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Transcranial magnetic stimulation: a new tool in the fight against depression

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Since its introduction to the clinical realm in 1985, transcranial magnetic stimulation (TMS) has rapidly developed into a tool for exploring central nervous system function in both health and disease. The antidepressant effects of TMS were initially observed in 1993. Since then, a solid body of evidence has accumulated suggesting antidepressant effects for both slow TMS (sTMS) and repetitive TMS (rTMS). This review is divided into four parts. First, it addresses the basic concepts governing TMS, and then, second, it discusses the technical parameters involved in administering TMS. Knowledge of these parameters is necessary for understanding how TMS is administered, and how manipulation of the technique impacts on the results obtained. Third, we review the most relevant studies on the antidepressant effects of sTMS and rTMS published to date. Finally, we discuss cortical excitability and how the understanding of this basic neurophysiological function of cortical neurons can be used for monitoring the effects of TMS. In our discussion, we conclude that the time has arrived for TMS to be offered to depressed patients as a treatment.

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Transcranial magnetic stimulation (TMS) was introduced by Barker in 1985[1] as a tool for noninvasively stimulating the central nervous system (CNS). The first experiments by Barker et al were aimed at inducing motor movements and measuring nerve conduction. These authors based their studies on previous reports that electromagnetic coils placed near the human head can give rise to neurological phenomena such as phosphenes and vertigo, and cause some to feel faint.[2]

The dramatic implications of this initial demonstration by Barker et al are becoming apparent with the exponential increase in the number of studies that use TMS as a tool for exploring CNS function in normal individuals and in disease.[3,4]

TMS is based on Faraday's principle of mutual induction, which states that electrical energy can be converted into magnetic energy, and vice versa. During TMS, a bank of capacitors repeatedly and rapidly discharges into an electric coil and produces a time-varying magnetic pulse. If the coil is placed near the head of a human or animal, the magnetic field penetrates unimpeded into the brain and induces an electric field in the underlying region of the cerebral cortex. This electric field in turn produces a charge across the excitable neuronal membranes and, if it is of sufficient intensity, induces neuronal depolarization and an action potential. The propagation of this action potential along nerve structures and neuronal networks constitutes the neuronal basis for TMS actions.[4] TMS has both local effects, by stimulation of interneurons, and distant effects through stimulation of axonal connections. The magnetic field induced during TMS declines logarithmically with distance from the coil. In humans, this limits the effects of TMS to cortical depolarization (about 2 cm below the skull).[5] It is possible that improvements in

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the manufacturing of coils will allow the delivery of magnetic pulses to deeper brain areas.

Effects similar to those of TMS can be obtained with electrical pulses (transcranial electrical stimulation); however, the impedance of the tissue requires the electrical charge administered to be large, and this stimulation is usually painful and disturbing for patients. In TMS, the magnetic pulse crosses the scalp almost painlessly.[4]

The study of the effects of TMS received a significant boost with the introduction of stimulators with more powerful capacitors that allowed the delivery of magnetic pulses at frequencies of up to 100 Hz. It is conventional to refer to pulses of 1 Hz or less as slow TMS (sTMS), and pulses of above 1 Hz as repetitive (or fast) TMS (rTMS). In humans, the risk of induction of seizures has limited the frequency of rTMS to a maximum of 25 Hz.[6,7] The only exception to this was the study of Lisanby et al[8] in which stimulations of 40 Hz were used during research into magnetically induced seizures.

TMS is a rapidly evolving technique with many applications in psychiatry, neurology, cognitive neurosciences, and basic neurosciences. In this review, we will focus on the importance of TMS as a tool in the treatment of depressive illness. We will discuss the relevant technical aspects of TMS, which are essential for understanding the effects of this treatment modality, and we will conclude with an update on the electrophysiological mechanisms of the action of TMS that are relevant for understanding its effects in depression.

