Applications of TMS to Therapy in Psychiatry

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Summary: Transcranial magnetic stimulation (TMS) has been applied to a growing number of psychiatric disorders as a noninvasive probe to study the underlying neurobiologic processes involved in psychiatric disorders and as a putative treatment. Transcranial magnetic stimulation is unparalleled in its ability to test the hypotheses generated by functional neuroimaging studies by modulating activity in selected neural circuits. As a focal intervention that may in some cases exert lasting effects, TMS offers the hope of targeting and ameliorating the circuitry underlying psychiatric disorders. The ultimate success of such an approach depends on our knowledge of the neural circuitry underlying these disorders, of how TMS exerts its effects, and of how to control the application of TMS to exert the desired effects. Although most clinical trials have focused on the treatment of major depression, increasing attention has been paid to schizophrenia and anxiety disorders. Many of these trials have supported a significant effect of TMS, but in some studies the effect is small and short lived. Current challenges in the field include determining how to enhance the efficacy of TMS in these disorders and how to identify patients for whom TMS may be efficacious. **Key Words:** DLPFC, dorsolateral prefrontal cortex; ECT, electroconvulsive therapy; FDG, fluorodeoxyglucose; HRSD, Hamilton Rating Scale for Depression; MT, motor threshold; OCD, obsessive compulsive disorder; PET, positron emission tomography; PTSD, post traumatic stress disorder; rCBF, regional cerebral blood flow; SPECT, single photon emission computed tomography; TMS, transcranial magnetic stimulation.
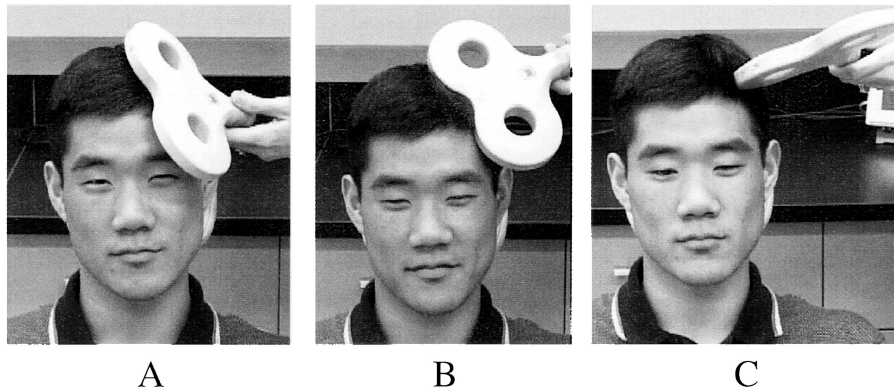
Soon after transcranial magnetic stimulation (TMS) was introduced as a noninvasive means of cortical stimulation in 1985, its potential utility as a therapeutic intervention in psychiatry was explored. Initial studies used single magnetic pulses administered at low frequencies with large stimulating coils to broad regions of the cortex. When repetitive TMS stimulators became available, attention shifted to higher frequencies of stimula-

tion, which appeared more effective in influencing higher cognitive functions such as language (Claus et al., 1993; Epstein et al., 1999; Michelucci et al., 1994; Pascual–Leone et al., 1991). Based on theories regarding focal brain regions involved in depression, subsequent trials used the more focal figure-of-eight coil. In distinction to the development of new psychopharmacologic agents, exhaustive animal studies on the behavioral effects of TMS did not precede clinical testing, although in recent years such animal work has been informative. Most clinical trials with TMS have involved small numbers of patients and have focused on major depression. The results of these trials, and of work in schizophrenia, anxiety disorders, and other potential applications are reviewed. Neuroimaging studies and animal models relevant to the potential mechanisms of action of TMS in

FIG. 1. Typical orientations for active and sham transcranial magnetic stimulation (TMS) with a figure-of-eight coil. **(A)** Active TMS is applied with the figure-of-eight coil tangential to the scalp. **(B)** Sham TMS with two wings of the figure-of-eight coil touching the scalp, but the intersection of the coil windings is tilted off the head by 45 deg. This orientation can still produce motor movement when positioned over the motor cortex with some manufacturers' coils. **(C)** Sham TMS with 1 wing of the figure-of-eight coil touching the scalp, and the intersection of the coil windings tilted off the head by 90 deg. This orientation does not elicit motor movement when positioned over the motor cortex. It is also easier to distinguish from active TMS as a result of less intensive contraction of scalp muscles.

psychiatric disorders are included whenever available. In this review we focus exclusively on relevant clinical studies. Preclinical studies have been reviewed extensively elsewhere (Lisanby and Belmaker, 2000; Post and Keck, 2001).

CLINICAL TRIAL DESIGN WITH TRANSCRANIAL MAGNETIC STIMULATION

The conventions in clinical trials on pharmaceutical agents in the treatment of psychiatric disorders do not translate perfectly to the study of TMS as a therapeutic intervention. Special challenges in clinical trial design with TMS include blinding, standardization of dosage, selection of a clinically appropriate target for stimulation, and navigation to that target.

There is currently no consensus on the ideal "placebo" condition for TMS to blind patients and investigators. Initial studies with TMS were open, uncontrolled investigations. Both patients and investigators knew that the patient was receiving a cutting-edge technology in which both parties placed a good deal of faith. The administration of TMS involves intense and frequent contact between doctor and patient of a sort that is not typical in conventional office-based psychiatric practice. To control for these ancillary aspects of the intervention, various "sham" TMS conditions have been adopted.

Sham TMS is typically applied by tilting the coil off the head such that the magnetic field grazes the scalp, stimulating the scalp muscles and producing a clicking noise, but not affecting the brain (Fig. 1). However, there is evidence that some types of sham manipulations used in clinical trials actually do exert some effects on the brain (Lisanby et al., 2001a; Loo et al., 2000). Even if a form of coil-tilt sham that does not exert measurable brain effects is used, studies rarely report data on the integrity of the blind on the part of the patients and raters. It is reasonable to assume that crossover trials with coil-tilt sham conditions are likely to be unblinded because active and sham TMS do not feel the same. In our work using a crossover design with a coil-tilt sham, patients could readily discriminate between active and sham TMS (Boylan et al., 2001). Although coil-tilt shams may be of some utility in blinding patients in parallel design studies, they nevertheless do not blind the investigator.

At least two manufacturers now offer sham coils that look the same and are held the same as active coils, but use mu-metal to shield the patient from the magnetic field. This strategy may become important for blinding the physician administering TMS, but their utility in blinding patients remains to be determined.

The difficulty in blinding TMS makes the comparison of TMS with a gold standard treatment (e.g., psychopharmacology or electroconvulsive therapy [ECT]) complex. In the case of pharmacologic agents, it would be possible to use a "double-dummy" design in which some patients would receive sham TMS plus active medication, whereas other patients would receive active TMS and a placebo pill. To date, no published studies have used this design, yet comparison of TMS with a gold standard is a necessary step in the evaluation of the potential clinical role of this intervention. Unfortunately, a double-dummy design is not possible with ECT. This represents a serious design limitation in studies that randomize patients to receive either ECT or TMS.

