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Review article

Neuropsychiatric Application of Transcranial Magnetic Stimulation: Review Article

Amal Salah Eldien El Motayam [1], Walid M. Reda Ashour [1], Ahmed E. Elsayed [2], Mohammed Samir Ibrahim [2], Rania S. Nageeb [1]
(1) Neurology Department, Faculty of Medicine, Zagazig University, Egypt
(2) Neurology Department, Kobri El-Koba Military Complex, Cairo, Egypt.

Corresponding author:
Mohammed Samir Ibrahim
Email:
drmsi200200@gmail.com,

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Abstract:

Repetitive trains of stimulation (rTMS), a noninvasive cortical stimulation method, is used to give transcranial magnetic stimulation (TMS). Neuronal cortical networks can be subject to various effects, such as activation, inhibition, or interference, based on the frequency, intensity, and configuration of the brain-induced electric field. It can be applied in a variety of ways to diagnose or treat certain neurophysiologic conditions. So **the aim** of this review was to present the most recent neurophysiologic applications of TMS. Regarding to the diagnosis, it is mainly dedicated to the recording of motor evoked potentials (MEPs). It is also a reliable method to perform functional mapping of muscle representation within the motor cortex. For therapeutic applications, especially in the domain of neuropsychiatric application. **Conclusion:** By modifying brain functions, with after-effects lasting beyond the time of stimulation, TMS opens exciting perspectives especially neuropsychiatric therapeutic applications, as in poststroke rehabilitation, depression and chronic pain syndromes.

Keywords: TMS, motor, rTMS.

Introduction:

Transcranial magnetic stimulation (TMS) is a non-invasive way by which evaluation of the function and structure of the central nervous system is implemented, via a stimulation coil which introduces a magnetic field over a specific area of a participant's scalp[1, 2]. The stimulation are administered as single pulses, usually with three to five seconds between every stimulus creating a secondary electrical current within cerebral parenchyma **[1].**

Stimuli can be administered at a single cranial site or systematically over a preset grid, a process known as "mapping," depending on the desired neuro-physiological indicator **[2].**

Mechanism of action: The basic idea underlying the TMS action mechanism is the same for all protocols and is based on Faraday's principle: an alternating electric field generates a few teslas of dynamic magnetic field, which in turn causes a perpendicular electric current to flow through nearby conductors, or a population of neurons **[3].**

Electrical fields (voltages measured between two places) are produced by the magnetic stimulation, and these electrical fields cause the body to swirl with electric currents. More specifically, a magnetic stimulator consists of a capacitor discharge system that is coupled to an external wire coil. This causes the coil to throb with electricity, producing a magnetic field pulse. This coil, meanwhile, is placed close to the body and allows currents to pass through the tissue as demonstrated in **figure *(1)* [4].**

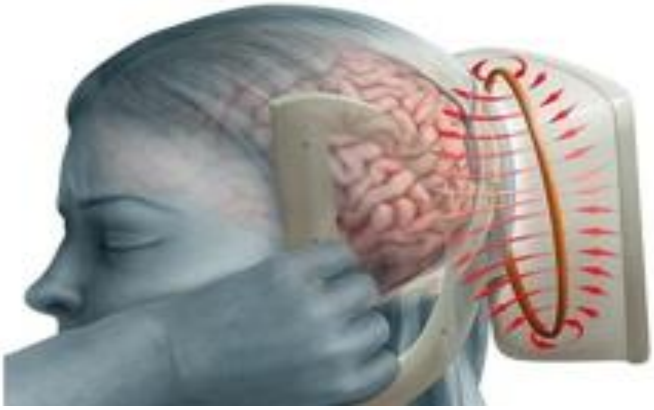

Figure (1): The basic principle of transcranial magnetic stimulation, showing a time-varying pulse of current in an external coil inducing currents in the brain. Inset: Time-varying pulse in TMS, with coil at occiput **[4].**

The action potential that is produced by these currents, provided they are of the right size, duration and site will depolarize neural tissue, which will then spread via the body's typical nerve conduction pathways [5]. In a clinical setting, the term "magnetic stimulation" is used to distinguish it from conventional electrical stimulation, which involves injecting current into the tissue by means of electrodes. However, since the stimulation taking place at the neuronal level is truly electrical, the word is misleading **[4].**

The TMS-evoked action in human brain tissue requires a primary current of four to eight kiloamperes Combined with a quick peak-to-peak rate of change of approximately 100–200 µs, a current of several hundred volts per meter can be induced (V/m), or 7–15 mA/cm2. Importantly, the induced current is directed perpendicular to the coil surface and has an intensity equal to the starting current despite being attenuated by bone, air, tissues, cerebrospinal fluid in subdural and subarachnoidal regions, and structural alterations to the cortex **[6].**

Applying TMS pulses to the motor cortex can cause twitches in the muscles whose representation is being activated by activating the corticospinal tract and associated circuits **[7].**

Targeted cortical areas can mediate physiological and/or behavioral activity that the TMS can counteract. Although they do not cause muscle contractions or subjective visual sensations, these Higher order cortical regions and their corresponding networks subtend higher order cognitive skills including language, memory, attention, visuomotor coordination, and TMS in a hierarchical manner. Nevertheless, they can interfere with firing encoding rhythms and proper processing and communication of associated regions within the activated network [3].

