possible to reduce the hallucination symptoms by suppressing pathological hyperactivity in this region through the use of low-frequency magnetic stimulation[41], but more in-depth studies are needed in the future. In patients with SZ, negative symptoms are often associated with social dysfunction, so it is important to improve negative symptom-based treatment. In 2022, a study of bilateral DTMS of the insula and prefrontal cortex using special H4 coils demonstrated the therapeutic effects of DTMS on psychotic symptoms. In functional magnetic resonance imaging (fMRI) analyses, resting-state connectivity between the insula and the default mode network showed a numerically greater change from baseline in the active DTMS group than in the sham group, consistent with a functional change in insular circuitry[42-44].

Although the current findings on the treatment of negative symptoms with DTMS have shown to be effective, the sample size of the studies is small, and more clinical studies are needed to confirm this in the future. DTMS was also compared to other brain stimulation techniques such as electroconvulsive therapy, transcranial direct current stimulation, vagus nerve stimulation, or standard TMS.

Substance use disorders

Substance use disorders (SUDs) are a group of disorders in which brain damage is caused by chronic use of alcohol and drugs. Substance use disorders are currently difficult to treat, medications are less effective, and the disease has a high relapse rate of 40%-60%[45]. Non-invasive brain stimulation can affect neuroplasticity in the cerebral cortex and throughout the brain, potentially reducing and controlling the compulsive craving for psychoactive substances by rewiring the brain's nerves[46]. Different substance use disorders are affected by similar neural circuits, and because the

Table 3 Development of deep transcranial magnetic stimulation in Schizophrenia

Ref.	Method	Result	Adverse events	Significance
Birdi *et al*[36], 2023	1 Hz DTMS stimulates LTPC	Significant improvement in AHRS score	Transient headache	DTMS treatment was effective for chronic auditory hallucinations in schizophrenic patients
Rosenberg *et al* [38], 2011	20 Hz DTMS stimulates PFC	Cognition and negative symptoms are improved	Transient headache and fatigue	DTMS can improve negative symptoms and cognitive deficits for schizophrenia patients
Rosenberg *et al* [38], 2011	1 Hz DTMS stimulates LTPC	Significant improvement in AHRS score	Mild and self-limiting headaches	DTMS had no significant effect on auditory hallucinations
Rabany *et al*[43], 2014	20 Hz DTMS stimulates PFC	SANS was significantly reduced	Unreported	DTMS was effective for negative symptoms, but the effect was moderate
Linsambarth *et al*[44], 2019	18 Hz DTMS stimulates bilateral PFC	SANS was significantly reduced	Temporary headaches, scalp aches, and toothaches	DTMS contributed to negative symptoms in schizophrenia
Moeller *et al*[42], 2022	10 HZ DTMS stimulates the insular and prefrontal cortices	The DTMS group had a more pronounced decrease in insula blood flow than the sham operation group	Unreported	DTMS in smoking patients with schizophrenia was effective

AHRS: Auditory Hallucinations Rating Scale; DTMS: Deep transcranial magnetic stimulation; PFC: Prefrontal cortex; SANS: Scale for the Assessment of Negative Symptoms; TPC: Temporoparietal cortex.

use of H-coils can alter the electrical field activity in deep subcortical brain regions, DTMS may be recommended for the treatment of different SUDs.

The evolution of DTMS applied to SUDs is shown in Table 4. Harel *et al*[47] intervened in patients with alcohol use disorders using high-frequency (10 Hz) DTMS and showed that the results were similar to sham. The results showed that the DTMS group had significantly lower levels of alcohol craving and relapse rates of alcohol use disorders compared to the sham-stimulation treatment group. In addition, resting-state network connectivity between the ACC and medial frontal cortex was reduced in the DTMS group during the 3 wk of treatment, and this altered connectivity may be related to substance-induced craving and relapse[47]. Dinur-Klein *et al*[48] evaluated the effects of bilateral prefrontal and insula cortical stimulation using DTMS in patients with nicotine use disorder. The investigators recruited 115 patients with nicotine use disorder (for whom prior treatment had been ineffective), randomizing patients to high-frequency and sham stimulation groups, and showed that high-frequency DTMS treatment significantly reduced patients' nicotine dependence, resulting in a 44% abstinence rate at the end of treatment and a 33% abstinence rate at the 6-mo follow-up, in contrast to the low-frequency DTMS (1 Hz) group, which was less effective[48-50].

In summary, it is clear from the few available studies that high-frequency DTMS may be effective in the acute phase of treatment for some SUD symptoms.

