Transcranial Magnetic Stimulation: A New Investigational and Treatment Tool in Psychiatry

Zafiris J. Daskalakis, M.D., Ph.D., F.R.C.P.C.
Bruce K. Christensen, Ph.D., C.Psych.
Paul B. Fitzgerald, M.B.B.S., M.P.M., F.R.A.N.Z.C.P.
Robert Chen, M.B.B.Chir., M.Sc., F.R.C.P.C.

Transcranial magnetic stimulation (TMS) is a new investigational technique used to explore various neural processes and treat a variety of neuropsychiatric illnesses. The most notable advantage of TMS is its ability to directly stimulate the cortex with little effect on intervening tissue. Single-pulse stimulation techniques can measure cortical inhibition, facilitation, connectivity, reactivity, and cortical plasticity, providing valuable insights into the cortical physiology. Repetitive TMS (rTMS) is currently being used to investigate cognitive processes and as a treatment tool in disorders such as depression and schizophrenia. Both TMS and rTMS are safe and well tolerated. The most serious side effect of high-frequency rTMS is seizures. TMS represents an exciting new frontier in neuroscience research, providing insights into the pathophysiology and treatment of various neuropsychiatric disorders.

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Transcranial magnetic stimulation (TMS) is a unique experimental tool that allows researchers to noninvasively study the cortex in healthy and diseased states.[1] It has been used as an investigational tool to measure a variety of cortical phenomena including cortical inhibition and plasticity,[2,3] as a probe to explore cognitive mechanisms,[4] and as a treatment tool in illnesses such as depression and schizophrenia.[5,6] In this article we review the role of TMS as an investigational and treatment tool in major mental illness. We also discuss safety issues, limitations, and directions for future research.

OVERVIEW OF TMS TECHNOLOGY

In 1831 Michael Faraday demonstrated that a current was induced in a secondary circuit when it was brought in close proximity to the primary circuit in which a time-varying current was flowing. Here, a changing electrical field produces a changing magnetic field that, consistent with Faraday's law, causes current to flow in a nearby conducting material. With TMS, electrical charge is stored in capacitors. Periodic discharge of this stored

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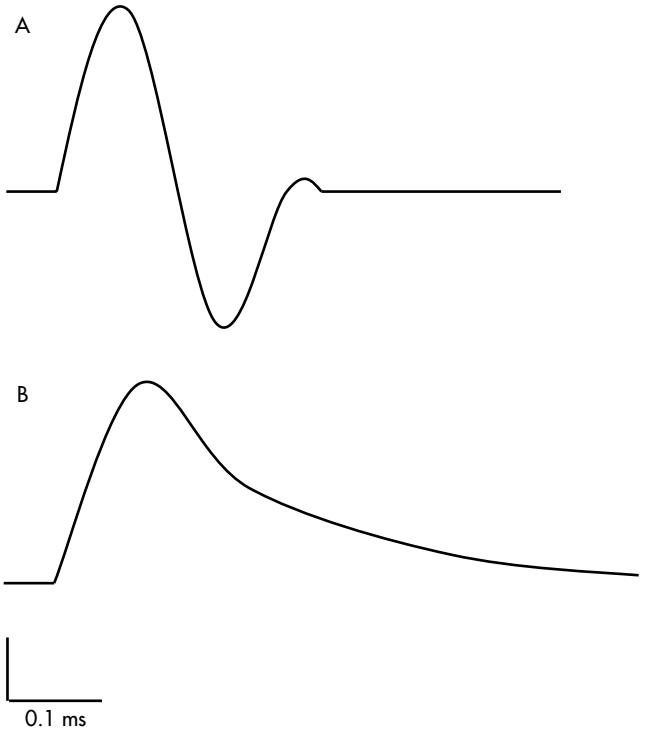
From the Centre for Addiction and Mental Health, University of Toronto, Ontario, Canada (Z.J.D., B.K.C.); Dandenong Psychiatry Research Centre, Dandenong, Victoria, Australia (P.B.F.); and Division of Neurology, Toronto Western Hospital, University of Toronto, Ontario, Canada (R.C.). Address correspondence to Dr. Daskalakis, Schizophrenia and Continuing Care Program, Centre for Addiction and Mental Health, 7th Floor, Clarke Division, 250 College Street, Toronto, Ontario, Canada. E-mail: Jeff_Daskalakis@camh.net.