Current research has examined the molecular and cellular processes that underlie TMS effectiveness, particularly rTMS. It created an electric field in neurons that stimulates the release of dopamine, glutamate, and gamma-aminobutyric acid [10], as well as the voltage-dependent calcium channels [8], N-methyl-Daspartate receptor [9], and calmodulin-dependent protein kinase II [8].

These changes trigger calcium influx, excitatory and inhibitory postsynaptic potentials, as well as the activation of molecular pathways that are essential for plasticity. These pathways include ribosomal protein S6, Akt/mammalian target of rapamycin, mitogen-activated Extracellular signal regulated protein kinase 1/2, extracellular signal regulated protein kinase, and protein kinase 1/2 [11].

TMS has been shown to affect the expression of inflammatory genes and glial fibrillary acidic protein in vitro, as well as to stimulate astrocytic intracellular calcium release in astrocytes [12]. Twenty Hz rTMS inhibited astrocyte growth and down-regulated neuronal nitric oxide synthase expression, which may be related to its advantageous effects on the alleviation of neuropathic pain [13]. Long-term low-frequency (LF) rTMS stimulation in microglia also aided in their polarization to the M2 phenotype without impairing their ability to proliferate [14].

Patterns of TMS are:

There are three different ways to apply TMS: single-pulse, double-pulse, and repeated. To ensure that the effects of each individual pulse do not compound over time, single-pulse consists of releasing one pulse at a time interval of at least four seconds (five to eight seconds for safety). The spatial distribution and somatotopic/retinotopic representations of muscles and visual receptor fields have been causally mapped using it extensively. Double pulse TMS, sometimes referred to as paired pulse TMS, involves the release of a test stimulus that is followed by a conditioning stimulus that is postponed by an interstimulus period. Its key applications have been in evaluating interregional interactions between two areas or local primary motor cortex (M1) intracortical modulatory mechanisms [3].

Any combination of more than two pulses delivered at a frequency of 0.5–1 Hertz with a time interval of two seconds or fewer is referred to as repetitive transcranial magnetic stimulation (RTMS). These combinations can have different effects from the solo pulses. This comprises lengthy periods of stimulation (up to 20–30 minutes) at a set frequency, with or without stimulation interference. Additionally, it entails the high-frequency (10–20 Hertz) transmission of short bursts or trains of three–four pulses, with a 50 millisecond gap between each pulse.-intervals of time without releases Within [15]

The safety of TMS usage: To maintain operator and subject safety, TMS's technical design, manufacturing process, use, and maintenance must all be optimized. It is advisable to take into account methods such as insulating high voltage, decreasing coil heating, friction, and vibration, and producing dependable magnetic fields in order to extend the device's lifespan [16].

The only significant reason why the participants should not use TMS is if they have metallic or ferromagnetic objects connected to the discharging coil (such cochlear implants or pacemakers). Under these circumstances, there is a chance that they will become hot and lose their function [15].

The quality of the device and the stimulation protocol play a major role in both the therapeutic and adverse effects of TMS. The secret to minimizing adverse effects and optimizing therapeutic benefit is control of the stimulation dose [17]. Seizures are the most serious adverse effect of TMS, with an overall reported rate of 0.31 per 10,000 sessions and 0.71 per 1000 patients [18].

The distribution of the electrical field, individual variations, and the strength, quantity, patterns, frequency, and waveforms of the pulses all affect the seizure threshold. It is consequently important for operators to consider these factors when doing TMS. For TMS-induced seizures using conventional devices, the lowest parameters are a single train at a frequency of 25 Hz and a maximum stimulator output of 100% for a maximum of 10 seconds. Seizures are rare when TMS is used within ideal parameters, which include stimulus dose and intensity, duration, frequency, pulse count, and session paradigms [15].

Clinical diagnostic and therapeutic applications of TMS:

TMS either modifies brain cortical parameters (such as hormone levels, receptor density, and excitability) or investigates the characteristics of the brain (e.g., location of brain function and connection, impact of medication on cortical excitability) in the brain cortical parenchyma. It has the ability to alter the cortical properties of the brain when distinct brain areas receive rapid sequences of stimulus delivery. Instead of using a single pulse, nearly All TMS applications that are intended to treat rather than investigate use either rapid frequency TMS (one Hz) or slow frequency TMS (one Hz) (ten Hz) [19].

The following TMS outcome parameters are more useful in evaluating Cortical silent period duration, motor threshold, motor evoked potential amplitude, central motor conduction time, short-interval intracortical inhibition, and intracortical facilitation are measures of the integrity of the motor cortex and corticospinal tract in a clinical context [20].

Examining cortical excitability in normal and psychopathological conditions as well as in response to different drugs and therapies, single- and paired-pulse TMS techniques are tools utilized to examine psychopathology and cortical characteristics in the brain. They can also be used to look into how different parts of the brain work together and how excitable they are, as well as how neurotransmitter systems affect perception and function [21].

