

# A REVIEW OF TRANSCRANIAL MAGNETIC STIMULATION

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## ABSTRACT

Transcranial magnetic induction is a promising and powerful tool in the field of neuropsychiatry and has widespread application in basic neurophysiological & neuropsychiatric research, treatment of depression and other psychiatric disorders. Since it is a relatively new technique approved by the FDA, more prospective studies and clinical trials are needed to provide more accurate data and help optimize the treatment.

**Key-Words:** Transcranial Magnetic Stimulation; Magnetic Induction; Psychiatry; Depression

## Introduction

Since its inception to modern medicine in the late 1980s, Transcranial magnetic stimulation (Transcranial Magnetic Stimulation) has been employed for nearly two decades as a non-invasive clinical tool in the treatment of patients with depressive disorders. It is a relatively novel form of treatment in the field of neurophysiology and its efficacy is based on electromagnetic induction of electric currents in the brain. As a therapy, it tends to be well-tolerated and painless and is used for stimulation and activation of neurons causing hyperpolarization or depolarization of the electro-physiologically active tissues.<sup>[1]</sup> Transcranial Magnetic Stimulation can measure various cortical phenomena, including cortical inhibition and plasticity<sup>[2]</sup> and it can also be employed in the diagnosis and treatment of certain neuropsychiatric disorders including depression, strokes and migraines amongst others. Transcranial Magnetic Stimulation serves as a means of perturbing the brain and effecting modulation of brain function. Electromagnetic induction can be applied solitarily as single induction or as repeated pulses at predetermined intervals over a time variable, which can be customized based on the underlying condition and treatment goals. This form of application is known as Repetitive Transcranial Magnetic Stimulation which is accepted as a functional variant application of

Transcranial Magnetic Stimulation.

In 2008 the US Food and Drug Administration (US FDA) approved Transcranial Magnetic Stimulation for the treatment of refractory Major Depressive Disorder in adults not responding to conventional pharmacological anti-depressant therapeutic modalities. Numerous studies have demonstrated significant anti-depressive properties of Repetitive Transcranial Magnetic Stimulation when in patients with Major Depressive Disorder.<sup>[3-5]</sup> Transcranial Magnetic Stimulation can also serve as an additional or adjuvant therapy in addition to antidepressant drugs, effectively hastening the clinical response to pharmacological management.<sup>[6]</sup> Transcranial Magnetic Stimulation has also been shown to improve depression in pregnant patients thus providing a hypothetically safer alternative by virtue of preventing fetal exposure to the drugs that cross the placental barrier.<sup>[7-9]</sup> Repetitive Transcranial Magnetic Stimulation Magnetic Stimulation exerts its antidepressant effect by augmenting the serotonergic system and by increasing monoamine levels in the brain.<sup>[10,11]</sup> Recently, Transcranial Magnetic Stimulation is preferred over Electroconvulsive Therapy because of the relative ease of application as an outpatient procedure and also because general anaesthesia is not required for Transcranial Magnetic Stimulation. Other advantages of Transcranial Magnetic Stimulation over ECT are

that it requires less energy and stimulation can be targeted without the need for convulsion.<sup>[6]</sup> A British study demonstrated that even unilateral electroconvulsive in people with treatment-resistant depression resulted in memory deficits, while Repetitive Transcranial Magnetic Stimulation was not accompanied by such impairments.<sup>[12]</sup> In the future Transcranial Magnetic Stimulation may play a bigger role in treatment of other neuropsychiatric disorders including, strokes, Parkinson's disease, bipolar disorder, schizophrenia, migraines, obsessive-compulsive disorder, schizophrenia and others.<sup>[13]</sup> This review focuses on the mechanism of action of Repetitive Transcranial Magnetic Stimulation and its applications in the field of psychiatry.

