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Recent Advances In Transcranial Magnetic Stimulation (TMS) for Mental Health Disorders: A Narrative Review

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ABSTRACT

Since its development in 1985, repetitive Transcranial Magnetic Stimulation (rTMS) has evolved from a novel neuromodulation technique to an FDA-approved treatment for several psychiatric conditions. The paper explains the basic principles of TMS, including its mechanism of action, stimulation parameters, and targeting methods. It details the FDA-approved protocols for three primary indications: major depressive disorder (MDD), obsessive-compulsive disorder (OCD), and smoking cessation. For MDD, multiple protocols targeting the left dorsolateral prefrontal cortex have shown response rates of 38-49%. In OCD, targeting the dorsomedial prefrontal cortex and anterior cingulate cortex has demonstrated a 45% response rate. For smoking cessation, stimulation of the prefrontal cortex and insula has shown promising results in achieving continuous abstinence. The paper also discusses future trends in TMS research and highlights challenges in implementing this technology in low-and-middle income countries like Nigeria, where barriers include insufficient funding, limited mental health infrastructure, and high treatment costs. It concludes that while rTMS offers promising opportunities for personalized treatment approaches, improved mental health services and policy changes are needed to increase its accessibility.

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INTRODUCTION

Transcranial magnetic stimulation (TMS) was developed by Anthony Barker and his team in 1985. This technique involves the noninvasive delivery of a magnetic field to the human motor cortex, which causes a motor response (1). Their work was inspired by Merton and his team's electrical stimulation of the brain and spinal cord and its effect on Parkinson's disease, multiple sclerosis, and pelvic neuropathy associated with urinary incontinence. Two years later, the possible effects of TMS on mood were incidentally found. Extensive studies verified the effectiveness of TMS as an antidepressant over the next few decades, and with the FDA's 2008 approval of repetitive transcranial magnetic stimulation (rTMS) for the treatment of depression, the modality has become widely used (2). Understanding rTMS is becoming increasingly important as it becomes a standard procedure for treating treatment-resistant depression and its other indications (2).

Currently, diagnoses from the American Diagnostic and Statistical Manual (DSM, 5th edition) or the International Classification of Diseases of the World Health Organization (ICD, 11th edition) are used to classify people with mental disorders. Diagnoses are made based on a collection of visible clinical symptoms for a predetermined time. This categorical ICD/DSM approach has several advantages, including high diagnostic reliability, standardization of the diagnostic procedure, and high practicability for clinicians (3).

Nevertheless, drawbacks include a significant degree of psychopathology variation within diagnostic categories and a limited capacity to uncover additional brain mechanisms underlying clinical complaints. This is believed to hinder the creation of more customized and possibly more effective treatments (3,4). Scientific

research has shown that rTMS is effective for a number of neurological and mental disorders during the past century. This paper aims to elucidate the current applications and use of rTMS in managing mental disorders.

BASIC PRINCIPLES OF TRANSCRANIAL MAGNETIC STIMULATION

Every TMS device has an electromagnetic coil attached to a stimulator. A pulse, or powerful but brief magnetic field, is produced by the stimulator's strong electric current flowing through the coil's windings. TMS can be given in trains, which consist of hundreds or thousands of magnetic pulses delivered in quick succession (rTMS), in pairs (paired-pulse TMS), or one pulse at a time (single-pulse TMS) (2). The main focus of this essay is rTMS, which has the most therapeutic usefulness in Psychiatry.

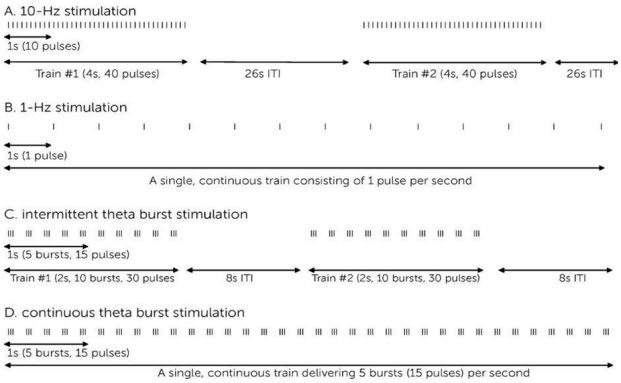
The magnetic field flows freely through the skull and scalp when the electromagnetic coil is positioned at the scalp during TMS. Local neurons get depolarized due to the time-based magnetic field's induction of a low-amplitude electrical current upon reaching the cortex (5). distinct sites have distinct effects: a single TMS pulse to the motor cortex induces a motor response, whereas a single pulse to the visual cortex causes phosphenes. The stimulation properties, such as pulse frequency and duration, influence the total stimulation impact, and can be excitatory or inhibitory (2). In most therapeutic applications, rTMS is given once a day, five days a week, for many weeks.

