20 Individual Differences in the Response to Transcranial Magnetic Stimulation of the Motor Cortex

Eric M. Wassermann

One of the most striking aspects of transcranial magnetic stimulation (TMS) is the degree to which individuals differ in the magnitude of their muscle responses to stimulation of the motor cortex. Much of the TMS literature is devoted to the study of differences in response between groups of neurological patients and healthy individuals, and these can be dramatic. However, the range of variation within the healthy population is also interesting, and no study of any amplitude-related measure of the motor evoked potential (MEP) has ever shown a difference in response between two populations that was greater than the normal range.

Normal variation in the MEP has been generally ignored or treated as a nonsytematic and uninformative source of variance. Neurophysiologists in particular, who tend to perform intensive investigations on small numbers of human or animal subjects, tend to neglect the issue of individual variability entirely. To behavioral scientists, geneticists, and clinicians, however, differences among individuals hold considerable importance. Moreover, when such differences are physiologically meaningful, robust, consistent, and readily quantified and scalar, as many interindividual differences are, they present a unique opportunity for study. In this chapter, I discuss some of the factors known to contribute to the individual variation in the response to TMS of the motor cortex in populations of motorically normal individuals.

Variability of Motor Evoked Potential Threshold and Amplitude

The MEP threshold is a very widely used measure of the excitability of the corticospinal system to exogenous stimulation with TMS. It is not a true threshold, but a probabilistic index of corticospinal and spinal neuron responsiveness to stimuli of low intensity. Perhaps a better overall measure of aggregate excitability in the corticospinal system is the input-output or recruitment curve[1] relating stimulation intensity at a range of levels to MEP amplitude. Nevertheless, the resting MEP threshold is deeply embedded in the TMS literature and provides a useful standard measure for comparison across studies.

The MEP threshold is relatively stable across time within individuals, but varies widely across the population (i.e., from about 30% to more than the maximum output of conventional stimulators and coils[2]) (Fig. 20–1). Similar variability is present in the threshold during a mild voluntary contraction of the target muscle. Based on a sample of 151 healthy individuals that contained 19 whose thresholds were determined on three different occasions,[2] I estimated that experimental error (i.e., mistaken estimation of the true threshold) contributed approximately 6% and 11% to the population variance for the resting and active conditions, respectively. The validity of the resting MEP threshold as a measure of corticospinal system excitability has been

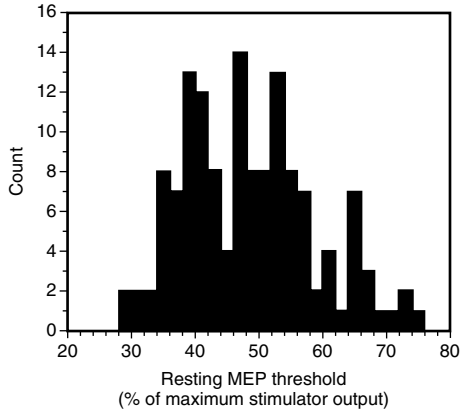

Figure 20–1 Histogram of the resting motor evoked potential thresholds in 151 healthy subjects. No counts are shown for individuals whose thresholds exceeded maximum stimulator output. (Adapted from Wassermann EM. Variation in the response to transcranial magnetic brain stimulation in the general population. Clin Neurophysiol 2002; 113:1165–1171.)

questioned because electromyographic silence does not imply the absence of excitatory traffic in the corticospinal tract. However, the MEP threshold measured during a standardized voluntary contraction is more variable than when measured at rest. Analogous dissociations between grip force and corticospinal cell activity have been described in primates.[3] The remaining 90% of the variance in our large group did not appear to be caused by measurement error or random variability and was likely to contain a substantial component related to stable biological differences between individuals and perhaps to experience, as in the increase in MEP amplitude found in individuals after motor learning.[4,5]