energy from the capacitors and through the conducting coil produces a time-varying electrical field. This electrical field produces a transient magnetic field that causes current to flow in a secondary conducting material, such as neurons. TMS discharge over the scalp induces a depolarization of the conducting neural tissue located just under the coil. Because intervening tissue between the coil and the cortex (i.e., scalp and skull) is largely nonconducting, the magnetic field that is produced penetrates these tissues virtually unattenuated.

Commercially available stimulators produce two pulse types: a biphasic pulse and a monophasic pulse (Figure 1). The biphasic pulse is sinusoidal and is generally of shorter duration than a monophasic pulse, which involves a rapid rise from zero followed by a slow decay back to zero. In commercially available stimulators, two types of coils are typically used: the circular and the figure-eight-shaped coil. In general, figure-eight-shaped coils produce a more focused magnetic field and a better spatial resolution of activation compared with circular coils.[7] In contrast, circular coils tend to be more powerful.

The orientation and intensity of the current that passes through the coil determine the type of tissue stimulated as well as the strength of that stimulation. By and large, in small figure-eight-shaped coils, neurons are activated in a cortical area of approximately 3 cm^2 and to a depth of approximately 2 cm.[8] In most studies, figure-eight coils are held over the cortex flat and at about 45° from the midline position, perpendicular to the central sulcus. This induces a current in the posterior-to-anterior direction, perpendicular to descending pyramidal neurons and parallel to interneurons, which modulate pyramidal cell firing.[9] It is the orientation between the coil and underlying neural tissue that allows researchers to selectively activate different groups of neurons, providing useful information regarding neuronal inhibition, excitation, and connectivity.

FIGURE 1. Time course of a biphasic magnetic field (A) and a monophasic magnetic field (B).



TMS AS A TOOL TO MEASURE CORTICAL INHIBITION

The ability to measure cortical inhibition rests on the ability of TMS to stimulate cortical inhibitory and excitatory interneurons in addition to corticospinal output neurons.[10,11] At low intensities, intracortical inhibitory and excitatory neurons are stimulated without any change in the excitability of corticospinal output neurons. The paradigms that demonstrate cortical inhibition include paired-pulse TMS (ppTMS),[2,12] cortical silent period TMS (CSP),[13,14] and transcallosal inhibition (TCI).[15] Paired-pulse TMS involves a subthreshold conditioning pulse followed by a suprathreshold test pulse. A high-intensity suprathreshold magnetic pulse activates cortical pyramidal neurons directly and indirectly, via excitatory interneurons, leading to corticospinal output that can be measured peripherally as a motor evoked potential (MEP) following stimulation of the motor cortex. In contrast, a low-intensity subthreshold pulse only excites cortical interneurons and, therefore, does not result in an MEP. By combining a subthreshold pulse with a suprathreshold pulse, one can assess the inhibitory effects of interneurons on cortical output.[2,16] That is, when a subthreshold pulse precedes the test pulse by 1 to 5 ms, inhibitory interneurons are recruited and the MEP response is inhibited by 50% to 90%[2] (Figure 2). Evidence for ppTMS inhibition originating in the cortex includes the reduction of descending corticospinal waves.[17,18] In addition, anodal transcranial electrical stimulation (TES), which directly activates corticospinal axons,[10,19] is not inhibited by a TMS conditioning pulse.[2] CSP experiments involve motor cortical stimulation superimposed on background electromyographic activity. At high stimulus intensities a cessation of all electromyographic activity occurs, producing a silent period (Figure 3). The first half of the silent period is in part due to spinal inhibition,[20] but the second half (>50 ms) is due to reduced cortical excitability.[13,17,20,21] In TCI,

