Transcranial Magnetic Stimulation and Major Depressive Disorder

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Introduction

Transcranial Magnetic Stimulation (TMS) is a neurophysiologic procedure that noninvasively stimulates neural tissue. It uses electromagnetic induction, which means an electric current is passed through a coil generating a magnetic field that penetrates the skull. Evidence suggests that TMS causes long-term inhibition and excitation of neurons in certain brain areas (Cirillo et al., 2019). The stimulation impacts how the brain is working, which seems to ease depressive symptoms and improve mood. Applying pulses repetitively results in depolarization of nerve cells, causing the release of neurotransmitters that corrects impaired cell functioning and aids in healing. Hypofunctioning of the dorsolateral prefrontal cortex (DLPFC) has been implicated in the pathology of depression and remains the preferred area for stimulation (Phillip et al., 2016).

Privileges to prescribe TMS vary by state. While psychiatrists can universally offer TMS treatment, many states allow other physicians, as well as nurse practitioners, physician's assistants, and prescribing clinical psychologists to do so, as well. Different insurance providers may define a different list of healthcare professionals that can provide and be reimbursed for TMS treatment. Appreciating which patients will benefit from TMS and when it is contraindicated, and most importantly, being aware of the current evidence-based clinical guidance for the use of TMS as a treatment for depression, are important navigation tools to guide clinical practice.

Summary of TMS and its inferred relevance to clinical practice

Transcranial magnetic stimulation is a biomedical application of Faraday's principle of electromagnetic induction. It is a safe, effective, noninvasive, and nonconvulsive neuromodulation therapy cleared by the U.S. Food and Drug Administration (FDA) in 2008, for the treatment of Major Depressive Disorder (MDD) that does not remit with pharmacotherapy (Cirillo et al., 2019). This outpatient noninvasive technique does not require anesthesia and uses a pulsed magnetic field to induce neuronal depolarization in a targeted brain region, typically the left dorsolateral prefrontal cortex (DLPFC) for MDD (Phillip et al., 2016). It works by generating strong and rapidly changing electric currents in a circular coil that is placed on the surface of the skull. This primary current generates a magnetic field that travels unimpeded through the hair, soft tissue, skull, and cerebrospinal

fluid until it reaches the neurons of the cortex. At this level, the magnetic field converts back into a secondary electrical current able to depolarize neurons and force an action potential, which will then travel from synapse to synapse across an entire functional circuit of interest (Camprodon & Pascual-Leone, 2016).

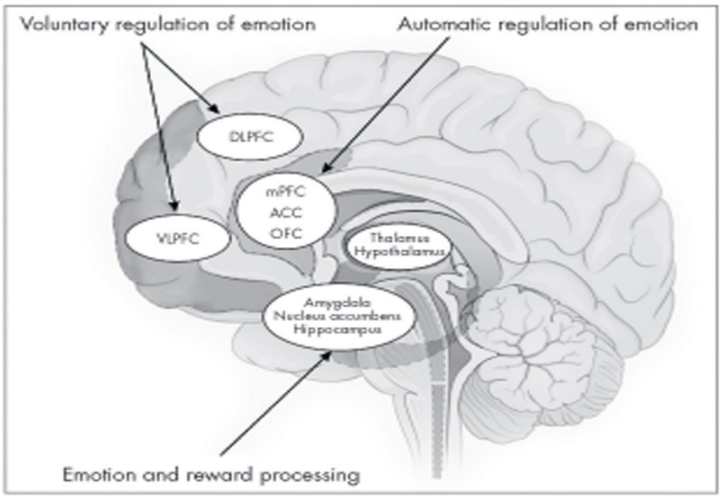
A typical treatment includes initial determination of an individual motor threshold which is an index of cortical excitability to which the treatment intensity is calibrated. The coil is then placed over the left DLPFC and 3,000 pulses are delivered at 10 Hz over 45 minutes. The side effect profile is generally benign, and includes scalp discomfort, twitching, and rarely, seizures (Phillip et al., 2019).

