South Asian Journal of Social Studies and Economics

Volume 21, Issue 8, Page 97-106, 2024; Article no.SAJSSE.119973
ISSN: 2581-821X

Repetitive Transcranial Magnetic Stimulation (rTMS) Therapy in Mood Disorders and Generalized Anxiety Disorder (GAD)

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/sajsse/2024/v21i8869

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/119973

Review Article

Received: 21/05/2024
Accepted: 24/07/2024
Published: 30/07/2024

ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neurostimulation technique increasingly investigated for its therapeutic potential in mood disorders and related brain conditions. This paper using content analysis reviewed literatures and summarized current research on the efficacy and safety of rTMS in treating mood disorders, including major depressive disorder (MDD), bipolar disorder (BD), and Generalized Anxiety Disorders (GAD). Studies suggest that rTMS may offer significant improvements in depressive symptoms and mood regulation, particularly in individuals who have not responded to traditional treatments. Mechanisms of action involve

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Cite as: *Ugbenin, Blessing Eseleose, and Chibuike Chinonso Mgbeanuli. 2024. "Repetitive Transcranial Magnetic Stimulation (rTMS) Therapy in Mood Disorders and Generalized Anxiety Disorder (GAD)". South Asian Journal of Social Studies and Economics 21 (8): 97-106. https://doi.org/10.9734/sajsse/2024/v21i8869.*

modulation of cortical excitability and neural circuitry implicated in mood regulation. While rTMS demonstrates promise as a well-tolerated intervention with minimal side effects, further research is needed to optimize treatment protocols, identify patient-specific predictors of response, and elucidate long-term outcomes. Understanding the role of rTMS in mood disorder management holds potential for advancing personalized treatment approaches and improving overall patient outcomes. The paper concludes that rTMS is a promising intervention for individuals with major depressive disorder (MDD), and generalized anxiety disorder (GAD). Finally, it was recommended that further studies should be conducted on the efficacy or rTMS on mood disorders generally.

Keywords: Transcranial magnetic stimulation; neuromodulation; mood disorders; neuropsychiatry; brain conditions.

1. INTRODUCTION

Neuromodulation techniques in neurotherapy and psychology have become increasingly prominent in neurology and psychiatry with the aim of tackling neuronal endophenotypes and significant health symptoms in neuropsychiatric contexts. The most frequent neuromodulation treatments are neurostimulation methods, which use external electronic equipment and electromagnetic fields to exogenously change the activity of sensitive cells. Neurofeedback techniques; a set of biological feedback systems that involve learning how to control cognitive and emotional states by voluntarily controlling certain brain waves with the aid of neural recording techniques that stimulates neurophysiology and brainwaves. Time cues such as visual or auditory signals enable the accurate detection of fixed neurofunctional states and time-dependent regional responses (Martz et al., 2020). These neuromodulation processes have an impact on the neural activity in particular brain regions and the functional circuits that link them. This affects cognition and behavior in measurable ways, allowing for experimental demonstrations of neural manipulation and behavior modification.However, during different mental or behavioral states, inference of brain-behavior relationships is typically achieved through observational neurophysiological monitoring techniques, which are used by neuroimaging techniques including functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and positron emission tomography (PET). As a result, neuromodulation is the only way to directly target, modify, and more importantly, restore unstable brain processing circuits that lead to abnormal behaviors [1]. Whether these methods are used alone or in combination with other sophisticated therapies, they can provide improvement or serve as an alternative to existing treatments**.**

Typical of most opulent societies, therapeutic innovations turn to biology and biotechnology to counter the decline in mental health and well-being. Three new brain stimulation techniques have emerged, including rTMS, magnetic seizure therapy (MST), and deep brain stimulation (DBS), Transcranial magnetic stimulation (TMS), a non-invasive method of neuromodulation was developed in the 1980s and rapidly implemented in healthcare services. Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive brain stimulation technique used in neuroscience and clinical settings to modulate brain activity. It starts with a brief; high-intensity magnetic field is generated by passing electric current rapidly through a coil. This magnetic field is crucial for the stimulation process (Rachid, 2018). The magnetic field created by the coil enters the scalp without obstruction and reaches the underlying cortex of the brain. This is essential because the target for stimulation lies within the brain's cortex [2]. When the magnetic field enters the target sheath within the cortex, it induces electrical currents. This phenomenon is based on the principles of electromagnetic induction [3]. Further, the induced electrical current causes depolarization of superficial cortical neurons below the coil and in linked locations. Depolarization refers to a change in the neuron's membrane potential, making it more likely to generate an action potential or electrical impulse. Multiple pulses are delivered in rapid succession, and this process is often repeated over the same area of the brain. These pulses are typically dispersed over the target region. The frequency of stimulation can vary, typically ranging from 1 to 20 Hz in rTMS and sometimes higher. This repetition and dispersion of pulses are crucial for the effectiveness of the stimulation and its ability to modulate brain activity over time.

