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Perspective

Efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Affective Disorders

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Transcranial magnetic stimulation (TMS) is a relatively noninvasive technique to interfere with the function of small cortical areas through currents induced by alternating magnetic fields emanating from a handheld coil placed directly above the targeted area. This technique has clear effects on a whole range of measures of brain function and has become an important *research tool* in neuropsychiatry. More recently, TMS has been studied in psychiatry mainly to assess its putative *therapeutic effects* in treatment refractory major depression. Most studies indicate that both low-frequency TMS and higher (20 Hz) frequency repetitive TMS may have some antidepressant properties. However, definite therapeutic effects of clinical significance still remain to be demonstrated.
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PRINCIPLE OF TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation (TMS) refers to a technique of delivery of magnetic pulses to the cortex using a handheld stimulating coil, which is directly applied to the head. The equipment necessary for delivering TMS consists basically of two parts: a stimulator that generates brief pulses of strong electrical currents whose frequency and intensity can be varied and a stimulation coil connected to the stimulator. The magnetic field generated at the coil passes unimpeded through scalp and skull and induces an electrical current in the underlying tissue, which depolarizes neurons. The main advantage of this stimulation method is its relative noninvasiveness and the possibility to stimulate very focused brain areas. With recent technology, single, paired or repetitive pulses can be delivered. Cortical excitability may be increased or decreased depending on the stimulation frequency (Hallett, 2000), and TMS has been shown to modify regional cerebral blood flow (Bohning *et al*, 2000; Catafau *et al*, 2001).

Barker first demonstrated the induction of muscle potentials by magnetic stimulation of the central nervous system in 1985 (Barker *et al*, 1985). He induced muscle twitching with a coil of 10 cm diameter placed on the scalp over the motor cortex. A brief pulse of 110 μs with a peak current of 4000 A was applied and pulses at a maximal rate of 0.33 Hz were delivered.

With the possibility of stimulating the motor cortex noninvasively, TMS replaced high-voltage transcutaneous electrical stimulation previously used in clinical studies to measure variables such as central motor conduction time. Altered conduction time may be associated with a variety of neurological disorders such as multiple sclerosis, amyotrophic lateral sclerosis, cervical myelopathy and degenerative ataxic disorders. TMS has great potential in the intraoperative monitoring of the integrity of motor tracts during surgery of the brain and spinal tract (Murray, 1991). TMS has found widespread diagnostic use in neurology for demyelinating disorders involving the excitability and the connections of the motor cortex with other parts of the nervous system involved in motor function (Ziemann and Hallett, 2000).

In 1987, Bickford extended the field of TMS research into neuropsychiatry: he described transient mood elevation in several normal volunteers receiving single-pulse stimulations to the motor cortex (Bickford *et al*, 1987). This was the starting point of the scientific investigation of effects of depolarizing magnetic fields in a variety of neuropsychiatric disorders. Soon after, open studies of the effects of TMS on patients with major depression were conducted using single-pulse stimulations at frequencies less than 0.3 Hz (Grisaru *et al*, 1994; Höflich *et al*, 1993; Kolbinger *et al*, 1995). In these studies, relatively large areas under the vertex were stimulated bilaterally and involved only very few subjects. More recent work has suggested that slow and fast repetitive TMS (rTMS) may have some value in depression.

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BASIC EFFECTS

Magnetic fields generated by TMS are interacting with an extremely complex biological system where essential interactions between brain and mind take place (Kandel, 1998, 1999). It is obvious that the impact of these fields on brain systems is difficult to evaluate, because monitoring functions of the living human brain is only possible by assessing summation responses that are determined by the action of tens of thousands or more cells. The actual psychopathological models of psychiatric disorders are integrating the so-called functional systems at molecular, cellular, neurotransmitter, organ, systemic or individual and social levels that are not understood in detail. Presenting the mechanisms of action of TMS both as a research or treatment tool challenges old hypotheses of brain function and, hopefully, allows the creation of new ones. Several acute and chronic alterations at different levels, ranging from changes in gene expression of cells in the central nervous system to alterations in mood and behavior have been documented during and after the application of TMS.