APPLICATION OF DTMS IN NEUROLOGICAL DISEASES

Alzheimer's disease

Alzheimer's disease (AD) is a common and persistent neurological disorder whose prevalence is increasing with the world's aging population. The pathological mechanism of AD may be the structural changes in the brain, abnormal protein deposition, and loss of cholinergic neurotransmission[51]. The functional networks closely related to memory in the brain of AD patients show large-scale disruptions and their plasticity is impaired, as confirmed by neurophysiological and fMRI studies[52]. Currently, there are several disease-modifying therapies such as monoclonal antibodies developed [53]. However, these therapies are specific to early AD stages and amyloid-related imaging abnormalities[54], and there is no effective treatment for AD patients[55]. Gamma oscillations function in information processing by modulating neuronal and glial cell responses to ameliorate AD[56], and pathological increases in gamma band power may be due to the disruption of GABAergic interneuronal networks, resulting in an imbalance between excitation and inhibition in the central nervous system[57]. Brain modulation techniques such as TMS can regulate this unbalanced state of excitation. Recently, brain stimulation to improve cognitive function has received much attention. Chang *et al*[58] first introduced TMS to the motor cortex, and it has now been suggested to be useful in improving cognitive function in AD patients, and the basic principle is that rTMS induces long-term potentiation to enable patients to have enhanced neuronal signaling and increased synaptic plasticity. High-frequency rTMS applied to the dorsolateral prefrontal cortex[59-61] or multiple brain regions[62,63] improves cognition in randomised controlled trials (RCTs) in AD, while functional performance and mood are unaffected[64]. DTMS is still in the early stages of investigation for the treatment of patients with AD.

The evolution of DTMS applied to AD is shown in Table 5. In 2016, Avirame *et al*[65] first applied DTMS to patients with moderate to severe AD, where the researchers used H2 coils to administer 20 DTMS sessions to the PFC of 11 patients with moderate to severe AD, and found that cognitive function improved in 60% to 77% of patients after

Table 4 Development of deep transcranial magnetic stimulation in substance use disorders

Ref.	Method	Result	Adverse events	Significance
Girardi *et al* [49], 2015	20 Hz DTMS stimulates DLFPC	Craving scores dropped significantly	Unreported	DTMS was well tolerated and found to be effective in AUD
Harel *et al* [50], 2022	10 Hz DTMS stimulates mPFC and ACC	A lower percentage of heavy drinking days	Moderate to severe headaches	DTMS was a safe and well-tolerated intervention, with promising initial evidence for efficacy in alcohol addiction

DLFPC: Dorsolateral prefrontal cortex; DTMS: Deep transcranial magnetic stimulation; SUD: Substance use disorders; mPFC: Medial prefrontal; ACC: Anterior cingulate cortices; AUD: Alcohol use disorder.

Table 5 Development of deep transcranial magnetic stimulation in Alzheimer's disease

Ref.	Method	Result	Adverse events	Study design	Significance
Avirame *et al* [65], 2016	10 Hz DTMS for PF stimulation	60%-70% of AD patients' cognitive function was improved	Light headache and occasional tiredness	Case series study	DTMS led to preservation and even improvement of cognitive functions
Leocani *et al* [66], 2020	10 Hz DTMS	ADAS-cog at 4 and 8 wk compared with baseline was improved	Temporary headaches	Double-blind, placebo-controlled pilot study	DTMS was feasible and safe in patients with probable AD

ADAS-cog: Alzheimer's disease assessment scale-cognitive; AD: Alzheimer's disease; DTMS: Deep transcranial magnetic stimulation; PF: Bilateral prefrontal regions.

treatment[65]. A randomized double-blind placebo-controlled trial by Leocani *et al*[66] showed that the DTMS group showed an improvement in AD Assessment Scale-Cognitive (ADAS-cog) scores compared with the sham-stimulation group at weeks 4 and 8 compared with baseline, but this effect diminished after 2 mo of treatment, suggesting that DTMS is effective in AD patients in a short period. However, most of the subjects included in the above two studies were patients with moderate to severe AD for whom DTMS was ineffective in improving cognitive function, and this may be related to the reduced neuroplasticity of the brain in patients with advanced AD. Patients with early AD respond better to DTMS.

Although DTMS is effective in improving cognitive function in AD patients, we need to further validate the efficacy of DTMS combined with cognitive training in early AD patients and conduct more relevant large-scale multicenter RCTs.