Other subregions of the prefrontal cortex, frontopolar cortex, and parietal cortex have also been investigated as potential rTMS brain areas.

The visual cortex may be a promising target for rTMS therapy in the MDD according to previous research. rTMS has been used to treat affective disorders like depression and bipolar disorder (BD), as well as to improve mood symptoms. rTMS is noninvasive, well tolerated, and generally safe in comparison to pharmaceutical therapy [4,5]. Despite mounting evidence that rTMS improves spontaneous brain activity and cerebral functioning in the general population, mild cognitive impaired individuals, and schizophrenia patients, no specific enhancing effects on some cognitive tasks have been observed in studies of rTMS therapy (Cristea et al., 2018). Previous research revealed that rTMS indeed displays therapeutic functions in Major Depressive Disorder (MDD) symptoms, and it can also effectively treat patients with concomitant physical disease, people who cannot endure the negative effects of medication therapy, and refractory BD patients when compared to pharmaceutical therapies and cognitive behavioral therapy.

2. LITERATURE REVIEW

rTMS is commonly given across one or both dorsolateral prefrontal cortices (DLPFC), although the response is still unpredictable [6]. Biological markers could be utilized to show how treatment affects brain function and provide information about therapeutic response pathways in subgroups of people, which could help clinicians make better treatment decisions. Recent meta-analyses have shown that high frequency rTMS to the left dorsolateral prefrontal cortex (LDLPFC), low frequency rTMS to the right dorsolateral prefrontal cortex (RDLPFC), and to a lesser extent bilateral rTMS [7] are more effective than sham for the acute treatment of moderately resistant depressive disorders. rTMS is a therapy option that is readily available in specialist treatment centers and has none of the systemic side effects associated with antidepressant drugs, according to current knowledge [8]. The frontoparietal network hypoconnectivity is linked to the default mode network's hyperconnectivity, which may increase negative emotional bias, disordered self-referential thinking, and rumination. In general, Low-frequency (LF) rTMS is expected to lower excitability in the targeted cortical region, while High-frequency (HF) rTMS is thought to increase it. Synaptic plasticity, a long-term potentiation and long-term depression pathways, play a role in the physiological effects of rTMS and other neuromodulatory approaches [9,10].

HF-rTMS has been shown to stabilize the functional balance amidst neural networks by stimulating the left DLPFC. For example, it has been demonstrated to reduce connection between the hippocampus and the salience network, as well as between the left DLPFC and insula and the default mode network, which has been linked to improved depressive symptoms [11,12]. For MDD, an acute course of rTMS usually consists of daily visits (Monday through Friday) for around 6 weeks. Unlike ECT, the mechanism of action does not necessitate the induction of a seizure or anesthesia. Because the effect is often immediate (within 1-2 weeks), the treatment is typically well tolerated, the treatment has no systemic effects, and there is no pharmaceutical exposure to the fetus and/or breastfeeding newborn, rTMS may be an appealing alternative treatment for perinatal depression [13]. HF-rTMS to the bilateral primary motor cortex (M1) appeared to improve motor symptoms in PD, while HF-rTMS to the DLPFC displayed to be an effective treatment for medication-resistant depression, including depression in PD (Fox et al., 2016). Each patient's treatment dose is unique, and is expressed as a percentage of their motor threshold (MT). Typically, the MT is determined by ocular observation or electromyography as the stimulus intensity that moves the contralateral abductor pollicis brevis 50% of the time. Its antidepressant impact in MDD has been proven in several big trials and meta-analyses. rTMS for MDD appears to be efficacious and well-tolerated in younger persons, according to preliminary open-label studies (Donaldson et al., 2014).