The technique of TMS

In TMS, the patient does not require special preparations besides the standard psychiatric and medical workup for depressive illness. It is important to follow the safety guidelines, and exclusion criteria have been produced by Lorberbaum and Wassermann[6] and Wassermann[7] for the safe administration of TMS. The main limitations of TMS relate to the presence of active neurological illness, or to the presence of metallic inserts in the body, particularly in the head. Although TMS has been administered during pregnancy,[9] it is considered to be a relative contraindication for TMS. The technical considerations for TMS are listed in *Table I*.

Motor threshold
Scalp-to-cortex distance
Subthreshold vs threshold or suprathreshold stimulations
Types of coil
Round coil
Figure-of-eight coil
Coil placement
Anatomical landmarks vs neuronavigation
Frequency of stimulation
sTMS vs rTMS
Total number of magnetic pulses administered
Per session
Per course of TMS
Total number of treatments per course

Table I. Relevant technical issues in the administration of transcranial magnetic stimulation (TMS). sTMS, slow TMS; rTMS, repetitive TMS.

Magnetic motor threshold and the power of stimulation

Magnetic motor threshold (MT) is defined as the minimal amount of machine power needed to induce a deflection of 50 µV in the electromyographic recordings in 5 out of 10 trials.[10] It has been argued that the difference between the MT (ie, electromyographic recording of motor evoked potentials [MEP]) and the twitch threshold (ie, hand movement that corresponds to the MEP) is minimal and probably clinically irrelevant.[11] However, current safety guidelines require monitoring by electromyography (EMG) for identification of afterdischarges or spreads of excitation, ie, the established forerunners of seizures.[12]

In sTMS, magnetic stimulations are usually administered at 100% machine power, whereas in rTMS the power ranges between 80% and 120% MT (usually about 40% to 70% of the stimulator's maximum). Initial studies with rTMS were performed with the power set at 80% to 90% MT. However, more recent studies generally use around 100% to 110% MT. Stimulation paradigms significantly above MT have been reported to be associated with the induction of seizures,[7] or have been used to induce seizures in a controlled setting.[8] It is important to note that, since the introduction of the safety guidelines for the administration of TMS, there has been no new report of seizures during TMS.[13]

MT may not be the best guiding principle for setting the power of stimulation when rTMS is performed over the frontal cortex. Indeed, what is appropriate for the motor cortex may not be appropriate for the frontal or prefrontal cortex. Kozel et al[14] and McConnell et al[15] pioneered the concept that the power of stimulation needs to be calculated on the basis of the scalp-to-cortex distance and not just as a function of MT. MT reflects more closely the scalp-to–motor cortex distance than the scalp-to–prefrontal cortex distance. In elderly patients in whom the scalp-to–frontal cortex is increased due to brain atrophy, calculations of the power of stimulation on the basis of scalp-to–motor cortex distance may underestimate the power needed to stimulate the frontal cortex in these individuals.

Coil used for administering TMS

Two main types of coil are used in TMS: the round coil and the figure-of-eight coil. It is unclear whether one is superior to the other, as positive results have been reported with both types. The round coil is more common in single-pulse and sTMS studies, while the figure-of-eight coil is used more commonly in rTMS studies. The magnetic field produced by the round coil is strongest around the perimeter of the coil and, therefore, it stimulates a larger but more diffuse cortical area. The magnetic field of the figure-of-eight-coil is concentrated over the area where the wings of the coil meet, providing a much more focused stimulation over a smaller area of the cortex.[5]

Coil placement

During TMS, small areas of the brain are stimulated locally under the coil and distally through axonal connections. Thus, TMS allows the study of both local and distal effects of magnetic stimulation.[16] The importance of specific brain areas and neuronal networks can be studied with TMS. In depression, studies have reported beneficial effects with rTMS when the coil is placed over the left dorsolateral prefrontal cortex (LDLPFC), and with sTMS when the coil is placed over the right dorsolateral prefrontal cortex (RDLPFC).[5] In studies with rTMS over the LDLPFC, the site for stimulation is located by placing the coil 5 cm rostrally and parasagitally to the motor cortex. This may not be accurate enough as individual variations in the anatomy of the cortex are not taken into account. The method of neuronavigation, which is commonly used in neurosurgery, relies on magnetic resonance imaging (MRI) and frameless stereotaxy to determine coil placement. This method improves the ability to target the LDLPFC accurately.[17,18]