Modifying synaptic strength or inducing structural changes, such as sprouting or modifications to dendritic spines, are necessary for long-lasting effects on the brain. The fundamental idea of TMS stimulation is to alter synaptic strength since long-term alterations in synaptic strength may very well lead to morphological changes [22].

In terms of diagnosis, the motor evoked potentials (MEPs) recording is the primary focus. This recording aids in the study of cortical motor control and corticospinal conduction time in clinical practice, particularly when image-guided neuronavigation techniques are employed. Functional mapping of the motor cortex's representation of muscles can also be accomplished with good results using this technique. With the use of different paired-pulse paradigms, TMS enables the assessment of brain circuit excitability or plastic changes affecting these circuits for therapeutic purposes. This allows an evaluation of the intracortical balance between excitatory and inhibitory controls mediated by glutamatergic and gamma aminobutyric acid neurotransmission and gamma aminobutyric acid. Numerous neurologic and psychiatric illnesses can now benefit from new therapy approaches because to rTMS's noninvasive ability to regulate target brain areas [23].

Therapeutic applications of TMS in Psychiatry:

Medication-resistant depression is the most well-known therapeutic indication at the moment. Increasing the left dorsolateral prefrontal cortex's (DLPFC) excitability is the primary objective of this TMS clinical application, since it allows for the local and network-wide modulation of activity [24].

Additional indications with prefrontal targets include addiction (right/left DLPFC), obsessive-compulsive disorder (left orbitofrontal cortex), anorexia nervosa (left DLPFC), negative symptoms of schizophrenia (right/left DLPFC), and posttraumatic stress disorder (right DLPFC) [25].

Therapeutic applications of TMS in Neurology:

Post stroke rehabilitation: The main process thought to cause the restoration of motor function is neuronal plasticity, which works by progressively reestablishing the connections between neural networks and between the brain and muscle. In conventional rTMS procedures, the low-frequency rTMS (LF-rTMS) applies < three Hz to produce an inhibitory effect, while the high-frequency rTMS (HF-rTMS) uses a frequency > three Hz to provide an excitatory influence. Because of its impact on controlling the cortex's excitability, rTMS is seen as a therapeutic method that enhances the recovery of motor function **[26].**

Post stroke aphasia: The language impairment caused by damage to particular language areas in the brain is known as aphasia. Most cases of stroke are shared by cerebrovascular stroke[27]. Patients with injuries display a variety of language deficiencies, such as difficulties understanding syntax, semantics, and the communicative use of these structural components**[28].**

Functional neuroimaging investigations have demonstrated the complicated the underlying pathophysiology of language dysfunction following a stroke, which includes motor cortex expression and overactivation of frontal areas in the right hemisphere [29]. As a result, the majority of post-stroke aphasia treatments seek to correct harmful perturbations of the excitatory balance between the hemispheres in addition to rearranging the language network. rTMS functions by adjusting the cerebral cortex's excitability **[30].**

It is believed that the therapeutic effects of neural activity modulation arise from the facilitation of the rearrangement both the repair of the brain's functional divisions and the networks that cause disruptions to neurological function. It is thought that brain network remodeling is the cause of the functional recovery brought about by rTMS at the behavioral level **[28].**

Post stroke dysphagia: Dysphagia is a common and serious consequence of stroke, as it increases the risk of pneumonia after the event. Moreover, it is associated with a longer hospital stay, a higher death rate, and unfavorable long-term results **[31].**

Exercises, swallowing techniques, and posture adjustments are all part of traditional dysphagia therapy. Despite being utilized in clinics all around the world, there is still a dearth of evidence supporting the usefulness of these interventions. With rTMS, one may precisely control brain activity in a cortico-subcortical network. In relation Applying three Hz and ten Hz rTMS across the cortical representation of the esophagus or mylohyoid muscle in the ipsilesional hemisphere demonstrated a significant improvement to the sham stimulation in dysphagia following stroke. In contrast to the cortical representation of the pharyngeal or mylohyoid muscles, the swallowing function improved at one Hz rTMS and five Hz rTMS in the contralesional motor cortex **[32].**

Parkinson's Disease: Parkinson's disease (PD) patients are increasingly considering transcranial magnetic stimulation (TMS), especially repetitive TMS, as a potential therapeutic strategy. Yang et al.'s thorough 2018 meta-analysis revealed the potential benefits of rTMS treatment for Parkinson's disease patients' motor recovery. They included 23 research with 646 participants in all, and they discovered both short- and long-term improvements in motor function were noteworthy. Significantly, whilst low frequency rTMS did not have the same influence on the improvement of motor function, high frequency rTMS did. Multisession rTMS targeting bilateral M1 areas was determined to be the most effective high-frequency rTMS intervention. This shows the necessity of customized therapies to enhance patient outcomes and showcases the largest impact size **[33].**

TMS in Migraine: The common and frequently incapacitating disorder known as migraine usually presents with moderate to severe headaches and related symptoms. Most people who suffer from migraine headaches will consult a doctor, and most of these patients will be given medication therapy [34]. TMS is helpful for the acute treatment of migraine headaches when administered during the aura phase, according to recent evidence from a randomized, sham-controlled clinical trial **[25].**

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