An Introduction to Transcranial Magnetic Stimulation and Its Use in the Investigation and Treatment of Depression

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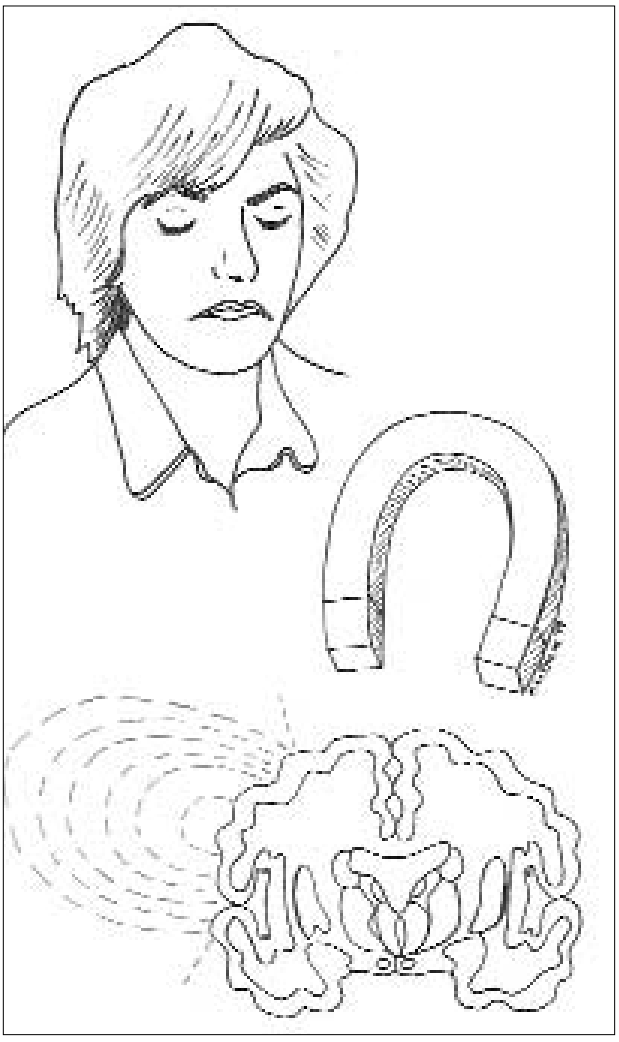
Abstract

Research during the past decade and a half has led to the development of Transcranial Magnetic Stimulation (TMS). In this procedure a pulsed magnetic field generated extracranially induces focal intracranial electrical discharges. TMS has been used in the investigation of neurological and neuropsychiatric disorders, and more recently has emerged as a tool in the study and treatment of depressed mood in the context of Major Depressive Disorder and Bipolar Disorder. Although data are limited and preliminary, early results are promising with regards to the efficacy of TMS in alleviating depressed mood. The antidepressant effect, however, is currently short-lived, lasting hours to weeks. TMS appears to be safe, with only minor side effects in both healthy and neurologically impaired individuals. However, a possible increased predisposition to generalized seizures may exist among those with multiple sclerosis, stroke, and epilepsy, both during and following the procedure. Ongoing research into optimization of hardware specifications, treatment protocols, and side-effects, may allow TMS to emerge as an alternative to psychoactive medications and electroconvulsive therapy in treating primary psychiatric disorders where depressed mood is prominent, as well as secondary and reactive depression arising in the context of medical conditions and surgical procedures.



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Transcranial Magnetic Stimulation – An Introduction

Following the discovery of the unified and interchangeable nature of electric and magnetic forces, it became evident that electric currents generate magnetic fields while changing magnetic fields generate electric currents. By this time it

had already been well established by Galvani's and Volta's classic experiments that electric currents were capable of stimulating neuronal tissues. The combination of these two concepts – the unity of electric and magnetic forces, and the responsiveness of neurons to electrical stimulation – is now being harnessed to study and manipulate the central nervous system (CNS) from both neurologic and psychiatric perspectives. A technique called Transcranial Magnetic Stimulation (TMS) uses an externally generated changing magnetic field to induce electric current intracranially. This is in contrast to the application of an electric current that is generated externally and transmitted to the brain through the skull (for example in electroconvulsive therapy). When electricity is forced to pass through the skull, the current used must be relatively large as the skull is a powerful insulator with an electrical resistance 8 to 15 times greater than that of soft tisues.[2] Furthermore, externally generated electric currents cannot be focally directed as the skull dissipates the electricity globally leading to massive depolarization of cortical and subcortical structures.[2] Such difficulties are minimized upon exposure of the skull to TMS, where the changing external magnetic field undergoes minimal attenuation in the skull tissues while inducing smaller, focally directed electric currents within the brain.[1,2]