Scalp-to-Brain Distance and Age-Related Influences on Motor Evoked Potentials

One potential source of variation in the amplitude and threshold of the MEP is the distance of the coil from the stimulation target in the motor cortex. One might expect the MEP to be particularly sensitive to this distance, because the intensity of the induced magnetic field falls with the third power of distance from the source. In 17 healthy individuals 19 to 75 years old, McConnell and colleagues[6] found that the MEP threshold increased with the distance from scalp to cortex as determined from MRI scans. Earlier, the same group found that age and scalp to motor cortex distance were highly correlated in a sample of depressed patients.[7]

Genetic Factors

Some determinants of the MEP threshold may be genetic. In a study of 17 healthy sib pairs, aged 18 to 76 years,[2] we found a significant correlation between the MEP thresholds in the right (dominant) hand during both rest ($r^2 = 0.55$; $P < .001$) (Fig. 20–2) and voluntary activation ($r^2 = 0.30$; $P < .05$). There was no relation of age or sex to threshold in this sample. Although the similarity in threshold between siblings could easily have been caused by a gross anatomical factor, such as scalp to cortex distance, it was considerably weaker for the left hand, suggesting that the inherited factor might affect the organization of the hand representation in the dominant hemisphere.

Neurologically Normal Patients with Behavioral Disorders

It is not surprising that many neurological disorders, particularly those affecting movement, can alter the amplitude and threshold of

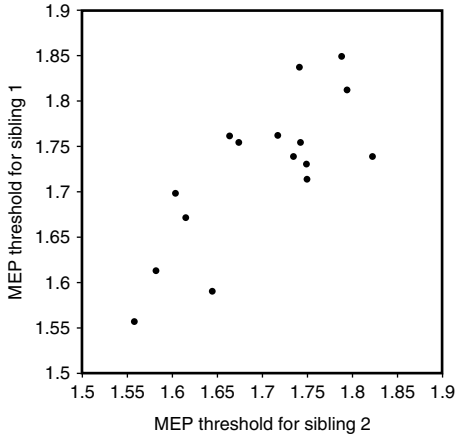

Figure 20–2 Plot showing the correlation of resting motor evoked potential thresholds between siblings. Axes are in logarithmic scale. (Adapted from Wassermann EM. Variation in the response to transcranial magnetic brain stimulation in the general population. Clin Neurophysiol 2002;113:1165–1171.)

the MEP. However, high-functioning psychiatric patients who have no clinically apparent neurological abnormalities can also differ from healthy individuals on various TMS measures of motor cortex function. For example, we studied a group of 16 patients with obsessive-compulsive disorder (OCD),[8] 11 of whom had no history or evidence of tics or any other neurological disorder and 7 of whom were on no medications. We found that, on average, these patients had MEP thresholds significantly lower than normal during rest and voluntary activation, and larger resting MEPs at a range of stimulation intensities (Fig. 20–3). The difference was apparent in the tic-free and the unmedicated patient subgroups when their data were analyzed separately and we have gotten similar results in subsequent studies.[9] The fact that the MEP threshold was reduced during both rest and overt voluntary contraction of the target muscle implies that the change was not due to subthreshold activation or disinhibition of the cortical output pathway, as might occur in anxious individuals. Rather, it implies a change located in series with the pathway conducting the stimulus from presynaptic cortical axon to muscle (i.e., located in a set of conducting synapses or neurons). The basis for this argument has been set forth elsewhere.[10,11]

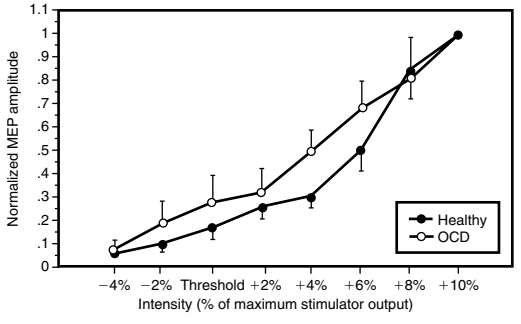

Figure 20–3 Recruitment curve showing the relation between stimulus intensity and motor evoked potential (MEP) amplitude in healthy individuals and patients with obsessive-compulsive disorder. The *x* axis is normalized to each individual's resting MEP threshold, and the units are the percent of maximum stimulator output. The *y* axis is normalized to each individuals largest MEP. *Bars* show the standard error.

