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Transcranial Magnetic Stimulation: An Overview of Mechanisms and Therapeutic Uses

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Transcranial Magnetic Stimulation: An Overview of Mechanisms and Therapeutic Uses

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Abstract: Transcranial magnetic stimulation, TMS, has been an innovative method of demure neuromodulation. This paper aims to delve into the different forms of its existence and to evaluate the use of TMS in five psychiatric disorders; Parkinson's disease, schizophrenia, obsessive-compulsive disorder, major depressive disorder, and major anxiety disorder. Literature pertaining to the use of TMS in treating these specific diseases will be analyzed, and its efficacy and mechanisms will be explored. The literature will be evaluated through sources with established facts and research studies demonstrating function, potency, or inefficacy. TMS poses a method to have a more explicit effect on the regions of the brain, and the exploration of its use in the treatment of psychiatric diseases poses new possibilities in the treatment of psychiatric disorders. Venturing into the options it could have in a sole or combinatorial setting could provide penetrating insight into innovative forms of treatment and research.

Keywords: OCD; TMS; obsessive-compulsive disorder; transcranial magnetic stimulation

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Selected abbreviations and acronyms
TMS**:** Transcranial Magnetic Stimulation
rTMS: Repetitive Transcranial Magnetic Stimulation
dTMS: Deep Transcranial Magnetic Stimulation
HFrTMS: High-Frequency Transcranial Magnetic Stimulation
LFrTMS: Low-Frequency Transcranial Magnetic Stimulation
PFC: Prefrontal Cortex
DLPFC: left dorsolateral prefrontal cortex
HD: Hypokinetic dysarthria
STG: superior temporal gyrus
LID: levodopa-induced dyskinesia
PD: Parkinson's Disease
OCD: Obsessive-Compulsive Disorder
MDD: Major Depressive Disorder
MAD: Major Anxiety Disorder
SMA: Superior Motor Area
MRS: Magnetic Resonance Spectroscopy
H-Coil: Hesed Coil

Introduction

Transcranial magnetic stimulation, or TMS, is a non-intrusive method that utilizes electrodes to stimulate brain regions to generate electric current (1). This method works by exploiting the properties of electromagnetic induction to cause changes in neural activity (2). Traditional transcranial stimulation, which was used to activate the motor cortex, utilized a coil placed on the head, creating an electric field that causes the transsynaptic activation of pyramidal cells, which evoke descending volleys on the corticospinal tract (3). Pyramidal cells are specialized cells that are the principal excitatory neuron in the brain that act in the corticospinal tract (4). The cells depolarize and lead to the activation of motor neurons, eventually eliciting a physical response (3). This was first performed in 1980 by Merton and Morton, who successfully stimulated the brain using non-invasive methods to produce movement in the arm (5). Although they were successful, it was not an entirely

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seamless method, and complaints of scalp discomfort were common (6). From there, research moved toward magnetic stimulation. In 1985, Barker introduced the use of magnetic stimulation that creates electric currents running in parallel with the magnetic coil to eliminate the issues with the scalp (6).

rTMS

rTMS was the traditional method that had the capability to penetrate 1-3 cm using superficial coils; the subsequent development of the H-coil led to the mastering of 4-6 cm infiltration from the scalp (6). Another type of coil is the figure-8 or butterfly coil, which can penetrate about 2-3 cm depending on the protocol used (2). There are various approaches used for TMS, and since its conception, TMS has branched into several different forms. One of these is called repetitive transcranial magnetic stimulation rTMS. This method, which utilizes either low (1 Hz) or high frequency (10-20 Hz), is capable of activating or inhibiting cerebral regions using the butterfly coil (2,7). The most significant difference from conventional TMS is the "repetitive" aspect, which delivers several pulses instead of a single pulse (7).

dTMS

Another method that diverged from TMS is deep transcranial magnetic stimulation, dTMS, which is a more recent application. This utilizes H-coils to promote bilateral stimulation of the brain regions (8). Due to the H-coils employed in dTMS having a more excellent penetration capability, it is able to have an impact at a different caliber compared to rTMS. rTMS has been used to treat several neurologic and psychiatric disorders containing major depressive disorder (MDD), Bipolar disorder, Schizophrenia, Obsessive-compulsive disorder (OCD), Post-traumatic stress disorder (PTSD), chronic pain, Parkinson's disease, Alzheimer's disease and Stroke rehabilitation (9). dTMS, being more contemporary, has been used to treat MDD (8).