Current science and evidence involving TMS

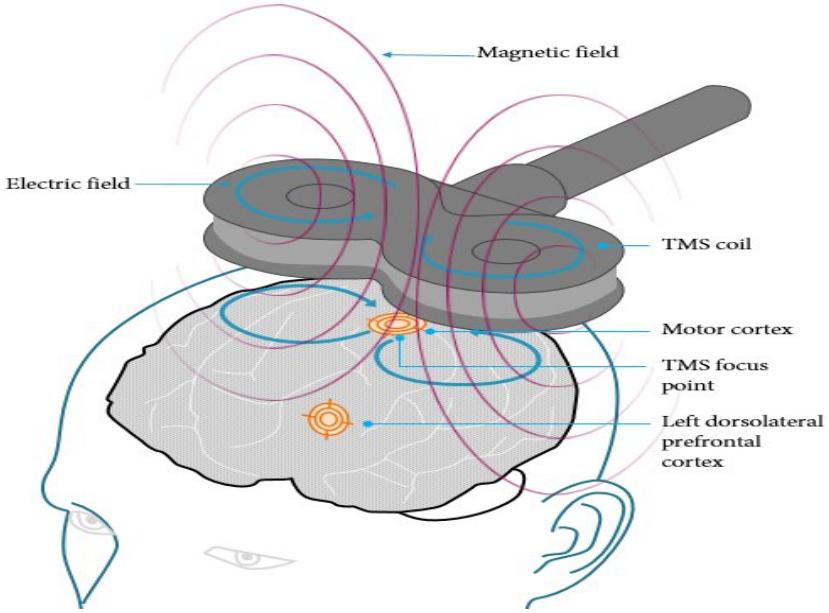
Bermudes et al. (2017) note that the pathogenesis of depression and the mechanism of action of antidepressant medications have focused on the level of cell-to-cell interaction and synaptic transmission, since the monoamine hypothesis theories were first proposed more than 50 years ago, with particular attention to serotonin, dopamine, and norepinephrine. Most antidepressant medications increase extracellular levels of these monoamine neurotransmitters and thereby alter synaptic signaling. Evidence suggests that enhanced neuroplasticity is a common feature of all antidepressant medications, as well as of neuromodulation treatments such as TMS. In contrast to medications, however, TMS is delivered at a very different level of brain organization. Rather than targeting synaptic proteins, TMS is applied to cortical circuits (Bermudes et al., 2017).

Research shows that the functional neuroanatomy of depression implicates the ventromedial and dorsolateral divisions of the prefrontal cortex (PFC) among other deeper brain regions. Connections to the ventromedial PFC (VMPFC) from the hypothalamus and the ventral striatum mediate activity associated with emotions, motivation and reward (Koenigs & Grafman, 2009). Dysfunction in the dorsolateral PFC (DLPFC) is also related to depression. This area is involved in cognitive or executive functioning associated with working memory, goal-orientated actions and abstract reasoning. Together, dysfunction in the VMPFC and DLPFC play important neurocognitive and neurobehavioral roles in depression (Koenigs & Grafman, 2009).

Transcranial magnetic stimulation (TMS) has emerged as a novel neuromodulation technique in the management of depression. It involves placing a small coil near the scalp that when engaged generates a magnetic field that induces an electrical field in the brain's outer cortex in regions that are close to the coil. Philip et al., (2016) note that TMS therapy is focused and can be used to target discrete locations like the DLPFC, where it is typically used to deliver magnetic pulses at either a 'high' frequency of 10-20 Hertz or a 'low' frequency of ≤1 Hertz. Low-frequency TMS reduces neuronal excitability, whereas high-frequency TMS increases cortical excitability (National Institute for Health and Care Excellence, 2015). The most common area targeted in depression is the DLPFC (Philip et al., 2016).



Depression circuit in the brain (https://neupsykey.com/transcranial-magnetic-stimulation-therapy-for-treatment-resistant-depression/



https://psychscenehub.com/psychinsights/transcranial-magnetic-stimulation-for-depression/

TMS treatment results in increased neuronal activity in the dorsolateral prefrontal cortex (DLPFC), which through cortico-subcortical trans-synaptic connections and fronto-cingulate networks suppresses hypothalamic and indirectly amygdala overactivity, resulting in corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) decreases and ultimately in decreased salivary cortisol concentrations. TMS appears to normalize the function of the hypothalamic-pituitary-adrenal axis and also appears to exert a neuroprotective effect by decreasing oxidative stress, thus increasing the level of brain-derived neurotrophic factor (BDNF) in the dentate gyrus of the hippocampus. In line with successful pharmacological interventions, successful TMS treatment results in normalization of the negative feedback system (Baeken & De Raedt, 2011).

Bermudes et al., (2017) note that Major Depressive Disorder (MDD) has been conceptualized as a syndrome of "thalamocortical dysrhythmia," marked by persistent resonance of rhythmic thalamocortical activity. TMS may directly modulate this rhythmic thalamocortical activity in a top-down fashion at the level of large-scale networks to influence neuronal firing rates, firing patterns, and other processes at the cellular level. Conversely, medications would appear to act in a bottom-up fashion by inducing changes at the level of the synapse followed by changes in neuronal firing rates and patterns, eventually affecting network activity (Bermudes et al., 2017).

Dubin (2017) posits that there is also evidence for neurotransmitter changes after TMS treatment. Stimulation of the DLPFC has been shown to increase dopamine levels in the striatum. There is also evidence that TMS over the left DLPFC modulates gamma aminobutyric acid (GABA) and glutamate systems which is correlated with response to treatment for depression (Dubin, 2017).