Variability of Paired-Pulse Motor Evoked Potential Measures

The amplitude of the MEP in paired-pulse TMS studies of the type described by Kujirai and colleagues[12] and refined by Ziemann and coworkers[13] has become a popular measure of the relative degrees of intrinsic cortical inhibition and facilitation that are evoked by a subthreshold conditioning TMS pulse. It is important to note that this technique measures only the activities *evoked* by the conditioning stimulus and not the absolute or ongoing levels of inhibition and facilitation. It is therefore critical to know whether the MEP to a single TMS pulse is affected (as by tonic inhibition) before attempting to interpret paired-pulse data. Another important point is that factors (e.g., $GABA_A$ agonists) that increase inhibition also reduce facilitation, sometimes to a greater degree.[14] In many circumstances, it is not possible to distinguish between alterations in facilitation and inhibition unless there is a strong predictive hypothesis or a simultaneous change in the response to single stimuli.

Like the MEP to single pulses, paired-pulse measures vary substantially from measurement to measurement[15] and between ostensibly healthy subjects.[2] Although there is a well-known tendency to show inhibition at short intervals and facilitation at longer ones, there is an appreciable number of healthy subjects who show facilitation at short intervals and or inhibition at longer intervals even when large numbers of trials are obtained and experimental conditions are carefully controlled (Fig. 20–4A). A significant portion of this variation appears to result from stable individual differences rather than experimental error, because individuals seem to show similar tendencies across inter-stimulus intervals (see Fig. 20–4B).

Age-Related Differences

Two small studies, each comparing two groups with different mean ages have found disparate results. In one,[16] an elderly group showed significantly less paired-pulse inhibition than a group of young adults. In the other,[17] a middle-aged group showed more paired-pulse inhibition than young adults.

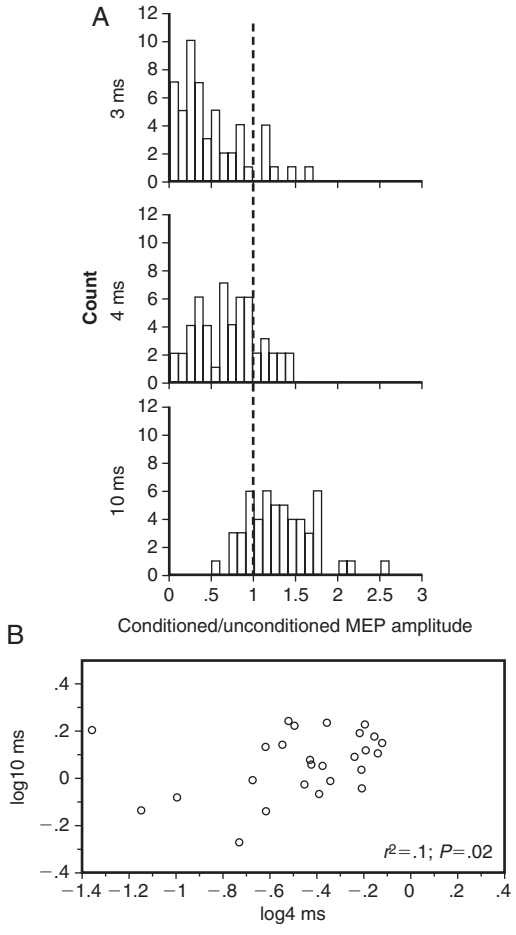

Figure 20–4 **A:** Histograms of the amplitude ratio of the mean conditioned to mean unconditioned motor evoked potential for 3, 4, and 10 ms from a paired-pulse transcranial magnetic stimulation study in 53 healthy subjects. **B:** Plot showing the correlation within individuals of the conditioned/unconditioned amplitude ratios at inter-stimulus intervals of 4 and 10 ms. (**A** adapted from Wassermann EM. Variation in the response to transcranial magnetic brain stimulation in the general population. Clin Neurophysiol 2002;113:1165–1171.)