Ji reported recently that one single train of rTMS applied to rats *in vivo* induced c-fos and c-jun expression in different brain including key regions controlling circadian biological rhythms (Ji *et al*, 1998). Similar stimulation parameters have earlier been shown to posses efficacy in an animal model of depression (Fleischmann *et al*, 1995). These findings might point to a possible antidepressant mode of action of TMS effects via circadian rhythms. The finding that immediate-early gene expression is modified by TMS has been replicated and further examined both *in vivo* and *in vitro* (Doi *et al*, 2001; Hausmann *et al*, 2001).

Keck measured modulatory effects of frontal rTMS in rat brain *in vivo* using intracerebral microdialysis (Keck *et al*, 2000). There was a continuous reduction in arginine vasopressin release of up to 50% within the hypothalamic paraventricular nucleus. In contrast, the release of taurine, aspartate and serine was selectively stimulated within this nucleus. Furthermore, in the dorsal hippocampus the extracellular concentration of dopamine was elevated in response to rTMS.

By using PET scanning, a reduction in ^{11}C raclopride binding to dopamine receptors in the left dorsal caudate nucleus was observed in eight volunteers after left dorsolateral prefrontal cortex (DLPFC) rTMS. This implies that rTMS can trigger dopamine release in these brain structures (Strafellea *et al*, 2001).

Several studies documented the effect of rTMS on plasma levels of a variety of hormones including cortisol, prolactin and thyroid stimulating hormone. Results from these studies are inconclusive but indicate that TMS might significantly affect neuroendocrine function (Cohrs *et al*, 1998; George *et al*, 1996; Szuba *et al*, 2001).

TMS can transiently disrupt or induce activity in focal brain regions, depending on the region stimulated. Applied to the visual cortex for example, strong TMS can produce phosphenes and stimuli of lower intensity induce transient scotomas (Hallett, 2000). Moreover, other functions, such as linguistic processing, can be investigated with rTMS (Flitman *et al*, 1998). A neuromodulatory effect of subthreshold high-frequency rTMS has been observed in 10 subjects. After 1250 stimulations at 90% motor threshold, an intracortical inhibition could be measured, which persisted for at least 10 min after the rTMS stimulation (Peinemann *et al*, 2000).

The combination of noninvasive stimulation of the brain coupled with functional neuroimaging techniques offers novel opportunities to investigate human brain function. It also allows visualization of the effects of TMS including those distant from the site of stimulation (Paus *et al*, 1997). For example, 10 medication-free subjects suffering from major depression (eight unipolar, two bipolar), received in a crossover, randomized study rTMS at the left prefrontal cortex (LPFC), at 100% motor threshold, at either 20 or 1 Hz. After 20 Hz, an increase in regions cerebral blood flow (rCBF) in the prefrontal cortex left $>$ right, cingulated gyrus left $\geqslant$ right, left amygdala, bilaterally insula, basal ganglia, hippocampus, parahippocampus, thalamus, cerebellum was observed, after 1 Hz only decreases in rCBF in right prefrontal cortex, left medial cortex, left basal ganglia and left amygdala was noted. Individuals whose depressive symptoms improved with one frequency worsened with the other (Speer *et al*, 2000).

The above-mentioned multidisciplinary results suggest that TMS has prominent and reproducible effects on the brain. This puts TMS apart from other putative approaches to treat neuropsychiatric disorders (Hallett, 2000). One problem shared with antidepressants is that the link between changes at cellular levels and complex behavioral changes—such as the ones observed in depression—has been very difficult to establish. The field of neuropsychiatric research in TMS has somewhat suffered from a 'top-down' approach in which early promising results in depression have led to an enthusiasm for clinical studies without sufficient basic neurobiologic rationale. Approaches integrating findings from all levels of brain—molecular to behavioral—systems are extremely important and should be undertaken in order to support ongoing clinical research.

EFFECTS ON MOOD

It is of obvious importance to elucidate the exact structural and functional bases of affect to understand the neurobiology of, and putative therapeutic interventions for, human disorders like depression and mania. Converging evidence from different areas of research support the hypothesis that mood is regulated by an interconnected network of brain regions encompassing prefrontal, cingulate, parietal, and temporal cortical regions as well as parts of the striatum, thalamus, and hypothalamus. Among them, the limbic system integrates external stimuli with internal drives and is part of a distributed neural network that marks stimuli and events with positive or negative value (Aggleton, 1993). Lesions of this network from tumor, infarction or transient disruption often result in mood changes. In addition, alterations of cerebral blood flow and metabolism in the dorsolateral, ventrolateral, orbitofrontal, and medial frontal regions, as well as the subgenual prefrontal and anterior cingulate cortex have been demonstrated in patients suffering from major depression (Mayberg, 1997; Soares and Mann, 1997). The prefrontal cortex has been implicated with mood generation and modulation, although this view is not universal (George *et al*, 1995a; Lane *et al*, 1997; Paradiso *et al*, 1997).

