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Transcranial magnetic stimulation

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The ability to stimulate the brain in awake alert adults without the need for anesthesia or open craniotomy is a significant advance that has long been a dream of clinicians and neuroscientists. The pioneering work of the neurosurgeons Penfield and Perot demonstrated the behavioral results of direct electric stimulation of epilepsy patients during open craniotomy. This work demonstrated how powerful and important direct brain electric stimulation might be for advancing understanding of the brain [1,2]. Their results were confined to epilepsy patients, however, and the testing was done during open craniotomy.

Transcranial magnetic stimulation (TMS) is the answer to this dream of noninvasive stimulation in awake individuals. TMS produces noninvasive direct cortical brain stimulation by creating a powerful transient magnetic field [3,4], which then induces electric currents in the brain. Because of its noninvasiveness, TMS has considerable promise as a research tool to understand brain-behavior relations. Although TMS is not limited to use by neurosurgeons and does not involve surgery, it is important for neurosurgeons to be familiar with this most powerful new tool for causing "electrodeless electric stimulation." Advances made with TMS promise to set the stage for other brain stimulation advances in neurosurgery. Moreover, information gleaned from TMS studies will likely inform us about the mechanisms of action of classic neurosurgical techniques like deep brain stimulation (DBS).

Despite TMS's promise and widespread use, there is still inadequate understanding of the exact mechanisms by which TMS affects the brain and

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Drs George, Nahas, and Kozel hold several TMS-related patents either alone or in combination. These are not in the area of TMS therapeutics but are for new TMS machine designs as well as combining TMS with MRI.

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how these effects change as a function of different TMS use parameters, such as intensity and frequency. Progress in this area is occurring by performing TMS in animal models and by combining TMS with functional neuroimaging. There has been much interest in using repeated daily administration of TMS as a potential treatment in a variety of neuropsychiatric disorders. The largest body of work has been done in the treatment of major depression. Although several meta-analyses of these antidepressant studies show that TMS has statistically significant effects greater than those of placebo, larger sample studies are still needed to clarify its clinical role. Additionally, TMS as a treatment for depression has not yet been approved by the US Food and Drug Administration (FDA), although pivotal trials geared for eventual FDA approval are currently underway. This article succinctly summarizes basic TMS physics and mechanisms and then critically reviews the potential clinical uses of TMS, particularly in the treatment of depression and other neuropsychiatric conditions.

Description of transcranial magnetic stimulation and mechanisms of action

TMS uses a powerful handheld magnet to create a time-varying magnetic field, where a localized pulsed magnetic field over the surface of the head depolarizes underlying superficial neurons [3–5]. High-intensity current is rapidly turned on and off in the electromagnetic coil through the discharge of capacitors (Fig. 1). It is important to realize that TMS, which produces powerful but brief magnetic fields that, in turn, induce electric currents in the brain, radically differs from the currently popular use of low-level static magnetic fields as alternative therapies. Constant exposure to static magnetic fields can have biologic effects [6]. TMS does not produce magnetic fields for long (microseconds), however, and they are relatively weak, except directly under the TMS coil. It is thus assumed that TMS produces its behavioral effects solely through the production of electric currents in the cortex of the brain. This assumption has not been proved, however. If TMS pulses are delivered repetitively and rhythmically, the process is called repetitive TMS (rTMS) [7]. rTMS can be modified by the term *fast* if the frequency is greater than 1 Hz [8]. Fast rTMS is currently limited to brief runs of approximately 25 to 30 Hz. Stimulation frequencies faster than this have an increased seizure risk, and most modern capacitors cannot keep delivering the needed energy before depleting. Thus, fast TMS is performed at frequencies that would be considered slow for DBS, where stimulation frequencies sometimes exceed 150 Hz.

The magnetic field induced by TMS declines rapidly with distance away from the coil. Thus, with current technology, TMS coils are directly and electrically only able to stimulate the superficial cortex and are not able to produce direct electric stimulation deep in the brain [9]. Although this limited depth of penetration is a limitation of the present technology, deeper brain structures can be influenced by cortical TMS because of the cortex's

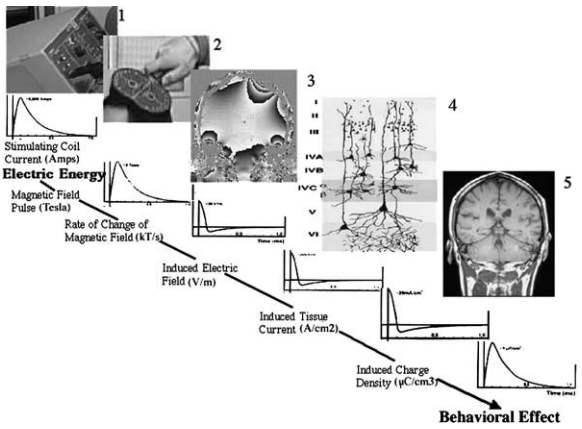

Fig. 1. Diagram of events leading to transcranial magnetic stimulation excitation. (*From* George MS, Belmaker RH. Transcranial magnetic stimulation in neuropsychiatry. Washington (DC): American Psychiatric Press; 2000; with permission).

massive interconnections and redundant cortical-subcortical loops [10]. Moreover, there are several groups working on novel TMS coil designs that might be able to reach deeper into the brain without overwhelming superficial cortical structures.

The amount of electricity needed to cause changes in the cortex varies from person to person and also from one brain region to the next [11]. One commonly used method for standardizing and adjusting the amount of electricity delivered and induced by TMS across different individuals is to determine each person's motor threshold (MT). The MT is commonly defined as the minimum amount of electricity needed to produce movement in the contralateral thumb when the coil is placed optimally over the primary motor cortex. MT can be determined either by using electromyographic (EMG) recordings [12] or, with less precision, by using visible movement [13].

TMS has been shown to produce immediate effects (within seconds), such as the movement of the thumb or direct inhibition of another TMS pulse followed shortly in time. These immediate effects are thought to result from direct excitation of inhibitory or excitatory neurons. There is some evidence to suggest that TMS at different intensities, frequencies, and coil angles excites different elements (eg, cell bodies, axons) of different neuronal groups (eg, interneurons, neurons projecting to other parts of the cortex, U fibers) [8,14–17]. This is further complicated by the complex six-layer arrangement of human neocortex along with the varying gyral folds, which places some aspects of the brain close to the surface and others far away in sulcal folds.

Another example of immediate TMS effects is called paired-pulse TMS. This technique involves delivering two TMS pulses to the same region with varying interpulse intervals (usually milliseconds long) and intensities [12]. Depending on the relative strength of the first pulse to the second and the interpulse interval, the first pulse can either inhibit or enhance the second pulse. Paired-pulse TMS over the motor area can be used to assess natural brain inhibitory and excitatory systems at rest in individuals with different disorders [18,19] as well as after the administration of different centrally active compounds or other treatments [20]. The different TMS use parameters (eg, frequency, intensity, length of stimulation, intertrain interval) are most certainly all biologically relevant and likely important. Particular attention has been focused on whether and to what degree different frequencies of TMS might have divergent biologic effects. For example, repeated stimulation of a single neuron at low frequency in culture produces long-lasting inhibition of cell-cell communications (called long-term depression [LTD]) [21–24]. Conversely, repeated high-frequency stimulation can improve cell-cell communication (called long-term potentiation [LTP]) [25]. With these cellular data on LTD and LTP as a background, there has been much interest in whether TMS, exciting hundreds or thousands of neurons in a pulse, can produce sustained inhibitory or excitatory effects [26,27]. Several studies have now shown that chronic low-frequency stimulation of the motor cortex can produce inhibitory intermediate-term effects (lasting for several minutes) after stimulation [28,29]. There is also some evidence that high-frequency stimulation can produce intermediate-term excitatory effects [30]. One of the most easily demonstrated immediate effects of TMS is speech arrest, where high-frequency TMS placed precisely over the Broca's area can immediately and transiently block fluent speech [31]. TMS used in studies like this can produce what are sometimes referred to as "virtual lesions." Importantly, none of these temporary lesion effects were demonstrated to persist beyond the time of active TMS administration. Thus, the lesions are truly virtual and temporary. This contrasts with observations that a train of repeated high-frequency stimulation can excite the brain so much that it results in seizure activity [32]. With knowledge of the appropriate limits of stimulation, seizures can be avoided safely.

Safety issues

Although there is minimal risk of a seizure when TMS is performed within the published safety guidelines, the most well-known critical safety concern with TMS is inadvertently causing a seizure [7]. It is important to realize that this TMS safety table was developed in a small subject sample using a surrogate end point for a seizure—spread of TMS-induced motor-evoked potentials (MEPs) beyond the target area of stimulation. Thus, the safety table exists only for stimulation of motor cortex and cannot readily be applied to using TMS over other brain regions. Finally, although the intensity and frequency of stimulation were examined, the intertrain interval was not. One of the inadvertent seizures was induced with stimulation trains that were within the safety guidelines but that were administered with an excessively short intertrain interval [33]. A general rule of thumb is

that one should have an intertrain interval at least as long as the period of stimulation. A known seizure disorder, history of epilepsy, or intracranial abnormality, such as a prior stroke, can all increase the risk of a TMS-induced seizure [34]. Although an inadvertent seizure is the main safety hazard associated with TMS, there have been only 12 reported cases since 1985 when cranial TMS began. It is, in fact, not easy to intentionally use TMS to produce a seizure, even in patients with epilepsy [35]. For example, an attempt to use TMS to produce a seizure intentionally in a patient with a focal epilepsy was not successful [35]. In addition, in a study exploring rTMS as a method to induce therapeutic seizures, stimulation parameters far above the published safety thresholds had to be used to reliably induce seizures [36].