An additional challenge in the design of clinical trials with TMS has to do with standardization of the dosage. Just as it is critical to control the dosage of medication administered during drug trials, it is likewise essential to control the amount of TMS administered and the location of the brain region stimulated. Unfortunately, these factors are controlled for poorly by the current standard methods. The convention is to administer an intensity that is set relative to the threshold for eliciting a motor evoked potential (or in some centers, a visible twitch) in a distal hand muscle. Although setting intensity relative to this measurable peripheral effect may be appropriate for motor stimulation, its relevance to thresholds for stimulation of other areas is unknown. Reliable methods for determining functional thresholds for other brain regions have yet to be determined. Imaging the effects of TMS in targeted regions (Bohning et al., 1999), and then linking those effects to a more readily available measure would be one such strategy. Because it is known that the strength of the magnetic field is determined by the distance from the coil to the target brain structure, one approach would be to set intensity based on coil-to-brain distance as measured on a structural MRI (Kozel et al., 2000; McConnell et al., 2001). Although magnetic field strength in target regions can be computed, the induced electrical field and current density depend on other factors, some of which cannot be measured noninvasively (Lisanby et al., 1998). Nevertheless, use of structural imaging and magnetic field modeling could only serve to improve the current practice.

Beyond issues of standardization of dosage, other factors that have been controlled poorly in clinical studies with TMS include the selection and localization of the particular cortical target to stimulate. Depression has been linked to abnormalities in a network of brain regions, many of which are not easily accessible to the TMS coil (Mayberg, 1997; Soares and Mann, 1997). The dorsolateral prefrontal cortex (DLPFC) figures prominently in depression models, but it also plays other roles in cognitive operations and is implicated in schizophrenia. The orbital prefrontal cortex and regions of the anterior cingulate have been recognized increasingly to play key roles in depression circuitry, but these are not directly accessible to the TMS coil. After the target region is selected, it is difficult to predict how a given frequency of TMS applied to that target will affect activity at the site of stimulation and in connected regions (Kimbrell et al., 1999). It is quite possible that the effect of TMS on the circuit may depend in part on the baseline activity in the region stimulated. Most psychiatric disorders are heterogeneous in their presentation and in their patterns of brain activity. Studies of the effects of TMS on functional connectivity in psychiatric disorders (reviewed later) are important in the selection of appropriate patients and appropriate stimulation paradigms to achieve the desired effects.

When the target region has been selected, navigating the coil to the scalp position nearest to that region is not a trivial problem. Most clinical trials in depression have targeted the DLPFC by moving the coil 5 cm anterior to the optimal site for stimulation of a distal hand muscle. Studies have shown this method to introduce a great deal of variability in ultimate coil position (Kozel et al., 2000). Frameless stereotaxic systems have been developed to guide the coil to regions selected on the individual's MRI, but such technology is expensive and of limited availability (Herwig et al., 2001; Krings et al., 1997; Krings, 1997; Paus, 1999; Paus and Wolforth, 1998). Herwig et al. (2001) compared the standard means of coil positioning with frameless stereotaxy and demonstrated that in only 7 of 22 subjects was the DLPFC targeted correctly with the standard means. In the remaining 15 subjects, the center of the coil was located more dorsally, over the premotor cortex (Herwig et al., 2001). When frameless stereotaxic positioning is not available, a better compromise may be to make use of scalp landmarks and the International 10-20 EEG positioning system, which takes into account variation in head size and for which studies have documented reasonable correspondence with underlying cortical structures (Homan et al., 1987).

MAJOR DEPRESSION

Trials with Single-Pulse and Low-Frequency Transcranial Magnetic Stimulation

The earliest studies of TMS in the treatment of major depression used single-pulse TMS (<0.3 Hz), usually administered with a large, round coil centered on the vertex (Geller et al., 1997; Höflich et al., 1993; Kolbinger et al., 1995; Menkes et al., 1999). In this position, the round coil stimulates broad regions of the bilateral frontal and parietal cortices. These early trials characteristically reported significant antidepressant effects of TMS. One of these studies was sham controlled (Kolbinger et al., 1995). Despite the promising results, these studies have not yet been followed up with larger controlled trials using large coils at slow frequencies. Large coils induce stronger electrical fields in the brain than small coils because the strength of the induced electrical field is proportional to the ratio between the size of the coil and the size of the brain (Weissman et al., 1992). Because the coil-to-brain ratio achieved in these studies
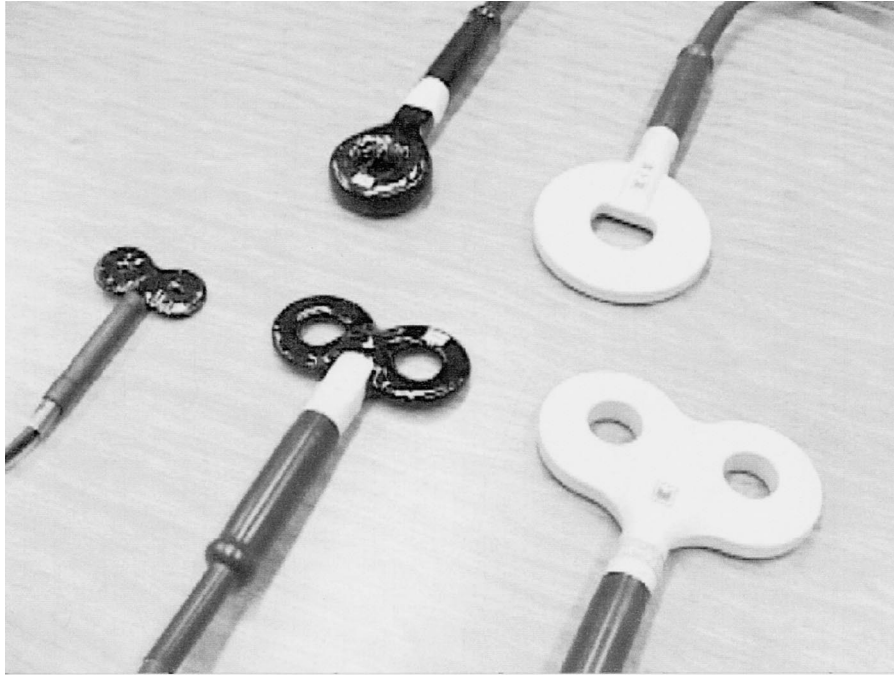
FIG. 2. Typical coil configurations used in human and animal trials. **(Top row)** Round coils (left, animal/pediatric; right, human). **(Bottom row)** Figure-of-eight coils (left, rodent; middle, nonhuman primate/pediatric; right, human).

matches more closely that achieved in most animal studies of TMS showing action consistent with antidepressant activity (Belmaker and Grisaru, 1998; Belmaker et al., 1997, 2000; Fleischmann et al., 1995; Lisanby and Belmaker, 2000), and because single-pulse TMS has a much better safety profile than repetitive TMS (Wassermann, 1998), it may be worth revisiting the utility of large coils and low frequencies. Typical coil designs for human and animal trials are illustrated in Fig. 2.

Using a slightly higher frequency (1 Hz) and a slightly smaller round coil positioned on the right prefrontal cortex, Feinsod et al. (1998) reported improvement in 7 of 14 depressed patients. The same group went on to perform a sham-controlled trial of 1-Hz TMS administered with a round coil positioned on the right prefrontal cortex for 10 daily sessions (Klein et al., 1999). In what remains the largest single-site TMS depression study to date, Klein et al. (1999) found a response rate of 31% percent with active TMS and 14% with sham. This difference was significant and represents one of the largest effect sizes reported. Like single-pulse TMS, 1 Hz carries a much lower seizure risk than frequencies more than 1 Hz (Wassermann, 1998). Therefore, the utility of low-frequency TMS in clinical treatment deserves further exploration.

