Repetitive transcranial magnetic stimulation in psychiatry

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive and relatively painless tool that has been used to study various cognitive functions as well as to understand the brain–behavior relationship in normal individuals as well as in those with various neuropsychiatric disorders. It has also been used as a therapeutic tool in various neuropsychiatric disorders because of its ability to specifically modulate distinct brain areas. Studies have shown that repeated stimulation at low frequency produces long-lasting inhibition, which is called as long-term depression, whereas repeated high-frequency stimulation can produce excitation through long-term potentiation. This paper reviews the current status of rTMS as an investigative and therapeutic modality in various neuropsychiatric disorders. It has been used to study the cortical and subcortical functions, neural plasticity and brain mapping in normal individuals and in various neuropsychiatric disorders. rTMS has been most promising in the treatment of depression, with an overall milder adverse effect profile compared with electroconvulsive therapy. In other neuropsychiatric disorders such as schizophrenia, mania, epilepsy and substance abuse, it has been found to be useful, although further studies are required to establish therapeutic efficacy. It appears to be ineffective in the treatment of obsessive compulsive disorder. There is a paucity of studies of efficacy and safety of rTMS in pediatric and geriatric population. Although it appears safe, further research is required to optimize its efficacy and reduce the side-effects. Magnetic seizure therapy, which involves producing seizures akin to electroconvulsive therapy, appears to be of comparable efficacy in the treatment of depression with less cognitive adverse effects.

Key Words

Long-term potentiation, long-term depression, neuropsychiatry, repetitive transcranial magnetic stimulation

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Introduction

The past century has witnessed huge strides in the understanding of normal functioning of the human brain as well as its different pathophysiological states mainly through the development of more efficient structural and functional neuroimaging tools and electrophysiological measures. Although we have come a long way, it seems that the complexities of the human brain demand as many novel ways to unravel these. The induction of finger and foot movements through a magnetic coil placed on the motor cortex by Barker *et al*.[1] opened up the possibility of a novel research tool in neurosciences. Transcranial magnetic stimulation (TMS) is a non-invasive and relatively painless tool that is used in the investigation of cortical functions and also has important therapeutic applications in various psychiatric disorders.

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Basic Principles of Transcranial Magnetic Stimulation

TMS works on the principle of "electromagnetic induction," involving a bank of capacitors that discharge very large current (peak current: Approximately 5000 amps), which rapidly flows through a simple circuit and then through a copper-wire coil. This subsequently results in the induction of a brief and pulsed magnetic field (rise time ~0.1 ms, field strength ~2 Tesla), which is perpendicular to the electric current. When the copper coil is held to the head of the subject, this induced magnetic field generates an electrical current, which is parallel to the

plane of the coil and of adequate intensity to cause localized depolarization of superficial cortical and subcortical neurons, generating a propagating action potential that is then used to study the various neuronal functions.[2] The application of TMS can produce immediate (within seconds) effects such as quick jerky movements and perception of flashes of light, etc. Different frequencies of TMS have been found to result in divergent intermediate-term (seconds to several minutes) biologic effects. Studies have revealed that repeated stimulation of a single neuron at low frequency produces long-lasting inhibition of cell–cell communications, which is called as long-term depression (LTD); conversely, repeated high-frequency stimulation can improve cell–cell communication by long-term potentiation (LTP).[3,4] Long term (days to weeks) effects have also been observed with TMS administration reflected as sustained changes in neurotransmitter release, signaling pathways and gene expression.[5]

Types of Transcranial Magnetic Stimulation

Various types of TMS have been devised depending on the frequency and type of magnetic pulse delivered. Single-pulse TMS discharges a single magnetic pulse at a given time, whereas repetitive pulse TMS (rTMS) delivers repeated single magnetic pulse of the same intensity to a discrete brain area.[6] In paired pulse TMS (ppTMS), a subthreshold stimulus is paired with a suprathreshold stimulus, with an interstimulus interval of 1–4 ms. When the interstimulus interval is 1–4 ms, there is intracortical inhibition (ICI) mediated by GABA and dopamine interneurons, whereas when the interstimulus interval is 5–30 ms, there is intracortical facilitation (ICF) mediated by excitatory NMDA interneuron.[7] Repeated paired pulse TMS (rppTMS) delivers paired pulse at a very low frequency (2 Hz). When the interval between the pairs of pulse is 3 ms, it has been found to reduce cortical excitability, and when the interval is 1.5 ms, it has been found to increase cortical excitability.[8] Theta Burst Stimulation (TBS) is a novel paradigm consisting of short bursts at 50–100 Hz stimulation frequency that are repeated at 5 Hz ("theta frequency"). It is based on theta burst protocols applied in experimental neurophysiology for inducing LTP, which were developed to resemble normal patterns of neural firing occurring in the hippocampus of rats during exploratory behavior.[9]