Frequency of stimulation and total number of pulses administered per treatment

Magnetic stimulation can be administered at frequencies ranging between less than 1 Hz and 100 Hz. In humans, there are no safety guidelines for stimulation above 20 Hz. The remarkable flexibility of this parameter may have far-reaching implications for the magnetic stimulation of the brain. It has been proposed and demonstrated that low-frequency stimulation of the motor cortex leads to brief inhibition of motor responses,[19] while higher frequency stimulation of the motor cortex leads to brief excitation of motor responses.[20] The total number of pulses administered during a treatment depends on the frequency of stimulation and the length of each treatment. Initial studies administered few magnetic pulses. More recent studies introduced the concept of trains of stimulation and also proposed that additional clinical benefits, especially in depressive illness, are obtained when the number of magnetic pulses is increased dramatically. For example, in previous communications from our laboratory, we have administered up to 24 000 stimulations per course of TMS; in an ongoing study, we are testing whether 160 000 stimulations per course would be more effective in the treatment of severe depression.

Number of treatments

The number of treatments has also varied greatly between the studies. The initial reports were based on a

single day's stimulation. More recently, studies report between 5 and 20 treatment days. The relevance of this difference remains to be established. We recently finished a study comparing the changes in depression ratings after 2 or 4 weeks of rTMS. Significant additional clinical gains were noted after 4 weeks (Grunhaus et al, unpublished data).

Use of sham controls

Open studies with TMS are difficult to evaluate, especially because of the placebo-like effects that treatment with magnets may have. However, it is difficult to mask the effects of the magnet. Two ways to cope with this problem have been considered: one is the use of sham-masked stimulations, and the other is the use of a sham coil. There has been considerable argument on whether a "true" sham or masked TMS exists. The one-wing, two-wing, 45-degree, and 90-degree positions have been explored and have nevertheless been found to induce a modest amount of magnetic field in the cortex.[21] The use of sham coils seems to be the preferred method (Neotonus, Marietta, Ga, USA), though there have been no published research using this coil.

Side effects associated with TMS and rTMS

Overall, TMS and rTMS have so far been remarkably safe. Initial concerns about the possibility of the induction of seizures have been allayed since the introduction of the guidelines for the safe administration of TMS. Additional concerns like headaches, cognitive effects, effects of irradiation, and local facial or scalp pain during the administration of TMS are rare.[7]

TMS studies in depression

Following the observations that TMS could provoke transient mood elevations or acute crying in normal volunteers,[22,23] several researchers described the antidepressant effects of single-pulse TMS in small sample of patients with major depression.[24-28]

Hoflich and collaborators from Germany published the first report on the antidepressant effects of TMS.[27] These authors treated two patients with delusional major depressive disorder (MDD) with 10 sessions of TMS (14-mm round coil, 250 stimulations at 0.3 Hz per day, at the vertex, and at 5% to 30% above MT) and followed

these treatments with 10 sessions of electroconvulsive therapy (ECT). ECT was superior to TMS in both patients; however, a mild antidepressant effect of TMS was observed in one of the patients. Additional sTMS studies are those of Kolbinger et al,[28] Grisaru et al,[26] Conca et al,[24] and Geller et al.[25] These studies were all performed with round coils, at relatively low frequencies, and with coil locations at either the vertex or the LDLPFC. The antidepressant effects of TMS in these studies were very modest.