stimulation of the ipsilateral motor cortex a few milliseconds prior to stimulation of the contralateral motor cortex inhibits the size of the motor evoked potential produced by contralateral motor cortical stimulation. It has been demonstrated that in normal control subjects ipsilateral cortical stimulation 6 to 15 ms prior to contralateral cortical stimulation inhibits the size of the MEP produced in hand muscles by 50% to 75%[15] (Figure 4). Ferbert et al.[15] have provided evidence that TCI represents a cortical inhibitory phenomenon by demonstrating that there was a clear inhibition of MEPs by magnetic test stimuli, whereas test responses, evoked by small anodal electrical shock that stimulates corticospinal axons, were not significantly inhibited by a contralateral magnetic conditioning stimulus.

FIGURE 2. **Mean cortical excitability curve in 15 healthy control subjects. Cortical excitability is expressed as a percentage of the mean unconditioned motor evoked potential (MEP) when the test stimulus is preceded by a conditioning stimulus at different interstimulus intervals (2, 4, 10, 15, or 20 ms). Values below 100% represent inhibition and values above 100% represent facilitation. Inhibition occurs at short interstimulus intervals (2, 4 ms) and facilitation at longer interstimulus intervals (10, 15, 20 ms).**

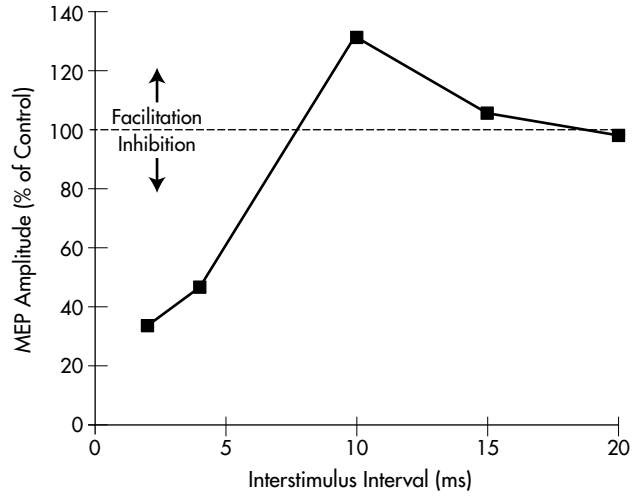
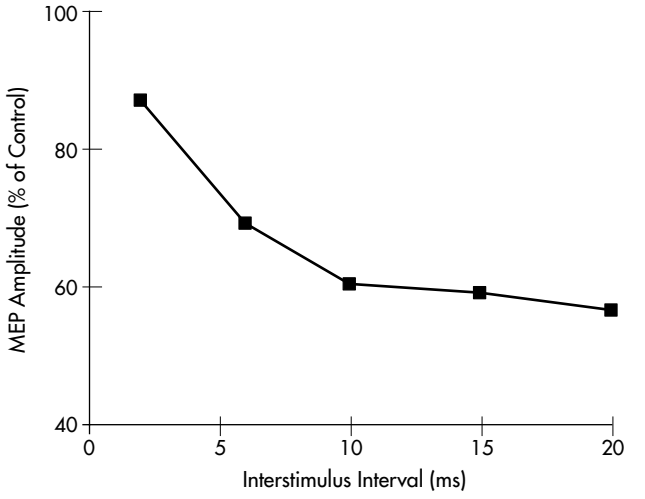


FIGURE 3. **Surface electromyogram recordings from the tonically active first dorsal interosseus muscle following 40% suprathreshold transcranial magnetic stimulation of a healthy control subject. The waveform represents the average of 15 trials. The silent period starts at the onset of the motor evoked potential and ends with return of motor activity, marked by the arrows.**