Efficacy of TMS

TMS is diverse in its application, as it can also be used to study the utility of pharmacological drugs and their efficacy in patients (10). Using a combinatorial method for select medicines and TMS, it is possible to see how TMS affects the brain and how drugs can affect brain circuits in conjunction (10). It can be used in tandem with other methods of stimulation, such as magnetic resonance spectroscopy (MRS), allowing for a bimodal method of stimulation to understand plasticity and neurotransmitter levels in the brain (11). MRS, also a non-invasive procedure, works by the same principles as magnetic resonance imaging (MRI); however, it provides information on chemical composition rather than imaging the body's internal structures (11).

The efficacy of TMS in treating psychiatric disorders is of great interest, as the non-invasive aspect proposes a method that can reduce the use of pharmacological drugs in the treatment of ailments. Meta-analysis data has found that in the treatment of schizophrenia, depression, dementia, Parkinson's disease, stroke, traumatic brain injury, and multiple sclerosis, there is significant data to prove that it is an effective method to improve cognitive functioning (12). Nevertheless, studies on the efficacy of psychiatric disorders pose to the use of TMS in conjunction with traditional methods of treatment rather than as an exclusive approach (13-15). Use in conjunction with conventional treatments has shown to have positive outcomes in psychiatric disorders such as depression and in neurological disorders such as those resulting in a decrease in corticospinal excitability (13-15).

This article will examine how TMS affects Schizophrenia, Parkinson's Disease, MDD, MAD, and OCD. These are all psychiatric disorders that have shown to be contenders in TMS research. They have differing exhibitions, which require compatibility with the different types of TMS.

Schizophrenia

Schizophrenia is characterized by psychotic symptoms which cause occupational and social decline (16). Its etiological characterization and treatment remain elusive (16). Schizophrenia is

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more prevalent in men than women and typically develops early in life (16). Cognitive decline is now recognized as a clinical feature of the disorder (16). In schizophrenia, there are also other changes that occur within the brain, such as lateral ventricular enlargement, brain functional changes, and neurochemical disturbances (16). Genetic contribution to schizophrenia is also now recognized to be caused greatly by multiple genes (16). Schizophrenia is treated normally by a combination of treatments such as dopamine antagonists, cognitive behavioral therapy, and psychological intervention (16).

TMS has been proposed for patients who display positive symptoms of schizophrenia in conjunction with their mainstay existing treatments (17). Positive Symptoms of schizophrenia are delusions, hallucinations, disorganized talking, and movements (17). Early results found an indication of a positive treatment effect of TMS on positive symptoms in schizophrenic patients (17). Memory improvements have also been noted after rTMS in combination with antipsychotics in the temporoparietal region of the brain (17). Negative symptoms associated with schizophrenia are flat affect, anhedonia, and catatonia (18). They do not respond to typical and atypical antipsychotics (19). Repetitive Transcranial Magnetic Stimulation (rTMS) applied over the prefrontal cortex (PFC) in the brain in conjunction with antipsychotics has been beneficial for the treatment of patients with negative symptoms (19). High-frequency (HF) rTMS has also been shown to improve cognition dysfunction and visual recognition memory in negative patients (20-21).

Schizophrenia has not only been noted to cause psychotic symptoms, but it also causes physiological symptoms such as obesity, and metabolic syndrome, which contribute to premature deaths due to cardiovascular disease complications (22). rTMS has been proposed as a potential treatment for obesity in schizophrenic patients as it has shown efficacy in non-psychiatric patients (22). rTMS has proven to be an adequately safe intervention in relation to verbal/speech function to treat neuropsychiatric conditions (23).