Conca et al[24] compared the effects of TMS as an add-on treatment to ongoing antidepressant medication in patients with MDD without delusions. The authors randomly assigned patients to one of two groups, one treated with sTMS and medication, and the other with medication alone. TMS was administered over several cortical regions with a round coil. The authors found a greater remission of depressive symptoms in the sTMS group after just three sTMS sessions; this difference was even more significant by the end of the 10th and final sTMS session. Conca et al repeated this design in a follow-up study of 12 MDD patients without delusions.[29] These authors administered 500 pulses a day for up to 10 days at maximal machine output, and over several cortical regions. They reported a significant response rate for sTMS-treated patients.

The most comprehensive study with sTMS published so far is by Klein et al,[30] who compared sTMS and sham TMS as an add-on treatment in a large population of nondelusional MDD patients (N=70). Klein and coworkers administered sTMS with a 9-cm round coil over the RDLPFC at 1 Hz and 110% MT. The authors administered two trains of 60 magnetic pulses each separated by a 3-min interval. The TMS course was given daily for 10 days. The authors found that over 50% of the sTMS-treated patients, but only 25% of the sham sTMS–treated patients (ie, a significant difference) achieved a greater than 50% decrease in the Hamilton rating scale for depression (HRSD) score during the trial.

Studies with rTMS

Following the introduction of rTMS, an increasing number of studies using rTMS in the treatment of depression are being published. George et al[31] published the first study using rTMS in medication-resistant MDD. These authors administered rTMS over the LDLPFC at 80% MT and 20 Hz for 5 sessions. They described a 26%

decrease in HRSD score. Two other studies of that period merit particular discussion because of the impact they have had on the field. Pascual Leone et al[32] published the first sham TMS/rTMS comparison in depressed psychotic patients. They tested the effects of rTMS (real and sham) on 16 patients at various scalp coil positions (LDLPFC, RDLPFC, and vertex). The sham coil was held at a 45°. In a crossover study, Pascual Leone et al administered one form of treatment daily for 5 days only and then observed the patients for 3 weeks. Only stimulation of the LDLPFC led to significant improvements in depression rating scales, and these lasted for approximately 2 weeks. Although there has been significant discussion regarding the methodology of this study, there can be no argument about the impact this publication has had on the field of rTMS. This landmark paper led to an explosion of studies in depression. Shortly thereafter, George et al[33] published a double-blind, single crossover, sham-controlled study of 12 patients with MDD, using the same parameters reported in their previous study. They found a modest decrease of 26% in HRSD score with real rTMS over the 2 weeks of the study.

Over the following years, a number of important studies were published, some of them supporting the antidepressant effects of rTMS and others finding that there was no difference from placebo or, at best, that there were mild antidepressant effects.[32-43] During the year 2000, three relatively large studies (Grunhaus et al,[38] George et al,[37] and Pridmore et al[42]) have reported significant antidepressant effects for rTMS administered over the LDLPFC. George et al conducted a parallel, double-masked, sham-controlled study of rTMS over the LDLPFC in patients with nondelusional MDD.[37] They studied 30 patients with MDD (21 unipolar and 9 bipolar), who were in the midst of an episode of illness. Patients were assigned to either the active or sham groups, and to either a 5-Hz or a 20-Hz group. Patients received 10 rTMS treatments at 100% MT, with 16 000 stimulations given to both cells. The antidepressant response was defined as a decrease of 50% or more in the HRSD score. The proportion of patients responding in the active treatment group was significantly larger (9 of 20) than that of the sham group (none of 10). However, there was no significant difference between the 5-Hz and 20-Hz groups. George et al concluded that rTMS significantly reduced depressive symptomatology.