Stimulation Site

The effects of TMS are dependent on the stimulation site and this varies between various psychiatric conditions. For instance, the left dorsolateral prefrontal cortex (DLPFC) is usually the target in the therapy of depression. In contrast, the dorsomedial prefrontal cortex (DMPFC) and anterior cingulate cortex (ACC) are targeted in the therapy of obsessive-compulsive disorder (2). Target localization research is still being conducted partly because it is thought that errors in target localization contribute to therapeutic nonresponse.

Stimulation Parameters

Examples of stimulation parameters are the number of pulses provided, the frequency of pulse delivery, the number of pulses given in a single train, the intertrain interval (the time between pulse trains), the total delivered pulses, and the stimulation strength. The excitatory or inhibitory nature of the stimulus is determined by its frequency (6). The phrase "high-frequency" refers to frequencies that are more than 5 Hz and are typically excitatory. In contrast, the word "low-frequency" refers to frequencies that are less than 1 Hz and are often inhibitory (7). There are several stimulation patterns to choose from. The most prominent stimulation patterns are intermittent theta burst stimulation (iTBS), continuous theta burst stimulation (cTBS), 10-Hz stimulation, and 1-Hz stimulation (8).



The motor threshold (MT), which represents the patient's unique cortical excitability level, dictates the therapy's extent. On the first day of treatment (and after that as needed), single TMS pulses are applied to the motor cortex to establish the MT, and the contralateral hand's thumb and fingers are watched for movement. When at least 50% of administered pulses produce a discernible motor response, the MT is the lowest stimulation intensity. Next, the percentage of the patient's MT (often 120%) is used to calculate the strength of the therapeutic stimulation (2).

APPLICATION OF RTMS IN MENTAL HEALTH DISORDERS

Currently, the FDA has authorized rTMS for treating three mental disorders: major depressive disorder (MDD), obsessive-compulsive disorder (OCD), and smoking cessation. For each FDA indication, there are one or more authorized protocols that use one or more approved devices (2).

Major Depressive Disorder

MDD is a very common mental illness that significantly reduces functionality and quality of life.

Between 2007 and 2017, the prevalence of MDD rose by over 13% worldwide (9). Major depressive episodes are characterized by core symptoms such as low mood, reduced drive, and loss of interest in previously pleasurable activities. Different levels of depression severity are defined by the co-occurrence of numerous accessory symptoms and the wide variation in the illness course (i.e., single, recurring, or chronic). As a result, MDD is a very heterogeneous condition with a wide range of symptom clusters and treatment outcomes. First-line therapies, which typically include combining cognitive-behavioral therapy with antidepressant medication, are not effective for 30 to 50% of patients (11).

Conventional antidepressants, which vary significantly in their effectiveness, target the primary neurotransmitter systems (such as serotonin, noradrenaline, and dopamine) that are known to be involved in MDD. Neuromodulation modifies brain circuitry dynamically instead of directly influencing neurotransmission. To assess changes in the excitability of specific brain areas, coils provide magnetic pulses of different shapes at different frequencies (often between 1 and 20 Hz) and intensities during rTMS. Cortical excitability is altered permanently by rTMS (11).