Neither of these studies controlled for any differences between the groups other than age. In our own sample of 53 individuals, my colleagues and I found no age-related differences in the paired-pulse response.[2]

Sex Differences and Hormonal Effects

Steroid hormones are potent modulators of neuronal excitability. Estradiol itself facilitates of glutamatergic transmission.[18,19] Progesterone and cortisol are metabolized to neurosteroids that bind to a site on a subunit of the $GABA_A$ receptor, increasing its activity in a manner analogous to the action of the benzodiazepines. The effects of androgens on this system are less well known, but testosterone may decrease excitability.[20,21] Studies have shown that drugs shifting the balance of GABA and glutamate activity in the cortex in the direction of GABA activity increase TMS paired-pulse inhibition and decrease facilitation at moderate doses.[22–24] Therefore, one might expect that the same technique would be sensitive to the actions of neurosteroids in healthy individuals. In women immediately after menstruation, the circulating levels of estradiol and progesterone are low. Estradiol rises gradually throughout the follicular phase and progesterone begins to be secreted in the luteal phase during which estrogen remains high. In two studies,[25,26] we performed paired-pulse TMS experiments in groups of healthy, ovulating women across the menstrual cycle and found that intracortical inhibition decreased and facilitation increased late in the follicular phase when high estradiol levels were unopposed by progesterone. Then there was a drop in facilitation and increase in inhibition in the luteal phase when progesterone was present. The magnitudes of the increase in excitability from the early to the late follicular phase and the subsequent drop in the luteal phase were comparable to effects described for behaviorally significant doses of drugs.[22]

Not all neurologically normal women, however, show the expected decrease in excitability in the luteal phase. In a sample of women meeting rigorous behavioral criteria for premenstrual syndrome and premenstrual dysphoric disorder, inhibition actually *decreased* and facilitation *increased* in the luteal phase.[27] An aberrant brain response to a normal circulating level of progesterone is consistent with current theories regarding the pathogenesis of this disorder[28] and could be caused by an alteration in a component of the $GABA_A$ receptor complex or in the cerebral metabolism of progesterone.

Although the effects of cortisol-derived neurosteroids on human cortical excitability have not been measured with TMS, there is

reason to believe that they act in a manner very similar to that of the neurosteroid metabolites of progesterone.[29] Cortisol levels vary in a circadian pattern that is lost in clinical depression, and the levels rise with exercise, illness, and other stressors. These factors should be taken into account in the composition of experimental groups and the timing of experiments and in explaining differences in the responses to paired-pulse TMS.

Neurologically Normal Patients with Behavioral Disorders

Tic-free and unmedicated patients with OCD have markedly reduced intracortical inhibition.[8] Similar findings exist in patients with attention deficit-hyperactivity disorder (ADHD),[30,31] and Gilbert and associates[32] found a strong inverse relationship between intracortical inhibition and impulsivity on scales for ADHD but not with the severity of tics or OCD in a group of children identified as having Tourette's syndrome. This is the first report of a direct correlation between a TMS measure and any index of disease. This reflection of behavioral abnormalities and traits in the motor cortex may not surprise behaviorally oriented clinicians. However, as discussed in the earlier section on MEP amplitude in OCD, the fact that the physiological disease phenotype can be expressed in the motor cortex, even in individuals without recognizable movement disorders, has potential importance for understanding the pathogenesis of neurobehavioral disorders and for the use of TMS as a measure of cortical function in healthy individuals and patients.

Personality and Paired-Pulse Cortical Excitability

In our study of OCD,[8] we found that the patients also had decreased intracortical inhibition relative to a sample of healthy individuals that had been screened with the Structured Clinical Interview for the DSM-IV[33] and interviewed by a psychiatrist. Individuals with high degrees of anxiety or a significant tendency for obsessions or compulsions, but who did not meet diagnostic criteria for OCD were excluded. By contrast, screening of healthy subjects in most neurophysiological and clinical studies involving motor cortex TMS consists at most of a brief medical history and physical examination. When we compared our OCD patients with the large general population sample mentioned earlier[34] who were screened only for psychiatric or neurological diagnoses, neurological abnormalities, and neuroactive medications, we found no such difference in excitability.