A potential area of great impact of rTMS is in popula-tions who are resistant to medications and are therefore candidates for ECT. ECT is an accepted treatment for medication-resistant MDD and also for MDD with delusions. Rates of response to ECT are highest in the latter group of patients.[44,45] However, ECT is a treatment with significant limitations. Patients and their relatives often object to it as a treatment because of a negative aura that surrounds ECT. In addition, and especially in the elderly or in medically ill individuals, ECT may be associated with significant morbidity particularly in the cardiovascular and respiratory systems. Finally, ECT often induces reversible memory changes, but on occasion may lead to permanent memory impairment.[45] TMS, on the other hand, is a procedure that is associated with few side effects; it does not induce memory impairments and does not require anesthesia. Thus, if TMS could lead to sustained antidepressant responses in patients with resistant or delusional MDD, then a significant therapeutic advance would be made. Zyss summarized this possibility well when he stated that "deep brain stimulation would be the end of ECT."[46]

We published the first study to compare the effects of ECT and rTMS in patients referred for ECT.[38] In this study, patients referred for ECT and suffering from treatment-resistant MDD were randomly assigned to a course of either ECT or rTMS (over the LDLPFC, at 90% MT, 20 treatment days, at 10 Hz, a total of 24 000 magnetic pulses). Response to treatment was analyzed according to both changes in the HRSD and increases in function as assessed by the global assessment of function (GAF) scale. Patients responded equally well to both treatments. However, when the response was analyzed according to the presence or absence of psychosis, ECT was clearly more effective in MDD patients with psychosis. We concluded that rTMS, according to the parameters used, was as effective as ECT in nonpsychotic MDD, but that ECT was clearly superior in psychotic MDD. Dannon et al[47] have performed a follow-up study on these patients and reported that relapse rates were comparable in both groups. Relapse rates were approximately 20% in the two groups. Thus, the beneficial response seen with rTMS persisted for at least 6 months. A replication study used the same rTMS and ECT methodology, but added restrictions on medication use (patients in both groups had to be free of psychotropic medication with the exception of lorazepam up to 3 mg per day) and required that raters be blind to treatment modality (Grunhaus et al, unpublished data). In this

study, we again found that rTMS and ECT had comparable results in nondelusional MDD.

The combined results of these two studies from our group are presented in *Table II*. These results show that ECT is the superior treatment when the whole sample is considered; however, this holds true in delusional MDD, but not in nondelusional MDD. In the latter group, ECT and rTMS have comparable treatment outcomes. Response to treatment was defined as a 50% or more decrease in the HRSD score and a final GAF of 60 points or more.

Pridmore et al[42] also compared ECT and rTMS. They studied 32 patients with MDD (it is not clear from their publication whether delusional patients were excluded), who had been resistant to a course of 4 weeks of antidepressant medication. They randomly assigned patients to one of the two treatment groups. Raters were blind to treatment group and response to treatment was assessed with the HRSD. Treatments were provided as needed, or up to a point when no further change was noted. rTMS was administered at 100% MT, 20 Hz, for 2 s, 30 to 35 trains per day. The rate of remission was the same for both groups, and the percentage of patients improving was above 55% in both groups, but favored ECT in a nonsignificant way. The authors concluded that rTMS had useful antidepressant effects approaching those of ECT. Janicak et al[43] randomly assigned 25 patients with a major depression deemed clinically appropriate for ECT to either rTMS (10-20 treatments, 10 Hz, 110% MT applied to the LDLPFC for a total of 10 000 to 20 000 stimulations) or a course of bitemporal ECT (4-12 treatments). They found that the percentage improvement on the baseline HDRS score did not significantly differ between the two treatments (ie, 55% for the rTMS group versus 64% for the ECT group [NS]). With response defined as a 50% reduction from baseline and a final score <8 on the HDRS, there was no significant difference between the two groups. These authors concluded that bitemporal ECT and rTMS have similar antidepressant effects.

In an attempt to conceptualize the state of the art of TMS in MDD, Sackeim[48] concluded that both sTMS and rTMS (to the left DLPFC) exert "important antidepressant effects over and beyond those of placebo contributions"; nonetheless he questioned whether enough evidence has accumulated to suggest clinical utility for TMS in MDD. He proposed two directions for research to clarify this question: (i) to attempt to identify individual differences in patients that are predictive of response; and (ii) to optimize the parameters for TMS delivery.