### **Mechanism of Action and Clinical Application of Transcranial Magnetic Stimulation in the Field of Neuropsychiatry**

The principle of Transcranial Magnetic Stimulation is based on the law of electromagnetic induction formulated by Faraday in 1831. This law expounds that when a time-varying current is flowing around a primary coil, it creates a changing electromagnetic field and induces a secondary current in conductors found within a predetermined physical proximity. According to Lenz's law, this secondary current will flow in an anti-parallel direction to the primary current.<sup>[14]</sup> The brain is capable of similar electrical conduction and therefore can be electrically stimulated using pulsed magnetism in immediate proximity. In 1985, Barker and colleagues developed a device capable of magnetic field generation of sufficient intensity to depolarize cortical neurons. This device was capable of generating a large electrical charge over a very short interval. This formed the basis of all modern devices.<sup>[15]</sup> In Transcranial Magnetic Stimulation, electrical charges stored in capacitors discharge in a programmed periodical manner directly over the scalp, producing a time-varying electrical field. This electrical field then produces a transient electromagnetic field causing an electrical current to flow in secondary conducting materials, in this case neurons, altering their electrical environment causing them to depolarize.<sup>[16]</sup> This periodical

discharge of electric charge generates a changing magnetic field that lasts approximately 100–300 milliseconds with intensity ranging from 1 to 2.5 Tesla. This intensity approximates that of magnetic resonance scanners and is 20,000 to 50,000 times more intense than the magnetic field of the Earth.<sup>[17]</sup> Once aligned and arranged, the magnetic field passes through the soft tissues of the head and the skull without resistance, and so inducing a secondary electrical current in the brain, which results in the depolarization of neurons but surpassing their depolarization threshold.<sup>[17]</sup>

The Transcranial Magnetic Stimulation apparatus consists of a concealed wire coil, placed on the subject's scalp over the targeted neural centers. The location on the scalp is chosen based on the patient's neuropsychiatric condition. The coil is connected to capacitors through electric cabling. The capacitors are charged by a power source and they then discharge through the coil when the device is triggered. The two most commonly used configurations are the "circular" configuration, and the "figure eight" configuration.. The circular arrangement tends prevents diminution of sheer power, "8" shaped coils produce a more focused magnetic field when placed tangentially over the target, bringing about better spatial resolution of activation.<sup>[18]</sup> The degree of response is directly proportional to the location and method of application of Transcranial Magnetic Stimulation. A single pulse Transcranial Magnetic Stimulation induces muscle twitches when applied to the motor cortex<sup>[19]</sup> but produces visual light flashes when applied to the occipital cortex by stimulating the visual centers of the brain.<sup>[20]</sup> Similarly high frequency Transcranial Magnetic Stimulation produces different effects based on the location for example, it produces short term memory impairment when applied to prefrontal cortex<sup>[21]</sup> and free recall of verbal material when applied to left mid-temporal cortex.<sup>[22]</sup> There are two pulse types produced by Transcranial Magnetic Stimulation stimulators: a single stimulus pulse or repeated pulses for seconds or minutes. When the stimulation frequency is more than one pulse per second (1Hz) it is known as rapid Repetitive Transcranial Magnetic Stimulation.<sup>[23]</sup> Single pulse being safe and well tolerated<sup>[24]</sup> produces a mild headache as side

effect. The risk of seizures with Repetitive Transcranial Magnetic Stimulation is very low especially at slow rates of 1 Hz and this is one of the reasons Repetitive Transcranial Magnetic Stimulation is preferred over ECT in some psychiatric disorders.