Aphasia

Approximately 1/3 of stroke patients are diagnosed with aphasia[67]. Aphasia is an acquired language disorder that has phonological, morphological, semantic, and syntactic deficits that negatively affect patients' functioning, emotions, quality of life, and social participation. Language deficits after stroke aphasia are heterogeneous, and each subtype of aphasia is associated with damage to specific cortical areas, with some extension to subcortical areas[68,69]. Studies have shown that TMS can significantly improve language outcomes in patients with aphasia[70]. H-coil stimulation of a large number of neural networks involved in language function may be more effective than conventional focal coils because of the extensive and non-selective stimulation of language areas in the brain, where aphasia is often due to damage to areas involved in language function[71].

The development of DTMS applied to aphasia is shown in Table 6. First, Spagnolo *et al*[72] utilized repetitive DTMS on a patient diagnosed with progressive supranuclear paralysis accompanied by aphasia. The patient exhibited enhancements across all cognitive domains, particularly in language function. Furthermore, 18-FDG-PET scans revealed notable clinical, neuropsychological, and metabolic improvements when compared to the pre-treatment phase. These findings suggest that DTMS elicits excitation in pertinent functional circuits beyond the intended area of stimulation. Moreover, the observed improvements endured for a minimum of 1 mo post-stimulation, as confirmed through telephone follow-up. In the same year, Trebbastoni *et al*[73] treated a patient with primary progressive aphasia with high-frequency DTMS in the left dorsolateral PFC and showed that the patient also showed transient but significant improvements in verbal fluency and writing ability. Chieffo *et al*[71] suggested that high-frequency DTMS can significantly improve naming ability in patients with chronic post-stroke aphasia.

Although the sample sizes of all the above studies are small and subject to some error, they provide new insights into the use of DTMS in aphasia.

Post-stroke motor dysfunction

Limb motor dysfunction is one of the most common sequelae after stroke. rTMS has been studied to improve motor dysfunction in stroke patients, but the results are somewhat mixed. Some scholars have suggested that an interhemispheric competition model is a basis for rTMS to promote motor recovery after stroke, in which the healthy hemisphere inhibits the diseased hemisphere, resulting in reduced dominance of the hemiplegic limb[74]. In recent years, some of the

Table 6 Development of deep transcranial magnetic stimulation in aphasia

Ref.	Method	Result	Adverse events	Significance
Spagnolo *et al*[72], 2013	10 Hz DTMS stimulates Broca's area and DLPFC	Improvement of language function	Unreported	This observation opens new possibilities for treatment of drug-unresponsive neurodegenerative disorders
Trebbastoni *et al*[73], 2013	hf-rTMS stimulates DLPFC	Improved language in LPPA	Unreported	DTMS improved the linguistic skills
Chieffo *et al*[71], 2014	10 Hz DTMS stimulates Broca's area	Significant improvement in the naming power	Unreported	Deep brain rTMS improved naming in right-handed chronic poststroke aphasic patients

LPPA: Primary progressive aphasia logopenic variant; DLPFC: Dorsolateral prefrontal cortex; DTMS: Deep transcranial magnetic stimulation; hf-rTMS: High frequency-repetitive transcranial magnetic stimulation; rTMS: Repetitive transcranial magnetic stimulation.

above-mentioned scientists have critically proposed a bimodal balance-recovery model, suggesting that the residual structural reserve of the corticospinal tract on the affected side also influences both the hemispheric balance and the degree of functional recovery. Diffusion tensor imaging studies have shown that the integrity of nerve fiber connections between primary and secondary motor areas is positively correlated with recovery of motor function after stroke[75]. DTMS helps to improve motor dysfunction after a stroke.

The development of DTMS applied to post-stroke motor dysfunction is shown in Table 7. Chieffo *et al*[76] applied DTMS to patients with lower limb motor dysfunction after chronic stroke, showing improved lower limb function in patients receiving treatment, and high-frequency DTMS has long-term effects on lower limb motor function in patients with chronic stroke. In 2018, this team again applied DTMS to the rehabilitation of upper limb motor dysfunction after chronic stroke and found that the recovery of upper limb function in patients treated with DTMS combined with exercise training was significantly better than that in patients treated with exercise training combined with sham stimulation, and this effect was more pronounced in patients with severe upper limb motor dysfunction, without serious adverse effects [77].