There is no doubt that the studies published over the past 2 years are offering increasing evidence of the efficacy of rTMS, especially in nondelusional MDD. Interestingly, several studies have found that rTMS can be as effective as ECT. No study has been published that simultaneously compares the clinical efficacy and the cognitive impact of either rTMS or ECT. However, from the evidence published so far it appears that rTMS is devoid of negative effects on cognition and memory,[49] while ECT has marked, and probably also prolonged, effects on these functions.[50-52] On the basis of the studies that we have reviewed, it appears imperative to include rTMS in the armamentarium of treatments offered to patients with severe depression, especially if ECT is being considered.

Effects of TMS on cortical excitability

How magnetic stimulation of discreet areas of the prefrontal cortex leads to antidepressant effect is a very interesting and puzzling question. The number of studies in laboratory animals looking at the mechanisms of ECT actions has been steadily increasing and the reader is referred to recent publications that have dealt comprehensively with this topic.[53-55] In this publication, we will limit ourselves to a review of the human studies dealing with cortical excitability as a correlate of TMS actions in humans.

	ECT group (N=40)		rTMS group (N=40)		P
	Responders	Nonresponders	Responders	Nonresponders	
Whole sample	28	12	19	22	0.03
Psychotic	9	5	3	10	0.03
Nonpsychotic	19	7	16	12	NS

Table II. Response to treatment. ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation.

Cortical excitability in MDD

Measuring cortical excitability can provide an assessment of the neurophysiological state of the brain. It is likely that the therapeutic effects of TMS are mediated by TMS-induced changes in the metabolism and excitability of the stimulated cortex.[56]

Cortical excitability in major depression can be assessed at baseline and following TMS treatments. The former provides information on the underlying state of the motor cortex in depression, while the latter reflects the effects of the treatment. Although in depression TMS is administered over the prefrontal cortex, it has been shown that LDLPFC stimulation has an impact on motor cortex excitability. Rollnick et al[57] have shown that rTMS given at 5 Hz and 90% MT over the LDLPFC led to decreases in MEP areas obtained with single-pulse TMS stimulations over the motor cortex. The authors speculated that this inhibitory effect was due to either an antagonism between the frontal and parietal lobes (prefrontal motor connections) or one that follows the activation of subcortical projections.

A number of methods can be used to assess cortical excitability.[13,56] In major depression, reports have included measurement of MT, changes in MEP amplitude with the input-output curve, postexercise facilitation of MEP, paired-pulse stimulation, and effects on the poststimulation EMG silent period. *Table III* presents definitions of the various cortical excitability tests that have been explored in major depression.

Motor threshold

Triggs et al[58] treated 10 MDD patients with rTMS (20 Hz, at 80% MT, 2000 stimulations per day for 10 days, over the LDLPFC) and reported a significant positive correlation between decreases in MT and HRSD scores with treatment. The changes in MT reported by Triggs et al were small but significant. In a study from our group (Dolberg et al, unpublished data), changes in MT were explored in a group of 46 patients with MDD treated with rTMS and in normal controls. No differences were identified in MT between patients and controls. In addition, MT did not change with treatment and showed no association with severity, age, or the presence of psychosis. It is possible that the differences observed in our study and those reported by Triggs et al were related to differences in the methods of determining MT. Triggs et al defined MT as

Test	Definition
Motor threshold	Minimal amount of TMS intensity that induces a deflection of 50 μV in electromyographic recordings (MEPs) in 5 out of 10 trials
Postexercise facilitation	Increase in MEP size observed after exercise
Silent period	Variable period of electromyographic silence observed after the occurrence of an MEP
Paired-pulse stimulation	Modifications of MEP amplitude by prestimulation challenges administered at variable intervals
Input-output curve	Averaged MEP area following a series of TMS stimulations or modifications of MEP amplitude induced by gradients of TMS stimulations

Table III. Definitions of tests used to assess cortical excitability in major depression. TMS, transcranial magnetic stimulation; MEP, motor evoked potential.