A muscle tension type headache and discomfort at the site of stimulation are less serious but relatively common side effects of TMS. In contrast to electroconvulsive therapy (ECT), no deleterious cognitive effects of 2 weeks of slow or fast rTMS have been found [37,38]. This is not surprising, because ECT induces a generalized seizure, whereas rTMS is being used at subconvulsive levels. Like MRI, TMS could cause the movement of paramagnetic objects in or around the head. For this reason, subjects with paramagnetic metal objects in the head or eye are generally excluded from TMS studies. TMS can cause heating of metallic implants and the inactivation of a pacemaker, medication pumps, or cochlear devices. In the United States, rTMS is an experimental procedure that requires an investigational device exemption (IDE) from the FDA for research. It should be kept in mind that modern TMS did not begin until 1985 [39] and that the total number of subjects or patients to receive TMS is likely still less than 10,000. Nevertheless, substantial experience to date suggests that at least in the short term (<10 years), TMS at moderate intensity has no other evident lasting adverse effects in adults.

Overview of research uses relevant to neurosurgery

As a research tool, TMS has been used to influence many brain functions, including movement [40], visual perception [41,42], memory [43,44], attention, speech [31,45], and mood [46–48]. A full review is beyond the scope of this article [49,50]. We discuss below the TMS uses germane to neurosurgery.

Interestingly, in light of the initial pioneering results of Penfield, stimulation with TMS has never evoked the type of complex behavioral symptoms reported with direct electric stimulation in human beings. TMS has never been reported to provoke a memory, smell, or song as reported by Penfield [1,2,51]. There may be several explanations for this difference between TMS and direct cortical stimulation. First, most TMS studies are in healthy subjects, whereas the Penfield results were from patients with refractory epilepsy requiring surgery. Complex behaviors have not been provoked by TMS, even when it has been used in epilepsy patients [35,52]. This area has not been systematically explored, however. Second, Penfield and Perot used high-intensity electric stimulation that even caused seizures in some instances. In other words, the initial electric stimulation likely spread to other regions through pathologically kindled neuronal circuits. Stimulation of these circuits led to the expression of auras. Thus, most importantly, all the complex behaviors reported by Penfield and Perot were actually auras commonly experienced by the patients. This fact is underappreciated but was recently confirmed by Perot (P. Perot, personal communication, 2002). Thus, it is likely that TMS does not produce complex behaviors like historic accounts of direct cortical electric stimulation because TMS has not been delivered in intensities high enough to cause spreading of a seizure discharge and elicitation of auras.

Use of transcranial magnetic stimulation and speech arrest to determine eloquent cortex

TMS delivered over the motor speech area can produce transient speech arrest. There was initial interest in whether TMS might be used to determine eloquent cortex. This information could be useful in patients about to undergo surgical resection of tumors or seizure foci. Initial reports found that TMS needed to be delivered at frequencies around 20 Hz, which was painful and might induce a seizure in a patient with a focal lesion or epilepsy [52–54]. A later study showed that TMS could be performed at lower frequencies, sometimes as low as 4 Hz [31]. There has not been a formal comparison of TMS speech arrest with the Wada test or functional MRI (fMRI) presurgical mapping. Some studies have found that the TMS-indicated region for motor cortex correlates well with fMRI-predicted motor cortex and later direct neurosurgical stimulation [55]. Further work

using TMS to help with presurgical planning for motor or speech areas is warranted [56].

Use parameter effects in animal models

Although TMS has been used quite effectively as a tool to investigate normal and pathologic brain function, its full and proper uses as a research tool and clinical treatment are still hampered by incomplete knowledge of the neurobiologic cascade of events triggered by TMS at different settings. Numerous animal studies have been important in trying to bridge this knowledge gap and improve our understanding of the modes of action of TMS.

TMS studies with intracranial electrodes in rhesus monkeys have provided information about the nature and spatial extent of the rTMS-induced electric field [57,58]. Corticospinal tract development, aspects of motor control, and medication effects on corticospinal excitability have been studied fairly extensively in nonhuman primates using single-pulse TMS [59–67]. Such work has yielded information about TMS neurophysiologic effects, such as the observation that TMS-evoked motor responses result from direct excitation of corticospinal neurons at or close to the axon hillock [67].

Rodent rTMS studies have reported antidepressant-like behavioral and neurochemical effects. In particular, rTMS enhances apomorphine-induced stereotypy and reduces immobility in the Porsolt swim test [68,69]. rTMS has been reported to induce electroconvulsive shock (ECS)–like changes in rodent brain monoamines, β-adrenergic receptor binding, and immediate early gene induction [69–71]. The effects of rTMS on seizure threshold are variable and may depend on the parameters and chronicity of stimulation [26,72]. Within the past year, Pope and Keck [73] have completed a series of studies using more focal TMS in rat models. They have largely replicated earlier TMS animal studies using less focal coils. Even with the attempt at focal rat stimulation, the effects involve an entire hemisphere and cannot readily be extrapolated to what is happening in human TMS using focal coils [74].

Combining transcranial magnetic stimulation with functional imaging

A critically important area that will ultimately guide clinical parameters is to combine TMS with functional imaging to monitor TMS effects on the brain directly and to thus understand the varying effects of different TMS use parameters on brain function. Because it seems that TMS at different frequencies has divergent effects on brain activity, combining TMS with functional brain imaging will better delineate not only the behavioral neuropsychology of various psychiatric syndromes but some of the pathophysiologic circuits in the brain. In contrast to imaging studies with ECT, which have found that ECT shuts off global and regional activity [75], most studies using serial scans in depressed patients undergoing TMS have found increased activity in the cingulate and other limbic regions [76–78]. However, two studies have now found divergent effects of TMS on regional activity in depressed patients, determined both by the frequency of stimulation and the baseline state of the patient [79,80]. In other words, for patients with global or focal hypometabolism, high-frequency prefrontal stimulation has been found to increase brain activity over time, with the opposite happening as well. Conversely, patients with focal hyperactivity have been shown to have reduced activity over time after chronic daily low-frequency stimulation. These two small sample studies have numerous flaws, however. They simultaneously show the potential and the complexity surrounding the issue of how to use TMS to change activity in defined circuits. They also point out an obvious difference from ECT, where the net effect of the ECT is to decrease prefrontal and global activity [75].

Over the past year, several studies combining TMS with other neurophysiologic and neuroimaging techniques have helped to elucidate how TMS achieves its effects. The Medical University of South Carolina (MUSC) group has pioneered and perfected the technique of interleaving TMS with blood oxygen level–dependent (BOLD) fMRI, allowing for direct imaging of TMS effects with high spatial (1–2 mm) and temporal (2–3 seconds) resolution [81–83] (Fig. 2). Another group in Germany has now succeeded in interleaving TMS and fMRI in this manner, replicating some of the earlier MUSC work [84]. Work with this technology has shown that prefrontal TMS at 80% MT produces much less local and remote blood flow changes than does 120% MT TMS [85]. Strafella et al [86] used positron emission tomography (PET) to show that prefrontal cortex TMS causes dopamine release in the caudate nucleus, and Paus et al [87] used the same modality to show that prefrontal cortex TMS has reciprocal activity with the anterior cingulate gyrus. Our group at the MUSC [76,77,88] as well as investigators in Scotland (K. Ebmeier, personal communication 2002) and Australia [80]

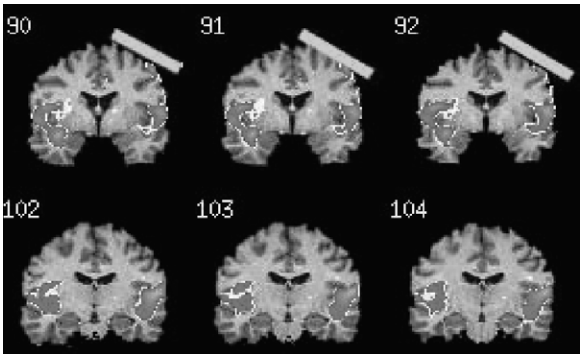

Fig. 2. Image of blood oxygen level–dependent (BOLD) functional MRI (fMRI) data from healthy adults, where transcranial magnetic stimulation (TMS) has been applied at 120% motor threshold over the prefrontal cortex. Note that although TMS initially affects only superficial cortex, cortical-subcortical connections cause changes in deeper limbic regions (8 individuals, $P < 0.001$, extent $P < 0.05$ for display on Talairach normalized MRI template). (*From* Nahas Z, Lomarev M, Roberts DR, et al. Unilateral left prefrontal transcranial magnetic stimulation (TMS) produces intensity-dependent bilateral effects as measured by interleaved BOLD fMRI. Biol Psychiatry 2001;50:712–720; with permission).

have all shown that lateral prefrontal TMS can cause changes in the anterior cingulate gyrus and other limbic regions in depressed patients.