The frequency of stimulation of rTMS can range from ≤1 to 20 or more per second. In low-frequency rTMS (or slow rTMS), stimulation of <1 Hz is applied for a longer duration (10–15 min), resulting in LTD of cortical neuronal, whereas high-frequency rTMS (or fast rTMS) involves >1 Hz frequency stimulation for a shorter duration, manifested as neuronal LTP.[6,10]

Neuronal Functional Measurements

Various parameters have been devised using TMS to measure the cortical and subcortical neuronal functions:

Motor threshold

A single magnetic pulse applied to the motor cortex generates a twitch in the corresponding muscle known as the motor-evoked potential (MEP). The intensity of the stimulus required to produce the response is the Motor Threshold (MT), which has been defined as the lowest stimulus intensity required producing MEPs of >50 μV peak to peak amplitude in at least 50% of successive trials in a resting or activated muscle.[11] TMS application to the occipital cortex can produce experience of flashes of light known as phosphenes, and the threshold of stimuli to elicit this response is called phosphenes threshold (PT), which is more variable than MT measures.[12]

Cortical silent period

The application of a suprathreshold stimulus can cause suppression of the background EMG activity after the production of MEP in a contracting muscle. This period of suppression from MEP to the return of voluntary muscle activity is known as the Cortical Silent Period (CSP). The first 50–60 ms of the CSP is partly due to Renshaw cell inhibition while the rest is contributed by the reduced cortical excitability.[13]

Transcallosal inhibition

TMS stimulation of the motor cortex can suppress the voluntary contraction of the muscle on the ipsilateral side beginning 10–15 ms after the minimum corticospinal conduction time to the recorded muscle. This inhibition is mediated through corpus callosal fibers and can be used to study the connectivity between different cortical regions.[14]

Central motor conduction time

The latency of motor response evoked by a single motor pulse gives an idea about the neuronal conduction velocity. The difference in conduction latency of MEP evoked with cortical and spinal TMS indicates the central motor conduction time.[15]

rTMS Studies in Normal Individuals

TMS has been used in normal individuals to map brain functions, measure cortical excitability and modulate functional neuronal networks and to study their interrelations.

Cortical and subcortical functions

Various brain properties and cortical and subcortical functions have been studied using TMS, including motor and sensory function, memory, language, visual information processing and saccades.[15]

Neural plasticity

Neural plasticity is defined as a functional reorganization of synaptic connections in response to environmental contingencies or due to disease. Compensatory plasticity is studied by creating virtual lesions with rTMS on one side of the cerebral cortex and observing the dynamic compensatory process in the opposite cerebral hemisphere. In deafferentation experiments, rTMS has been used to study cortical plasticity and the underlying mechanisms.[16]

Brain mapping

This is a method to establish a causal relationship between neuronal activity in a discrete brain region and a particular cognitive, behavioral or neurophysiological phenomenon. This relationship is studied by generating virtual lesions in specific cortical areas, and studying the deterioration in the

performance of the corresponding event, as well as the exact timing of the same (known as causal chronometry). In the process of creating virtual lesions, functional neuroimaging tools such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and single photon emission computed tomography (SPECT) are used to locate the probable cortical area implicated in a cognitive task thus facilitating the exact TMS coil positioning; this method is called imaging-guided TMS neuronavigation.[17]

Neuroendocrinal effects of TMS

The effect of rTMS on the plasma levels of a variety of hormones, including cortisol, prolactin and thyroid stimulating hormone, has been documented in several studies. Although results of these studies were not conclusive, they indicate that TMS might affect neuroendocrine function.[18,19]

Therapeutic Uses of rTMS in Psychiatric Disorders

The pathophysiology of psychiatric disorders is conceptualized in terms of dysfunction of neuronal circuits. Therefore, rTMS holds the potential of being able to selectively modulate activities in brain areas involved in various psychiatric disorders.