100-μV MEP deflections in the EMG, whereas we used the more widely accepted cutoff of 50 μV.

Postexercise facilitation

It is well established that muscular activation increases the size of the MEPs during TMS. Samii et al[59] and Shajahan et al[60,61] explored this paradigm in patients with acute depression, in recovered depressed patients, and in normal controls. They found that patients in the acute stage of the illness had significantly less postexercise facilitation than normal controls or recovered patients. They speculated that this lack of facilitation in depressed patients is due to decreased cortical excitability (which may be secondary to increased inhibitory outflow from interneurons), and that the normalization seen with recovery reflects the normalization of underlying neurobiological processes.

Silent period

A variable period of EMG absence follows an MEP. This period is referred to as the silent period and it is believed to be, at least in part, secondary to increased inhibitory forces in the motor cortex.[13] Steele et al[62] looked at the post-TMS silent period in patients with

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depression and compared it with that of normal controls. They found that depressed patients had longer post-TMS silent periods than normal controls. They concluded that their findings were indirect evidence for the presence of state-dependent increased inhibitory mechanisms in the motor cortex, and possibly other areas of the brain, in depression. It has not been reported whether recovery from depression was associated with a normalization of the silent period.

Paired-pulse stimulation

Paired-pulse stimulation of the motor cortex is considered today to be the gold standard of motor cortex excitability.[13,56,63] The paired TMS stimulations are given with short intervals between them (interstimulus intervals [ISIs]). The effects depend on the intensity of the conditioning and test stimulus, and on the ISI. Short ISIs are believed to reveal inhibitory cortical mechanisms, whereas long ISI are thought to reveal excitatory cortical mechanisms. Paired-pulse stimulation has been studied extensively in neurology, but much less in depression. Maeda et al[63] studied eight subjects with major depression with the paired-pulse paradigm and compared their responses with that of normal controls. They found significant interhemispheric differences in MT and in the paired-pulse response, both showing lower excitability in the left hemisphere.

Input-output curve

The input-output curve is obtained either by stimulating with progressively increasing TMS intensities or by measuring MEP size following a set number of suprathreshold TMS stimulations to the motor cortex. Input-output curves can be obtained during a course of TMS without major changes to the treatment protocol. In a sample of 16 patients with major depresssion, we tested the hypothesis (Grunhaus et al, unpublished data) that excitatory responses to rTMS (10 Hz, 90% MT, LDLPFC, 1200 pulses per treatment) would be associated with positive clinical response. We did not identify an association between the input-output curve and response to rTMS. We did, however, find a clear age effect, in which older patients had overall lower MEP size responses. This association suggests that older individuals may require more intense TMS stimulations to respond to rTMS.

In summary, cortical excitability can be readily studied in patients with major depression. The studies published so far suggest that decreased cortical excitability, and possible left to right differences, predominate in major depression. The negative correlation between age and MEP response reported by our group provides some indication that higher TMS intensities are needed for response in older patients. Future studies need to look into possible associations between cortical excitability and clinical variables like psychosis, response to treatment, and gender.

Discussion

The idea of using TMS as an antidepressant treatment is less than 10 years old. It is remarkable that in this short period of time the technique of TMS has developed so impressively, particularly in view of the large number of parameters that may have an impact on how TMS affects the brain. Most, but not all, of the publications exploring the antidepressant effects of TMS have found at least a moderate degree of positive results. Of particular interest are those studies that have found TMS comparable to ECT in the treatment of MDD. Follow-up of small samples following TMS suggests that the therapeutic effects of TMS extend for as long as those of ECT.