DTMS is effective in restoring motor function in the limbs after stroke, but the exact mechanism of action remains to be explored. Does DTMS somehow improve the language of patients with aphasia? At this time, we have not found any studies to provide a reference. Existing studies show clinically beneficial effects of TMS with or without combined speech and language therapy on overall language function and expressive language (including naming, repetition, writing, and comprehension) in patients with post-stroke aphasia[70]. In the assessment of aphasia and why not in aphasia therapy, spontaneous and semi-spontaneous speech analysis may be useful[78]. We recommend that future DTMS research on aphasia could be more involved in this gap area.

PD

PD is the second most common neurodegenerative disease in the world, and patients most commonly suffer from abnormal motor symptoms due to the loss of dopaminergic neurons in the substantia nigra[79]. The gold standard treatment for PD is oral levodopa, but the long-term efficacy of levodopa is mostly not maintained[80]. Some reports suggest that the excitability of cortical-mediated pathways may be altered in PD patients, resulting in dyskinesia[81]. Several studies have shown that stimulation of the motor cortex with high-frequency rTMS can improve dyskinesia in PD patients and that the effects can be sustained for a longer period of time[82]. However, some studies suggest that cortical inhibition is impaired in PD patients[83] and perhaps low-frequency stimulation may be more beneficial for PD patients, whereas DTMS is used to act on a wider range of cortical and deeper brain areas.

The development of DTMS applied to PD is shown in Table 8. In 2013, by treating 27 PD patients with movement and high-frequency rDTMS to the prefrontal cortex, Spagnolo *et al*[84] found that the Unified PD Scale (UPDRS) score of PD patients improved significantly after treatment compared to before treatment. Spagnolo *et al*[85] conducted a randomized, sham-controlled trial to evaluate whether high-frequency TMS with an H5 coil is safe and effective for PD patients, and the results showed that patients who received rTMS (M1-PFC and M1 combination) had better results in tremor and hemilateral scores than those in the sham stimulation group. There was no significant difference in safety and efficacy between the two groups, suggesting that gh-frequency rTMS with the H-coil is a safe and effective intervention. It has been suggested that high-frequency rTMS acting on the M1 or PFC may, on the one hand, induce the release of endogenous dopamine in the ipsilateral dorsal striatum[86]. On the other hand, it may promote the production of dopaminergic neurons[87-90].

Studies today have shown that PD patients tolerate DTMS well and no serious adverse effects have been reported in these patients, but there are still some side effects such as transient headache, dizziness, and involuntary movements. However, DTMS can be used to improve the symptoms of dyskinesia in PD patients, and high-frequency stimulation may be more effective than low-frequency stimulation. In the future, RCTs with larger sample sizes and long-term follow-up are needed to determine the optimal treatment parameters and duration of the effect of DTMS.

Table 7 Development of deep transcranial magnetic stimulation in post-stroke motor dysfunction

Ref.	Method	Result	Adverse events	Significance
Chieffo *et al* [76], 2014	20 Hz DTMS	Significant improvement in lower limb motor function	Unreported	DTMS could induce improvements in lower limb functions in the chronic post-stroke period
Chieffo *et al* [77], 2018	20 Hz DTMS	Upper limb motor function improved significantly	Transitory dizziness, toothache, and muscle twitches	DTMS combined with exercise training is more effective (upper limb motor function)

DTMS: Deep transcranial magnetic stimulation.

Table 8 Development of deep transcranial magnetic stimulation in Parkinson's disease

Ref.	Method	Result	Adverse events	Significance
Spagnolo *et al* [84], 2014	10 Hz DTMS for PF stimulation	UPDRS was improved	Slight and transitory hypotension and headache	DTMS might be a safe treatment for PD motor symptoms
Cohen *et al*[87], 2018	M1 + PFC or M1	M1 + PFC OR M1 group was improved in T-UPDRS and M-UPDRS	Mild and transient head discomfort, transient fatigue, and rare mild visual transient hallucinations during stimulation	DTMS improved PD motor symptoms but the effect was moderate
Torres *et al*[80], 2015	M1 + PFC	UPDRS was improved	Sleepiness, headaches, and nausea	DTMS improved motor, postural, and motivational symptoms of PD patients
Cohen *et al*[88], 2016	1 Hz DTMS M1 and 10 Hz DTMS PFC	UPDRS was improved	Headache, dizziness, pain in the head or neck during treatment; nausea, general weakness, and transient aggravation of gait disturbance	DTMS improved motor, but no advantage compared to sham treatment
Spagnolo *et al* [85], 2020	M1 + PFC or M1	UPDRS was improved	Mild, not-distressing, and transient dyskinesias	DTMS was a safe and potentially effective procedure
Cohen *et al*[87], 2018	1 Hz M1 or 10 Hz PFC	UPDRS was improved	Headache, nausea, and discomfort of the eye region or tearing of the eyes during stimulation	DTMS can decrease the subjective motor symptom severity and depression