Barker *et. al.* first described in 1985 the use of a pulsed (i.e. changing) magnetic field focused over specific regions of the cerebral cortex to induce muscle action potentials.[3,4] The use of pulsed magnetic fields to induce electrical activity in peripheral nerves had been described much earlier, in the 1960's.[1] The mathematical framework describing how pulsed magnetic fields may be used to generate electrical currents in the human brain was subsequently described by Barker in 1987.[1] The technique requires a hand-held coil shaped as a circular disc (or more recently as a figure-8), with an inner diameter of approximately 60 millimeters (mm) and an outer diameter of approximately 130mm. The coil is held near the patient's head, and is connected to a power-source which generates an electric current that is switched on and off repeatedly producing a changing magnetic field in the vicinity of the coil. The frequency at which the current (and hence magnetic field) is pulsed varies from as low as 1-5 Hz to as high as 25-30 Hz. The higher frequency technique has been found to be particularly effective in psychiatry and has been termed Rapid Rate Transcranial Magnetic Stimulation (rTMS).[1,5,6] rTMS is believed to be unique in that rapid pulsation can induce electrical currents within neurons while they are in the refractory period, although how this relates to an altered clinical manifestation is unclear. The magnetic field, passing largely unimpeded through the skull, induces a current within the brain tissue.[1] Depending on the region of the brain over which the coil is physically placed, specific circumscribed areas can be stimulated. This avoids generalized seizure-like discharge and global stimulation of cortical and subcortical structures. TMS has been used for multiple purposes in the field of neurology including establishing hemispheric language dominance, localization of epileptogenic foci, and the study of motor pathways originating at the cerebral cortex and relevant motor pathway physiology.[1,2,6,7] It has also been utilized in neuropsychiatry in the mapping of attention, memory, movement, speech, and vision.[8] Clinically, TMS has been combined with electromyographic studies (EMG) to determine impairment in CNS conduction pathways by measuring differences in the rates of muscle activation upon electromagnetic stimulation at the cerebral cortex in comparison with similar stimulation at spinal nerve roots.[1,9,10] This assessment is useful in the diagnosis and prognostication of demyelinating diseases such as multiple sclerosis. More recent efforts have focused on the use of TMS in the symptomatic improvement of Parkinson's disease.[9,11,12]

Being a relatively new technique, optimization of parameters such as frequency of pulsing of the magnetic field, size of the coil utilized, strength of the magnetic field generated, and duration of induction of electrical current has yet to be established.[13,14] Furthermore, it is likely that such parameters will vary substantially depending on the specific neurological or psychiatric applications.

Use of TMS in the Treatment of Primary Mood Disorders

Several serendipitous findings in the course of neurological and psychoneurological testing have suggested that TMS may be useful in the study and treatment of primary psychiatric mood disorders. Grisaru *et. al.* noted an improvement in the mood of two Parkinsonian patients following TMS while measuring nerve conduction times, while studies of hemispheric language dominance using rTMS have found affective reactions in a considerable number of patients following dominant frontal cortex stimulation.[7,15,16] Given that TMS is focally applied, however, the question arose as to which specific regions of the brain should be stimulated. Dysfunction in the frontal lobes, particularly involving the left prefrontal cortex, has been implicated in the development of major depressive episodes.[13,17,20] Furthermore, studies of patients with strokes causing damage in the left prefrontal cortex have suggested an increased risk of developing depression, while studies of patients with multiple sclerosis have shown a greater number of plaques in the left frontal lobe of those who have comorbid depression in comparison to patients with similarly severe multiple sclerosis but no depression.[17,20] Findings from functional neuroimaging studies, Computed Tomography, and Magnetic Resonance Imaging have also described abnormalities in the left prefrontal cortex in both primary and secondary depression.[17,19] The observation that TMS may affect mood states, and the implication of the frontal lobes in the pathogenesis of depression have led investigators to examine the efficacy of TMS applied to regions of the frontal cortex in studying

and treating depression arising in the context of Major Depressive Disorder (MDD) and Bipolar Disorder (BD).[13,17,18]

George *et. al.* in 1995 reported an open study of six patients with treatment resistant depression, who were subjected to rTMS of the left prefrontal cortex over the course of one week.[17] All patients had primary mood disorders, five being BD type II and one suffering from MDD. All were in the midst of a major depressive episode. For the group as a whole a significant improvement in mood was noted, with a decrease in the mean Hamilton Depression Rating Scale score from 23.8 to 17.5 on the 17-item scale.