Parkinson's Disease

Parkinson's Disease (PD) has been noted as one of the most prevalent neurodegenerative disorders, with prevalence and incidence rates of approximately 108-257/100,000 and 11-19/100,000 per year, respectively (24). Even though Parkinson's etiology is unknown, successful identification of 5-15% of familial forms of PD have been achieved (24). Some common symptoms in PD are motor symptoms which are tremors, postural instability, bradykinesia/akinesia, and rigidity (24). PD is primarily diagnosed in a clinical setting, while pathologically, it is categorized by the loss of dopaminergic neurons, which are in the substantia nigra (24). Current treatment options for PD aim to target motor symptoms without being able to modify the progressivity of it (24). A TMS study has been shown to improve cognition and focused task performance when being conducted over the left dorsolateral prefrontal cortex (DLPFC) and caudate nucleus (25). Hypokinetic dysarthria (HD) is a motor speech disorder; there is imprecise articulation and it occurs in 90% of PD patients (26). Abnormal activation and connectivity of subcortical and cortical brain areas have been linked with HD. Previous research has shown the superior temporal gyrus (STG) to be an essential modulator of the motor aspects of speech in PD patients (26). Low-frequency sessions of (rTMS) over the right (STG) have proven to have clinical and long-lasting relevant effects on motor speech impairments caused by PD (26). Levodopa is the drug of choice when treating PD (27). Long-term use of levodopa has been noted to cause levodopa-induced dyskinesia (LID) and converts patients from being in an akinetic state to a hyperkinetic state (27). Significant negative changes have been reported to occur at 4-6 years and increase after 15 years (27). TMS has been used since 2005, and positive results have been obtained in improving neuromodulation in LID (27). A study was conducted in which 10 PD patients with LID were subjected to 15-minutes of low frequency (1Hz) rTMS (LF-rTMS) stimulation over the supplementary motor area (SMA) after levodopa intake for five consecutive days; this study included sham control and no rTMS condition (27). There was a decrease in dyskinesia onset with multiple sessions of LF-rTMS in comparison to sham control (27).

In addition to motor symptoms caused by PD, there are nonmotor symptoms that occur, such as cognitive dysfunction, autonomic dysfunction, and depression (28). Repetitive TMS in

 doi:10.20944/preprints202407.1755.v1

conjunction with dopaminergic medication, has been proposed as a form of treatment for cognitive impairment in PD patients who have Alzheimer's and dementia (29). Findings suggest that high-frequency rTMS (HF-rTMS) of the left DLPFC may be potentially effective in treating depressive symptoms while targeting the primary motor cortex (M1) and is shown to be effective in motor symptom improvement (30). An analysis of twelve studies with 381 patients was pooled in order to examine rTMS efficacy on motor function improvement (30). Their findings in the motor scales were 0.51 ($p<0.0001$) and were not distinctively heterogeneous ($I^2 = 29\%$) (30). Findings of rTMS and motor function improvement were significant (30). A similar approach was used to analyze the efficacy of rTMS and its anti-depressive effects (30). Five studies with 202 patients were also pooled, and their findings on depression score scales were 0.42 ($P = 0.004$); it was also not distinctly heterogeneous ($I^2 = 25\%$), which indicates rTMS has an anti-depressive effect (30). TMS has shown to be useful as a sole therapy or in conjunction with dopaminergic medication and has shown promise in the treatment of motor and non-motor symptoms in PD patients (31). Minimal risks in PD patients have been established due to it causing potential seizures, small transient headaches, and scalp pain (31).

Obsessive/Compulsive Disorder

Obsessive-compulsive disorder, which is also known as OCD, can be a disorder that disrupts someone's entire life through obsessions and compulsions (32). Obsessions can be seen differently among different people (32). They can mainly be seen as issues with cleanliness or worrying about something harming that person, or issues with the environment that are not symmetrical (32). Compulsions are mainly repetitive behaviors that people need to perform to feel more at ease (32). The person with OCD believes that acting on these compulsions is necessary (32). Some people may also develop OCD after a streptococcal infection also known as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection or PANDAS (33). Many times the symptoms that accompanied this disorder involve intrusive thoughts, checking things multiple times, having symmetry, and having thoughts that compel them to do something often or clean things (32). All of these symptoms can lead to a very disrupted life (32). To be diagnosed with OCD, a person must have obsessions and compulsions that consume time in their day. This would be for at least one hour or more a day (34).