Open Trials of High-Frequency Transcranial Magnetic Stimulation

Several open studies have offered support for antidepressant efficacy of TMS, but the possibility of placebo response must be kept in mind in interpreting these results. George et al. (1995) reported that five daily sessions of TMS delivered to the left DLPFC at 20 Hz, 80% of motor threshold (MT), 2-second trains, 20 trains per day, reduced depression scores in four of six medication-resistant depressed patients (George et al., 1995). The effects of five daily session of TMS delivered to the left DLPFC at 10 Hz, 110% of MT, 5-second trains, 10 trains per day were reported by Epstein et al. (1998). Fifty-six percent of patients met response criteria. Extending the treatment to 10 days and increasing the number of pulses per day to 2,000 (20 Hz, 80% of MT, 2-second trains, 50 trains per day), Triggs et al. (1999) reported a 50% response rate in 10 medication-resistant unipolar depressed patients. Pridmore et al. (1999) advocated extending the period of treatment to 3 or 4 weeks. In their open study of 22 patients with melancholic depression referred for ECT treated with 1,250 pulses per day (10 Hz, 90 to 100% of MT, 5-second trains, 25 trains per day), TMS to the left DLPFC

resulted in remission in 88% of patients. Although placebo response may have contributed to this effect, it may be that longer treatment is more effective or that patients with melancholic subtype are more responsive to TMS. Of note, the psychomotor symptoms of melancholia predict response to ECT (Hickie et al., 1990). Others have also observed normalization of the dexamethasone suppression test, a marker for endogenous depression, after TMS (Pridmore, 1999; Reid and Pridmore, 1999).

Another strategy that has been explored to enhance efficacy is to combine high-frequency TMS to the left DLPFC with low frequency to the right DLPFC. In a small open study of 10 medication-resistant patients, Cohen et al. (personal communication, May 2002) found that up to 2 weeks of treatment with 20-Hz TMS to the left DLPFC followed by 1-Hz TMS to the right DLPFC was well tolerated and resulted in a 40% response rate. It is possible that the response rate may have been even better had the treatment period been extended to 3 or 4 weeks.

A recent meta-analysis of the open trials of TMS in depression found an effect size of 1.45 (Burt et al., 2002). Although significant, the degree of clinical improvement was modest, with an average 37.0% (standard deviation, 29.2%) improvement in depression ratings.

Transcranial Magnetic Stimulation versus Electroconvulsive Therapy

In many centers, the patients who volunteer for TMS are seeking an alternative to ECT. Although ECT is extremely effective in treating severe depression, its cognitive side effects limit its use. Three groups have performed direct comparisons between ECT and TMS.

Grunhaus et al. (2000) randomized 40 patients to receive ECT or up to 40 weeks of high-frequency TMS to the left DLPFC. Overall, patients responded better to ECT. This advantage was primarily the result of the subgroup with psychotic depression, in which ECT was clearly superior. For nonpsychotic patients there was no difference between ECT and TMS. Unfortunately the rater in this study was not blinded. In a study using blinded raters, Pridmore et al. (2000) randomized 32 patients to receive TMS or right unilateral ECT. The number of treatments was not predetermined but was selected by the patient's treating psychiatrist. The response rate based on change in the Hamilton Rating Scale for Depression (HRSD) score was identical in both groups (66%), but ECT was superior in terms of self-report measures. The same group compared the efficacy of six ECT treatments with two ECT treatments in combination with eight TMS sessions (Pridmore, 2000).

Although they found no difference between ECT and ECT + TMS, it is important to note that administration of only six unilateral ECT treatments is not optimal treatment. Using bilateral ECT, Janicak et al. (2002) completed a similar randomized study involving 25 patients, and again failed to find a difference in efficacy between ECT and TMS.

A recent meta-analysis of these comparisons failed to find a significant difference in efficacy between the groups (Burt et al., 2002), however none of these studies can be considered truly blinded. Another limitation is that the response rate to ECT in these studies was unusually low. On the other hand, TMS could still become a useful treatment even if it falls short of matching the efficacy of ECT, considering its much more benign side effect profile.

Blinded Trials of Transcranial Magnetic Stimulation

A series of sham-controlled trials have examined the efficacy of TMS in depression. The first controlled trial (Pascual–Leone et al., 1996) is still the only published trial to have compared the antidepressant efficacy of high-frequency TMS applied to different cortical regions. It bears remembering that the optimal stimulation site for antidepressant effects may not have been identified yet. Pascual–Leone et al. (1996) treated 17 medication-resistant psychotic, depressed patients with 1 week of daily TMS (10 Hz, 90% MT, 10-second trains, 20 trains per day) or sham TMS to each of three different locations (vertex, left or right DLPFC). At 100% of MT, the longest train recommended by safety guidelines is 5 seconds, so the 10-second trains administered during this study represent quite robust stimulation. Only the active stimulation of the left DLPFC resulted in improvement. Eleven of 17 patients were improved significantly. Although their improvements diminished within 2 weeks, such an impressive and rapid clinical response in this severely ill group of patients is remarkable. As an intrasubject crossover trial, it is quite likely that the patients became unblinded to the treatment condition. Indeed, subsequent studies have failed to find benefits of TMS in psychotic depression (Grunhaus et al., 2000).

Also using a sham-controlled crossover design, George et al. (1996) found a significant effect of 2 weeks of active 20-Hz TMS to the left DLPFC in 12 depressed patients. Although significant, the effect size was small in comparison with that of the Pascual–Leone (1996) trial (average 5-point drop in depression scores with active and 3-point increase with sham). Again, the pos-

sibility of unblinding resulting from the crossover design must be considered.

Results in studies using a parallel group design have been mixed. Loo et al. (1999) failed to find a difference between 2 weeks of sham and active TMS (10 Hz, 110% MT, 5 seconds, 30 trains) in 18 medication-resistant depressed patients. Given that both groups improved, the question has been raised regarding whether the sham used (45-deg coil tilt) may have been somewhat active (Lisanby et al., 2001a; Loo et al., 2000). Berman et al. (2000) was able to detect a difference between sham and active TMS (20 Hz, 80% MT, 2 seconds, 20 trains) in 20 medication-resistant depressed patients. Although they also used a 45-deg coil tilt, the coil they used was enclosed in a thick casing (used for water cooling of the coil, which elevates the coil windings approximately 0.5 cm off the scalp). The clinical response was significant but modest in magnitude (14-point drop in HRSD score with active and 0-point drop in sham).

Two parallel group studies of TMS in the elderly have been negative. Manes et al. (2001) found response rates of 30% with sham and 30% with active TMS (20 Hz, 80% MT, five daily treatments) in 20 elderly, depressed patients (Manes and Crespo–Facorro, 1999). Using a higher intensity of 100% of MT and 2 weeks of treatment, Mosimann et al. (2000) failed to find a difference between active and sham TMS in 25 elderly patients. These controlled observations confirm open data from Figiel et al. (1998), who reported that only 23% of patients older than 65 years responded to TMS, compared with 56% of younger patients. It has been suggested that lower response rates in the elderly may result from inadequate dosing (Kozel et al., 2000). Alternatively, cerebral atrophy would increase the distance from the coil to the brain, thereby decreasing the strength of the induced electrical current. Dosing relative to MT may not compensate adequately for this increase in distance because cortical atrophy is not necessarily symmetric in all brain regions.