Generally, rTMS therapy for depression uses excitatory stimulation of the left DLPFC. This goal is partially based on earlier functional MRI research that

Target site	Protocol	Typical course	Outcomes
Left DLPFC	10 Hz High-Frequency Left (HFL) Protocol: Total pulses: 3,000 Frequency: 10 Hz Train configuration: 75 trains, each 4 seconds long with 40 pulses Inter-train interval (ITI): 26 seconds Target intensity: 120% of motor threshold (MT)	Session length: 37.5 minutes Standard course: 36 sessions Initial phase (6 weeks): 5 sessions per week Taper phase (3 weeks): Week 7: 3 sessions Week 8: 2 sessions Week 9: 1 session	Response rate: 47%, Remission rate: 27%.
Left DLPFC	Modified 10 Hz HFL Protocol: Total pulses: 3,000 Frequency: 10 Hz Train configuration: 75 trains, each 4 seconds long with 40 pulses Inter-train interval: variable (11-25 seconds) Target intensity: 120% of motor threshold (MT)	Identical to HFL, Session length: variable (19-36 minutes), dependent on selected ITI	The modified HFL protocol exhibits equivalent safety and effectiveness compared to conventional 10 Hz treatment.
Left DLPFC	Theta Burst Stimulation (TBS) / Intermittent TBS (iTBS) parameters: 600 pulses at 200 bursts (3 pulses at 50 Hz each) Burst frequency: 5 Hz Train duration: 2 seconds 8-second rest between trains Intensity: 120% motor threshold (MT)	Session length: 3 minutes Standard course: 36 sessions Initial phase (6 weeks): 5 sessions per week Taper phase (3 weeks): Week 7: 3 sessions Week 8: 2 sessions Week 9: 1 session	Response rate: 49%, Remission rate: 32%

Left DLPFC	1,980 pulses at 18 Hz 55 trains, each 2 seconds long with 36 pulses 20-second rest between trains Intensity: 120% of motor threshold (MT)	Session length: 20 minutes Acute treatment phase: 4 weeks, with 5 sessions per week Maintenance treatment phase: up to 12 weeks, with 2 sessions per week	Response rate: 38% Remission rate: 33%

MT, motor threshold, DLPFC, dorsolateral prefrontal cortex; ITI, intertrain interval; iTBS, intermittent theta burst stimulation

Table 1. An overview of the rTMS therapy protocol for MDD authorized by the FDA (2)

showed depressive patients to have left prefrontal hypometabolism (12). Furthermore, the default mode network nodes and the left DLPFC are functionally related and constitute a significant part of the central executive network. These nodes have been linked to the pathophysiology of depression (13). The FDA authorized 10-Hz stimulation, the first depression therapy program, in 2008. A significant advancement occurred in 2018 when the FDA approved iTBS, a procedure that shortens treatment duration from 37.5 to 3 minutes. Currently, the FDA has approved four therapy regimens for the management of depression (2).

Obsessive-Compulsive Disorder

According to DSM5 and ICD10 diagnostic criteria, obsessive-compulsive disorder (OCD) is defined by "intrusive, obsessive, and repetitive compulsive symptoms" (14,15). The chronic, waxing and waning nature of OCD and its detrimental impact on quality of life are well-known. The lifetime prevalence is constant across cultures, ranging from 1.6% to 2.3% (16). A significant number of patients encounter delays in diagnosis and treatment, and a significant proportion of patients do not attain complete clinical remission even with treatment (17).

Global recommendations for treating OCD show that both pharmaceutical and psychosocial interventions are beneficial. First-line recommendations include exposure/response prevention cognitive behavioral therapy and serotonin-reuptake inhibitors (SRIs) or selective SRIs (SSRIs). (18). Just one-third of patients exhibit a clinically significant response to an SRI after switching to a different one, whereas the majority of patients (40–60%) do not (19). Additional approaches to treatment involve the use of complementary therapies including exercise, motivational interviewing, cognitive therapy, acceptance and commitment therapy, and augmentation with antipsychotics. Although many people still experience symptoms and impairment (20). Thus, there has long been interest in

Target	Protocol	Typical Course	Outcome
Bilateral DMPFC and ACC	2,000 pulses at 20 Hz 50 trains, each 2 seconds long with 40 pulses 20-second rest between trains Intensity: 100% of leg motor threshold (MT)	Each 18-minute treatment session is preceded by a 3-5 minute symptom provocation procedure. The standard treatment protocol includes: Frequency: 5 sessions per week Duration: 6 weeks (total of 30 sessions)	Efficacy outcomes at 1-month follow-up: Response rate: 45% Partial response rate: 60%

ACC, anterior cingulate cortex; DMPFC, dorsomedial prefrontal cortex; MT, motor threshold

Table 2. An overview of the rTMS therapy protocol for OCD authorized by the FDA (2)

alternative approaches, particularly those that directly affect the neuro-circuitry underlying OCD.