Pascual-Leone *et. al.*, in 1996, described a multiple cross-over, randomized, placebo-controlled trial studying rTMS stimulation of the left dorsolateral prefrontal cortex in drug resistant depression.[13] Seventeen patients with MDD, multiple relapses of major depressive episodes, and psychotic features were studied. The patients received 5 courses of TMS, each lasting five days. These included real left frontolateral TMS, real right frontolateral TMS, placebo TMS of these two regions, and real TMS of the mid-frontal region. Both the Hamilton Depression Rating Scale and the Beck Depression Inventory were used to assess depressed mood at baseline and following treatment. Nine of the patients were found to experience improvement in mood only following administration of real left frontolateral TMS, while three patients reported improvement in mood following both administration of left frontolateral and mid-frontal TMS. Two patients reported subjective improvement in mood following only real left and real right frontolateral TMS. In all patients the lowest Beck and Hamilton scores (i.e. least depressed mood) followed administration of left frontolateral TMS, and represented a statistically significant improvement over baseline. TMS stimulation of all other areas of the brain demonstrated no statistically significant improvement (and at times an increase) in Hamilton and Beck scores versus baseline. The average duration for which patients reported a significant improvement in mood following left frontolateral TMS was limited to 2 weeks following cessation of stimulation of this area.

Pascual-Leone *et. al.* studied 10 healthy volunteers and assessed subjective perception of five emotional domains on visual analogue scales.[20] These domains included "happiness", "anxiety", "tiredness", "pain and discomfort", and "sadness". TMS was applied over the course of 3.5 hours, with 5 minute sessions and 30 minute intervals between sessions. After each session participants were required to fill in the five analogue scales, noting the intensity of each of the above emotions. The TMS sessions involved right prefrontal, left prefrontal, and mid-frontal regions, applied in varying order to correct for possible sequential effects of the treatment. The authors concluded that no clinically apparent mood changes were evoked by rTMS applied to any scalp position when compared to baseline. However, left prefrontal TMS did result in a significant increase in the "sadness" rating on the visual analogue scale, and a significant decrease in the "happiness" rating when compared to the right- and mid-prefrontal regions.

George *et. al.* also demonstrated a lateralization in their study of 10 healthy volunteers, although left prefrontal stimulation was again found to be associated with a worsening of mood.[21] After applying rTMS to the right, left, and mid-frontal corteces, as well as to the occipital and cerebellar regions, left prefrontal stimulation was found to be associated with an increase in self-rated feelings of sadness, while right prefrontal stimulation was found to be associated with an increase in self-rated feelings of happiness.[21] The results of these two studies are inconsistent with the previously described studies which showed improvement in mood when the left prefrontal cortex was stimulated. The difference may stem from variability in the physical parameters and settings of the TMS equipment, and the protocol used. Furthermore, these two latter studies assessed healthy patients over the course of hours while the previously described two studies assessed pathologically depressed patients over the course of several weeks. This raises the possibility that TMS may impact differently on healthy individuals as compared to those who are depressed. It is worth noting that all studies implicate the frontal lobes as important in the maintenance of mood states and point to a lateralization of mood within them.

Assessment of the value of TMS in the management of mood disorders has also been attempted within the context of laboratory models. Fleischmann *et. al.* in 1995 described the effects of TMS on rat brains in behavioural models of depression.[18] Their findings suggested that TMS had neurological and behavioural effects similar to those induced by electroconvulsive shocks.