CORTICAL INHIBITION DEFICITS IN NEUROPSYCHIATRIC ILLNESS

Recent studies using these TMS paradigms have demonstrated altered cortical inhibition in neuropsychiatric illnesses such as obsessive-compulsive disorder (OCD),[22] Tourette's disorder,[23] and schizophrenia.[24] For example, Greenberg et al.[22] compared 18 patients with OCD and 11 healthy control subjects and demonstrated that the patient group had significantly less cortical inhibition, as indexed by ppTMS, compared with healthy control subjects. Similarly, Ziemann et al.[23] demonstrated that 20 patients with Tourette's disorder have cortical inhibition deficits compared with 21 healthy control subjects in both ppTMS and CSP measures of inhibition. We have completed a cross-sectional study that measured cortical inhibition, using TMS in unmedicated patients, medicated patients, and healthy control subjects. Unmedicated patients with schizophrenia demonstrated significantly less cortical inhibition compared with normal control sub-

FIGURE 4. **Mean transcallosal inhibition curve in 15 healthy control subjects. Transcallosal inhibition is expressed as a percentage of the mean unconditioned motor evoked potential (MEP) when the test stimulus is preceded by a conditioning stimulus from the contralateral motor cortex at different interstimulus intervals (2, 6, 10, 15, or 20 ms).**



jects on ppTMS, CSP, and TCI inhibitory paradigms.[24] Medicated patients, however, had greater cortical inhibition compared with unmedicated patients. Collectively, these studies provide new insights into the pathophysiology of neuropsychiatric conditions. For example, recent evidence suggests that ppTMS and CSP inhibition reflect the function of $GABA_A$ and $GABA_B$ neurotransmission, respectively.[25–27] Moreover, several authors have suggested that impaired cerebral inhibitory processes are responsible for the symptoms seen in OCD,[28] Tourette's disorder,[29] and schizophrenia.[30] Swerdlow et al.[30] demonstrated that patients with schizophrenia have deficits in pre-pulse inhibition (PPI). They suggest that deficient PPI in schizophrenia patients is a measure of the loss of inhibitory gating, which may lead to sensory flooding, cognitive fragmentation, and possibly psychosis. Whether a relationship between cortical inhibition deficits and these impaired cognitive processes exists remains to be seen.

TMS AS A TOOL TO MEASURE NEURAL PLASTICITY

Another application of TMS is the measurement of neural plasticity. Broadly, plasticity is defined as a functional reorganization of synaptic connections in response to environmental contingencies or due to disease. Classen et al.[3] recently described a paradigm to directly measure neural plasticity by using TMS. This is accomplished through 1) measuring the spontaneous direction of individuals' TMS-induced thumb movement; 2) training the individuals to perform a simple motor task opposite to the direction of TMS-induced thumb movement; and 3) evaluating subsequent directional changes in TMS-induced thumb movement over time. Classen et al.[3] demonstrated that immediately after training, the direction of TMS-induced movements follows the direction of training, but that over the next 40 minutes the direction of thumb movement returns to its pre-training orientation. It is this process of organization in response to training, and subsequent return to baseline, that is thought to represent neural plasticity.[3,31] Other TMS paradigms for measuring neural plasticity have also been described.[32]

Abnormalities in neural plasticity have been hypothesized as a key pathophysiological process underlying neuropsychiatric illnesses such as depression and schizophrenia. For example, Petrie et al.[33] and Olney et al.[34] have suggested that dysfunctional plasticity arises out of impaired NMDA receptor function in depression and schizophrenia, respectively. With TMS, we now have the ability to directly test such hypotheses.