There is little doubt that TMS is in the process of becoming a much more complex technical procedure. Post and Speer[64] have described nearly 10 parameters that need to be explored in order to optimize the antidepressant effects of TMS. The technique of neuronavigation based on MRI and stereotactic positioning of the coil[17,18] will improve our ability to reliably replicate the coil positioning over the selected cortical areas. Calculations of TMS intensity based on scalp-to-cortex distance[14,15] will require precise methodology combining MRI and clinical psychiatry. Finally, imaging methods such as single photon emission computed tomography (SPECT), functional MRI (fMRI), or positron emission tomography (PET) may provide evidence for the presence of hyper- or hypometabolic states in major depression. Speer et al[65] have shown that optimization of TMS parameters in the treatment of depression may depend on precise knowledge of the underlying physiological state of the brain.

Future administration of TMS will most probably involve more extensive stimulation paradigms and longer treatment periods. It would be invaluable to have

bedside methods for monitoring the effects of the magnetic trains on the cortex. Cortical excitability studies show some promise in providing this kind of information. However, the prefrontal cortex, the area of the brain most commonly stimulated in major depression, cannot be assessed with the usual cortical excitability probes. A neurophysiological method that is yet to be tested extensively during TMS is quantitative electroencephalography (qEEG). Preliminary studies suggest that the effects of TMS can indeed be monitored with qEEG.[66,67]

The final and most relevant question continues to be whether TMS is ready to be offered as a treatment to patients with major depression. The evidence accumulated during the recent past strongly supports a positive answer to this question. ❑

La estimulación magnética transcraneal: una nueva herramienta en la lucha contra la depresión

Desde su introducción al campo clínico en 1985, la estimulación magnética transcraneal (EMT) se ha desarrollado rápidamente como una herramienta para explorar la función del sistema nervioso central tanto en el sujeto sano como en el enfermo. Los efectos antidepresivos de la EMT se observaron inicialmente en 1993. Desde esa fecha se ha acumulado un cuerpo sólido de evidencias que sugiere los efectos antidepresivos para la EMT lenta (EMT l) y la EMT repetitiva (EMT r). Esta revisión está dividida en cuatro partes. La primera parte se orienta hacia los conceptos básicos que rigen la EMT y en la segunda se discuten los parámetros técnicos que participan en la administración de la EMT. El conocimiento de estos parámetros es necesario para entender cómo se administra la EMT y cómo la manipulación de la técnica afecta los resultados obtenidos. En la tercera parte se revisan los estudios más relevantes de los efectos antidepresivos de la EMT l y de la EMT r publicados hasta la fecha. Finalmente se discute la excitabilidad cortical y cómo la comprensión de esta función neurofisiológica básica de las neuronas corticales se puede usar para monitorear los efectos de la EMT. En la discusión se concluye que ha llegado el tiempo para que la EMT sea ofrecida a los pacientes depresivos como un tratamiento.

La stimulation magnétique transcrânienne : un nouvel outil dans la lutte contre la dépression

Depuis son introduction en clinique en 1985, la stimulation magnétique transcrânienne (SMT) s'est rapidement développée en outil d'exploration de la fonction du système nerveux central malade ou sain. Les effets antidépresseurs de la SMT furent reconnus dès 1993. Depuis lors, les effets antidépresseurs de la SMT lente (SMTl) comme de la SMT répétitive (SMTr) ont été solidement confirmés. Cette mise au point est divisée en quatre parties. Après avoir abordé les grands concepts à la base de la SMT, nous passons en revue les paramètres techniques conditionnant l'administration de la SMT. La connaissance de ces paramètres est nécessaire pour comprendre l'administration de la SMT et comment le mode d'utilisation de cette dernière influe sur les résultats obtenus. En troisième partie, cet article traite des études les plus pertinentes sur les effets antidépresseurs de la SMTl et de la SMTr publiées jusqu'à maintenant. La dernière partie, enfin, examine l'excitabilité corticale et comment la compréhension de cette fonction neurophysiologique de base des neurones corticaux peut être utilisée pour contrôler les effets de la SMT. La conclusion qui s'impose est qu'il est grand temps de proposer la SMT dans le traitement des patients déprimés.

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