Safety of TMS

Barker *et. al.*, describing TMS in its early days, believed this technique to be relatively safe.[1] They calculated the amount of thermal energy deposited in tissues as a result of the procedure to be very small. They described the peak magnetic field used in the procedure as being similar in magnitude to the static fields used in magnetic resonance imaging scanners, and noted that no adverse effects had yet been attributed to such magnetic fields. Consistent with this view is the report by Pascual-Leone *et. al.*, whereby none of the seventeen patients in their study reported adverse effects other than minor headaches which were relieved with mild analgesics.[13] Bridgers and Delaney assessed 30 healthy adults for cognitive and motor performance following TMS.[22] No statistically significant declines in story recall, word association, visual recall, or grip strength were observed. A study of 9 normal volunteers by Pascual-Leone *et. al.* found that

rTMS was not associated with significant changes in neurological examination findings, cognitive performance, EEG, electrocardiogram, or levels of anterior pituitary hormones.[23] However, the highest intensity stimulus of TMS did produce a focal seizure in one patient, which secondarily became generalized. Chokroverty *et. al.* concluded that TMS was not associated with any apparent deleterious effects in the short term and in long term follow-up of 16 to 24 months, after assessing EEG data, psychometric test results, anterior pituitary hormone levels, and onset of fatigue in normal subjects undergoing this procedure.[24] Transient decline in delayed recall was noted, resolving 2 weeks after the procedure.

Several authors raised the possibility of seizure induction during or following TMS in healthy subjects and in those with neurological conditions such as epilepsy and stroke.[2,25,26,27,30] The majority of reports, however, have been anecdotal. Others contend that TMS is a safe procedure in both healthy and neurologically impaired persons. Kandler reports on a 3 to 21 month post-TMS survey sent to patients with multiple sclerosis, Parkinson's disease, or stroke, assessing various aspects of physical health.[28] Of 133 patients who responded, only one experienced a single seizure and another experienced two seizures in the month following TMS (both had multiple sclerosis). The only other side effects noted by Kandler were headache in five respondents, and transient memory loss in three. Homberg *et. al.*, while describing their experiences with a patient who developed a seizure during a course of TMS, note that this patient may have represented a unique subgroup having a large ischemic scar following a middle cerebral artery infarction.[26] They suggest that the risk of epileptic seizures in most individuals is low, even in patients with previously known epilepsy or stroke. They also note that in approximately 2000 TMS examinations over the course of 2 years at the National Hospital for Nervous Diseases in London, England, no seizures occurred. Tassinari *et. al.* report on a study of 58 patients with partial or generalized epilepsy who had transcranial magnetic stimulation (TMS) of the brain motor regions.[31] Short-term monitoring demonstrated that stimulation did not provoke seizures or EEG changes in any patient, and long-term follow-up showed that the epileptic condition was not made worse by TMS. Their conclusion was that TMS, at least as used for monitoring conduction in central motor pathways, does not induce seizures in drug-treated epileptic patients. Gates *et. al.* assessed histopathalogically the temporal lobes of two patients who received TMS and subsequently underwent lobectomy for medically intractable epilepsy two or four weeks following TMS.[32] They concluded that no lesions were attributable to TMS in these specimens.

Conclusion

TMS is a relatively new technique, currently standing at the threshold between experimental investigation and clinical application. It holds prospects as both a research tool and a therapeutic modality in psychiatric mood disorders. Reports of the effectiveness of TMS in treating depression are limited, however, and most are either anecdotal or open-study based with small heterogeneous sample sizes. Furthermore, no studies have directly compared TMS to conventional therapies. Therefore, replacement by TMS of antidepressant medication in MDD, mood stabilizers in BD, or ECT in both of these conditions, cannot be advocated. Moreover, the effects of TMS currently appear to be short-lived, necessitating frequent repetition of the treatment. Further investigation and refinement of the equipment and treatment protocols, and more detailed and well controlled studies are required before TMS may be considered for routine clinical use. This is evident in the variability of treatment protocols reported in the literature, and in the uncertainty regarding the optimal parameters to use. Nevertheless, this technique opens a new frontier in mood disorder research and patient management, and provides impetus for further investigation into novel methods of managing these often complex conditions. TMS appears to be a safe procedure, particularly among those individuals with no previous neurological conditions. Therefore, its ongoing use in this population for the purposes of further investigation and preliminary treatment efforts appears justified. Even among those with a history of neurological conditions such as multiple sclerosis, epilepsy, and stroke, TMS appears to be safe and these conditions do not as yet pose an absolute contraindication to the procedure. Given the reports of seizure induction in these patients, however, further study and cost-benefit assessment are required before routine use can be advocated. The applications of TMS may not be limited to primary mood disorders. Other psychiatric conditions where mood symptoms are prominent, such as schizophrenia, schizoaffective disorder, and post-traumatic stress disorder, may respond to the procedure. Furthermore, TMS may prove useful in the management of reactive depression arising in the context of a multitude of medical illnesses and surgical procedures.

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