Several groups have examined the utility of TMS as an add-on to pharmacotherapy in the treatment of depression. Although an open study by Conca et al. (1996) suggested that single-pulse TMS to multiple scalp locations in addition to various medications was more effective than medications alone, a sham-controlled trial by Garcia–Toro et al. (2001) failed to find a benefit with left DLPFC 20-Hz TMS augmentation of sertraline therapy. Lisanby et al. (2001d) placed 36 patients on sertraline and randomized them to receive 10 daily sessions of sham, 1-Hz TMS to the right DLPFC or 10-Hz TMS to the left DLPFC (Lisanby et al., 2001d). The therapeutic results were disappointing, with effect sizes of only 0.24

for 20 Hz and 0.20 for 1-Hz TMS. Patients who were classified as not medication resistant at baseline showed substantial improvement regardless of TMS condition, whereas medication-resistant patients showed little change. There was an indication that medication-resistant patients showed a small but significant benefit in the 10-Hz TMS left DLPFC condition. In all three of these studies, antidepressant medications were initiated concurrently with TMS (Conca et al., 1996; Garcia-Toro et al., 2001; Lisanby et al., 2001d).

Although there is not convincing evidence that TMS can speed onset of action, better effects may be seen with TMS as an add-on to ongoing pharmacotherapy to augment response. Indeed, most studies of TMS in depression have allowed patients to remain on stable doses of antidepressant medications during the TMS trial. Garcia–Toro et al. (2001) randomized depressed patients on stable doses of antidepressant medications for 6 weeks to receive sham or active TMS (20 Hz), and found a modest clinical benefit to active TMS (drop in depression scores of 7 points with active and 2 points with sham; response rates of 25% with active and 5% with sham).

Meta-analysis revealed that across the 23 controlled comparisons, the combined effect size was 0.62, indicating a moderate to large effect (Burt et al., 2002). Although this effect size is significant, the magnitude of the effect in most studies was modest and of doubtful clinical importance. The average percent improvement with active TMS was 28.94% (standard deviation, 23.19%) and with sham was 6.63% (standard deviation, 25.56%). Relatively few patients met standard criteria for response (e.g., 50% reduction in HRSD scores) or remission (e.g., final HRSD score ≤ 8 points). The presence or absence of concomitant antidepressant medications did not alter the effect size.

Meta-analysis failed to find a significant difference between effect sizes in low-frequency and high-frequency studies (Burt et al., 2002). However, some head-to-head comparisons suggest low frequency may actually fare better than high frequency (George et al., 2000; Kimbrell et al., 1999; Padberg et al., 1999). Kimbrell et al. (1999) reported a trend toward better improvement after 2 weeks of 1-Hz TMS compared with 20 Hz to the left DLPFC (drop of 6 points in HRSD score with 1 Hz, and increase of 1.2 points with 20 Hz) in a crossover design. A negative correlation was found between clinical response to 1 Hz and 20 Hz, and there were suggestions that baseline metabolic activity in the DLPFC correlated with response. George et al. (2000) randomized patients to active TMS at 5 Hz, 20 Hz, or sham to the left DLPFC. Response rates were 60% with 5 Hz, 30% with 20 Hz, and 0% with sham. If lower frequencies

are indeed as effective (or even more effective) than higher frequencies, this would have significant safety implications because lower frequencies carry less risk of seizure.

Magnetic Seizure Therapy

All of the previously mentioned studies involved the use of levels of TMS that were below the threshold for inducing seizure. Subconvulsive TMS is administered without the need for anesthesia and is generally performed as an ambulatory procedure. In parallel with work on subconvulsive forms of TMS, there has been some interest in exploring the uses of convulsive levels of TMS in the treatment of depression. In 1994, Sackeim (1994) postulated that magnetically induced seizures might have some advantages over conventional ECT. Conventional ECT is highly effective, but it carries a substantial risk of memory loss and other side effects. Electroconvulsive therapy research during the past few decades has indicated that the efficacy and side effects of ECT depend in part on the site of seizure onset and patterns of seizure spread (Lisanby et al., 2000; Luber et al., 2000; Sackeim et al., 1993, 2000a, b). There is little hope of controlling these factors with conventional ECT because the application of electricity through the scalp is inherently imprecise. The scalp and skull act as effective resistors to the flow of electricity, causing the stimulation to diffuse (Sackeim et al., 1994). Transcranial magnetic stimulation, on the other hand, passes through tissue without impedance, permitting a more localized stimulation. Transcranial magnetic stimulation presents the possibility of using noninvasive magnetic fields to induce focal seizures, thereby sparing other regions of the brain involved in amnestic side effects.

This method was first developed and tested in rhesus monkeys (Lisanby et al., 2001c), and was recently subjected to the first clinical trials. The procedure is performed under anesthesia of the sort used in conventional ECT. The first open case report of magnetic seizure therapy in the treatment of major depression documented a 40% improvement in depression ratings after four treatments (Lisanby et al., 2001e). The treatments were well tolerated with minimal side effects. Subsequently, Lisanby et al. (2001b) performed a controlled clinical trial of 10 patients with major depression. Each patient received a course of convulsive therapy in which two of the first four treatments were induced magnetically (counterbalanced order), and the remaining were induced electrically (Lisanby et al., 2001b). Acute cognitive side effects were measured with blinded neuropsychological batteries, and subjective side effects were compared.

Treatments were well tolerated with no adverse events. Magnetic seizure therapy had fewer subjective side effects and patients recovered orientation more quickly than with ECT. Magnetic seizure therapy was superior to ECT on some but not all cognitive measures. This study demonstrated that magnetic seizure therapy in patients with depression is feasible, and appears to be a well-tolerated method for performing convulsive therapy. More work is needed to establish whether magnetic seizure therapy will have comparable antidepressant efficacy with ECT.

Relevant Imaging Studies

The mood-elevating effects of TMS seen in some studies may reflect changes in activity in regions remote from the site of direct stimulation. Szuba et al. (2001) found that a single session of TMS to the left DLPFC in depressed patients increased thyroid-stimulating hormone in peripheral blood, suggesting an effect on the hypothalamus–pituitary–thyroid axis. Similar findings were reported by George et al. (1996) in normal volunteers. It is not clear whether this thyroid effect is related to the mood effects, because the two were uncorrelated in both studies. Functional neuroimaging using oxygen (O^{15}) or fluorodeoxyglucose (FDG) positron emission tomography (PET), single photon emission computerized tomography (SPECT), or functional MRI provides a more precise method of mapping the effect of TMS on depression circuitry.

Activation of brain regions removed from the stimulation site can provide information on the functional connectivity of cortical and subcortical structures relevant for understanding the neural circuits involved in depression (Fox et al., 1997; Siebner et al., 2000, 2001). For example, proximal brain activation effects obtained during TMS are generally thought to reflect local cortical excitability, whereas distal effects may reflect connectivity to the stimulated region. Imaging at multiple time points can also provide information on the time course of activation of various brain regions. Like antidepressant medications, TMS probably produces dynamic changes (both acute and chronic), the full extent of which cannot be captured by imaging at only a few time points.