PF: Bilateral prefrontal regions; M1 + PFC: Sequential stimulation of low frequency over the primary motor cortex and then high frequency over the prefrontal cortex; M1: Low-frequency stimulation over the primary motor cortex alone; UPDRS: Unified Parkinson's Disease Rating Scale; M-UPDRS: Motor UPDRS; T-UPDRS: Total UPDRS; DTMS: Deep transcranial magnetic stimulation; PFC: Prefrontal cortex; PD: Parkinson's disease.

DISCUSSION

The results of our review suggest that the DTMS technique is safe and effective when applied to various neurological and psychiatric disorders, with no serious adverse effects identified other than transient headache and fatigue. However, the biology of the efficacy of DTMS is not yet clear, so its efficacy is mostly assessed by psychometric scales such as the UPDRS and HDRS-24[13], and biological indicators are lacking. A comparison of DTMS with other brain stimulation techniques[90] such as magnetic shock therapy, electroconvulsive therapy[91], transcranial direct current stimulation, vagus nerve stimulation, or deep brain stimulation would provide better clinical evidence for patients.

The advantage of DTMS over conventional TMS is that the H-coil can stimulate deeper areas of the brain without increasing the intensity of the stimulation[92], thus ensuring the continuous stimulating effect of DTMS. There are currently more than 20 H-coils available, of which the H1/H2 coil is FDA cleared for bilateral PFC stimulation. DTMS can stimulate deeper and wider areas of the brain and modulate neurological function through the H-coil, which is effective and safe in the treatment of PD, AD, SZ, and depression. Based on the above tables, it can be seen that DTMS is currently most commonly used in PD, OCD, and depression, with high levels of patient acceptance and efficacy. Some of the other neurological and psychiatric disorders treated with DTMS are still in the early stages of research, and although some have shown significant efficacy, more research is needed to validate them in the future. It is believed that with the continued optimization of the DTMS coil device and further understanding of the etiology of neurological and psychiatric disorders, as well as the resolution of some ethical and legal issues related to these disorders, the use of DTMS with different coils and parameters for different disorders can be explored in the future, thus creating a standardized treatment plan for patients with different disorders, which will facilitate the treatment of patients who have failed or cannot take medication for a long time. This will facilitate the use of DTMS for patients who have been on medication for a long time or are unable to take medication.

CONCLUSION

A large number of studies have shown that DTMS technology is generally safe and tolerable, with mild side effects, and can be used to rehabilitate mental and nervous system disorders. DTMS regulates neural function by directly stimulating deeper and wider brain regions, and currently the evidence for DTMS in the treatment of depression and OCD should be strong. However, for other neurological disorders (particularly neurodegenerative disorders), there are very preliminary results and small sample sizes. RCTs with larger sample sizes should be warranted.

However, DTMS research is still in the exploratory stage, and several issues need to be addressed and determined: (1) Consistency of efficacy: Although some studies have shown that DTMS is effective in certain diseases, the results of these studies are variable and the effects are unpredictable. Further studies are needed to determine the consistency of efficacy and to identify patients who are best suited for this treatment modality; (2) Long-term safety and side effects: The long-term safety and potential side effects of DTMS are not fully understood, and although some studies have shown that the technique is relatively safe and well tolerated in the short term, the potential for adverse effects and potential risks associated with long-term use needs to be further evaluated; (3) Determining optimal stimulation parameters: DTMS involves the selection of stimulation site, stimulation frequency, stimulation intensity, and other parameters; it is unclear which stimulation parameters are most effective, and further research is needed to determine the optimal stimulation parameters and to ensure their consistency and reproducibility in clinical applications; (4) Disease-specific mechanism of action: The mechanism of action of DTMS on various diseases is not fully understood. A deeper understanding of its mechanism of action may help us to better understand and optimize its clinical application; and (5) Development of individualized therapeutic strategies: Since each patient's situation is unique, there is a need to develop methods for individualized therapeutic strategies that can better guide treatment and improve treatment efficacy by combining information from brain imaging technology and biomarkers. Addressing and identifying these issues will advance the use of DTMS in clinical practice and provide more effective options for the treatment of psychiatric and neurological disorders.

FOOTNOTES

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