Nevertheless, this general population sample proved interesting: Because the difference in intracortical inhibition that we found between the psychiatrically screened normal subjects and the OCD patients could have been an artifact of the screening procedure, we looked at the unscreened general population sample for correlations between paired-pulse excitability and a range of scaleable differences between individuals, including measures of intelligence and temperament. The only correlation of any magnitude or statistical significance was between paired-pulse excitability (lower inhibition or higher facilitation) and the tendency to experience anxiety and other negative emotions (i.e., *neuroticism*, a dimension in the five-factor model of personality as tested with the NEO-PI-R inventory).[35] The association of cortical excitability and negative emotionality (common in OCD and related disorders) could have contributed to our paired-pulse findings in OCD. Interestingly, there was no effect of personality on MEP threshold, suggesting that the threshold change in OCD might be associated with actual pathology.

Conclusion

The fact that TMS of the motor cortex is sensitive to hidden but systematic differences among neurologically normal individuals has important implications for research using TMS. First, it should alert investigators to the importance of screening experimental subjects for individual factors known to influence cortical excitability (e.g., psychopathology) and balancing experimental groups for sex and demographic factors such as age and education that may produce unwanted differences. At the same time, this sensitivity to individual differences also opens new fields of study to motor neurophysiologists. For example, individual variation in the response to

substances and the environment are increasingly acknowledged as major factors in the treatment and etiology of brain disease. Many of these are genetically determined. Physiological studies with TMS could prove particularly useful in identifying the physiologic phenotypes associated with genetic variations that affect behavior, the susceptibility to disease, and the response to chemical agents.

REFERENCES

1. Ridding MC, Rothwell JC. Stimulus/response curves as a method of measuring motor cortical excitability in man. Electroencephalogr Clin Neurophysiol 1997;105:340–344.
2. Wassermann EM. Variation in the response to transcranial magnetic brain stimulation in the general population. Clin Neurophysiol 2002;113:1165–1171.
3. Fetz EE, Cheney PD. Functional relations between primate motor cortex cells and muscles: fixed and flexible. Ciba Found Symp 1987;132:98–117.
4. Pascual-Leone A, Grafman J, Hallett M. Modulation of cortical motor output maps during the development of implicit and explicit knowledge. Science 1994;263:1287–1289.
5. Pascual-Leone A, Dang N, Cohen LG, et al. Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. J Neurophysiol 1995;74:1037–1045.
6. 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;49:454–459.
7. Kozel FA, Nahas Z, deBrux C, et al. How coil-cortex distance relates to age, motor threshold, and antidepressant response to repetitive transcranial magnetic stimulation. J Neuropsychiatry Clin Neurosci 2000;12:376–384.
8. Greenberg BD, Ziemann U, Corá-Locatelli G, et al. Altered cortical excitability in obsessive-compulsive disorder. Neurology 2000;54:142–147.
9. Smith MJ, Jean-Mary J, Grafman J, et al. Abnormal cortical excitability in motor learning in OCD. Biol Psychiatry 2002;51(Suppl):81S.
10. Ridding MC, Rothwell JC. Reorganisation in human motor cortex. Can J Physiol Pharmacol 1995;73:218–222.
11. Touge T, Gerschlager W, Brown P, et al. Are the after-effects of low-frequency rTMS on motor cortex excitability due to changes in the efficacy of cortical synapses? Clin Neurophysiol 2001;112:2138–2145.
12. Kujirai T, Caramia MD, Rothwell JC, et al. Corticocortical inhibition in human motor cortex. J Physiol (Lond) 1993;471:501–519.
13. Ziemann U, Rothwell JC, Ridding MC. Interaction between intracortical inhibition and facilitation in human motor cortex. J Physiol (Lond) 1996;496:873–881.
14. Ziemann U, Lonnecker S, Steinhoff BJ, et al. The effect of lorazepam on the motor cortical excitability in man. Exp Brain Res 1996;109:127–135.
15. Boroojerdi B, Kopylev L, Battaglia F, et al. Reproducibility of intracortical inhibition and facilitation using the paired-pulse paradigm. Muscle Nerve 2000;23:1594–1597.
16. Peinemann A, Lehner C, Conrad B, et al. Age-related decrease in paired-pulse intracortical inhibition in the human primary motor cortex. Neurosci Lett 2001;313:33–36.
17. Kossev AR, Schrader C, Dauper J, et al. Increased intracortical inhibition in middle-aged humans; a study using paired-pulse transcranial magnetic stimulation. Neurosci Lett 2002;333:83–86.
18. Wong M, Thompson TL, Moss RL. Nongenomic actions of estrogen in the brain: physiological significance and cellular mechanisms. Crit Rev Neurobiol 1996;10:189–203.
19. Woolley CS. Electrophysiological and cellular effects of estrogen on neuronal function. Crit Rev Neurobiol 1999;13:1–20.
20. Beyenburg S, Stoffel-Wagner B, Bauer J, et al. Neuroactive steroids and seizure susceptibility. Epilepsy Res 2001;44:141–153.
21. Edwards HE, Burnham WM, MacLusky NJ. Testosterone and its metabolites affect afterdischarge thresholds and the development of amygdala kindled seizures. Brain Res 1999;838:151–157.
22. Ziemann U, Steinhoff BJ, Tergau F, et al. Transcranial magnetic stimulation: its current role in epilepsy research. Epilepsy Res 1998;30:11–30.
23. Ziemann U, Chen R, Cohen LG, et al. Dextromethorphan decreases the excitability of the human motor cortex. Neurology 1998;51:1320–1324.
24. Schwenkreis P, Witscher K, Janssen F, et al. Influence of the N-methyl-D-aspartate antagonist memantine on human motor cortex excitability. Neurosci Lett 1999;270:137–140.
25. Smith MJ, Keel JC, Greenberg BD, et al. Menstrual cycle effects on cortical excitability. Neurology 1999;53:2069–2072.
26. Smith MJ, Adams LF, Schmidt PJ, et al. Ovarian hormone effects on human cortical excitability. Ann Neurol 2002;51:599–603.