The diagnosis of OCD has been around for some time now, so there are multiple options of treatment other than TMS. One of the main treatments is cognitive-behavioral therapy (35). This involves seeing a therapist that can work with someone on their specific obsessions and compulsions through exercises and how they respond (35). Another treatment related to cognitive-behavioral therapy is exposure therapy, where a patient is put into a situation that makes them want to perform compulsions or obsess about things and is told not to act on their obsessions or compulsions (35). Medications are also a route for treatment. The main kinds of medications prescribed for OCD are SRI clomipramine and SSRIs (36). SSRIs are tolerated the best and have a decent risk and benefit ratio (36). A combination of an SSRI and an antipsychotic has also been used and is recommended over just SSRI use alone. Patients should be starting their treatment journey here with therapy and medication rather than starting with TMS because around 70% of patients benefit from therapy or medication first (37).

Transcranial magnetic stimulation for patients with OCD has been used as an effective treatment after other treatments, such as the previous therapies and medications mentioned, have not worked (38). For OCD patients specifically, rTMS is used on the pre-supplementary motor area, dorsomedial prefrontal cortex, and bilateral and right dorsolateral prefrontal cortex (38). It can decrease the desire for compulsive urges (39). However, this form has seen negative effects. dTMS is also used on the dorsomedial prefrontal cortex and the anterior cingulate cortex. dTMS has been approved by the FDA for the treatment of OCD (38). A major study in 'The American Journal of Psychiatry' showed results that dTMS in the anterior cingulate cortex and the medial prefrontal cortex could help reduce OCD symptoms for patients that have used other methods of treatment previously (40). The focus of TMS is also on the "resting state" of the functional network in the brain

 doi:10.20944/preprints202407.1755.v1

(41). The "resting state" shows the brain's functional framework and is not dependent on how a patient does regarding completing tasks (41). It can be used to predict behavior, psychopathology, and task-induced neural activity (41). An increased "resting state" between the striatum and the prefrontal cortex has been seen to cause increased symptom severity (41). Therefore these are areas that TMS can target and decrease the severity of symptoms (41).

The effectiveness of TMS has been mainly positive. Patients who are on other medications for OCD have seen great improvement in symptoms (42). While patients are on other medications or using cognitive-behavioral therapy, they have been seen to have better success with the dTMS (42). This is due to the rewiring of the neural connections happening faster than those who have not gone through any kind of treatment and who have a long time of seeing results from the dTMS (42). Even though TMS has been seen as effective for most symptoms through many trials, it is also important to continue research, especially on how TMS can affect executive functions (43). TMS has been approved for effective treatment by the Food and Drug Administration (FDA) (44). Ever since 2008, the FDA has approved TMS for issues such as headaches and depression but after reviewing a study of 100 patients split between a treatment and sham group where the treatment group saw improvement in symptoms, they approved the use of TMS for OCD (45).

Overall, TMS has been helpful for patients with OCD that have tried other treatments that were not successful (40). Patients that used the TMS as their first type of treatment also showed symptom improvement (46). TMS treatments can last up to three months and can help with OCD patients' anxiety and depression (46).

Major Depressive Disorder and Major Anxiety Disorder

Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) are two of the most common psychiatric conditions experienced in the modern world. Over time, cultural shifts away from the stigmatization of MDD, GAD, and psychiatric disorders, in general, have allowed people to share in their relevant life experiences, consequently illuminating a previously hidden mental health epidemic affecting people of all nations. Given the prevalence of treatment-resistant MDD and GAD in the American population, the pressure to pursue alternate and unconventional therapies has rapidly increased with time. Multiple studies have been conducted to establish the usefulness of dTMS treatment, both in isolation and in conjunction with conventional alternatives (antidepressants, psychotherapy, and alternative forms of transcranial stimulation). These studies have largely focused on the stimulation of the DLPFC and ACC: current literature generally demonstrates that dTMS is not particularly harmful when used regularly and generally improves outcomes in patients if it has any significant effect - it is currently approved for the treatment of depression by the FDA (47). A large number of double-blinded randomized controlled trials have been performed, demonstrating that active dTMS treatment is more effective than sham treatment ($p=0.006$) (47). At the circuit level, one study found that the activation of specific connections in the DLPFC is related to the attenuation of specific symptoms - with depression, suicidal ideation, and apathy being treatable via the targeted activation of one circuit, and anxiety, inhibited sexual drive, and insomnia by another (48). Outside of a few studies, however, there exists relatively little information about the mechanisms underpinning the effects of dTMS on either a circuitous or pharmacological level - a gap that must be filled for it to truly be considered a valid procedure.