Possible adverse effects of rTMS include mild headaches, localized soreness at the stimulation site, neck discomforts vertigo, syncopal vagal episodes, mania, and seizures. Mild, self-limiting holocephalic headaches, especially at the start of treatment, temporary dizziness, and occasional paresthesia at the treatment site are the most common adverse effects in non-pregnant patients. Treatment termination owing to side effects is quite uncommon so far Baeken et al., [8] Kozel, [14].

2.1 Applications of rTMS in Mood Disorders

MDD has a lifetime frequency of 14.6% in high-income nations and the most prevalent cause of serious illness and death worldwide [15]. Only one-third of patients react to their first suggested

antidepressant drug at the right dose and duration, despite the fact that effective antidepressant medications, electroconvulsive treatment (ECT), and psychotherapy lessen the average duration of episodes of depression [16] while only two-thirds of patients achieve remission after several trials of antidepressants and multi-drug regimens [17]. To prevent recurrence and recurrence in remission patients, continuity and care therapy are required, and the rehabilitation phase may last indefinitely. TMS makes use of a coil to deliver a high-intensity electromagnetic pulse [18].

TMS is applied in the treatment of major depressive disorder MDD by using induced current created from strong magnetic field to modify rapidly changing activity of specific brain areas in depressed individuals [19,20]. By passing electricity via a coil to create an alternating magnetic field, a TMS machine may stimulate neurons in a specific area of the brain. Upon application of this magnetic field to the scalp, it travels across the skull, causing electrical impulse in specific neurons. TMS magnetic pulses can be administered repeatedly to generate lasting alterations in brain activity, and the frequency and pattern of pulse administration can be modified to modify the effects of TMS on cortical activity, i.e., inhibition versus excitation [21]. When Grunhaus et al., [22] reported two such cases, rTMS was first studied for the treatment of depression. Since then, depression has been the primary focus of rTMS treatments, with guidelines for its safe and effective administration created.

The first high frequency rTMS (10Hz) of the left dorsolateral prefrontal cortex (DLPFC) to treat depression was approved in 2008 by the US Food and Drug Administration [7]. It targeted the left dorsolateral prefrontal cortex with 10 Hz stimulation at 120% MT, DLPFC. After then [23] the FDA approved five additional rTMS devices and expanded the use of the first rTMS device to treat a wider group of treatment-resistant MDD patients. In addition to efficacy studies for MDD, further investigations have confirmed the effectiveness of rTMS in a variety of situations outside of randomized trials. Numerous other neuropsychiatric disorders, such as posttraumatic stress disorder (PTSD) (Chen, generalized anxiety disorder (GAD) [24] and both stages of bipolar disorder, are being examined with rTMS, because of its success in MDD cases and significant safety profile [6,25]. Response and remission to rTMS monotherapy in populations receiving medication or psychotherapy as a first-line treatment are comparable to antidepressant drugs monotherapy. Nonetheless, experts all across the world are working to improve depressed patients' response and remission rates [8].

The DLPFC – the major center of the frontoparietal network – is the most significant rTMS target region in MDD, and it is hypoactive when clinically depressed. It is important in controlling various activities such as decision-making, functional memory, and attention [26]. The frontoparietal network's hypoconnectivity is linked to the default mode network's hypoconnectivity, which can encourage negative emotional bias, passive self-referential processing, and romanticism. High-frequency (HF) rTMS has been proposed to equalize the functional balance across neural networks by stimulating the left DLPFC, for example, down-regulate connectivity in the default mode network, the left DLPFC and insula, and the salinity network, by stimulating the left DLPFC [27,28].

After a patient has responded to treatment, a variety of measures can be used to prevent recurrence of depression. Continuous or maintenance rTMS, as well as recurrent cycles of rTMS (during relapse) or following a favorable response to acute rTMS from long-term antidepressant medication and/or psychotherapy, may be beneficial to patients. Following a good response to an acute course of rTMS, maintenance rTMS should be regarded a potential complement to therapeutic treatments for treatment-resistant unipolar or bipolar depression, based on the encouraging outcomes of previously described studies. Unfortunately, no precise stimulation parameters for maintenance rTMS have yet been established [29,30].

rTMS applied to the L-DLPFC has previously been found to be a safe and effective treatment for MDD in people who have not responded to antidepressant medication. Early rTMS open label studies in teenagers with MDD revealed that the treatment is effective and well tolerated [31,32].