Although it is not clear to what extent findings obtained with normal subjects can be extrapolated to depressed patients, imaging studies in normal control subjects can shed light on the underlying connectivity of the stimulated region. One, 2, and 5-Hz TMS over motor cortex concurrent with neuroimaging has been shown to produce regional cerebral blood flow (rCBF), regional cerebral glucose metabolic rate, and blood oxygenation

level-dependent increases at the stimulation site in normal subjects (Bohning et al., 1999; Fox et al., 1997; Siebner et al., 2000, 2001), yet different patterns are observed in normal subjects after left prefrontal TMS (George et al., 1999; Nahas et al., 2001a, b). George et al. (1999) performed a SPECT study of eight subjects before DLPFC stimulation, during 10 to 20 seconds of a 2-minute train of 10-Hz TMS, and during a 2-minute train of TMS after a prior 18 minutes of TMS. Although no increase in perfusion was produced at the coil site, increases were observed in the orbitofrontal cortex and the hypothalamus at both 2 minutes and 20 minutes (20 > 2), and in the thalamus at 20 minutes. At 20 minutes, decreases were observed in the right PFC, bilateral anterior cingulate, and temporal cortices. The authors suggest that the cingulate effects may explain the mood-altering effects of TMS observed in depressed patients.

The only study using functional MRI to measure cerebral effects of interleaved TMS was performed by (Nahas et al., 2001). A 1.5-T MRI scanner was used to image five normal subjects during short trains of 1-Hz left prefrontal TMS at 80%, 100%, and 120% of MT. Subjects performed a continuous performance task throughout scanning that required them to lift their index finger at the sound of a tone, leading to significant activation of auditory cortex and right insula. There was a significant increase in perfusion under the coil at 120% of MT when compared with rest. Increases were also observed in the right orbitofrontal cortex at 120% of MT, and in the prefrontal cortex at both 100% and 120% of MT. The only significant cingulate effects were left-side increases, and were observed only when 120% MT was compared with 80% MT. The task performance may also have influenced the activations observed.

The first functional imaging study of a depressed patient undergoing TMS treatment was performed by George et al. (1995). A baseline FDG PET scan revealed global hypometabolism that normalized after treatment of depressive symptoms by 20-Hz TMS (80% of MT). A further increase in metabolism was observed when FDG injection occurred during concurrent stimulation. It is important to recognize that changes observed in activation patterns may be the result of TMS effects, resolution of depressive symptoms, or both. Nonetheless it has been suggested that the antidepressant effect of high-frequency TMS could be the result of activation of such hypofunctional areas.

Kimbrell et al. (1999) performed a quantified FDG PET study comparing randomized 20-Hz (80% of MT), 1-Hz, and sham left DLPFC TMS in 13 unipolar (medication free) and bipolar (one of four medication free) depressed patients and found that better antide-

pressant response to 20-Hz TMS was associated with greater baseline hypometabolism in the bilateral temporal, anterior cingulate, occipital, and cerebellar regions, whereas response to 1-Hz treatment, although nonsignificant, was associated with global baseline hypermetabolism. These findings may also be consistent with the hypotheses of Mayberg et al. (1999) that it is not a specific change in activity in any given region that mediates resolution of depressive symptomatology, but a reconfiguration of prefrontal and cingulate interactions. Further studies should be carried out to determine whether pretreatment activation patterns may predict whether patients would respond better to high- or low-frequency TMS. Consistent with this idea, a possibly related phenomenon was observed in two separate studies performed by the same group (Speer et al., 2000; Kimbrell et al., 1999). Patients whose depression improved with 1-Hz TMS tended to worsen with 20-Hz TMS, and vice versa ($r = -0.78$, $P < 0.005$ [Speer et al., 2000]; $r = -0.80$, $P < 0.004$ [Kimbrell et al., 1999]). These findings suggest that, just as some patients respond better to one antidepressant medication than another, so might they respond better to one frequency of TMS than another.

Seemingly contradictory effects were observed with low-frequency stimulation in another study, however. Conca et al. (2002) imaged four drug-resistant (medicated) depressed patients with SPECT and FDG PET before and one day after 10 sessions of alternating right- and left-hemisphere single-pulse TMS. In contrast to the baseline hypermetabolism associated with response to low-frequency TMS observed by Kimbrell et al. (1999), in this study a moderate hypofrontality (medial frontal gyrus) was observed in the baseline FDG PET images that disappeared with remission of symptoms. Glucose uptake and rCBF also increased significantly in bilateral prefrontal regions of interest corresponding to the coil location, and decreased in left orbitofrontal regions. These findings are more difficult to interpret than those of Kimbrell et al. (1999), however, given the small sample size, concurrent antidepressant medications, and particular stimulation parameters used.

Teneback et al. (1999) also observed a correlation between response to TMS and brain activity patterns. In this study, 22 largely medication-resistant unmedicated unipolar or bipolar depressed patients received either 2 weeks of active (n = 13) 20-Hz (100% of MT), 5-Hz (100% of MT), or sham (n = 9) left prefrontal stimulation and underwent SPECT scanning 3 days before and 3 to 4 days after treatment. At baseline, depression severity was correlated inversely with activity in the left prefrontal cortex and the bilateral medial temporal lobe and

caudate, which normalized in TMS responders after treatment. Yet when compared with nonresponders, responders exhibited increased inferior frontal activity at baseline and further increases with treatment, and also showed decreased activity in the right medial temporal lobe with treatment. Regional CBF also changed in limbic regions as a function of mood improvement in sham responders.

High-frequency (>1-Hz) TMS is thought to induce cerebral excitation whereas low-frequency (≤1 Hz) TMS is thought to induce cerebral depression, yet few neuroimaging studies of depressed patients have tested this hypothesis by directly comparing high- and low-frequency TMS. In a study by Speer et al. (2000), 10 medication-free depressed patients received 2 weeks of either 20-Hz (100% of MT), 1-Hz (100% of MT), or sham TMS over the DLPFC in a crossover design (those receiving sham first next received 20 Hz, whereas those who received active TMS first were crossed over to the other frequency) at 100% of MT. Quantitative O[15] PET images were acquired at baseline and 72 hours after completion of the last TMS treatment at each frequency. As in normal subjects, 20-Hz TMS produced widespread, mainly left-side increases in rCBF in the prefrontal and cingulate cortices. Increases also occurred in the left amygdala, and bilateral insula, basal ganglia, uncus, hippocampus, parahippocampus, thalamus, and cerebellum. One-Hertz TMS produced only decreases that were much smaller in spatial extent in the right prefrontal cortex, left medial temporal cortex, basal ganglia, and amygdala.

Speer et al. (2000) suggest that the differential effects of high- versus low-frequency TMS may be analogous to the effects of stimulation on cortical, hippocampal, and cerebellar slice preparations, in which high-frequency stimulation leads to long-term potentiation, whereas low-frequency stimulation produces long-term depression (Christie and Abraham, 1994; Malenka, 1994; O'Dell and Kandel, 1994).

Variable results have also been obtained in studies that examined high-frequency stimulation alone. Nahas et al. (2001) measured rCBF with SPECT in 23 unipolar or bipolar depressed patients (three of whom were on concomitant mood stabilizers) during sham or left DLPFC TMS (100% of MT) at 20 Hz or 5 Hz for 10 days. Scanning occurred before TMS treatment and again during the fifth treatment session. Increases in rCBF associated with active TMS were observed at the stimulation site. The right medial frontal lobe increases, and the anterior cingulate and anterior temporal pole decreases, were similar to the results obtained by George et al. (1999) in normal subjects. Twenty-Hertz and 5-Hz

TMS also produced differential effects, although with their method of analysis, the authors could not determine how they differed.