It is thus clear that TMS delivered over the prefrontal cortex has immediate effects in important subcortical limbic regions. The initial TMS effect on cortex and the secondary synaptic changes in other regions likely differ as a function of mood state, cortical excitability, and other factors that would change resting brain activity. The MUSC group thus wondered whether these TMS-induced limbic effects might be modified by medications that are known to treat or stabilize mood. Would a medication that inhibits cortical spreading of electric stimulation change the TMS-induced limbic effects? To answer this, we recently designed and completed a study in 12 healthy young men, where we measured the TMS MT as well as performed TMS/fMRI on 2 separate days [89]. On the first day, subjects received one single oral dose of 325 mg of lamotrigine or placebo. On the other day 1 week later, in a randomized fashion, they received whatever they did not receive during the first session. Lamotrigine is a use-dependent sodium channel inhibitor with broad-spectrum anticonvulsant, antidepressant, and mood-stabilizing effects. As with many central nervous system (CNS) active compounds in which much is known about the pharmacology, little is known about how lamotrigine works within brain circuits to achieve its clinical effects, particularly its mood-stabilizing and antidepressant effects. On the day that subjects received lamotrigine, their TMS MT was elevated by 15% compared with the day they received placebo. This demonstrates that lamotrigine has an inhibitory effect on motor cortex. TMS/fMRI images showed that lamotrigine markedly reduced the secondary effects of TMS in other cortical regions. In direct contrast, however, lamotrigine increased the TMS-induced effects in limbic regions. This proof of concept study highlights several key points in understanding TMS brain effects. First, it is abundantly clear that prefrontal TMS has direct modulating effects on limbic structures. Second, these TMS effects are easily seen with the interleaved TMS/fMRI and other imaging techniques. Most importantly, factors like medications and probably diseases like depression modify the TMS-induced limbic effects.

The interleaved TMS/fMRI technique shows promise as a useful new method for understanding the regional brain effects of CNS active compounds, particularly those with inhibitory mechanisms. Further studies are needed to determine if this technique is useful in new compound development or in monitoring or predicting clinical efficacy.

Uses of transcranial magnetic stimulation as therapy

Depression

Although the functional anatomy of mood regulation is not nearly as well understood as the

circuitry of the visual or motor systems, most scientists agree that certain brain regions are consistently affected in depression and, to a lesser extent, mania. Although there is controversy and much more work is needed, certain regions have consistently been implicated in the pathogenesis of depression and mood regulation [90–99]. These include the medial and dorsolateral prefrontal cortex, the cingulate gyrus, and other regions commonly referred to as limbic (ie, amygdala, hippocampus, parahippocampus, septum, hypothalamus, limbic thalamus, insula) and paralimbic (ie, anterior temporal pole, orbitofrontal cortex).

The notion of using something like TMS as an antidepressant dates back at least to the turn of the century, when a patent was filed in Vienna in 1902 [100]. In more modern times, there were two open studies in Europe in the early 1990s using nonfocal round coils centered over the vertex to deliver TMS to broad frontal and parietal regions in an attempt to treat depression [101,102]. Reasoning that prefrontal and limbic regions were more important for mood regulation than the brain regions near the vertex and that theories of ECT action emphasize the role of prefrontal cortex effects [103], one of us (M.S.G.) performed the first open trial of prefrontal TMS as an antidepressant in 1995 [104], followed immediately by a cross-over double-blind study [105]. The theory behind this work was that chronic, frequent, subconvulsive stimulation of the prefrontal cortex over several weeks might initiate a therapeutic cascade of events in the prefrontal cortex as well as in connected limbic regions. Thus, beginning with these prefrontal studies, modern TMS was specifically designed as a focal, nonconvulsive, circuit-based approach to therapy. TMS was conceived of and launched to serve as a bridge from functional neuroimaging advances in circuit knowledge to the bedside as a focal noninvasive treatment.

Since the initial studies, there has been continued high interest in TMS as an antidepressant. Multiple trials have been conducted by researchers around the world. In general, there is not a large industry sponsoring or promoting TMS as an antidepressant (or therapy for other disorders), and the funding for these trials has largely come from foundations and governments. The samples sizes in these antidepressant trials are thus small (in all, less than 100 subjects per trial) compared with industry-sponsored pharmaceutic trials of antidepressants. A thorough review of all of these trials is beyond the scope of this article. An initial study from Spain from a group not involving a psychiatrist and without prior treatment trial experience in depression found profound antidepressant effects in psychotically depressed patients with only 1 week of left prefrontal treatment [106]. The design of this trial was unorthodox for studying depression, involving 1 week of therapy per month repeated over 6 months. Nevertheless, it generated much interest in the field. The findings of rapid response after only 1 week have not been replicated despite numerous attempts, and many early TMS trials were designed using this study to determine the sample size and treatment algorithms, leading to small underpowered studies using an inadequate stimulation intensity (80% of MT). Since then, most of approximately 20 studies have found modest antidepressant effects that take several weeks to build. Not all TMS antidepressant treatment studies have been positive, however [107].

Meta-analyses of transcranial magnetic stimulation antidepressant effect

There have now been five independent meta-analyses of the published or public TMS antidepressant literature (Table 1). Each of these meta-analyses has used different methods of selecting studies as well as different methods of performing the statistical analysis of the literature. Their different approaches are summarized in Table 1. Their results are the same: daily prefrontal TMS delivered over several weeks has antidepressant effects greater than sham treatment. An initial meta-analysis by McNamara et al [108] of 5 sham-controlled studies found that TMS was statistically significantly superior to sham TMS and that this difference was robust. In a different meta-analysis, Burt et al [109] examined 23 published comparisons for controlled TMS prefrontal antidepressant trials and found that TMS had a combined effect size of 0.67, indicating a moderate to large antidepressant effect. A subanalysis was done on those studies directly comparing TMS with ECT. The effect size for TMS in these studies was greater than in the studies comparing TMS with sham, perhaps reflecting subject selection bias. The authors suggested that perhaps TMS works best in patients who are also clinical candidates for ECT. Holtzheimer et al [110] analyzed both published and some unpublished sham-controlled studies and concluded that, overall, prefrontal TMS was superior to sham and that

Table 1
Meta-analysis of transcranial magnetic stimulation antidepressant literature

Study	Selection method	No. studies	No. subjects	TMS effect size	Remarks
McNamara et al, 2001	R and L PFCX, DB	5	81	Active 43% greater than sham	
Holtzheimer et al, 2001	R and L PFCX, DB, published and unpublished	12	210	Overall, Cohen's D = 0.81 Left, Cohen's D = 0.9, right = 0.7	
Burt et al, 2001					
	Open published and unpublished	9	248	Cohen's D = 1.37	
	DB, published and unpublished	16	432	Cohen's D = 0.67	
	Compare with ECT, published	3	112	Cohen's D = 0.21 favoring ECT	
Kozel and George, 2002	Left PFCX, DB, data available	12	230	Hedge's D = 0.53	Funnel plot shows publication bias, 25–50 negative studies needed to change results
Martin et al, 2002	DB, published and unpublished	14 overall			
	Left PFCX	9	197	2 weeks, TMS WMD-0.35 greater than sham	Does not allow for adjustment for difference
	Right PFCX	1		2 weeks, TMS WMD-6.0 greater than sham	
	Compare ECT	1	40	2 weeks, ECT WMD 1.7 greater than TMS	

Abbreviations: TMS, transcranial magnetic stimulation; DB, double-blind; PFCX, prefrontal cortex; R, right; L, left; ECT, electroconvulsive therapy; WMD, weighted mean difference.

left-sided treatment had a nonsignificantly greater effect size. Yet another meta-analysis was recently conducted by Kozel and George [111]. This analysis was confined to published double-blind studies with individual data using TMS over the left prefrontal cortex. The summary analysis using all 10 studies that met criteria revealed a cumulative effect size of 0.53 (Cohen's D) (range: 0.31–0.97), with the total number of subjects studied being 230. The authors used a funnel plot technique to assess whether there was a publication bias in the literature to date and whether this bias might affect the results of the meta-analysis. This technique assumes that with small sample studies, there is a large chance of both erroneous positive and negative results. As the sample size of studies increases, the effect sizes should begin to converge, resembling a funnel. The funnel plot (Fig. 3) indicates that a publication bias is likely and that there are more positive small sample studies in the TMS antidepressant literature than should occur by chance. These authors then used techniques to determine how large this publication bias would have to be to change the results of the meta-analysis. The fail-safe results indicated that there would have to be 56 nonsignificant unpublished studies of approximately the same average sample size as the published studies to change the cumulative meta-analysis effect to a nonsignificant result (56 studies with Rosenthal's method, 22 studies with Orwin's method). The most critical meta-analysis of the TMS antidepressant field was recently conducted using the guidelines put forth in the Cochrane Library [112]. This study cannot be compared directly with the other meta-analyses because it looks at the field from a completely different angle. Cochrane reviews typically try to establish the clinical value of a given therapy using stringent guidelines. The method is not well suited to look at small effects, which are scientifically important but are of lesser value in establishing clinical significance. In addition, Cochrane study