In adolescents, non-invasive brain stimulation treatments such as rTMS may offer long-term therapeutic options. Although the US Food and Drug Administration has approved rTMS treatment for adults, particularly adolescents, little is known about its mechanism of action or

target engagement. More study is being done to better understand the pathophysiology of MDD and how rTMS changes patients underlying neurophysiology to make it easier to provide a specific aid through brain stimulation treatment [33,34].

2.2 rTMS In the Treatment of Bipolar Disorder

Bipolar disorder is a severe illness that affects nearly 2.5% of the population and results in significant morbidity and mortality. Bipolar disorder can be divided into two types: bipolar I and bipolar II. It is necessary to experience a history of manic periods for bipolar I illness, however these are typically followed by depressive episodes. Contrarily, bipolar II disorder requires the conjunction of a hypomanic and a significant depressive episode. rTMS therapy has been investigated for manic/hypomanic, depressive, and mixed bipolar disorder episodes (Kessler et al., 2012). Early in the development of rTMS as a clinical tool, Grisarus co-authored a publication in 1998 that contrasted left and right DLPFC 20Hz rTMS for mania. They found that the severity of improvement in manic symptoms was much higher when rTMS was applied to the right DLPFC as opposed to the left DLPFC (Grisaru, Chudakov, et al., 1998). In a subsequent study conducted in 2003, this team put right DLPFC 20Hz rTMS and sham rTMS in front of 19 participants: in contrast to sham stimulation, right-sided stimulation had no impact on mania symptoms. After that, in 2004, two small case investigations using rTMS at 10Hz and 20Hz over the right DLPFC discovered that manic symptoms considerably decreased. Two further randomised controlled studies using high-frequency rTMS over the right DLPFC have yielded conflicting results on the efficiency of rTMS in the treatment of mania. In another study (Praharaj et al., 2009), it was observed that that 20Hz rTMS across the right DLPFC for 10 days resulted in a significantly larger reduction in manic symptoms than sham rTMS in adults. The treatments were well tolerated, however one of the active stimulation patients experienced moderate depression during the research, whereas no one in the sham group did. However, using a similar design with adolescent participants, Pathak et al. (2015) found that physical stimulation did not lead to a greater decline in mania ratings in people between the ages of 12 and 17. Due to the small sample sizes, it is impossible to determine whether the observed discrepancies are brought on by age group differences or some other factor. There are definitely conflicting results when using rTMS to treat mania. The use of rTMS to treat mania is currently not backed by any strong data. Large-scale clinical randomized controlled trials demonstrating efficacy are necessary before rTMS can be recommended for mania in a therapeutic setting [35,36].

Patients with bipolar disorder and MDD were included in several trials undertaken to investigate rTMS for depression (Carnell et al., 2017). Early trials had insufficient populations to assess for differences in responsiveness or safety between the settings, but rTMS appeared to function equally in both. One of the first randomized studies with rTMS was conducted in 2002, especially for depressive episodes in people with bipolar disorder (bipolar depression), according to a report (Dolberg et al., 2002). Their pilot study of rTMS against sham showed a substantial improvement for rTMS over sham at two weeks, but not at four weeks. The study did not take into account a number of significant rTMS treatment factors. Similarly, in another article that was published, a randomised controlled trial of 5Hz left DLPFC rTMS versus sham at 110% MT for 2 weeks in 2003 found no significant difference in outcome between the two groups but was well tolerated with no hypomanic symptoms (Nahas et al., 2003). Both trials were, however, underpowered in terms of the number of treatments and participants. A different approach was taken by Tamas et al., 2007, who employed 100 stimuli of 1Hz right DLPFC rTMS at 95% MT twice weekly for four weeks. The number of subjects was too low to conduct a statistical analysis, despite the fact that the 5 participants who received active rTMS compared to the 1 participant who received sham rTMS exhibited improvement. Using a combination of 1Hz right DLPFC rTMS followed by 10Hz left DLPFC rTMS (sequential bilateral rTMS) both at 110% MT, Fitzgerald et al. (2016) reported a well-designed RCT comparing active versus sham rTMS for 20 sessions over 4 weeks in the treatment of bipolar depression. Even though there was no clinical difference between the two groups, both groups significantly improved after four weeks. 2016 saw the publication of a study that randomly assigned people beginning treatment with quetiapine to one of three rTMS groups: 10Hz left DLPFC rTMS, 1Hz right DLPFC rTMS, or sham rTMS (Hu et al., 2016). 20 sessions of rTMS were performed, each with 1200 pulses at an intensity of 80% MT. The coil