Zheng et al. (2000) measured rCBF with SPECT following 10-Hz left DLPFC TMS (110% of MT) in five drug-resistant depressed patients. Scans acquired 48 hours after treatment were compared with baseline and, as in other studies (e.g., Speer et al., 2000), an increase was observed in the left anterior cingulate. Although visual inspection of individual patients' SPECT images showed both increased and decreased rCBF in different regions, no significant change in either direction was observed in any other region when analyzed across subjects, most likely because of the small sample size and high individual variability in response.

Catafau et al. (2001) examined seven medication-resistant medicated depressed patients (two of whom were also resistant to ECT) with SPECT at baseline, during the first TMS session, and 1 week after 10 daily 20-Hz left DLPFC TMS (90% of MT) sessions. Significant increases in rCBF were observed in a left prefrontal region of interest after the final TMS treatment, but no significant changes were observed after the first treatment. No other regions demonstrated significant changes from baseline, again possibly because of the small sample size and high individual variability in response.

In summary, the many variables that must be accounted for in interpreting the cerebral activation effects of TMS on depressed patients make it difficult to integrate the findings across studies. Larger and better controlled studies are needed that control for intersubject variability in a depressive state, response to TMS, and concomitant medications, all of which may affect pre- and posttreatment perfusion patterns. The cerebral activation patterns produced by stimulation have also been shown to vary with coil placement (Paus et al., 1997, 1998), intensity of stimulation (Bohning et al., 1999; Nahas et al., 2001), frequency (Nahas et al., 2001), and number of pulse trains administered (Paus et al., 1998). In addition, the number of treatments before imaging, time between imaging and TMS sessions, and whether stimulation was performed before or during neuroimaging may also affect results.

More work is needed to resolve the apparent paradoxes in the TMS neuroimaging literature. Nonetheless, the regional brain activity changes produced by TMS may provide important information regarding the underlying neuronal circuitry responsible for mood regulation and mediation of antidepressant response.

MANIA

Compared with depression, relatively few studies have examined systematically the clinical effects of TMS in mania. Grisaru et al. (1998b) randomized 16 manic patients to receive high-frequency TMS to the left or right DLPFC with a round coil for 2 weeks. Manic symptoms improved significantly only in the right TMS group. This study suggested that the laterality of effects in mania with high frequency may be opposite to those in depression. However, more controlled trials in both disorders comparing right- with left-side stimulation would be needed to confirm this theory. There was some concern that the differential effects between right and left TMS may have been complicated by the fact that medications were initiated soon before the trial began. As such, a difference between the two groups could indicate that left-sided stimulation impeded the action of the medications. A sham-controlled trial may help to clarify this point.

The same group has examined the effects of TMS in an animal model of mania: the amphetamine hyperactivity model (Shaldivin et al., 2001). Daily TMS treatments in rats exerted behavioral effects similar to those seen with lithium, but twice-daily treatments produced the opposite effects, suggesting dose dependency in the action of TMS. Dosage effects may at least partially explain the failure of Clark et al. (2000) to find evidence of activity of a single right 20-Hz TMS session on an amphetamine model of mania in humans. In summary, the effects of TMS in mania are unclear, but further work is warranted.

SCHIZOPHRENIA

Although most of the clinical work to date with TMS has focused on depression, several of the earliest studies of TMS in psychiatric populations included schizophrenic patients. These studies used single-pulse TMS administered with a large round coil to the vertex, thereby stimulating broad regions of bilateral prefrontal and parietal cortices. Geller et al. (1997) reported that 6 of 10 medicated chronic schizophrenic patients showed some transient improvement after a single session of single-pulse TMS in an open study. Using 2 weeks of 1-Hz TMS with a somewhat smaller round coil positioned on the right prefrontal cortex, Feinsod et al. (1998) reported that 7 of 10 schizophrenic patients improved moderately or markedly, and psychosis ratings dropped significantly. However, when the same group followed up their findings with a sham-controlled trial in 35 schizophrenic patients, TMS did not differ from sham.

Hoffman et al. (1999, 2000) had better success with 1-Hz TMS in schizophrenia when the coil was positioned over the left temporoparietal cortex—a region that has shown selective activation during auditory hallucinations (Silbersweig et al., 1995). This trial was based on the hypothesis that low-frequency TMS may dampen excitability in the region implicated in this specific symptom. In an initial crossover study of three patients, significant reductions in hallucinations were noted with 4 days of active TMS compared with sham (Hoffman et al., 1999). Two patients experienced near-total cessation of hallucinations for at least 2 weeks. Of note, all three patients correctly identified which condition was active—a common occurrence in crossover studies with TMS. The same group also conducted a larger crossover trial with 12 patients (Hoffman et al., 2000). Again, active TMS reduced hallucinations significantly compared with sham. The effect was less marked in patients on concomitant anticonvulsant medications. However, it is not known whether these patients differed in other ways from those not on these medications. Other positive and negative symptoms did not change with treatment. It will be critical to determine whether other groups can replicate this finding using a parallel group design to rule out definitively placebo effects.

Other groups have examined the effects of high-frequency TMS applied to the prefrontal cortex on the theory that high-frequency TMS may be useful in reversing the hypofrontality observed in schizophrenia. Cohen et al. (1999) reported an open study of six patients who received 20-Hz TMS to the midline prefrontal cortex for at least 2 weeks. They observed a significant reduction in negative symptoms, but other symptoms and tests of neuropsychological function were essentially unchanged. Nahas et al. (1999) administered a single session of 20-Hz TMS to the left DLPFC in 15 patients in a sham-controlled crossover trial. Improvement was noted in negative symptoms the day after treatment. Continuing the treatment for 2 weeks, another group reported that active TMS decreased psychotic symptoms significantly in a crossover study of 12 patients (Rollnik et al., 2000). That study did not specify whether the improvement was in positive or negative symptoms. Interestingly, concomitant depressive symptoms did not improve. A parallel design study of high-frequency TMS to the DLPFC in schizophrenia would be important to follow up on these promising results.

ANXIETY DISORDERS

Post Traumatic Stress Disorder

Limited open studies have been conducted on post traumatic stress disorder (PTSD). One session of single-pulse TMS at 100% of stimulator output was applied to 10 PTSD patients (Grisaru et al., 1998a). Each patient received 15 stimuli to the vertex with a round coil for 15 minutes. A significant improvement was found 24 hours after treatment, but symptoms returned to baseline by 7 days.

McCann et al. (1998) treated two women with PTSD openly with 1-Hz TMS to the right frontal cortex at 80% of MT, with a figure-of-eight coil. Post traumatic stress disorder symptoms improved during the final week in one subject and during weeks 2, 3, and 5 in the other subject. Scores returned to baseline after the conclusion of treatment. Both patients had prefrontal hypermetabolism on PET that reversed with treatment, most markedly in the right prefrontal cortex. These PET data are interesting in light of a study by Rauch et al. (1996), who reported increased blood flow to right-side limbic, paralimbic, visual, and frontal areas in patients with PTSD. More recent functional neuroimaging studies have found more bilateral blood flow decreases in the medial frontal (anterior cingulate) regions and increases in the orbital frontal cortex during symptom provocation paradigms in PTSD patients compared with control subjects (Bremner et al., 1999a, b; Shin et al., 1999). Two of these studies have also shown a decrease in left inferior frontal cortex in PTSD patients (Rauch et al., 1996; Shin et al., 1999).