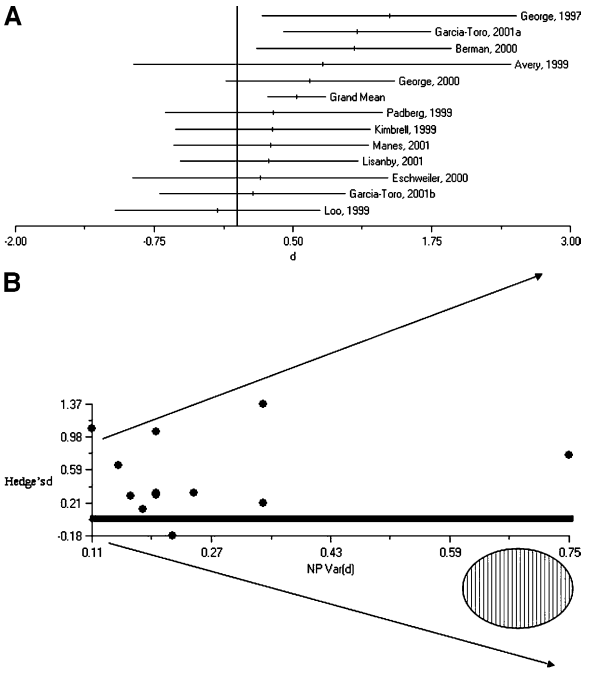

Fig. 3. Summary of transcranial magnetic stimulation (TMS) sham-controlled antidepressant studies, with effect sizes (A) and funnel plot (B). Note that there are insufficient small sample negative studies (shaded oval in B), which would be predicted by chance. This indicates there is likely a publication bias in the current TMS antidepressant literature.

groups try to include unpublished negative data to correct, at least in part, for publication bias. Moreover, the Cochrane method does not allow for within-study adjustments for between-group differences in illness baseline and instead uses raw illness variables. Thus, unequal initial distribution of illness severity, especially in small studies, can introduce significant bias into the results and conclusions. Even this stringent meta-analysis included 14 trials suitable for analysis, however [112]. Importantly, these investigators found "No difference. . .between rTMS and sham TMS using the Beck Depression Inventory or the Hamilton Depression Rating Scale, except for one time period (after 2 weeks of treatment) for left dorsolateral prefrontal cortex and high frequency; and also for right dorsolateral prefrontal cortex and low frequency, both in favor of rTMS and both using the Hamilton scale" [112]. In summary, all five meta-analyses of the TMS published literature concur that repeated daily prefrontal TMS for 2 weeks has antidepressant effects greater than those of sham.

Although there is general consensus that TMS has statistically significant antidepressant effects, a more important question is whether these effects are clinically significant. The meta-analyses discussed previously concur on an effect size of Cohen's D of 0.65, which is a moderate effect in the same range as the effects of antidepressant medications. For example, small to medium effect sizes (0.31–0.40) are common in randomized controlled trials of novel antidepressants [113,114]. Thus, with respect to whether or not TMS has clinical significance, an important clinical issue is whether TMS would be clinically effective in patients referred for ECT. This question has been addressed in a series of studies in which ECT referrals were randomized to receive either ECT or rTMS. In an initial study, Grunhaus et al [115] compared 40 patients who presented for ECT treatment and were randomized to receive either ECT or TMS. ECT was superior to TMS in patients with psychotic depression, but the two treatments were not statistically different in patients without psychotic depression. This same group recently replicated this finding in a larger and independent cohort with an improved design (L. Grunhaus, personal communication, 2001). Recently, Janicak and colleagues [116] reported a similar small series finding near equivalence between TMS and ECT. The major differences between these studies and the rest of the controlled studies of TMS efficacy are the

patient selection (suitable for ECT), length of treatment (3–4 weeks), lack of blinding, and lack of a sham control. Unfortunately, none of the studies explicitly measured differences in cognitive side effects, although, presumably, TMS has no measurable cognitive side effects, whereas ECT has several. In a similar but slightly modified design, Pridmore [117] recently reported on a study comparing the antidepressant effects of standard ECT (three times per week) and ECT given one time per week followed by TMS on the other 4 weekdays. At 3 weeks, he found that both regimens produced similar antidepressant effects. Unfortunately, detailed neuropsychologic testing was not performed, but one would assume that the TMS and ECT group had less cognitive side effects than the pure ECT group. Finally, an Israeli group recently published their finding that relapse rates in the 6 months after ECT or rTMS were similar [118]. For both treatments to maintain maximal benefit, some form of maintenance therapy is recommended. In sum, TMS clinical antidepressant effects are in the range of those of other antidepressants and persist as long as the clinical effects after ECT.

Although the literature suggests that prefrontal TMS has an antidepressant effect greater than that of sham and that the magnitude of this effect is at least as large as that of other antidepressants, many issues are not resolved. For example, it is unclear how best to deliver TMS. Most but not all [119] studies have used focal coils positioned over the left prefrontal cortex. It is still not known whether TMS over one hemisphere is better than that over another hemisphere or whether there are better methods for placing the coil. For the most part, the coil has been positioned using a rule-based algorithm to find the prefrontal cortex, which was adopted in the early studies [46,104–106]. This method was shown to be imprecise in the particular prefrontal regions stimulated directly underneath the coil, depending largely on the subject's head size [120]. Additionally, most studies have stimulated with the intensity needed to cause movement in the thumb (MT). There is now increasing recognition that higher intensities of stimulation might be needed to reach the prefrontal cortex, especially in elderly patients, where prefrontal atrophy may outpace that of motor cortex, where MTs are measured [121–123]. There are also emerging data that TMS therapeutic effects likely take several weeks to build. Consequently, many of the initial trials, which lasted only 1 to 2 weeks, were likely too brief to generate maximum clinical antidepressant effects.

Maintenance transcranial magnetic stimulation to prevent depression relapse after recovery

Because of its noninvasiveness and positive safety and cognitive profile, TMS is potentially attractive as a maintenance treatment. At MUSC recently, seven treatment-resistant bipolar depressed patients who had responded to an acute TMS trial were offered admission into a 1-year maintenance therapy of weekly TMS [124]. TMS was performed 1 day per week over the left prefrontal cortex at 110% MT and 5 Hz for 8 seconds for 40 trains. During this follow-up period, four subjects dropped out of the maintenance study and were labeled nonresponders (average of 25 weeks of treatment). Three subjects completed 1 full year of weekly TMS without a depression relapse. These data suggest that TMS might eventually be used as a maintenance tool in depression and that one treatment per week might be a good first attempt at a maintenance schedule. Much more work is needed, however.

Transcranial magnetic stimulation to treat mania

Grisaru and his colleagues in Israel [125,126] reported on an interesting study using either right or left prefrontal TMS in bipolar affective disorder (BPAD) manic patients admitted to their hospital for mania. TMS was given daily in addition to the standard treatment for mania. After 2 weeks, the group receiving right-sided TMS was significantly more improved than the group that had received left-sided TMS. The authors concluded that TMS might be useful as an antimanic agent. This same group has attempted to replicate these findings but has not found similar results (N. Grisaru, personal communication, 2001). Additionally, although subjects were assigned to the two groups at random, the left-sided group was more ill than the right-sided group on several measures. Further work is needed.

Current state of transcranial magnetic stimulation clinical practice for depression

In summary, TMS is a promising tool for treating depression acutely. It likely can also induce mania or hypomania in BPAD patients or susceptible patients. Its antimanic properties remain to be explored. Although it is approved in Canada and Israel as a treatment, it is still considered investigational in the United States by the FDA. Much work remains to understand the optimum

dosing strategy for the antidepressant effect of TMS. It is unlikely that the initial combinations of intensity, frequency, coil shape, scalp location, number of stimuli, or dosing strategy (daily, twice daily) are the most effective for treating depression. Some US and European psychiatrists are using TMS in clinical practice to treat depression under their general license to practice.

Important unanswered clinical questions

It is not clear which, if any, medications work well with TMS or interfere with its therapeutic effects. Despite these major unanswered questions, since the first use of prefrontal TMS as an antidepressant in 1995, this tool has clearly opened up new possibilities for clinical exploration and treatment of depression. Many parameters, such as intensity, location, frequency, pulse width, intertrain interval, coil type, duration, numbers of sessions, interval between sessions, and time of day, remain to be systematically explored. Although there are suggestions of antidepressant effects of TMS, there are questions about how it might be used in treatment algorithms. It will perhaps always be easier to see a clinician occasionally and take daily medication rather than traveling to a treatment facility for TMS on a daily basis. Thus, the ultimate clinical role of TMS in treating depression may be in medication-refractory cases, those who would otherwise receive ECT, or in patients who are unable to tolerate systemic therapy because of pregnancy [127] or a medical condition.

Other conditions

TMS has also been investigated as a possible treatment for a variety of neuropsychiatric disorders. In general, the published literature on these conditions is much less extensive than for TMS as an antidepressant; therefore, conclusions about the clinical significance of effects must remain tentative until large sample studies are conducted.

Movement disorders

Some initial studies found positive effects in Parkinson's disease [128]; however, one of these early results could not be replicated [129], and some of the methods described were actually not credible. Moreover, a recent study found that TMS delivered over the supplementary motor area (SMA) actually worsened Parkinson's disease symptoms [130]. Three other recent studies [131–133], however, as well as a study from Japan using TMS over the prefrontal cortex at low frequencies and doses [134,135] report that TMS may improve effects in Parkinson's disease. Further studies are needed. It should be remembered that only a small portion of the combinations of use parameters, brain regions, and dosing schedules have been tried.