TMS AS A TOOL TO MEASURE CORTICAL CONNECTIVITY

The recent marriage of TMS with electroencephalogram (EEG) recordings has afforded neuroscientists the ability to measure cortico-cortical connectivity. This has required the development of unique amplifiers and electrode caps designed to minimize artifacts from magnetic stimuli. With these modifications, Ilmoniemi et al.[35] have been able to record cortical potentials immediately after TMS and follow the transmission of such potentials across the cortex. Recordings are made from a modified electrode cap that records cortical potentials following TMS. With conventional TMS, a large artifact is produced that saturates the recording EEG amplifier and thus precludes any measurement during the first 100 ms, the time of greatest interest from a neurophysiological perspective. Ilmoniemi et al.[35] have shortened the intensity and duration of this artifact by using three modifications to standard stimulation and recording techniques: 1) a smaller stimulation coil is used (40 mm diameter per wing) that carries a biphasic pulse to minimize the effects of the magnetic pulse on the recording electrodes; 2) the electrode cap is built with Ag/AgCl electrodes with larger hollowed centers to minimize movement and heating artifacts on the cap; and 3) the amplifier uses a lock-and-hold switch that prevents any recording during TMS stimulation and consequently avoids saturation of the recording amplifier. Their experiments demonstrate that stimulation of the motor cortex results in activation of the contralateral homologous motor cortex in approximately 20 ms. Such experiments provide information regarding site, strength, and duration of cortico-cortical connections and hold promise for neuroscientists interested in testing connectivity and cortical neurocircuitry in healthy and diseased brains. An example of a potential application for this investigational tool is the measurement of corpus callosum connectivity in illnesses such as schizophrenia, in which the pathophysiology has been closely linked to dysfunctional cerebral connectivity.[36]

OVERVIEW OF REPETITIVE TMS TECHNOLOGY

Repetitive transcranial magnetic stimulation (rTMS) involves stimulation of the cortex by a train of magnetic pulses at frequencies between 1 Hz and 50 Hz, in contrast to single-pulse TMS, in which the frequency of stimulation is less than 1 Hz.[37] Higher frequencies are achieved because the bipolar stimulus is shorter than a unipolar stimulus and requires less energy to produce neuronal excitability. Thus capacitors can charge and

discharge rapidly, thereby achieving high stimulation rates. It is the ability to achieve such high stimulation rates that has made rTMS a valuable tool in investigation and treatment of many neuropsychiatric disorders.

Repetitive TMS can either activate or inhibit cortical activity, depending on stimulation frequency. Low-frequency (~1 Hz) stimulation for a period of approximately 15 minutes induces a transient inhibition of the cortex.[38] The mechanisms behind such inhibition are unclear, although there are similarities to long-term depresssion.[38] In contrast, stimulation at frequencies above 1 Hz has been shown to induce increased cortical activation.[39] The mechanisms by which such activation occurs are less clear, although some authors suggest that it may be due to a transient increase in the efficacy of excitatory synapses.[40] Stimulating at high frequencies has been shown to produce transient "functional" lesions in cortical areas receiving stimulation.[4,41] Therefore, rTMS may be used as a neurophysiological probe to test the functional integrity of different cortical regions by either activating these regions or inhibiting them.

REPETITIVE TMS AND COGNITION

Repetitive TMS is also currently being used to evaluate cognitive processes. As a result of its ability to selectively disrupt cortical areas, cognitive functions can be selectively impaired. For example, Pascual-Leone et al.[41] were able to produce speech arrest with 8–25 Hz rTMS to the left cortex. Claus et al.[42] demonstrated interference in language comprehension from 50 Hz rTMS to the left hemisphere but not from similar application to the right hemisphere. Similarly, Flitman et al.[4] and Wassermann et al.[43] found that rTMS produced naming errors and impaired memory performance following stimulation over the left anterior cortex. Other rTMS studies have provided information about cortical specialization. Pascual-Leone et al.[44] investigated the role of the dorsolateral prefrontal cortex (DLPFC) in implicit procedural learning. In this study, low-intensity rTMS was applied to the DLPFC, to the supplementary motor area, or directly to the ipsilateral hand used in testing. It was demonstrated that DLPFC stimulation markedly impaired implicit procedural learning, whereas stimulation of the other areas did not impair learning. Similarly, Terao et al.[45] used rTMS for mapping the topography of cortical regions active during saccadic eye movement as well as for constructing a physiological map to visualize the temporal evolution of functional activities in the relevant cortical regions. Thus, rTMS is useful for evaluating the cortical circuitry involved in generating cognition and other functions.