Major Depression or unipolar depression is a strikingly common condition, and is estimated to be vastly underdiagnosed worldwide. In the US alone, each year about nine million adults suffer from clinical depression. The majority of patients with depression respond well to pharmacological treatment but refractory depression is not uncommon. Since its approval by FDA, Transcranial Magnetic Stimulation has progressed tremendously in its capacity to treat depression in subjects who does not respond sufficiently to pharmacological therapy. Evidence shows that Repetitive Transcranial Magnetic Stimulation applied to the dorsolateral prefrontal cortex (DLPFC) produces significant positive outcomes and could be an effective treatment strategy for alternative management of clinical depression.<sup>[25,26]</sup> Consecutive applications of prefrontal rTMS has the potential to induce lasting EEG potentiations resulting in improved cognitive and depressive symptoms. Even though current studies report Transcranial Magnetic Stimulation to have superior outcomes compared to placebo, to date no clear mechanism has been proposed as to how treatment with Repetitive Transcranial Magnetic Stimulation could result in a normalization of mood in depressed patients. In animal models it was found that Repetitive Transcranial Magnetic Stimulation, in similar mechanism to ECT affects levels of dopamine levels and other neurotransmitters producing comparable effects. This effect is particularly noted in the hippocampus and nucleus accumbens.<sup>[27]</sup> Studies also shows that Repetitive Transcranial Magnetic Stimulation normalizes the function of the Hypothalamic-Pituitary-Adrenal axis and like anti-depressants, decreases Corticotropin-Releasing Hormone and Adrenocorticotrophic Hormone.<sup>[28-30]</sup> It was also shown in animal studies that Repetitive Transcranial Magnetic Stimulation exerts a Neuroprotective effect by decreasing oxidative stress<sup>[31]</sup> and by increasing the level of Brain Derived Neurotropic

Factor in the Gyrus Dentatus and the Hippocampal area.<sup>[32]</sup> The Dorsolateral Prefrontal Cortex has been implicated in mood regulation, cognitive control over stress and emotion responsiveness.<sup>[33]</sup> Most clinical studies involving Repetitive Transcranial Magnetic Stimulation target this area and have reported that in clinical depression patients, daily delivery of high frequency Repetitive Transcranial Magnetic Stimulation to the left Dorsolateral Prefrontal Cortex or low frequency Repetitive Transcranial Magnetic Stimulation applied to the right DLPFC effectively reduced symptoms.<sup>[34-36]</sup> Low frequency Repetitive Transcranial Magnetic Stimulation ( $\leq 1\text{Hz}$ ) inhibits regional cortical activity while High frequency Repetitive Transcranial Magnetic Stimulation ( $> 1\text{Hz}$ ) activates areas in the cortex.<sup>[37,38]</sup>

Most clinical studies in depression target the left Dorsolateral Prefrontal Cortex with high frequency stimulation. Brain imaging research shows prefrontal abnormalities in patients with clinical depression.<sup>[39,40]</sup> Decreased neuronal activity in the Dorsolateral Prefrontal Cortex is often reported in these patients and this decreased frontal neuronal activity results in the symptoms of depression like apathy, fatigue, psychomotor slowness and impaired functioning. This is part of the rationale behind application of high frequency Repetitive Transcranial Magnetic Stimulation over the Dorsolateral Prefrontal Cortex to stimulate the cortical neurons, which could result in symptomatic improvement in patients with depression.

Repetitive transcranial magnetic stimulation has been shown to induce remission in depressed patients and induce temporary mood and disposition changes in healthy subjects.<sup>[41-43]</sup> A meta-analysis revealed that in depressed subjects, high-frequency (i.e. 5–20 Hz) Repetitive Transcranial Magnetic Stimulation applied for 5–20 days over the left Mid-Dorsolateral Prefrontal Cortex resulted in improvement in depression ratings in about 41% of the study sample.<sup>[44]</sup> High-frequency Repetitive Transcranial Magnetic Stimulation when applied over the left Mid-Dorsolateral Prefrontal Cortex addresses the fact