There are two small positive studies showing that TMS can benefit writer's cramp, a form of focal dystonia [136]. After publication of a positive small abstract, two groups have used TMS to investigate and possibly treat Gilles de la Tourette syndrome [137]. One study found modest and transient beneficial effects on tics when applied over prefrontal cortex (M. Trimble, personal communication 2002). Another study at MUSC also found positive effects on tics and obsessive-compulsive disorder (OCD) symptoms [137]. Further work is needed in this promising area.

The TMS MT is reduced in patients with untreated epilepsy [138], hinting at widespread problems in cortical excitability. Therapeutically, there is one report of potential beneficial effects of slow rTMS in action myoclonus [139]. Additionally, TMS has been used to examine cortical excitability and inhibition in Tourette's syndrome, dystonia, and OCD [18,19]. Reduced intracortical inhibition has been reported in all three illnesses.

Schizophrenia

Several studies have used TMS to investigate schizophrenia without consistent replication of early findings, which were compounded by medication issues [140,141]. A 1-day prefrontal TMS challenge study by Nahas and colleagues [142] at MUSC failed to find significant effects on negative symptoms. Hoffman and colleagues [143,144] have used low-frequency TMS over the temporal lobes to treat hallucinations in patients with schizophrenia. Although they have replicated their earlier study, another group has tried to replicate this effect without success (K. Ebmeier, personal communication 2002).

Anxiety disorders

In a randomized trial of left and right prefrontal and midoccipital 20-Hz stimulation in 12 patients with OCD, Greenberg et al [145] found that a single session of right prefrontal rTMS decreased compulsive urges for 8 hours. Mood was also transiently improved, but there was no effect on anxiety or obsessions. Using TMS probes, the

same group reported decreased intracortical inhibition in patients with OCD [146], which has also been noted in patients with Tourette's syndrome [19]. Somewhat surprisingly, OCD patients had a lowered MEP threshold in one study [147], which was unrelated to intracortical inhibition and seems to replicate (E.M. Wassermann, personal communication 2002). Only two other studies have examined possible therapeutic effects of rTMS in OCD. A double-blind study using right prefrontal slow (1 Hz) rTMS and a less focal coil failed to find statistically significant effects greater than those of sham [148]. In contrast, a recent open study in a group of 12 OCD patients refractory to standard treatments, who were randomly assigned to right or left prefrontal fast rTMS, found that clinically significant and sustained improvement was observed in one third of patients [149]. Clearly, further work is warranted testing TMS as a potential treatment for OCD.

McCann et al [150] reported that 2 patients with posttraumatic stress disorder (PTSD) improved during open treatment with 1 Hz of rTMS over the right frontal cortex. Grisaru et al [151] similarly stimulated 10 PTSD patients over motor cortex and found decreased anxiety. Grisaru and colleagues also reported a positive TMS study in PTSD patients (N. Grisaru, personal communication, 2001). Further work is needed.

A potential new way of using transcranial magnetic stimulation–magnetic seizure therapy as an antidepressant

The discussion throughout this article has focused on using TMS to change brain function without inadvertently causing a seizure. As mentioned previously, TMS at high frequencies and intensities can cause seizures. ECT produces a seizure through direct electric stimulation, under anesthesia, of the scalp and skull. Although ECT is the most effective antidepressant, it has cognitive side effects and does not work in up to half of treatment-resistant patients. If one used TMS to induce an ECT-like seizure, one might be able to focus the point of origin of the seizure and thus spare some brain regions from unnecessary exposure to electric currents and to seizure spread. This is possible with TMS, because magnetic fields pass through the scalp and skull unimpeded, whereas the direct application of electricity to the scalp with ECT loses focality and power as a result of the impedance of the overlying tissue. After a proof of concept demonstration in primates [152], Lisanby et al [36] used an enhanced device with four times the usual number of charging modules to induce seizures in depressed patients referred for ECT. Further clinical and preclinical work with this exciting technique called magnetic seizure therapy (MST) has proceeded. An initial safety study found that MST seizures were briefer in duration than ECT seizures, that patients awoke from anesthesia much faster with MST, and that their acute cognitive side effects were much less with MST [153]. Further work is underway to determine whether this technique has antidepressant effects. Because MST induces a seizure, it still requires repeated episodes of general anesthesia.

The long-held dogma in the field of convulsive therapy was that a seizure was necessary and sufficient to constitute an effective treatment for depression. Recent research in ECT and new work in TMS have challenged both aspects of that theory with respect to the antidepressant potential of brain stimulation. First, it was demonstrated that it was possible to generate seizures with ECT that lacked efficacy; thus, a seizure cannot be sufficient [154,155]. What we have learned about the features that distinguish effective from ineffective seizures has guided the development of MST as a more targeted way of producing an effective treatment that should be less contaminated by the consequences of generalization to regions of the brain linked to cognitive side effects (medial temporal structures). Because MST offers a focal means of inducing seizures, it is possible to use MST to examine the roles of the location of seizure onset and patterns of seizure spread in the antidepressant effects and cognitive side effects more precisely than one could do with ECT.

In addition to not being sufficient, recent work with TMS has challenged the theory that a seizure is necessary at all [156]. This radical notion was not easily accepted by the field as recently as 8 years ago, because it challenged the then widely held dogma that a seizure was needed for ECT, and by extension, any form of transcranial stimulation to be effective in treating depression. The recent suggestions of antidepressant effects of vagus nerve stimulation (VNS) in treatment-resistant depressed patients [157–159] as well as in comorbid epilepsy and depression patients [160,161] add weight to the notion that somatic treatments can improve mood without causing a seizure (VNS does not cause seizures and is, in fact, an anticonvulsant treatment method). Additionally, the recent reports of mood effects with DBS also underline the point that nonconvulsive

stimulation can powerfully change mood [162]. The recent studies with MST, although perhaps a radical improvement over the current methods of inducing seizures, still work within the paradigm that a seizure is needed for antidepressant effects. If MST has clinically significant antidepressant effects that are not associated with side effects, one could imagine eventually doing a direct comparison of MST versus TMS over the same region and finally settling the argument over the necessity of the seizure to treat depression. While debating the theory can be useful in refining our perspective on the modes of action of antidepressant treatment, it is important to recognize that these various brain stimulation techniques for depression are not in competition; rather, each may be helpful for specific subpopulations of depressed patients. Demonstrating that a subconvulsive form of stimulation can be effective in depression does not necessarily make convulsive forms of treatment obsolete. The goal has been to expand our therapeutic options for severely ill and resistant patients and, in the process, to illuminate the brain circuitry and common mechanisms underlying antidepressant action.

Summary

TMS is a powerful new tool with extremely interesting research and therapeutic potentials. Further understanding of the ways by which TMS changes neuronal function, especially as a function of its use parameters, will improve its ability to answer neuroscience questions as well as to treat diseases. Because of its noninvasiveness, it does not readily fit under the umbrella of neurosurgery. Nevertheless, it is important for neurosurgeons to be aware of TMS, because findings from TMS studies will have implications for neurosurgical approaches like DBS and VNS. Indeed, it is possible to think of using TMS as a potential noninvasive initial screening tool to identify whether perturbation of a circuit has short-term clinical effects. In the example of chronic refractory depression or OCD, which is generally a chronic illness, it might then follow that rather than having daily or weekly TMS for the rest of their lives, patients would have DBS electrodes implanted in the same circuit.

Whatever road the future takes, TMS is an important new tool that will likely be of interest to neurosurgeons over the next 20 years and perhaps even longer.

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References

[1] Penfield W, Perot P. The brain's record of auditory and visual experience: a final summary and discussion. Brain 1963;86:595.
[2] Penfield W, Jasper H. Epilepsy and the functional anatomy of the human brain. Boston: Little, Brown and Company; 1954.
[3] George MS, Belmaker RH. Transcranial magnetic stimulation in neuropsychiatry. Washington (DC): American Psychiatric Press; 2000.
[4] George MS, Lisanby SH, Sackeim HA. Transcranial magnetic stimulation: applications in neuropsychiatry. Arch Gen Psychiatry 1999;56:300.
[5] Barker AT, Freeston IL, Jarratt JA, Jalinous R. Magnetic stimulation of the human nervous system: an introduction and basic principles. In: Chokroverty S, editor. Magnetic stimulation in clinical neurophysiology. Boston: Butterworth; 1989. p. 55.
[6] National Research Council. Possible health effects of exposure to residential electric and magnetic fields. Washington (DC): National Academy Press; 1996.
[7] Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 1998;108:1.
[8] Roth BJ, Saypol JM, Hallett M, Cohen LG. A theoretical calculation of the electric field induced in the cortex during magnetic stimulation. Electroencephalogr Clin Neurophysiol 1991;81:47.
[9] Bohning DE. Introduction and overview of TMS physics. In: George MS, Belmaker RH, editors. Transcranial magnetic stimulation in neuropsychiatry; Washington (DC): American Psychiatric Press; 2000. p. 13.
[10] Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357.
[11] Stewart LM, Walsh V, Rothwell JC. Motor and phosphene thresholds: a transcranial magnetic stimulation correlation study. Neuropsychologia 2001;39:415.
[12] Ziemann U, Hallett M. Basic neurophysiological studies with, TMS. In: George MS, Belmaker RH, editors. Transcranial magnetic stimulation in neuropsychiatry. Washington (DC): American Psychiatric Press; 2000. p. 45.
[13] Pridmore S, Filho JAF, Nahas Z, Liberatos C, George MS. Motor threshold in transcranial