Recent evidence also suggests that rTMS may be an effective tool for enhancing cognitive function. For example, Mottaghy et al.[46] demonstrated that rTMS at a frequency of 5 Hz, applied to Wernicke's area in right-handed healthy males, led to a brief facilitation of picture naming by shortening linguistic processing time immediately after rTMS was applied. This was not found when rTMS was applied to the right hemisphere homologue of Wernicke's area, Broca's area, or the visual cortex. Similarly, Boroojerdi et al.[47] demonstrated that rTMS, applied to the left prefrontal cortex in 16 right-handed healthy volunteers, led to enhanced analogic reasoning processes (i.e., the ability to determine the similarity between different stimuli, scenes, or events). This study also strengthened the previous findings of the role that the left prefrontal cortex plays in analogic reasoning.[48] Thus, rTMS can potentially be used to enhance cognition. More work, however, clearly needs to be undertaken before its utility in this regard can be established.

REPETITIVE TMS IN THE TREATMENT OF PSYCHIATRIC DISORDERS

Repetitive TMS has also shown promise as a potential treatment for psychiatric disorders, such as depression, in which the pathophysiology has been linked to disrupted cortical function. Treatment studies can be broadly grouped into two categories based on stimulation frequency and location: 1) high-frequency rTMS (10–20 Hz) to the left prefrontal cortex and 2) low-frequency rTMS (≤1 Hz) to the right prefrontal cortex. Before we proceed to a discussion of these studies, it is important to note that the majority of treatment studies are of the high-frequency, left prefrontal cortex group. Therefore this category has the greatest number of both positive and negative findings.

Several studies using high-frequency (10–20 Hz) rTMS over the left prefrontal cortex have demonstrated efficacy in the treatment of depression. George et al.[49] initially reported modest improvement (mean Hamilton Rating Scale for Depression [Ham-D] score decreased from 23.8 to 17.5) in 6 treatment-refractory depressed patients in an open study using rTMS. Two of these 6 patients had significant improvement in depressive symptoms, and 1 patient experienced a complete remission of depressive symptoms. Very promising results were also reported by Pascual-Leone et al.,[5] who showed rTMS was effective at treating depressive symptoms in 17 patients with medication-resistant depression and psychotic features when applied daily for 1 week. This was a multiple crossover, randomized, placebo-

controlled study with sham rTMS and stimulation of different cortical areas used as control conditions. Similarly, George et al.[50] and Figiel et al.[51] reported significant improvement in depressive symptoms in a group of patients with major depression in 2-week placebo-controlled crossover trials of real and sham high-frequency rTMS. Grunhaus et al.[52] recently compared rTMS and ECT in 40 patients with major depressive disorder (MDD) in an unblinded study, which did not include a placebo control group. They found that rTMS was less effective than ECT in patients with MDD and psychosis but was equal to ECT in patients without psychosis. Several other studies have also reported positive results with high-frequency rTMS over the left prefrontal cortex.[53,54]

Some studies have demonstrated the efficacy of low-frequency (≤1 Hz) rTMS over the right prefrontal cortex in depression. For example, in a large double-blind study of 70 depressed patients, Klein et al.[55] examined the therapeutic efficacy of right prefrontal slow rTMS. Patients were randomly assigned to receive rTMS or sham rTMS. After 2 weeks of treatment, 49% of rTMS-treated patients were classified as responders (i.e., >50% reduction in Ham-D score), whereas only 25% of patients treated with sham rTMS were responders. Other studies have also demonstrated right low-frequency rTMS to be useful in depression.[56–58]

In contrast, other rTMS trials in depression have been equivocal or have shown lack of efficacy. For example, Berman et al.[59] reported only a modest reduction in depressive symptoms following a 10-day course of high-frequency rTMS to the left prefrontal cortex. This study was conducted in a double-blind placebo (i.e., sham)-controlled manner. Similarly, Loo et al.[60] failed to find a significant difference between real and sham high-frequency rTMS to the left prefrontal cortex in 18 patients with depression after 2 weeks of treatment. Other studies have also reported negligible results.[61,62]