rTMS in depression

The therapeutic effects of rTMS have been robust in the field of depression. The efficacy studies of rTMS in depression, including open trials, sham-controlled studies and comparison studies, have involved different methodological designs using various stimulation parameters (frequency, intensity, stimulation site, number of stimuli, duration of treatment, etc.) and heterogeneous sample characteristics (age, unipolar vs. bipolar depression, level of treatment resistance). Two major categories of rTMS have been used in most of the studies: High frequency to the left prefrontal cortex (PFC) and low frequency to the right PFC. Both strategies are found to have similar antidepressant effect, while low-frequency rTMS of right PFC is better tolerated with lower risk of seizure.[20] Several randomized sham-controlled trials[21-23] have reported the antidepressant effect of left prefrontal high frequency rTMS over sham, but some results were negative.[24] In a sham-controlled study involving 40 patients with unipolar or bipolar depression, significant improvement was noted in depression and psychosis rating scores following high-frequency rTMS of left PFC.[25] Metaanalysis of the studies[20,26] further support the antidepressant effects of left prefrontal high-frequency rTMS with small to medium effect size. In contrast, few studies have found superior antidepressant properties of right prefrontal low-frequency rTMS as compared with high-frequency or sham group.[27,28] A 5-week, randomized, double-blind, placebo-controlled trial involving 10 daily applications of high-frequency rTMS to the left PFC in 54 drug-resistant depressed patients revealed rTMS to be an effective and safe adjunctive treatment for drug-resistant major depression.[29] Positive predictors of antidepressant response include patients who are younger, non-psychotic, with shorter duration of depressive episode, low level of treatment resistance and history of previous response to electroconvulsive therapy (ECT) and/or rTMS. Patients with significantly higher level of psychomotor retardation and lower level of agitation at baseline, along with a high level of sleep disturbances, have also shown good response to rTMS. Subjects with depressed mood and feeling of guilt are less likely to benefit from rTMS. Elderly subjects, with psychotic depression, having more treatment resistance and longer duration of depressive episode, respond poorly to rTMS.[30]

rTMS in mania

Studies on the therapeutic efficacy of rTMS in the manic phase of bipolar disorder are few. In the initial therapeutic study of rTMS in mania, comparative effect of high-frequency rTMS of right versus left PFC, as an adjunct to mood stabilizers and neuroleptics, was studied in 18 bipolar mania patients; significantly more improvement was observed with right prefrontal rTMS as compared with left side, and a worsening of mania was noted with left prefrontal rTMS, suggesting that the therapeutic effect of rTMS in mania may show a laterality effect opposite to that in depression.[31] An open-label, prospective study reported therapeutic efficacy of right prefrontal rapid rTMS in nine patients with either bipolar mania or mixed episodes.[32] In another open-label study, add-on 10-Hz rTMS of right PFC demonstrated significant improvement in manic symptoms in bipolar patients.[33] A sham-controlled study involving 41 bipolar manic patients has revealed significant improvement in manic symptoms following high-frequency rTMS application to the right PFC.[34]

rTMS in schizophrenia

In schizophrenia, hypoactivity of prefrontal cortex plays a role in the pathophysiology of negative symptoms,[35] for which high-frequency rTMS of prefrontal cortex has been used; whereas for positive symptoms such as hallucinations, which are associated with hyperactivity of temporoparietal areas,[36] low-frequency rTMS has been studied.

Left prefrontal rTMS for negative symptoms: The effects of rapid TMS of the prefrontal cortex on negative symptoms were studied initially by Cohen *et al*.[37] in an open trial of 20-Hz left prefrontal rTMS for 2 weeks on six schizophrenic patients with chronic negative symptoms. They found a significant reduction in negative symptoms. Subsequently, several open-label, randomized sham-controlled studies and crossover designs have demonstrated the efficacy of high-frequency rTMS of the left PFC in reducing negative symptoms of schizophrenia and producing functional improvement.[38-40] A review of the studies on the effect of rTMS on the negative symptoms of schizophrenia support a selective effect of high-frequency rTMS over PFC on negative symptoms, with more consistent results demonstrated by the open studies as compared with controlled trials.[41]