that depressed patients exhibit hypo perfusion and hypo metabolism in the lateral and medial prefrontal cortices. This facilitates its use in mood related disorders.<sup>[45-48]</sup> High frequency Repetitive Transcranial Magnetic Stimulation also increases cortical excitability although the neurophysiological changes underlying mood changes as a result of it are poorly understood. Repetitive Transcranial Magnetic Stimulation along with affecting the site of stimulation also stimulates the distal regions connected to the primary site. This shows that Repetitive Transcranial Magnetic Stimulation Magnetic Stimulation acts on entire neural circuits involved in the regulation of mood, not just neural material in closest physical proximity to the instrument. This hypothesis is supported by the fact that Mid-Dorsolateral Prefrontal Cortex is comprised of cytoarchitectonic areas 9, 46 which are richly interconnected with regions in the brain implicated in mood, motivation and arousal such as the striatum, thalamus and the anterior cingulate cortex.<sup>[49]</sup> One study shows that Repetitive Transcranial Magnetic Stimulation plus placebo has the same efficacy as fluoxetine plus sham Repetitive Transcranial Magnetic Stimulation Magnetic Stimulation for treating depression in patients with Parkinson's disease but is better tolerated.<sup>[50]</sup>

Transcranial Magnetic Stimulation has also been used in post stroke patients along with physical therapy for rehabilitation. The technology also measures neuroplastic changes secondary to physical therapy. In a study done in post stroke patients by Kim et al, it was found that the study group which received Repetitive Transcranial Magnetic Stimulation showed significant improvement in movement accuracy and speed compared to those who received placebo.<sup>[51]</sup> A recent study showed that Repetitive Transcranial Magnetic Stimulation in conjunction with Physical therapy resulted in better clinical improvement in stroke patients than just physical therapy alone.<sup>[52]</sup> Several other studies support the benefits of Transcranial Magnetic Stimulation for neuro-rehabilitation in post-stroke patients.<sup>[53-55]</sup>

This technology serves as a diagnostic tool in dementia and age related cognitive decline. It shows changes in intra-cortical excitation and

inhibition.<sup>[56]</sup> This could help differentiate mild cognitive defects from Alzheimer's disease<sup>[57-59]</sup>, fronto-temporal dementia<sup>[60]</sup>, subcortical vascular dementia<sup>[61]</sup> as well as normal and abnormal aging<sup>[62]</sup>. Several studies show that Transcranial Magnetic Stimulation could also improve memory function in elderly patients.<sup>[63-66]</sup> The other areas where Transcranial Magnetic Stimulation has been tried with some success are in treatment of Parkinson's disease, schizophrenic hallucinations, tinnitus, migraine, Obsessive-compulsive disorder (OCD) and Post traumatic stress disorder.<sup>[67]</sup> In studies by Hoffman et al. it was shown that Repetitive Transcranial Magnetic Stimulation delivered to left temporoparietal area resulted in reduction of auditory hallucinations in schizophrenics. This effect persisted for an extended duration even after stopping the treatment.<sup>[68,69]</sup> Transcranial Magnetic Stimulation improves tinnitus though a similar mechanism by acting on the temporoparietal cortex. Several studies confirm the application of Transcranial Magnetic Stimulation in anxiety disorders like Obsessive Compulsive Disorder and Post Traumatic Stress Disorder. The area targeted was the Dorsolateral Prefrontal Cortex. Patients with Parkinson's disease when treated with high frequency Transcranial Magnetic Stimulation improved reaction time, movement time and performance.<sup>[67]</sup> Transcranial Magnetic Stimulation also helps Parkinson's patients by stimulating dopamine secretion in the caudate nucleus.<sup>[70]</sup> Several prospective studies are needed in these areas.

Another interesting potential application for transcranial magnetic stimulation is in the alleviation of chronic neuropathic pain. Single-session repetitive TMS has demonstrated some evidence suggestive of therapeutic potential albeit transient in the management of intractable neuropathic pains. The findings of one study showed that daily high-frequency rTMS over the primary motor cortex is tolerable to the patient, and provides modest pain relief in neuropathic pain patients. The nature of the relief has been transient thus far but more data is needed.<sup>[71]</sup>



## Conclusion

Transcranial magnetic induction is a promising and powerful tool in the field of neuropsychiatry and has a wide application in basic neurophysiological & neuropsychiatric research, treatment of depression and other psychiatric disorders. Since it is a relatively new technique approved by the FDA, more prospective studies and clinical trials are needed to provide more accurate data and help optimize the treatment.

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