rTMS has been used in healthy subjects to help elucidate the basic neurophysiology of mood generation and modulation by stimulating the DLPFC. Six studies are available in which the effect of prefrontal rTMS on mood systems in normal volunteers was investigated. In half of the studies, rTMS over the LPFC transiently induced a decrease in self-rated happiness and an increase of sadness compared to the effects of right prefrontal cortical rTMS (Dearing *et al*, 1997; George *et al*, 1996; Pascual-Leone *et al*, 1996). Three more recent studies (Cohrs *et al*, 1998; Mosimann *et al*, 2000; Nedjat *et al*, 1998) failed to demonstrate any effects on mood in healthy volunteers.

EFFECTS ON MAJOR DEPRESSION

Owing to its ability to interfere focally with neuronal circuits, rTMS has been proposed and subsequently researched as a putative therapeutic approach in refractory major depression (Nemeroff, 1996; Nestler, 1998). As in the studies of mood modulation by rTMS, the DLPFC has been the most important target for stimulation in major depression studies. George reported the first open study of the effects of rTMS in six patients with refractory depression treated with five daily rTMS sessions to the left DLPFC (George *et al*, 1995b). He reported that two patients in this study experienced improvement as assessed by a reduction of 26% in the Hamilton Rating Scale for Depression (HRSD) scores. Open and blinded studies of rTMS to the left DLPFC followed with varying results. A relatively large open study demonstrated that 42% of 56 patients responded to five daily rTMS sessions; the elderly exhibited a considerably lower response rate (Figiel *et al*, 1998). A 2 weeks treatment study resulted in a 41% decrease in HRSD scores in another open trial (Triggs *et al*, 1999). However, there are open studies that have failed to demonstrate any antidepressant activity of rTMS (Schouten *et al*, 1999).

In the sham-controlled, single-blinded studies of rTMS in treatment-resistant depression, effect sizes have varied considerably. In a within-subject crossover, sham-controlled study of 12 depressed patients treated for 2 weeks with stimulation to the left DLPFC only somewhat modest antidepressant efficacy of rTMS was found (George *et al*, 1997). In a more recent study, an antidepressant effect in 20 subjects that was statistically different from sham stimulation using similar stimulation parameters in a parallel design, but still only of modest clinical impact, was demonstrated (Berman *et al*, 2000). In some studies, a low stimulation intensity of 80% of motor threshold was used. Generally, it seems that higher intensity may be more effective, although Loo *et al* (1999) found no differences between active and sham rTMS using a much higher stimulation intensity (110% of motor threshold). In a large sham-controlled trial with 71 patients that utilized low-frequency rTMS, it was demonstrated that 1 Hz stimulation to the *right* DLPFC was significantly more effective than sham stimulation (Klein *et al*, 1999). It is unclear whether stimulation of the *left* DLPFC at these parameters would have had the same effect. The effect of frequency was compared in a study in which 18 patients were randomized to single-pulse TMS, 10 Hz rTMS and sham rTMS delivered to the left DLPFC. A mild antidepressant effect with single-pulse TMS was demonstrated (Padberg *et al*, 1999). Recently, a sham-controlled trial in which 20 patients were randomly assigned to receive an equivalent number of pulses at 5 Hz or 20 Hz over 2 weeks was reported in which both active groups experienced a 45% reduction in depression severity ratings and none of the patients responded to the sham stimulation (George *et al*, 2000). This suggests that lower frequencies may have therapeutic efficacy as well, which is important because slow rTMS is associated with a lower seizure risk. An analysis of treatment response and cerebral metabolism suggests that patients with hypometabolism at baseline may respond better to high-frequency stimulation (20 Hz), whereas those with baseline hypermetabolism respond better to 1 Hz stimulation (Kimbrell *et al*, 1999). However, the effects of rTMS on mood examined in this study were not statistically significant.