Left temporoparietal rTMS for auditory hallucinations (AH): Hoffman *et al*.[42,43] conducted preliminary studies on patients with schizophrenia who had frequent AH, with 1-Hz TMS at 80% of MT to the left temporoparietal cortex using a figure-of-eight coil. In a double-blind crossover design, 12 medicated patients underwent active and sham TMS each for 4 days and the stimulation duration was gradually increased from 4 to 16 min/day. Eight of the patients reported a significant improvement in AH with TMS, and the improvement reached significance following the third and fourth days of stimulation. Low-frequency rTMS (1 Hz, 90% motor threshold) application to the left temporoparietal cortex for 10 days has

been reported to produce significant improvement in auditory hallucinations.[44] A review of the studies on the effect of rTMS on AH concluded rTMS to be overall active enough in reducing AH in schizophrenic patients.[41] The two aspects of AH that showed significant improvement with active rTMS compared with sham stimulation were frequency and attentional salience, whereas other AH parameters such as number of voices, loudness, duration of voices and levels of distress were not affected by any condition.[41] Few case reports have also demonstrated the efficacy of rTMS in reducing refractory AH.[45,46] There are case reports suggesting reduction in catatonic symptoms with application of rTMS in schizophrenic patients,[47] although randomized studies are lacking.

rTMS in obsessive compulsive disorder

Studies evaluating the therapeutic efficacy of rTMS in OCD are limited, and the results have been rather inconsistent. Greenberg *et al*.[48] administered 2 Hz rTMS at 80% of MT to left prefrontal, right prefrontal and midline occipital cortex in 12 patients with OCD; compulsive urges were reduced by right prefrontal stimulation up to 8 h after single stimulation, whereas left prefrontal stimulation and occipital stimulation did not produce these improvements. In another sham-controlled study, involving 42 patients of OCD, 10 adjunctive rTMS sessions (10 Hz, at 110% of MT, 20 trains for 5 s) were applied to the right PFC; there was no significant difference in improvement of obsessive-compulsive symptoms between the two groups; nevertheless, there was significant reduction in secondary depression in those receiving active rTMS.[49]

rTMS for craving in substance dependence

Studies have also revealed the potential anticraving effects of rTMS in substance dependence. In a randomized sham-controlled study, 11 nicotine-dependent subjects were randomly assigned to a course of active- and sham-rTMS on consecutive days; craving was significantly decreased after active-stimulation compared with sham-stimulation intraindividually.[50] Similarly, in a study involving 14 smokers, a single session of active high-frequency (20 Hz) rTMS application to the left PFC was found to produce reduction in craving, but was not significant.[51] In a recent outpatient randomized, double-blind, sham-controlled study, 48 chronic smokers were randomly allotted to real and sham rTMS stimulation (10 Hz over the left PFC, at 100% of MT, 20 trains/day, 50 pulses/train, intertrain interval 15 s for 10 days), each group again being randomly presented with either smoking-related or neutral pictures just before TMS intervention. There was significant reduction in cigarette consumption, as evaluated objectively by measuring nicotine levels in urine samples and subjectively by participants' self-reports; furthermore, the treatment blocked the craving induced by presentation of smoking cues.[52] In another randomized cross-over study involving six right-handed patients with cocaine dependence, two sessions of 10-Hz rTMS at 90% of MT was applied on the left or right PFC. The right, but not left, PFC rTMS was found to transiently reduce craving by 19% from baseline, which disappeared after 4 h.[53] Mishra *et al*.[54] in a prospective, single-blind, sham-controlled study, involving 45 patients with alcohol dependence, compared active and sham rTMS with the right PFC (10 Hz, 4.9 seconds/train, intertrain interval of 30 s, 20 trains per session, total 10 sessions). Right PFC high-frequency rTMS was found to have significant anticraving effects in alcohol dependence, with high effect size.[54]

rTMS in other anxiety disorders

Use of rTMS in panic disorder was based on the observation that panic and anxiety increased after fast rTMS over the left or right PFC.[55] In an open case series, three patients with treatment-resistant panic disorder showed modest improvement with 10 rTMS sessions (1 Hz, 110% of MT, 30 trains of 60 s duration) to the right PFC.[56] Alternating low-frequency rTMS to the right PFC with 20-Hz rTMS to the left PFC failed to produce further benefits. Grisaru *et al*.[57] were the first to administer rTMS in post-traumatic stress disorder (PTSD); 10 patients received 0.3 Hz rTMS to both left and right motor cortex at maximum power of the stimulator, 15 pulses to each side; transient improvement in avoidance behavior and overall clinical state was noted. In a placebo-controlled, cross-over design of imaginal exposure therapy with rTMS (1 Hz) versus sham in nine subjects with chronic, treatment-refractory PTSD, active rTMS resulted in significant improvement in hyperarousal symptoms, with an increase in 24-h urinary norepinephrine, serum T_4 and decreased serum prolactin levels.[58]