was positioned vertical to the skull in the sham condition, which used the left 10Hz parameter. Although there was a considerable improvement in all groups over the duration of the trial, there was no significant difference between them, which may have been caused by the low-dose (80% MT) stimulation that was employed [37,38].

As a result of the severe nature of bipolar disorder, multiple researchers have published modest case studies suggesting the safety and long-term effects of rTMS for bipolar depression (Nahas et al., 2003). Although there have been case reports of rTMS inducing mania/hypomania in bipolar depression, the actual incidence is low and comparable to rates reported with conventional mood stabilizers. Bipolar depression treatment with rTMS appears to be generally well tolerated. Importantly, whilst the development of mania/hypomania has been recorded in healthy individuals and persons with psychiatric conditions other than mood disorders, it may be more frequent in people with bipolar disorder (Rachid, 2018). Although rTMS is frequently recommended as a secure treatment for bipolar depression, it is still unclear whether it has therapeutic value. The majority of the evidence does not come from randomized controlled studies, despite the fact that there is some evidence to suggest the usefulness of rTMS for bipolar depression in the short and long terms. Randomized controlled trials have so far either failed to demonstrate a benefit or have only demonstrated a transient effect. This can be the result of methodological issues with the study's design, including low potential or a short therapy period. However, randomized controlled trials with sufficient potential are needed before rTMS can be advised for bipolar depression.

2.3 Clinical Application of rTMS in Generalized Anxiety Disorder (GAD)

GAD is a common mental disorder that affects about 3.1% of the population on average over the course of a year and has significant rates of depression comorbidity. Not only is GAD prevalent, but it also significantly increases the risk of morbidity in patients, particularly when it coexists with depression. (Kessler et al., 2005). Although there are various effective psychotherapy and pharmacological therapies, a large percentage of patients do not respond to these treatments. Given that MDD and GAD have many characteristics and that rTMS has been shown to be effective for treating MDD, researchers have been studying what role rTMS might play in treating GAD (Reinhold et al., 2011). One of the earliest experiments on GAD employed an open design to examine whether six sessions of 1Hz right prefrontal rTMS may lessen anxiety symptoms in 10 people with GAD alone and no other mental illness. They used a gambling challenge to identify the target region inside each subject's right prefrontal cortex during functional MRI acquisition. For three weeks, participants received 90% MT with 900 pulses twice per day. Six out of ten subjects met the remission requirements, and there was a significant decrease in anxiety ratings (Bystritsky et al., 2008). Due to the potential effectiveness of treating GAD symptoms alone with rTMS, numerous research has examined the implications of GAD symptoms on the treatment of MDD. 32 patients in a case series received 10-Hz left DLPFC rTMS that was titrated up to 130%MT over the course of around 31 treatments. Both the symptoms of anxiety and sadness improved to the same degrees in patients with and without anxious depression (Diefenbach et al., 2013). Right DLPFC rTMS was employed in a GAD randomized control study, however high-frequency (20 HZ) stimulation rather than low-frequency (1 Hz) stimulation was used. The participants in the active treatment group received 3600 pulses per day at 110 % MT for 9 seconds of stimulation and 51 seconds of inter pulsetrain interval. Treatments were given five days a week for four weeks, then tapered off for a total of twenty-five treatments. The coil was held at a 90-degree angle to the skull for the sham group, who underwent the same procedure as the control group. The right prefrontal cortex was stimulated by moving the coil 5 cm anteriorly from the point used to calculate the MT. The anxiety symptoms were significantly reduced in the active stimulation group while they were barely noticeable in the sham stimulation group. A generalised tonic-clonic seizure was experienced by one member of the active group. Although there is not much information now available on rTMS for GAD, it is gradually being developed. Since rTMS are mostly used in the context of treating MDD, open research and case reports demonstrate that rTMS is useful in treating GAD.