magnetic stimulation: a comparison of a neurophysiological and a visualization of movement method. J ECT 1998;14:25.
[14] Amassian VE, Eberle L, Maccabee PJ, Cracco RQ. Modelling magnetic coil excitation of human cerebral cortex with a peripheral nerve immersed in a brain-shaped volume conductor: the significance of fiber bending in excitation. Electroencephalogr Clin Neurophysiol 1992;85:291.
[15] Cohen LG, Roth BJ, Nilsson J, et al. Effects of coil design on delivery of focal magnetic stimulation. Technical considerations. Electroencephalogr Clin Neurophysiol 1990;75:350.
[16] Saypol JM, Roth BJ, Cohen LG, Hallett M. A theoretical comparison of electric and magnetic stimulation of the brain. Ann Biomed Eng 1991;19:317.
[17] Davey KR, Cheng CH, Epstein CM. Prediction of magnetically induced electric fields in biologic tissue. IEEE Trans Biomed Eng 1991;38:418.
[18] Greenberg BD, Ziemann U, Harmon A, Murphy DL, Wassermann EM. Reduced intracortical inhibition in obsessive-compulsive disorder on transcranial magnetic stimulation. Lancet 1998;352:881.
[19] Ziemann U, Paulus W, Rothenberger A. Decreased motor inhibition in Tourette's disorder: evidence from transcranial magnetic stimulation. Am J Psychiatry 1997;154:1277.
[20] Ziemann U, Steinhoff BJ, Tergau F, Paulus W. Transcranial magnetic stimulation: its current role in epilepsy research. Epilepsy Res 1998;30:11–30.
[21] Bear MF. Homosynaptic long-term depression: a mechanism for memory? Proc Natl Acad Sci USA 1999;96:9457.
[22] Linden DJ. The return of the spike: postsynaptic action potentials an the induction of LTP and LTD. Neuron 1999;22:661.
[23] Artola A, Brocher S, Singer W. Different voltage dependent thresholds for inducing long-term depression and long-term potentiation in slices of rat visual cortex. Nature 1990;347:69.
[24] Stanton PK, Sejnowsky TJ. Associative long-term depression in the hippocampus induced by hebbian covariance. Nature 1989;339:215.
[25] Malenka RC, Nicoll RA. Long-term potentiation: a decade of progress? Science 1999;285:1870.
[26] Wang H, Wang X, Scheich H. LTD and LTP induced by transcranial magnetic stimulation in auditory cortex. Neuroreport 1996;7:521.
[27] Post RM, Kimbrell TA, McCann UD, Osuch EA, Speer AM, Weiss SR. Repetitive transcranial magnetic stimulation as a neuropsychiatric probe tool: present status and future potential. J ECT 1999;15:39–59.
[28] Chen R, Classen J, Gerloff C, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48:1398.
[29] Wassermann EM, Wedegaertner FR, Ziemann U, George MS, Chen R. Crossed reduction of motor cortex excitability by 1 Hz transcranial magnetic stimulation. Neurosci Lett 1998;250:141.
[30] Wu T, Sommer M, Tergau F, Paulus W. Lasting influence of repetitive transcranial magnetic stimulation on intracortical excitability in human subjects. Neurosci Lett 2000;287:37.
[31] Epstein CM, Lah JJ, Meador K, Weissman JD, Gaitan LE, Dihenia B. Optimum stimulus parameters for lateralized suppression of speech with magnetic brain stimulation. Neurology 1996;47:1590.
[32] Wassermann EM. Report on risk and safety of repetitive transcranial magnetic stimulation (rTMS): suggested guidelines from the International Workshop on Risk and Safety of rTMS (June 1996). Electroencephalogr Clin Neurophysiol 1997;108:1.
[33] Wassermann EM, Cohen LG, Flitman SS, Chen R, Hallett M. Seizures in healthy people with repeated safe trains of transcranial magnetic stimuli. Lancet 1996;347:825.
[34] Lorberbaum JP, Wassermann EM. Safety concerns of transcranial magnetic stimulation. In: George MS, Belmaker RH, editors. Transcranial magnetic stimulation in neuropsychiatry. Washington (DC): American Psychiatric Press; 2000. p. 141.
[35] Jennum P, Winkel H. Transcranial magnetic stimulation. Its role in the evaluation of patients with partial epilepsy. Acta Neurol Scand Suppl 1994;152:93.
[36] Lisanby SH, Schlaepfer TE, Fisch HU, Sackeim HA. Magnetic seizure therapy for major depression. Arch Gen Psychiatry 2001;58:303.
[37] Little JT, Kimbrell TA, Wassermann EM, et al. Cognitive effects of 1 and 20 Hz repetitive transcranial magnetic stimulation in depression: preliminary report. Neuropsychiatry Neuropsychol Behav Neurol 2000;13:119.
[38] Nahas Z, DeBrux C, Lorberbaum JP, et al. Safety of rTMS: MRI scans before and after 2 weeks of daily left prefrontal rTMS for the treatment of depression. J ECT 2000;16:380.
[39] Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of the human motor cortex. Lancet 1985;1:1106.
[40] Desmurget M, Epstein CM, Turner RS, Prablanc C, Alexander GE, Grafton ST. Role of the posterior parietal cortex in updating reaching movements to a visual target. Nat Neurosci 1999;2:563.
[41] Epstein CM, Verson R, Zangaladze A. Magnetic coil stimulation suppresses visual perception at an extra-calcarine site. J Clin Neurophysiol 1996;13:247.
[42] Ray PG, Meador KJ, Epstein CM, Loring DW, Day LJ. Magnetic stimulation of visual cortex: factors influencing the perception of phosphenes. J Clin Neurophysio 1998;4:351.

[43] Grafman J, Wassermann E. Transcranial magnetic stimulation can measure and modulate learning and memory. Neuropsychologia 1999;37:159.
[44] Boroojerdi B, Phipps M, Kopylev L, Wharton CM, Cohen LG, Grafman J. Enhancing analogic reasoning with rTMS over the left prefrontal cortex. Neurology 2001;56:526.
[45] Flitman SS, Grafman J, Wassermann EM, et al. Linguistic processing during repetitive transcranial magnetic stimulation. Neurology 1998;50:175.
[46] George MS, Wassermann EM, Williams W, et al. Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation of the prefrontal cortex. J Neuropsychiatry Clin Neurosci 1996;8:172.
[47] Martin JD, George MS, Greenberg BD, et al. Mood effects of prefrontal repetitive high-frequency TMS in healthy volunteers. CNS Spectrums 1997;2:53.
[48] Mosimann UP, Rihs TA, Engeler J, Fisch HU, Schlaepfer TE. Mood effects of repetitive transcranial magnetic stimulation of left prefrontal cortex in healthy volunteers. Psychiatry Res 2000;94:251.
[49] Grafman J. TMS as a primary brain mapping tool. In: George MS, Belmaker RH, editors. Transcranial magnetic stimulation (TMS) in neuropsychiatry. Washington (DC): American Psychiatric Press; 2000. p. 115.
[50] Walsh V, Cowey A. Transcranial magnetic stimulation and cognitive neuroscience. Nat Rev Neurosci 2000;1:73.
[51] Penfield W. The mystery of the mind. A critical study of consciousness and the human brain. Princeton: Princeton University Press; 1975.
[52] Jennum P, Friberg L, Fuglsang-Fredericksen A, Dam M. Speech localization using repetitive transcranial magnetic stimulation. Neurology 1994; 44:269.
[53] Pascual-Leone A, Gates JR, Dhuna A. Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. Neurology 1991;41:697.
[54] Michelucci R, Valzania F, Passarelli D, et al. Rapid-rate transcranial magnetic stimulation and hemispheric language dominance: usefulness and safety in epilepsy. Neurology 1994;44:1697.
[55] Roberts DR, Vincent DJ, Speer AM, et al. Multimodality mapping of motor cortex: comparing echoplanar BOLD fMRI and transcranial magnetic stimulation. J Neural Transm 1997;104:833.
[56] Stewart L, Walsh V, Frith U, Rothwell JC. TMS produces two dissociable types of speech disruption. Neuroimage 2001;13:472.
[57] Lisanby SH, Luber B, Finck D, et al. Primate models of transcranial magnetic stimulation [abstract]. Biol Psychiatry 1998;41:76s.
[58] Lisanby SH, Luber B, Schroeder C, et al. Intracerebral measurement of rTMS and ECS induced voltage in vivo. Biol Psychiatry 1998; 43:100s.
[59] Amassian VE, Quirk GJ, Stewart M. A comparison of corticospinal activation by magnetic coil and electrical stimulation of monkey motor cortex. Electroencephalogr Clin Neurophysiol 1990; 77:390.
[60] Olivier E, Edgley SA, Armand J, Lemon RN. An electrophysiological study of the postnatal development of the corticospinal system in the macaque monkey. J Neurosci 1997;17:267.
[61] Flament D, Hall EJ, Lemon RN. The development of cortico-motoneuronal projections investigated using magnetic brain stimulation in the infant macaque. J Physiol 1992;447:755.
[62] Edgley SA, Eyre JA, Lemon RN, Miller S. Excitation of the corticospinal tract by electromagnetic and electrical stimulation of the scalp in the macaque monkey. J Physiol 1990;425:301.
[63] Lemon RN, Johansson RS, Wrestling G. Modulation of corticospinal influence over hand muscles during gripping tasks in man and monkey. Can J Physiol Pharmacol 1996;74:547.
[64] Baker SN, Olivier E, Lemon RN. Task-related variation in corticospinal output evoked by transcranial magnetic stimulation in the macaque monkey. J Physiol 1995;488:795.
[65] Ghaly RF, Stone JL, Aldrete A, Levy W. Effects of incremental ketamine hydrochloride doses on motor evoked potentials (MEPs) following transcranial magnetic stimulation: a primate study. J Neurosurg Anesthesiol 1990;2:79.
[66] Stone JL, Ghaly RF, Levy WJ, Kartha R, Krinsky L, Roccaforte P. A comparative analysis of enflurane anesthesia on primate motor and somatosensory evoked potentials. Electroencephalogr Clin Neurophysiol 1992;84:180.
[67] Baker SN, Olivier E, Lemon RN. Recording an identified pyramidal volley evoked by transcranial magnetic stimulation in a conscious macaque monkey. Exp Brain Res 1995;99:529.
[68] Fleischmann A, Steppel J, Leon A, Belmaker RH. The effect of transcranial magnetic stimulation compared with electroconvulsive shock on rat apomorphine-induced stereotypy. Eur Neuropsychopharmacol 1994;4:449.
[69] Fleischmann A, Sternheim A, Etgen AM, Li C, Grisaru N, Belmaker RH. Transcranial magnetic stimulation downregulates beta-adrenoreceptors in rat cortex. J Neural Transm 1996;103:1361.
[70] Ben-Sachar D, Belmaker RH, Grisaru N, Klein E. Transcranial magnetic stimulation induces alterations in brain monoamines. J Neural Transm 1997;104:191.
[71] Fujiki M, Steward O. High frequency transcranial magnetic stimulation mimics the effects of ECS in upregulating astroglial gene expression in the murine CNS. Mol Brain Res 1997;44: 301.