rTMS in neuropsychiatric disorders

Various studies have demonstrated the efficacy of low-frequency rTMS (0.33–1 Hz) in treating epilepsy and other manifestations of cortical hyperirritability.[59-61] Bae *et al*.[62] reviewed 30 studies of rTMS application in epilepsy, including open-label and controlled trials; significant reduction in seizure frequencies was seen in a majority of the studies with low-frequency rTMS; however, few studies did not demonstrate any seizure reduction. Low-frequency rTMS has been reported to reduce epileptic cortical myoclonus;[63] rTMS delivered in high-frequency (20–100 Hz) bursts or as prolonged low-frequency (1 Hz) trains, over the seizure focus, has been found to produce brief (20–30 min) pause in epilepsia partialis continua.[63] The therapeutic effect of rTMS has been suggested in Parkinson's disease and in other movement disorders. Studies reveal that rTMS application over the primary motor cortex and PFC, with a frequency range from 0.2 Hz to 5 Hz and varying intensity of stimulus (20–120% of MT), frequency of sessions (once a week for 8 weeks to twice a day for 10 days), produced improvement in motor functions, cumulative improvement of gait and bradykinesia by repeating the rTMS sessions.[64]

rTMS In Special Populations

Children and adolescents

There are no controlled trials conducted on the efficacy of rTMS for treatment of any disorder in children and adolescents. However, there are case reports of improvement with rTMS in bipolar disorder, unipolar depression, schizophrenia and seizure disorders such as epilepsia partialis continua, action myoclonus and progressive myoclonic epilepsy.[65] In attention deficit/hyperactivity disorder (ADHD), there is a dysfunction in dopamine neuronal circuitry and rTMS has been suggested as a treatment modality that requires further investigation.[66] There is a need to initially evaluate the safety of rTMS in the child and adolescent population before studying it for therapeutic applications.

rTMS in the geriatric population

The application of rTMS has been little studied in the geriatric population. High-frequency stimulation to the left and right dorsolateral prefrontal cortex (DLPFC) has been found to improve accuracy in action naming in Alzheimer's disease.[67] It has also been found to be useful in late-onset depression, post-stroke depression and depression in Parkinson's disease.[68]

Side-effects of rTMS

Transient headache is the most common adverse effect of rTMS, which resolves spontaneously or requires mild analgesics. Severe adverse effects have been reported rarely. High-frequency rTMS has been reported to induce seizures,[62] induce manic switch and delusions in patients with depression.[69] There is a report of transient increase in auditory threshold upon exposure to single-pulse TMS.[70] In studies of speech arrest involving stimulation of the motor speech area, unexplained crying and laughter has also been observed.[6,68] Local pain and scalp burns from surface EEG electrodes during rTMS sessions have also been documented.[6] Histotoxicity due to rTMS results from mass hyperexcitation of cortical neurons as well as ohmic heating of poorly perfused cortical tissues. Single-pulse TMS has been found to produce distinct immunological effects by producing changes in the CD8+ lymphocyte subset.[6]

Magnetic Seizure Therapy

The latest version of rTMS is Magnetic Seizure Therapy (MST), in which intense level of rTMS is applied for induction of seizures. In an FDA-approved trial, MST was administered to 21 depressed individuals, and all the patients showed response to therapy and had a milder side-effect profile as compared with ECT. Keeping in view these advantages over ECT, it could be thought of replacing the same in the near future.[71]

Conclusion

It is evident that rTMS is a unique tool in the history of psychiatry, which has got a wide range of research and therapeutic uses. We need to know more about the patients who benefit from rTMS, the optimal form of treatment delivery, the magnitude of therapeutic effects and risks of treatment. It seems that a new era has begun with the advent of rTMS, in which we have novel options of physical treatment and non-invasive brain modulations.

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