3. ETHICAL CONSIDERATIONS

Ethical considerations are paramount in research involving neuromodulation techniques including rTMS, particularly when studying their application

in neuropsychiatric disorders such as MDD. The pursuit of happiness has become one of the fundamental purposes of our life in a society devoid of poverty and war. The term "happy" is commonly used in ordinary speech to describe a psychological and emotional situation where a person has a long-lasting pleasant feeling of joy and or contentment. In current social sciences, 'happy' is also being adopted as an abstract concept for intricate models, particularly relevant to the field of positive psychology. As indicated by the growing global burden of mental health illnesses, joyful situations, progressing prosperity, and quality psychological well-being are hard to come by. To combat the perceived loss in psychological well-being in opulent worlds, certain individuals are increasingly turning to scientific researches and innovations (Delle Fave et al., 2016).

Philosophically and ethically, we can consider if it is good to be continually content and cheerful, or desire a society such that individual moods can be altered based on personal preferences or social standards. Devices that can actively interact with the brain can serve multiple functions, from detecting and preventing panic episodes to suppressing sensations in people with anxiety disorders in order to keep a person in a happy frame of mind. As this form of deliberate mental condition calibration can be exploited in a number of ways resulting in violation of core biomedical ethics concepts and human rights, the appropriate use of such interventions is critical. Besides the advantages, emotional development can have a number of drawbacks for both individuals and society. To begin with, after we achieve eternal joy, we may lose our true grasp of the meaning of some blissful moments. While repeated challenging occurrences may ward off environmental and social awareness, the manner with which we express particular emotions can have an impact on social relations with other individuals. Consider political discussions as an illustration of how this can have far-reaching repercussions for deciding or affecting the outcome of social interactions. It is debatable whether self-reported happiness is related to a lack of interest in society and human growth. This can certainly be a barrier to settling for fair means of combating major societal issues like climate change, poverty, or social inequality (Kushlev et al., 2020). Finally, whether a pleasant mood is linked to creativity is debatable: an extremely cheerful culture without emotional ups and downs is likely to turn less creative, resulting in 'social and cultural mediocrity'.

The ethical, legal, and social consequences that accompany the implementation of emerging technologies in affective engineering must be addressed in a systematic and thorough manner. It will have to consider both human and psychological dimensions, as well as the importance of 'negative' emotions like dread and grief. It will need to be turned into policy once there is a solid moral and social agreement on how to deal with effective engineering. Given the expanding worldwide influence of technology developments, international legislation with stringent oversight should be implemented immediately practice commence. The engineering approach seems a promising strategy to reduce the terrible agony and suffering caused by mental health issues, although it is also compelling to use this technology to improve everyday mood and long-term well-being (Pemberton & Fuller Tyszkiewicz, 2016).

4. CONCLUSION

In summary, neuromodulation techniques such as rTMS have emerged as promising interventions in the fields of neurology and psychiatry, aiming to address neuronal endophenotypes and significant health symptoms in neuropsychiatric disorders. These techniques, including neurostimulation methods and neurofeedback, offer the means to directly target and modify brain activity, thereby influencing cognition and behavior. While observational neurophysiological monitoring techniques like fMRI and EEG provide insights into brain-behavior relationships, neuromodulation stands out as a direct means to modify and restore unstable brain processing circuits associated with abnormal behaviors. The application of rTMS, particularly in the treatment of MDD, has shown promising results. By targeting specific brain regions, such as the DLPFC, rTMS can induce lasting alterations in brain activity, offering an alternative or adjunctive therapy for individuals who do not respond well to traditional treatments like antidepressant medications. The effectiveness of rTMS extends beyond MDD, with ongoing research exploring its potential in other neuropsychiatric disorders such as PTSD and bipolar disorder. Despite its efficacy, rTMS is not without side effects, which can include headaches, discomfort at the stimulation site, and in rare cases, seizures.

However, the overall safety profile of rTMS makes it an appealing option for individuals who may not tolerate or respond to conventional treatments. Moving forward, further research is needed to elucidate the mechanisms of action of rTMS and to optimize its application in various neuropsychiatric conditions, with special attention to the adolescent population. By better understanding the underlying neurophysiological changes induced by rTMS, clinicians can tailor treatment approaches to individual patients, ultimately improving outcomes and quality of life for those affected by neuropsychiatric disorders.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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