Strengths, Weaknesses, Opportunities and Threat Analysis of TMS

TMS represents an important breakthrough in the treatment of depression for a variety of reasons. Below is a S.W.O.T analysis of TMS:

Strengths: some of the strengths of TMS noted by Bermudes et al (2017) include:

- Effectiveness for patients who fail to respond to antidepressant medications.
- Office-based procedure that requires no anesthesia or sedation, unlike electroconvulsive therapy like ECT.
- Does not cause cognitive side effects like ECT.
- Does not cause systemic side effects such as weight gain or sexual dysfunction, that are commonly associated with medications.
- Observed procedure during which the clinician can ensure proper administration.
- No issues with non-adherence and patient error, that are often associated with medication usage.

Weaknesses: Kar (2019) notes some negative predictors associated with TMS:

- Higher baseline severity of both depressive and anxiety symptoms was associated with a lower chance of achieving remission
- Feelings of guilt
- Depressed mood
- Somatic symptoms
- Greater number of treatment failures
- Non-response to ECT

Opportunities: Trevizol et al. (2020) posit that predictors of response may be linked to illness

characteristics, nature of depression and severity which is relevant to the use of TMS in melancholic depression. They note the following positive predictors of response:

- Psychomotor retardation
- Younger patients with cognitive and affective symptoms (< 45 years)
- A low score of treatment resistance
- High levels of sleep disturbance
- Short duration of episode (<4 years)
- Employment
- Higher levels of extraversion

Threats: Some of the threats or potential side-effects involved with TMS, as per Hardy et al. (2017) include:

- Seizure induction
- Transient acute hypomania
- Syncope
- Transient headaches
- Neck pain and local discomfort
- Transient hearing changes
- Transient cognitive changes.

Local pain, headache and neck pain are generally mild and discontinuation rates due to these symptoms are low. Taylor et al., (2018) further note that although seizures have a very low incidence, the risk is increased with high-frequency treatment and more intense treatment protocols, pre-existing neurological conditions, adolescent patients, substance use and concurrent medication changes that may all impact seizure threshold. The risk for hearing impairment can be managed with adequate hearing protection. There is a very low risk for affective switch and psychosis, although there is an increased risk in those with Bipolar affective disorder, past manic switch or psychotic symptoms.

Evidence-based Guidance of TMS for Clinical Practice

TMS is recommended in all relevant depression treatment guidelines as an approach that should be considered in the standard care of patients with depression. Perera et al., (2016)

outline the recommended clinical practice essentials for TMS that may help guide and inform providers as they navigate practice issues. The following pre and post-treatment guidelines briefly summarize some of the information regarding good clinical practice.

Pre-Treatment Planning

Pre-treatment, as per Perera et al., (2016), involves planning a treatment regime that will provide symptomatic relief of MDD only in patients who have failed to achieve a satisfactory improvement after receiving antidepressant medications. TMS therapy can also be applied to patients who have had TMS therapy previously and have either benefitted from treatment or are currently experiencing a recurrence of depressive symptoms. Safety considerations should include analysis of the chance of a seizure with all staff and providers aptly trained to respond to such an event. Training is device specific and is a needed requirement for all staff as well as showing a complete understanding of device-specific standard operating procedures for administering TMS therapy.

Post-Treatment Planning

Perera et al., (2016) and NICE (2015) posit that the cessation of TMS treatment is likely to ideally involve the provision of a period of weaning off of therapy, usually with a decreasing schedule of sessions over a number of weeks. Post-treatment planning after TMS therapy includes the requirement to evaluate how to minimize the risk of relapse in successfully treated patients. This can include relevant antidepressant medication or additional TMS if depressive symptoms re-emerge. Evaluation should use relevant health questionnaires to determine what effect if any, TMS therapy had on depressive symptoms. Maintenance TMS schedules seem to have a meaningful benefit in reducing relapse. Due to the resistant nature of depression, non-responders may have treatment extended by 1-2 weeks. An alternative approach in non-responders is to switch and conduct a trial of low-frequency stimulation applied to the right DLPFC. Outpatient provision is considered safe and has the benefits of allowing slow weaning of therapy and reduced dislocation of patients from their home environment.

Conclusion

TMS is a safe and effective computerized medical device that delivers non-invasive and focal magnetic stimulation to the DLPFC over a brief duration of time. It represents a major advance in noninvasive therapeutic neuromodulation with proven efficacy in the treatment of Major Depressive Disorder. Its safety and benign side-effect profile make it a viable treatment alternative for patients who do not respond to standard treatments. Evidence suggests that its therapeutic effects are the result of neuroplastic changes in thalamocortical circuits involved in the expression of core symptoms of major depression. These findings, together with those derived from other lines of research, such as neuroimaging, may shed light on the pathophysiology and circuit dysfunction associated with other neuropsychiatric disorders. Research also suggests that other cortical sites, such as the ventromedial prefrontal cortex, may eventually become therapeutic targets. Modifications in TMS techniques and improvements in TMS technology, including the development of new stimulation coils, may further enhance clinical efficacy.

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