There is some indication that TMS stimulation at higher amplitudes might be more efficacious. Recently, a negative correlation between the distance from the coil to the cortex and antidepressant response expressed as the percentage of HRSD rating decrease before and after treatment in a relatively older patient group with treatment refractory major depression was reported (Mosimann *et al*, 2002). This study demonstrated that there might be a process of prefrontal atrophy that outpaces motor cortex atrophy in chronically depressed middle-aged subjects. This observation together with the established fact that therapeutic seizures have a strong and reliable effect in depression lead to the development of another method that uses rTMS at *convulsive* levels as a more targeted form of convulsive therapy. Efficacy and side effects of electroconvulsive therapy (ECT) seem to be dependent upon the path of the current passed through the brain (Sackeim, 2000; Sackeim *et al*, 1993). Therefore targeting seizures to focal cortical areas, such as regions of the prefrontal cortex, may reduce some of the side effects of convulsive treatment. Magnetic seizure therapy (MST) has now been tested in proof of concept studies both in nonhuman primates and patients (Lisanby *et al*, 2001b) and preliminary results on cognitive side effects of the treatment compared to those of ECT have been obtained (Lisanby *et al*, 2001a). Much additional research is obviously needed to evaluate the putative clinical efficacy of this approach and to determine if it has significant advantages over ECT.

DISCUSSION

Today, data on clinical efficacy of rTMS in mood disorders are certainly not unequivocal but nevertheless interesting and encouraging. Rigorously controlled, double-blinded multicenter trials are needed in order to address adequately the question of the clinical efficacy of TMS. Prior to such studies, technical problems in the application of TMS have to be solved, for example, more satisfactory sham conditions must be developed. Today, using analogies to antidepressant drug development, valid phase II trials must be conducted. Crucial unanswered questions remain including the long-term efficacy of TMS, prevention of relapse and long-term side effects. The key findings in the acute treatment of depression have not been systematically

replicated, and effect sizes have often been small and variable. Sources of variability across studies include differences in stimulation parameter settings, concomitant medications, and different characteristics of patient samples. In addition, simple and economical methods for precise and reproducible coil placement are needed, as this factor is likely to be important for effectiveness (Kozel *et al*, 2000). In much of this work, the magnitude of antidepressant effect, while often statistically significant, has been below the threshold of clinical usefulness (Berman *et al*, 2000) and has not lived up to expectations raised by encouraging results in animal studies. Furthermore, the persistence of antidepressant effects beyond the 1–2 week treatment period has rarely been examined. Initial evidence suggests that the beneficial effects may be transitory, making the development of maintenance strategies important if rTMS is to become clinically applicable.

Establishing whether nonconvulsive rTMS has antidepressant properties aside from its clinical usefulness is of theoretical importance, because positive data support the notion that focally targeted manipulations of cortical function can result in mood improvement. Nonetheless, the future of rTMS is far from certain in its usefulness as a clinical addition to the antidepressant armamentarium. A recent systematic review of published and unpublished studies on the effectiveness of rTMS in the treatment of refractory major depression demonstrated both a relative lack in the overall quality of studies (compared to drug registration trials) and the lack of a main effect (Martin *et al*, 2002).

There is no consensus about the exact mechanisms of action of how rTMS might induce antidepressant effects. However, this is also the case for other antidepressant treatments including ECT, bupropion and the SSRIs and SNRIs. Research on rTMS has mainly been empirical. There are many variables of rTMS application and a large parameter space has therefore to be carefully explored in order to find the most efficacious treatment. This process will most likely be slow, because there is little funding available for such studies. Nevertheless, rTMS has clearly effects on the brain—which is certainly remarkable—and it might be that rTMS is a treatment modality in search of a suitable application in psychiatry.

However, from the viewpoint of the *neuroscientis*t, TMS is a methodology with great potential as a research tool (Hallett, 2000; Lisanby *et al*, 2000). This technique, by itself and combined with other methods such as EEG and neuroimaging, may be useful to test functional connectivity, neuroplasticity, information processing (eg in the visual system), indirect and direct motor control, and aspects of mood control. It affords testing of either general hypotheses of the function of the brain at different levels and hypotheses of the underlying pathology of neuropsychiatric disorders. Even if the early enthusiasm, which prevailed after early studies of clinical effects in the treatment of mood disorders settled down somewhat, rTMS will be even more useful as an investigational tool of basic and clinical research.

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