Several explanations may account for these discrepant findings. First, the majority of patients included in these studies were treatment-resistant and thus may represent a subset of patients who generally are poor responders to all forms of treatment. Second, stimulation parameters, including frequency, intensity, and duration, vary from study to study, making direct comparisons between these studies very difficult. Third, the concomitant use of medications in these studies obfuscates the independent effects that rTMS may have on mood symptoms, making it unclear whether improvement was related to rTMS alone, medication, or the two combined. Fourth, no consistent method for precisely localizing the prefrontal cortex has been devised, and therefore different cortical areas may be stimulated between subjects and between studies. A recent study by Kimbrell et al.[63] attempted to clarify these issues. The authors examined the possibility that a subset of depressed patients with cerebral hypometabolism would respond to high-frequency rTMS whereas patients with cerebral hypermetabolism would respond to low-frequency rTMS. In doing so, these authors attempted to target treatment to underlying cerebral pathophysiology. They found that patients with baseline hypometabolism did respond better to high-frequency rTMS stimulation than patients with baseline hypermetabolism, who had a better response to low-frequency rTMS. It is clear, therefore, that rTMS represents a promising new treatment modality for depression. More research, however, is necessary before definitive conclusions regarding its efficacy as an adjunct or alternative treatment in depression can be made. Future studies designed to examine the efficacy of high-frequency left prefrontal rTMS compared with low-frequency right prefrontal rTMS are needed. Further information about rTMS trials in the treatment of depression has been compiled by Avery, George, and Holtzheimer and is available at *www.ists.unibe.ch.*

In contrast to the larger number of depression studies, relatively few studies have been conducted to evaluate the efficacy of rTMS as a treatment tool for schizophrenia. Hoffman et al.[64] demonstrated that rTMS at 1 Hz, delivered to a site between the left temporal and left parietal regions, was effective at reducing auditory hallucinations in 3 patients with schizophrenia in a double-blind crossover design. In contrast, Klein et al.[65] did not find a significant effect of 1 Hz right prefrontal rTMS in 35 actively psychotic patients with schizophrenia or schizoaffective disorder. This study evaluated general psychotic symptomatology as opposed to hallucinations alone. It also incorporated a double-blind placebo-controlled design in a much larger sample. Hoffman et al.,[6] in a double-blind crossover trial, reported that 1 Hz transcranial magnetic stimulation to the left temporoparietal cortex significantly reduced hallucinations relative to sham stimulation in 12 patients with schizophrenia. More recently, Rollnik et al.[66] used high-frequency rTMS to the left DLPFC in a 2-week double-blind crossover design to treat 12 patients with schizophrenia. They demonstrated a significant reduction in symptoms as rated by the Brief Psychiatric Rating Scale. The same criticisms can be made of these studies as of the rTMS studies in depression. For example, factors such as location, frequency, intensity, and duration would have to be standardized between studies in order to best determine how to optimize treatment outcomes in this illness.

SAFETY OF TMS

In numerous studies, single-pulse TMS has been found to pose no significant health risk to humans. Prospective studies designed to systematically evaluate health effects have found no changes in EEG, blood pressure, heart rate, serum cortisol, serum prolactin, cerebral blood flow, memory, or cognition.[67–69] Single-pulse TMS is now in routine clinical diagnostic use in many neurophysiological laboratories worldwide. Wassermann et al.[70] concluded that stimulation at less than 1 Hz carries only a remote likelihood of seizure. Nevertheless, seizures have been reported in patients with recent stroke who were receiving single-pulse TMS for clinical evaluation. Therefore, subjects should be notified of the remote risk of a seizure. The most commonly reported side effect of TMS is headache (5%). Subjects may experience some discomfort under the coil due to muscle contraction and stimulation of nerves on the scalp; however, if a subject develops headache, it is usually easily managed with standard analgesics. Earplugs may be used during TMS sessions to prevent discomfort from the clicking noise generated by the stimulation. However, no hearing loss has been found in humans exposed to TMS, even with extensive exposure to repeated stimulation over several years.[71] Coil heating can be a risk within the stimulation parameters to be used in some protocols. However, most stimulators are equipped with temperature sensors that disable the device if the coil temperature exceeds a threshold level. Magnetic fields are virtually unattenuated by human tissue. The peak magnetic field strength induced by magnetic stimulation is about 2 tesla, similar to the static magnetic field strength of clinical magnetic resonance imaging (MRI) scanners. The total time of exposure to the magnetic field for TMS procedures is extremely brief in comparison to a clinical MRI. The maximal magnetically induced charge density (expected to be in the range of 2–3 $\mu C/cm^2$) is below the threshold for neuronal injury (about 40–100 $\mu C/cm^2$).[72] It is important to note that subjects with metallic or electronic implants should be excluded because of the risk that magnetic field exposure may exert torque, affect the functioning of such implants, dislodge clips, and result in bleeding.