In a study of 12 patients who had comorbid depression and PTSD, Rosenberg (personal communication, May 2001), found that 75% of patients had at least a 50% decrease in HRSD score, but no decrease in PTSD symptomatology, after 10 days of either 1-Hz or 5-Hz TMS at 90% of MT to the left DLPFC. At the 2-month follow up, the antidepressant effects were maintained in half the patients. Although PTSD is often treated with antidepressant medications (Pearlstein, 2000), this study suggests the independence of the neural substrates of these illnesses.

These preliminary studies do not allow us to conclude that TMS is an effective treatment for PTSD. However, these results, and the demonstrated effect that TMS can have on the hypothalamus–pituitary–adrenal axis (Evers et al., 2001b; Post and Keck, 2001), warrant further sham-controlled trials.

Obsessive Compulsive Disorder

In the first study on the effects of TMS on obsessive compulsive disorder (OCD) symptoms, 12 patients were treated with 20-Hz stimulation at 80% of MT for 20 minutes (2 seconds on/58 seconds off) (Greenberg et al., 1997). Transcranial magnetic stimulation was delivered on three separate days to the left prefrontal cortex, right prefrontal cortex, and midline occipital cortex using a figure-of-eight coil. While receiving stimulation to the right or left prefrontal (but not occipital cortex) compulsions were decreased significantly. The decrease in compulsions was greater for right-side stimulation than left, and the effect persisted for 8 hours. After receiving stimulation to the right prefrontal cortex, participants also had improved mood that lasted for at least 30 minutes. There were no changes in obsessions and no significant differences in compulsions from baseline after left prefrontal or midline occipital stimulation.

The effect of a longer treatment course in OCD was explored by Sachdev et al. (2001). Ten daily treatments with 30 trains of 10-Hz TMS (5 seconds on/25 seconds off) at 110% of MT were given to 12 treatment-resistant OCD patients to either the left or right prefrontal cortex, with a figure-of-eight coil. There was no difference between the two sites of stimulation. Both groups demonstrated a reduction in obsessions and compulsions as long as 1 month after treatment. Thirty-three percent of the subjects (n = 4) had a clinically significant improvement in their OCD symptoms.

Extending treatment to 6 weeks, Alonso et al. (2001) performed a double-blind, placebo-controlled trail in which patients received either right prefrontal active or sham 1-Hz TMS. Stimulation was delivered three times a week for 6 weeks using a round coil at 110% of MT. During the sham condition the coil was tilted 90-deg and the intensity was 20% of MT. Neither group showed any significant improvement in OCD symptoms.

Regions most often implicated in functional neuroimaging studies of OCD include the orbital frontal cortex and the anterior cingulate gyrus (Saxena and Rauch, 2000). Studies on the effects of TMS on OCD have shown promising results, even though TMS technology does not allow the direct stimulation of those areas. Transsynaptic effects on the orbital frontal cortex or the anterior cingulate gyrus represent a mechanism by which TMS may influence OCD symptoms (Cummings, 1995; Paus et al., 2001). Further double-blind, sham-controlled studies are needed to determine the clinical efficacy of TMS in OCD.

TABLE 1. *Cases of seizure and spread of excitation in depressed patients*

Reference	Gender	Age, y	Frequency, Hz	Duration, sec	Intensity	Site of Stimulation	Description
Pascual–Leone, personal communication	Female	40	10	10	90% MT	Left DLPFC	Secondarily generalized seizure
Conca et al., 2000	Female	36	20	10	110% MT	Left DLPFC	Frontal complex partial seizure
Figiel et al., 1998	Male	66	10	5	110% MT	Left DLPFC	Brisk proximal right arm contractions during TMS
Figiel et al., 1998	Female	44	10	5	110% MT	Left DLPFC	20 Minutes of motor tics after TMS

DLPFC, dorsolateral prefrontal cortex; MT, motor threshold; TMS, transcranial magnetic stimulation.

COGNITIVE DISORDERS

To date, no studies have examined the use of TMS as a treatment for patients with cognitive disorders. Different frequencies of TMS can both decrease and increase motor cortical excitability (Chen et al., 1997; Pascual–Leone et al., 1998; Wu et al., 2000) and exert differential effects on cerebral activity (Kimbrell et al., 1999; Post et al., 1999a). This suggests that it has the potential to be used not only to inhibit brain function, but also to facilitate it. There are also preliminary animal studies suggesting that TMS may promote the release of neuroprotective agents such as brain-derived neurotrophic factor and secreted amyloid precursor protein (Muller et al., 2000; Post et al., 1999b). Several controlled studies have been conducted that illustrate an enhancing effect of TMS on cognitive function. Single-pulse TMS applied to Wernicke's area at 35% and 55% of stimulator output, 500 msec before stimulus presentation facilitated picture naming (Topper et al., 1998). Stimulation of the parietal or temporal lobe with single-pulse TMS has been shown to speed reaction time in a visual object working memory task (Oliveri et al., 2001). In patients with left temporal lobe epilepsy, single-pulse TMS delivered to the left temporal lobe at 120% of MT increased recall for recent words in a list (Duzel et al., 1996). Boroojerdi et al. (2001) reported improved performance on an analogic matching task following 5-Hz TMS at 90% of MT to the left DLPFC. It has also been reported that 20-Hz TMS applied to the left prefrontal cortex can speed reaction time and decrease P300 latency in a visual odd ball task (Evers et al., 2001a). These studies all produced significant, but small and short-lived changes in selected cognitive operations. Although a TMS paradigm may be identified that could enhance performance on a particular cognitive task in subjects without cognitive impairment (as illustrated earlier), it is not clear how the stimulation would affect other functions subserved by the region stimulated, nor is it clear how improvement on a particular task would generalize into clinically meaningful improvement in a population with cognitive impairment. More work must be done to elucidate what role, if any, TMS may play in the treatment of cognitive disorders.

SAFETY OF TMS IN PSYCHIATRIC DISORDERS

Studies in Normal Volunteers

Until recently, data on the safety of TMS was comprised exclusively of studies in normal volunteers, typically receiving a single TMS session (Jahanshahi et al., 1997; Pascual–Leone et al., 1993; Wassermann et al., 1996b) Those studies identified seizure as the most serious known risk of TMS. These seizures have been self-limited and have not had adverse sequelae. Risk factors for seizure include the presence of a structural brain injury, history of seizure, and family history of epilepsy. When administered at a sufficiently high frequency or intensity, a long enough duration, or with a short enough intertrain interval, TMS can induce seizure independently of these risk factors (Wassermann et al., 1996a). Guidelines exist to aid the selection of parameter combinations that are not associated with spread of excitation within the motor cortex, considered to indicate that one is near the seizure threshold. However, the relationship between motor spread and magnetic seizure threshold has not been examined directly (Wassermann, 1998). Other less serious side effects of TMS include headache, scalp pain from stimulation of scalp muscles, and neck pain. Hearing loss is a theoretical risk, and so earplugs are recommended (Counter, 1994).