Current understanding of the neuroscience of OCD has led to the successful treatment of the disorder by neuromodulation techniques. Different parts of the cortical-striatal-thalamo-cortical circuit are targeted by TMS therapy for OCD. The first TMS regimen approved by the FDA for adjunctive treatment of OCD was one that used the H7-coil and was developed by BrainsWay (Jerusalem) in 2018 (21). The DMPFC and ACC were the intended targets of the coil employed in this treatment. In 2020, the FDA authorized a second OCD therapy plan that made use of MagVenture's (Farum, Denmark) Cool D-B80 coil.

Smoking Cessation

Throughout history, smoking has been one of the most common and enduring addictions. According to WHO estimates, tobacco smoking results in over 6 million annual fatalities and over half a trillion dollars' worth of economic harm (22,23). Most smokers recognize the detrimental effects of tobacco use and want to minimize or quit. Regrettably, the majority of people who attempt to quit without help relapse within a week, with a recurrence rate of over 85% (24). Many drugs for tobacco dependence, such as varenicline, bupropion, and nicotine replacement therapy, have been shown to increase the incidence of rapid cessation. Long-term results, however, are not very good; the abstinence rate after six months ranges from 19% to 33% (25).

The activities of nicotine in the central nervous system are the primary cause of the addictive effects

Target	Protocol	Typical Course	Outcome
Prefrontal cortex and insula	1,800 pulses at 10 Hz 60 trains lasting 3 seconds with 30 pulses 15-second rest between pulses. Intensity: 120% of the motor threshold (MT)	Each 20-minute treatment session is preceded by a controlled craving provocation procedure. The treatment regimen comprises: Initial phase (3 weeks): daily sessions, 5 times a week Consolidation phase (3 weeks): weekly sessions	Among treatment completers with high levels of nicotine addiction, 28% attained four weeks of continuous abstinence

MT, motor threshold

Table 3. An overview of the rTMS therapy protocol for smoking authorized by the FDA

of smoking. Nicotine causes long-lasting neuro-adaptations and changes cortical excitability. It also modifies the ability of gamma-aminobutyric acidergic pathways to regulate dopaminergic activity (26). rTMS, which may both generate long-lasting changes in neuronal excitability and trigger dopamine release, is one method that may be able to alter this circuitry (24).

In 2020, the FDA authorized a TMS regimen for people with smoking addiction that makes use of the BrainsWay H4-coil as a short-term smoking cessation assistance (2). The insula and prefrontal cortex, which have been linked to the pathophysiology of tobacco use disorder and other drug use disorders, are stimulated by the H4-coil (27).

FUTURE TRENDS

The field of TMS is fast developing, and numerous noteworthy rTMS paradigms are now in development. Research on improving the effectiveness and efficiency of rTMS therapy for MDD, OCD, and smoking cessation is underway. Beyond the FDA-approved indications, TMS may also be useful in the treatment of other neuropsychiatric disorders. TMS has shown promise in treating a variety of neurological and psychiatric conditions, including posttraumatic stress disorder, schizophrenia, drug addiction, mild cognitive impairment, Alzheimer's disease, and others (28–30).

Local Trends

The use of TMS in the management of mental health disorders is not common in low-and-middle income

countries (LMICs) such as Nigeria. This is essentially due to the pre-existing barriers to mental health services which include insufficient funding for mental health services, complexities of integrating mental health care with primary health care services, low numbers of mental health professionals, poor infrastructure, and overburdened systems (31). Another major challenge is the lack of health care insurance for the treatment of mental disorders and patients have to pay out-of-pocket. According to reports, an entire course of TMS therapy generally entails 20–30 sessions, with a single session costing between $300 and $500. This suggests that the overall expense of TMS treatment may vary between $6,000 and $15,000 (32). Only few can afford this form of therapy.

CONCLUSION

The use of rTMS to mental health disorders presents encouraging opportunities for specialized treatment approaches through the identification and use of neurophysiological and neuroimaging biomarkers. rTMS can potentially improve treatment results in neuropsychiatric illnesses by tailoring therapy tactics to individual patients. The application of TMS in treating mental health disorders can be encouraged by improving mental health services in Nigeria. This may be done through community-based mental health awareness initiatives, national advocacy for pushing changes in mental healthcare policy, and research and innovation for improving mental health therapies.

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