27. Smith MJ, Adams LF, Schmidt PJ, et al. Abnormal luteal phase excitability of the motor cortex in women with PMS. Biol Psychiatry 2003;54:757–762.
28. Schmidt PJ, Nieman LK, Danaceau MA, et al. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. N Engl J Med 1998;338:209–216.
29. Majewska MD. Neurosteroids: endogenous bimodal modulators of the $GABA_A$ receptor. Mechanism of action and physiological significance. Prog Neurobiol 1992;38:379–395.
30. Moll GH, Heinrich H, Rothenberger A. Methylphenidate and intracortical excitability: opposite effects in healthy subjects and attention-deficit hyperactivity disorder. Acta Psychiatr Scand 2003;107:69–72.
31. Moll GH, Heinrich H, Trott G, et al. Deficient intracortical inhibition in drug-naive children with attention-deficit hyperactivity disorder is enhanced by methylphenidate. Neurosci Lett 2000;284:121–125.
32. Gilbert DL, Bansal AS, Sethuraman G, et al. Association of cortical disinhibition with tic, ADHD, and OCD severity in Tourette syndrome. *Mov Disord* 2004;19:416–425.
33. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM–IV Axis I Disorders, Research Version, Non-patient Edition (SCID-I/NP). New York, Biometrics Research, New York State Psychiatric Institute, 1997.
34. Wassermann EM, Greenberg BD, Nguyen MB, et al. Motor cortex excitability correlates with an anxiety-related personality trait. Biol Psychiatry 2001;50:377–382.
35. Costa PT, McCrae RR. Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI) Professional Manual. Odessa, FL, Psychological Assessment Resources, 1992.