Seizure and Spread of Cortical Excitation

There have been two reports of seizure in depressed patients with stimulation of the prefrontal cortex (Table 1). In both cases, stimulation parameters exceeded the safety guidelines. In the first case, a 40-year-old woman with depression receiving a maintenance course of high-

frequency TMS (10 Hz, 10 seconds, 90% of MT) to the left DLPFC experienced a secondarily generalized seizure during the first train of stimulation. This was attributed to initiation of haloperidol (15 mg) and amitriptyline (20 mg) immediately before that TMS session without the knowledge of the investigators (Pascual–Leone, personal communication, June 1996). Importantly, the MT had not changed, suggesting that MT and seizure threshold are not necessarily correlated. Of note, safety guidelines suggest that the longest train at 10 Hz and 100% of MT should be 5 seconds. The longest safe train at 90% of MT is not known, but it may be prudent to adopt the limits for 100% of MT as a conservative measure, and screen patients carefully for changes in their medications before each TMS session.

A second seizure in a depressed patient was reported by Conca et al. (2000) in a 36-year-old woman during her third train of stimulation at 20 Hz, 10-second duration, 110% of MT. The longest recommended train at 20 Hz and 110% of MT is 1.6 seconds. After a sensation of nausea (consistent with an aura), the patient lost consciousness, demonstrated oral automatisms lasting 8 seconds, and experienced postictal amnesia for these events. There was no motor spread, suggesting this was a frontal complex partial seizure. Concomitant medications were trazodone (500 mg/day), citalopram (30 mg/day), lorazepam (3 mg/day), and thyroxin (100 μg/day). Of note, the patient had a history of maprotiline-induced generalized seizure in the past. It may be wise to consider patients with a history of seizure, even medication-induced, at increased risk for TMS-induced seizure. These two patients also illustrate that extrapolating above the safety guidelines carries a real risk of seizure. If guidelines are exceeded, there should be careful justification for doing so, and patients should be informed of their increased risk of seizure.

There have been two reports of TMS-induced spread of excitation (see Table 1). A 66-year-old depressed man experienced brisk right upper extremity contractions during TMS (with stimulation parameters that were within suggested safety guidelines), which ended when stimulation was stopped (Figiel et al., 1998). Depending on the latency of the movements relative to each TMS pulse, this could either represent motor spread or direct stimulation of the motor cortex. Direct motor cortex stimulation could be observed if the intensity was high enough or if the coil were being held too close to the motor cortex (such as in the case of difficulty in locating the optimal site for hand stimulation). Motor spread is a distinct possibility because the coil used in this study is a more powerful coil (iron-core coil, Neotonus) than that used to create the safety guidelines. Because the volume of tissue stimulated depends on the coil design, it is not clear that normalizing to the MT is adequate to ensure that the safety guidelines are directly scalable to all coil designs and all devices. In another patient in the study by Figiel et al. (1998) who had a history of motor tics, TMS triggered 20 minutes of repeated motor tics that subsided after intravenous lorazepam.

Cognition

Recently, several studies have systematically examined the neuropsychological effects of repeated sessions of TMS in clinical psychiatric samples. In an open study of 10 unipolar depressed patients receiving a robust amount of high-frequency TMS for 10 days (2000 pulses per day), Triggs et al. (1999) found no impairment in performance on a variety of neuropsychological tests. In fact, some improvements in function were noted, which may be the result of practice effect or to improved mood. Likewise, Little et al. (2000) found no cognitive impairments in 10 depressed patients after 2 weeks of high- or low-frequency TMS to the left DLPFC given at 80% of MT. Performance on list recall actually improved. The same group examined the effects of TMS given at 100% of MT in 18 depressed patients with similar results (Speer et al., 2001). In another controlled trial, Loo et al. (2001) examined the effects of as long as 4 weeks of TMS in 18 depressed patients. They also found trends for improvements in neuropsychological tests, which were attributed to practice effects. No evidence of deterioration in performance was noted, but it is important to remember that practice effects could mask subtle TMS-induced cognitive impairment.

Mania

The induction of manic symptoms is a recognized risk of most antidepressant treatments, including ECT. There have now been several reports of TMS-induced hypomania and mania. Nedjat and Folkerts (1999) reported three cases of TMS (high frequency to the left DLPFC) inducing hypomanic symptoms lasting 24 hours in a study of 50 normal volunteers with no history of psychiatric illness. There have also been four reported cases of manic symptoms induced by TMS in unipolar and bipolar patients. George et al. (1995) reported that a unipolar depressed patient receiving open TMS at 20 Hz to the left prefrontal cortex developed hypomanic symptoms after nine daily treatments, which resolved when the frequency of treatments was reduced to once every other day. Garcia–Toro (1999) reported that 20 Hz to the left DLPFC induced manic symptoms reproducibly in a bi-

polar patient, despite concomitant mood stabilizer medications. Dolberg et al. (2001) reported TMS-induced mania in two bipolar patients, despite concurrent treatment with therapeutic levels of valproic acid. In the first case, frank manic symptoms began to manifest during the third week of daily treatment with high-frequency TMS to the left DLPFC, and worsened during the fourth week of treatment. Of note, the patient was withdrawn from haloperidol immediately before initiating TMS, and responded promptly to haloperidol once it was restarted after TMS. In the second case, manic symptoms developed 5 days after the end of the 4 week course. It is difficult to know whether this switch was triggered by the TMS or rather by the natural history of the illness. Nevertheless, this collection of cases and the evidence in normal volunteers suggest that manic symptoms are a potential risk of TMS about which prospective patients should be informed.

Other Side Effects

Structural MRI performed before and after 2 weeks of high-frequency TMS to the left DLPFC in depressed patients failed to show any volumetric changes (Nahas et al., 2000). Two depressed patients showed mild high-frequency hearing loss after 6 weeks of exposure to the TMS auditory artifact, despite the use of earplugs (Loo et al., 2001). Hearing returned to baseline within a month. Sedation was noted as a side effect of high-frequency TMS by Pridmore et al. (1999), and has been seen occasionally in our experience with some patients actually falling asleep during high-frequency TMS sessions.

CONCLUSIONS

Transcranial magnetic stimulation remains an investigational intervention that has not yet gained approval by the Food and Drug Administration for the clinical treatment of any disorder. Despite a growing number of promising studies on depression, it is still unresolved whether the magnitude of the effect will turn out to be clinically important. Effect sizes are consistently higher in patients referred for ECT, which may indicate something about proper patient selection to enhance efficacy. Studies in schizophrenia on both positive and negative symptoms with TMS administered to the temporoparietal cortex and DLPFC respectively are encouraging, and illustrate that TMS may be able to influence symptom clusters selectively with distinct neural circuitry. A parallel group study is now needed to confirm the results to date in schizophrenia, which have all been crossover trials.

Considering the relatively primitive methods used to determine dosage and localization of the TMS coil in most clinical studies, it is noteworthy that any significant effects were found. Further functional imaging studies and animal models are needed to illuminate the effects of TMS on brain function so that we may then apply these effects in a selective way to modulate the circuitry underlying psychiatric disorders. A critical issue is the selection of TMS dosage. To have adequate power to detect group differences, clinical trials are limited in the number of dosages that they can compare head to head. Dose-finding studies with animals and with functional neuroimaging could aid selection of the most effective parameters to test clinically.

Beyond issues of dosage, the reliability of TMS delivery in the clinical setting could be improved. Currently available figure-of-eight coils are flat and couple poorly to the curved surface of the scalp. Slight changes in the angle between the plane of the coil and the scalp can produce large variation in brain effects. Technology already exists to direct the TMS coil to the scalp position overlying the target cortical structure, but it has not yet been adopted widely in the clinical setting. Any method that could improve the precision and reliability of coil placement would serve to reduce the noise in the clinical trials and give the field a clearer picture of the true clinical potential of TMS.

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