Studies, both older and more recent, have found that (rTMS) is notably reliable for treating MDD and GAD, especially when combined with conventional therapeutics (48-51). rTMS has a longer history of use in treating mental health disorders; however, dTMS is considered to be somewhat advantaged over rTMS due to its ability to both penetrate deeper and target more focused areas (52). The newest variation on rTMS and dTMS is intermittent theta burst stimulation (iTBS), which is more time efficient than conventional TMS therapies (53). The novel nature of this treatment renders it somewhat suspect, but what data has been made public indicates a similar efficacy and side effect profile to TMS. In general, the nature of dTMS compared to alternative, similar treatments suggests that it is not necessarily better or worse at improving patient outcomes. Conversely, a different analysis of dTMS studies focusing on multiple different neurocognitive disorders found that dTMS

 doi:10.20944/preprints202407.1755.v1

had a significant effect on OCD symptoms in most cases, but its effects on depression were remarkably inconsistent (54). In fact, many studies found that dTMS has no significant effect on depressive symptoms at all (55). More often than not, research suggests that rTMS is more effective for treating depression than dTMS (51, 56-57). This casts doubt on its use as a co-therapy for MDD specifically, although it does not preclude use for comorbidities. Those that cast doubt on the use of dTMS for treating MDD also suggest that it may simply be a matter of how many stimulation sessions a patient sits through. Conversely, other studies have findings that indicate dTMS as being extremely effective at treating comorbid MDD and GAD at the same time ($p=0.009$) and noted that the severity of initial symptoms often predicted the degree of improvement (i.e., patients with more severe symptomatology improved more significantly) (58).

In general, the methodology of TMS-based MDD/GAD treatment is similar to that of other conditions. A device is used to stimulate the designated region of the brain; dTMS therapies use H-coils, and rTMS therapies use infinity coils (another name for figure-eight or butterfly coils) (50, 52). Both methodologies have proven to be effective at ameliorating the symptoms of treatment-resistant depression and anxiety, albeit with varying results as to the efficiency of either process (52, 59-60). As an example of this variance in success - one study found that comorbid depression/anxiety was effectively treated by repeated treatments of rTMS, but also found that this success was limited in its treatment of psychological anxiety symptoms (as opposed to physical anxiety symptoms) (52). The subset of these studies that have gone out of their way to investigate the safety of these processes have often found that the ancillary effects of both conventional forms of TMS are minimal, if they are at all present (61). However, multiple studies contradict this by demonstrating that repeated use of dTMS has the potential to cause transient side effects, including scalp pain, dizziness, insomnia, headaches, and increased difficulty in thinking (56). Notably, while a substantial amount of literature has been produced validating the efficacy of various H-coil subtypes, practically nothing has been written about the potential variance in side effects produced by these different coils, a gap in the literature that must be filled in order to fully understand dTMS as a treatment (60).

Summarily, dTMS has been notably useful in the treatment of General Anxiety Disorder, both independent of other conditions and comorbid with PTSD or OCD. However, there remains substantial doubt as to its efficacy in the treatment of depression (both isolated and comorbid). Due to the inconsistency of results in this area, larger and longer-scale studies are a necessity to truly understand how useful it can really be. More literature is also needed to map out the circuitry behind any effect dTMS may have on cognition, in order to both target it more accurately and minimize the risk of painful side effects.

Conclusion

To conclude, the different forms of TMS have distinct uses. While there is significant overlap between the conditions treatable by dTMS and rTMS, the former's use in alleviating depression symptoms remains dubious, while the latter has been validated for use for a variety of disorders, including MDD. However, the ability of both rTMS and dTMS to ameliorate the symptoms of OCD, Parkinson's disease, schizophrenia, and GAD appear to be well supported by the available literature. There are gaps in the literature regarding the use of TMS. Little is known about how TMS would work for the children and adolescent population dealing with mental disorders. Although there are, some studies on long-term effects are modest. Further research into TMS, including the possibility of it being the sole form of treatment and the efficacy that would have in early treated diseases should also be of great interest.

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