[72] Jennum P, Klitgaard H. Effect of acute and chronic stimulations on pentylenetetrazole-induced clonic seizures. Epilepsy Res 1996;23:115.
[73] Pope A, Keck ME. TMS as a therapeutic tool in psychiatry: what do we know about neurobiological mechanisms? J Psychiatr Res 2001;35:193.
[74] Weissman JD, Epstein CM, Davey KR. Magnetic brain stimulation and brain size: relevance to animal studies. Electroencephalogr Clin Neurophysiol 1992;85:215.
[75] Nobler MS, Oquendo MA, Kegeles LS, et al. Decreased regional brain metabolism after ECT. Am J Psychiatry 2001;158:305.
[76] Teneback CC, Nahas Z, Speer AM, et al. Two weeks of daily left prefrontal rTMS changes prefrontal cortex and paralimbic activity in depression. J Neuropsychiatry Clin Neurosci 1999; 11:426.
[77] Nahas Z, Teneback CT, Kozel AF, et al. Brain effects of transcranial magnetic stimulation delivered over prefrontal cortex in depressed adults: the role of stimulation frequency and distance from coil to cortex. J Neuropsychiatry Clin Neurosci 2001;13:459.
[78] Shajahan PM, Glabus MF, Gooding PA, Shah PJ, Ebmeier KP. Reduced cortical excitability in depression–Impaired post-exercise motor facilitation with transcranial magnetic stimulation. Br J Psychiatry 1999;174:449–54.
[79] Speer AM, Kimbrell TA, Wasserman EM, et al. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. Biol Psychiatry 2000;48:1133.
[80] Mitchel P. 15 Hz and 1 Hz TMS have different acute effects on cerebral blood flow in depressed patients [abstract]. Int J Neuropsychopharmacol 2002;5:S7.
[81] Shastri A, George MS, Bohning DE. Performance of a system for interleaving transcranial magnetic stimulation with steady state magnetic resonance imaging. Electroencephalogr Clin Neurophysiol Suppl 1999;51:55.
[82] Bohning DE, Shastri A, McConnell K, et al. A Combined TMS/fMRI study of intensity-dependent TMS over motor cortex. Biol Psychiatry 1999;45:385.
[83] Bohning DE, Shastri A, Wassermann EM, et al. BOLD-fMRI response to single-pulse transcranial magnetic stimulation (TMS). J Magn Reson Imaging 2000;11:569.
[84] Baudewig J, Siebner HR, Bestmann S, et al. Functional MRI of cortical activations induced by transcranial magnetic stimulation (TMS). Neuroreport 2001;12:3543.
[85] Nahas Z, Lomarev M, Roberts DR, et al. Unilateral left prefrontal transcranial magnetic stimulation (TMS) produces intensity-dependent bilateral effects as measured by interleaved BOLD fMRI. Biol Psychiatry 2001;50:712.
[86] Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. J Neurosci 2001; 21:RC157.
[87] Paus T, Castro-Alamancos MA, Petrides M. Cortico-cortical connectivity of the human mid-dorsolateral frontal cortex and its modulation by repetitive transcranial magnetic stimulation. Eur J Neurosci 2001;14:1405.
[88] George MS, Stallings LE, Speer AM, et al. Prefrontal repetitive transcranial magnetic stimulation (rTMS) changes relative perfusion locally and remotely. Hum Psychopharmacol 1999;14:161.
[89] Li X, Teneback CC, Nahas Z, et al. Lamotrigine inhibits the functional magnetic resonance imaging response to transcranial magnetic stimulation in healthy adults [abstract]. Biol Psychiatry 2002; 51:8S.
[90] Kimbrell TA, Ketter TA, George MS, et al. Regional cerebral glucose utilization in patients with a range of severities of unipolar depression. Biol Psychiatry 2002;51:237.
[91] George MS, Ketter TA, Gill D, et al. Brain regions involved in recognizing facial emotion or identity: an O15 PET study. J Neuropsychiatry Clin Neurosci 1993;5:384.
[92] George MS, Ketter TA, Post RM. SPECT and PET imaging in mood disorders. J Clin Psychiatry 1993;54:6.
[93] George MS, Huggins T, McDermut W, Parekh PI, Rubinow D, Post RM. Abnormal facial emotion recognition in depression: serial testing in an ultra-rapid-cycling patient. Behav Modif 1998;22:192.
[94] George MS. An introduction to the emerging neuroanatomy of depression. Psychiatr Ann 1994; 24:635.
[95] George MS, Ketter TA, Parekh PI, et al. Regional brain activity when selecting a response despite interference: An H215O PET study of the Stroop and an emotional Stroop. Hum Brain Mapping 1994;1:194.
[96] George MS, Ketter TA, Parekh PI, Horwitz B, Herscovitch P, Post RM. Brain activity during transient sadness and happiness in healthy women. Am J Psychiatry 1995;152:341.
[97] George MS, Ketter TA, Post RM. What functional imaging studies have revealed about the brain basis of mood and emotion. In: Panksepp J, editor. Advances in biological psychiatry. Greenwich (CT): JAI Press; 1996. p. 63.
[98] George MS, Ketter TA, Parekh PI, et al. Blunted left cingulate activation in mood disorder subjects during a response interference task (the Stroop). J Neuropsychiatry Clin Neurosci 1997;9:55.
[99] Ketter TA, Andreason PJ, George MS, et al. Anterior paralimbic mediation of procaine-induced emotional and psychosensory experiences. Arch Gen Psychiatry 1996;53:59.