The risks of rTMS are similar to those of single-pulse TMS with the exception of seizure induction. It has previously been demonstrated that seizures may be induced at stimulation frequencies of 25 Hz in healthy subjects.[73] The risk is heightened in subjects with an underlying seizure disorder.[74] Pascual-Leone et al.[75] demonstrated that in contralateral muscles, trains of rTMS applied to the motor cortex induced a spread of cortical excitability. This spread of excitability depended on the intensity and frequency of the stimuli and probably constituted an early epileptogenic effect of rTMS. Recommendations for safe ranges of rTMS stimulation parameters to avoid seizure induction have been published elsewhere by Chen et al.[76] These authors suggested that at stimulation frequencies of 20 Hz and intensities of 110% above the resting motor threshold, the train duration should not exceed 1.2 seconds.[76] In fact, a recent report of a seizure in a patient receiving rTMS for depression treatment used stimulation parameters in excess of this.[77] Despite these guidelines, some authors advocate the use of simultaneous EEG during rTMS to monitor for any early seizure activity.[78]

Repetitive TMS has not been shown to result in any permanent changes in neurological examination findings, cognitive performance, electroencephalogram or electrocardiogram readings, or hormone levels (prolactin, adrenocorticotropic hormone, thyroid-stimulating hormone, luteinizing hormone, and follicle-stimulating hormone).[75] For example, Little et al.[79] showed that there were no gross deleterious cognitive effects following 2 weeks of 1-Hz or 20-Hz rTMS at 80% of motor threshold over the left prefrontal cortex in 10 subjects with depression who received 2 weeks of either low-frequency (1 Hz) or high-frequency (20 Hz) rTMS and then were crossed over to the other treatment condition. In fact, several of the aforementioned rTMS–cognition studies demonstrated that any changes induced were brief (minutes to hours). Moreover, Nahas et al.[80] assessed 22 depressed adults who received daily left prefrontal rTMS for the treatment of depression in a 2-week double-blind, placebo-controlled trial with T_1- and T_2-weighted volumetric MRI scans for structural changes. They demonstrated that no structural differences were observed before and after treatment and concluded that 10 days of daily prefrontal rTMS does not cause observable structural changes on MRI scans in depressed adults. These studies, however, are limited by a small sample size and therefore need to be replicated before any firm conclusions regarding safety are made.

CONCLUSION

TMS represents a safe and effective method for evaluating aspects of the cortex in healthy and diseased states. Direct measurement of cortical excitability, inhibition, plasticity, and connectivity is now possible with this investigational tool. Using TMS and EEG, efforts are currently being made to measure cortical inhibition and plasticity from multiple cortical areas rather than just the motor cortex. This may have a tremendous impact on future research efforts in a variety of neuropsychi-

atric disorders whose pathophysiology has been closely linked to the integrated function of multiple cortical areas. Moreover, rTMS represents an exciting new tool for probing the functional integrity of the brain as well as offering a new dimension in the treatment of a variety of neuropsychiatric disorders including depression and schizophrenia. Here too, studies are currently under way evaluating TMS not only as a tool to treat neuropsychiatric illnesses without seizure induction, but also as a tool to induce seizures from different cortical areas in an effort to mitigate any prolonged cognitive effects. Given its relative safety and tolerability, its likely utility will be to augment the effects of psychotropic medications or as an alternative treatment option to ECT in treatment-resistant cases.

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