[100] Beer B. Uber das Auftretten einer objectiven Lichtempfindung in magnetischen Felde. Klinische Wochenzeitschrift 1902;15:108.
[101] Kolbinger HM, Hoflich G, Hufnagel A, Moller H-J, Kasper S. Transcranial magnetic stimulation (TMS) in the treatment of major depression—a pilot study. Hum Psychopharmacol 1995;10:305.
[102] Grisaru N, Yarovslavsky U, Abarbanel J, Lamberg T, Belmaker RH. Transcranial magnetic stimulation in depression and schizophrenia. Eur Neuropsychopharmacol 1994;4:287.
[103] Nobler MS, Sackeim HA, Prohovnik I, et al. Regional cerebral blood flow in mood disorders, III. Treatment and clinical response. Arch Gen Psychiatry 1994;51:884.
[104] George MS, Wassermann EM, Williams WA, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport 1995;6:1853.
[105] George MS, Wassermann EM, Williams WE, et al. Mood improvements following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. Am J Psychiatry 1997;154:1752.
[106] Pascual-Leone A, Rubio B, Pallardo F, Catala MD. Beneficial effect of rapid-rate transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 1996;348:233.
[107] Loo C, Mitchell P, Sachdev P, McDarmont B, Parker G, Gandevia S. A double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. Am J Psychiatry 1999;156:946.
[108] McNamara B, Ray JL, Arthurs OJ, Boniface S. Transcranial magnetic stimulation for depression and other psychiatric disorders. Psychol Med 2001; 31:1141.
[109] Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation. Int J Neuropsychopharmacol 2002;5:73–103.
[110] Holtzheimer PE, Russo J, Avery D. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. Psychopharmacol Bull 2001;35:149.
[111] Kozel FA, George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. J Psychiatr Pract 2002;8:270–5.
[112] Martin JLR, Barbanoj MJ, Schlaepfer TE, et al. Transcranial magnetic stimulation for treating depression. The Cochrane Library. Oxford: Update Software; 2002.
[113] Thase ME. The need for clinically relevant research on treatment-resistant depression. J Clin Psychiatry 2001;62:221.
[114] Thase ME. Studying new antidepressants: if there were a light at the end of the tunnel, could we see it? J Clin Psychiatry 2002;63:24.
[115] Grunhaus L, Dannon PN, Schreiber S, et al. Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. Biol Psychiatry 2000; 47:314.
[116] Janicak PG, Dowd SM, Martis B, et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial. Biol Psychiatry 2002;51:659.
[117] Pridmore S. Substitution of rapid transcranial magnetic stimulation treatments for electroconvulsive therapy treatments in a course of electroconvulsive therapy. Depress Anxiety 2000;12:118.
[118] Dannon PN, Dolberg OT, Schreiber S, Grunhaus L. Three and six-month outcome following courses of either ECT or rTMS in a population of severely depressed individuals—preliminary report. Biol Psychiatry 2002;51:687.
[119] Klein E, Kreinin I, Chistyakov A, et al. Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. Arch Gen Psychiatry 1999;56:315.
[120] Herwig U, Padberg F, Unger J, Spitzer M, Schonfeldt-Lecuona C. Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. Biol Psychiatry 2001;50:58.
[121] McConnell KA, Nahas Z, Shastri A, et al. The transcranial magnetic stimulation motor threshold depends on the distance from coil to underlying cortex: a replication in healthy adults comparing two methods of assessing the distance to cortex. Biol Psychiatry 2001;49:454.
[122] Kozel FA, Nahas Z, DeBrux C, et al. How the distance from coil to cortex relates to age, motor threshold and possibly the antidepressant response to repetitive transcranial magnetic stimulation. J Neuropsychiatry Clin Neurosci 2000;12:376.
[123] Mosimann UP, Marre SC, Werlen S, et al. Antidepressant effects of repetitive transcranial magnetic stimulation in the elderly: correlation between effect size and coil-cortex distance. Arch Gen Psychiatry 2002;59:560.
[124] Nahas Z, Oliver NC, Johnson M, et al. Feasibility and efficacy of left prefrontal rTMS as a maintenance antidepressant [abstract]. Biol Psychiatry 2000;48:57.
[125] Belmaker RH, Grisaru N. Does TMS have bipolar efficacy in both depression and mania [abstract]? Biol Psychiatry 1998;48:157.
[126] Grisaru N, Chudakov B, Yaroslavsky Y, Belmaker RH. TMS in mania: a controlled study. Am J Psychiatry 1998;155:1608.
[127] Nahas Z, Bohning DE, Molloy M, Outz JA, Risch SC, George MS. Safety and feasibility of repetitive transcranial magnetic stimulation in the treatment

of anxious depression in pregnancy. J Clin Psychiatry 1999;60:50.
[128] Pascual-Leone A, Valls-Sole J, Brasil-Neto JP, Cohen LG, Hallett M. Akinesia in Parkinson's disease. I. Shortening of simple reaction times with focal, single-pulse transcranial magnetic stimulation. Neurology 1994;44:884.
[129] Ghabra MB, Hallett M, Wassermann EM. Simultaneous repetitive transcranial magnetic stimulation does not speed fine movement in PD. Neurology 1999;52:768.
[130] Boylan LS, Pullman SL, Lisanby SH, Spicknall KE, Sackeim HA. Repetitive transcranial magnetic stimulation to SMA worsens complex movements in Parkinson's disease. Clin Neurophysiol 2001; 112:259.
[131] Mally J, Stone TW. Therapeutic and "dose-dependent" effect of repetitive microelectroshock induced by transcranial magnetic stimulation in Parkinson's disease. J Neurosci Res 1999;57:935.
[132] Mally J, Stone TW. Improvement in Parkinsonian symptoms after repetitive transcranial magnetic stimulation. J Neurol Sci 1991;162:179.
[133] Siebner HR, Rossmeier C, Mentschel C, Peinemann A, Conrad B. Short-term motor improvement after sub-threshold 5-Hz repetitive transcranial magnetic stimulation of the primary motor hand area in Parkinson's disease. J Neurol Sci 2000;178:91.
[134] Shimamoto H, Morimitsu H, Sugita S, Nakahara K, Shigemori M. Therapeutic effect of repetitive transcranial magnetic stimulation in Parkinson's disease. Rinsho Shinkeigaku 1999;39:1264.
[135] Shimamoto H, Takasaki K, Shigemori M, Imaizumi T, Ayabe M, Shoji H. Therapeutic effect and mechanism of repetitive transcranial magnetic stimulation in Parkinson's disease. J Neurol 2001; 248(Suppl):III48.
[136] Siebner HR, Tormos JM, Ceballos-Baumann AO, Auer C, Catala MD, Conrad B, et al. Low frequency repetitive transcranial magnetic stimulation of motor cortex in patients with writer's cramp. Neurology 1999;52:529.
[137] Chae JH, Nahas Z, Wassermann EM, et al. A pilot study using rTMS to probe the functional neuroanatomy of tics in Tourette syndrome. Neuropsychiatry Neuropsychol Behav Neurol [in press]
[138] Reutens DC, Puce A, Berkovic SF. Cortical hyperexcitability in progressive myoclonus epilepsy: a study with transcranial magnetic stimulation. Neurology 1993;43:186.
[139] Wedegaertner F, Garvey M, Cohen LG, Hallett M, Wassermann EM. Low frequency repetitive transcranial magnetic stimulation can reduce action myoclonus [abstract]. Neurology 1997;48: A119.
[140] Feinsod M, Sreinin B, Chistyakov A, Klein E. Preliminary evidence for a beneficial effect of low-frequency, repetitive transcranial magnetic stimulation in patients with major depression and schizophrenia. Depress Anxiety 1998;7:65.
[141] Puri BK, Davey NJ, Ellaway PH, Lewis SW. An investigation of motor function in schizophrenia using transcranial magnetic stimulation of the motor cortex. Br J Psychiatry 1996;169:690.
[142] Nahas Z, McConnell K, Collins S, et al. Could left prefrontal rTMS modify negative symptoms and attention in schizophrenia [abstract]? Biol Psychiatry 1999;45:37.
[143] Hoffman R, Boutros N, Berman R, Krystal J, Charney D. Transcranial magnetic stimulation and hallucinated "voices" [abstract]. Biol Psychiatry 1998;43:93s.
[144] Hoffman RE, Boutros NN, Hu S, Berman RM, Krystal JH, Charney DS. Transcranial magnetic stimulation and auditory hallucinations in schizophrenia. Lancet 2000;355:1073.
[145] Greenberg BD, George MS, Dearing J, et al. Effect of prefrontal repetitive transcranial magnetic stimulation (rTMS) in obsessive compulsive disorder: a preliminary study. Am J Psychiatry 1997; 154:867.
[146] Cora-Locatelli G, Greenberg BD, Harmon A, et al. Cortical excitability and augmentation strategies in OCD [abstract]. Biol Psychiatry 1998; 43:77s.
[147] Greenberg BD, Ziemann U, Cora-Locatelli G, et al. Altered cortical excitability in obsessive-compulsive disorder. Neurology 2000;54:142.
[148] Alonso P, Pujol J, Cardoner N, et al. Right prefrontal TMS in OCD: a double-blind, placebo-controlled study. Am J Psychiatry 2001;158:1143.
[149] Sachdev PS, McBride R, Loo CK, Mitchell PB, Malhi GS, Croker VM. Right versus left prefrontal transcranial magnetic stimulation for obsessive-compulsive disorder: a preliminary investigation. J Clin Psychiatry 2001;62:981.
[150] McCann UD, Kimbrell TA, Morgan CM, et al. Repetitive transcranial magnetic stimulation for posttraumatic stress disorder [letter]. Arch Gen Psychiatry 1998;55:276.
[151] Grisaru N, Amir M, Cohen H, Kaplan Z. Effect of transcranial magnetic stimulation in posttraumatic stress disorder: a preliminary study. Biol Psychiatry 1998;44:52.
[152] Lisanby SH, Luber B, Sackeim HA, Finck AD, Schroeder C. Deliberate seizure induction with repetitive transcranial magnetic stimulation in nonhuman primates [letter]. Arch Gen Psychiatry 2001;58:199.
[153] Lisanby SH, Luber B, Barriolhet L, Neufeld E, Schlaepfer T, Sackeim HA. Magnetic seizure therapy (MST)—acute cognitive effects of MST compared with ECT [abstract]. J ECT 2001;17:77.
[154] Sackeim HA, Decina P, Kanzler M, Kerr B, Malitz S. Effects of electrode placement on the efficacy of titrated, low-dose ECT. Am J Psychiatry 1987; 144:1449.

[155] Sackeim HA, Prudic J, Devanand DP, et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. N Engl J Med 1993;328:839.
[156] George MS, Wassermann EM. Rapid-rate transcranial magnetic stimulation (rTMS) and ECT. Conv Ther 1994;10:251.
[157] Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: A multicenter study. Biol Psychiatry 2000;47:276.
[158] Sackeim HA, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects and predictors of outcome. Neuropsychopharmacology 2001;25:713.
[159] Marangell LB, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for major depressive episodes: longer-term outcome. Biol Psychiatry 2002; 51:280.
[160] Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Res 2000;42:203.
[161] Harden CL, Pulver MC, Ravdin LD, Nikolov B, Halper JP, Labar DR. A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. Epilepsy Behav 2000;1:93.
[162] Limousin P, Krack P, Pollak P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 1998;339:1105.