21 Potential Therapeutic Uses of Transcranial Magnetic Stimulation in Psychiatric Disorders

Mark S. George, Ziad Nahas, F. Andrew Kozel, Xingbao Li, Kaori Yamanaka, Alexander Mishory, Sarah Hill, and Daryl E. Bohning

The potential therapeutic uses of transcranial magnetic stimulation (TMS) in psychiatry are simultaneously perhaps the most interesting and the most complex. Since its modern inception in 1985, TMS has been largely initially used as a research and clinical tool in clinical neurophysiology, as described in other chapters in this book. This chapter critically summarizes the studies using TMS as a potential therapeutic tool in psychiatry.

Limitations

Therapeutic uses of TMS in psychiatry have lagged behind the clinical neurophysiologic uses for several potential reasons. The first reason for a lag may be hearing about and becoming familiar with a new technology. TMS was developed in its modern form as a clinical neurophysiological tool, and information about the technology flowed out from these initial uses. It took several years for psychiatrists, as opposed to clinical neurophysiologists, to learn about TMS and begin to formulate how to use it therapeutically. More importantly however, the structural and functional neuroanatomy of several of the major psychiatric disorders is still inadequately understood, particularly compared with classic neurological disorders such as Parkinson's disease or amyotrophic lateral sclerosis. A major limitation in developing TMS as a psychiatric therapy has been to understand where to apply TMS for specific psychiatric disorders, given an inadequate understanding of the relevant functional anatomy. Although psychiatrists have used electroconvulsive therapy (ECT) for more than 60 years, most psychiatrists are not familiar with classic neurophysiological techniques, and there is a learning curve associated with using TMS for diagnosis, research, or therapy. With these caveats in mind, there is a large and rapidly growing literature on the therapeutic psychiatric uses of TMS.

Another major limitation of using TMS therapeutically is that there is inadequate understanding of what TMS is doing at a neurophysiological and neuropharmacological level, especially as a function of the use parameters. In an attempt to gain understanding in this area, psychiatric researchers have used TMS in animal models or combined TMS with functional imaging. Animal or imaging work has the promise of efficiently providing information about how TMS might work in a psychiatric condition, compared with the slow pace and high cost of a clinical trial.

Psychiatrically Relevant Animal Studies

Animal TMS studies offer many advantages over human clinical work. However, all studies are plagued by two major concerns. First, does the animal model validly reflect the human condition? Second, is TMS being applied in these animals in a way analogous to what is being done in humans? Although all animal models are vulnerable to the first question, the problem of the size of the TMS coil in small animals compared with humans is specific to TMS research and particularly worrisome. Even the smallest animal coils are several times larger relative to the brain size than human focal TMS coils. Nevertheless, initial rodent repetitive TMS (rTMS) studies reported significant antidepressant-like behavioral and neurochemical effects. In particular, rTMS enhances apomorphine-induced stereotypy and reduces immobility in the Porsolt swim test.[1] rTMS has been reported to induce electroconvulsive shock (ECS)-like changes in rodent brain monoamines, beta-adrenergic receptor binding, and immediate early gene induction.[2] The effects of rTMS on seizure threshold are variable and may depend on the parameters and chronicity of stimulation.[3] Pope and Keck have completed a series of studies using more focal TMS in rat models.[4] They have largely replicated earlier TMS animal studies using less-focal coils. However, even with the attempt at focal rat stimulation, the TMS-induced effects involve an entire hemisphere and cannot readily be extrapolated to what is happening in human TMS using focal coils.[5] In summary, TMS studies in animal models of stress, anxiety and depression have demonstrated antidepressant effects similar to those seen with ECS (analogous to human ECT) and other antidepressants. These studies, with one exception,[6] have not been very informative regarding the appropriate TMS use parameters for human clinical trials.

Several groups are considering performing analogous TMS animal studies using focal electrical stimulation, assuming that the induced electrical stimulation is actually what conveys the biological activity of TMS. However, creating electrodes that match the TMS field is a challenge, and the approach is subject to questions of comparative validity. A research group has designed TMS coils that weigh about 1 lb and are more focal than those currently produced (Epstein C, Davey K, Bohning D, personal communication, December 2002).[7] These may prove useful in animal TMS studies, with more focal stimulation than is currently done. At least one TMS manufacturer is advertising a small TMS coil for use with small animals such as mice or rats.

Combining Transcranial Magnetic Stimulation with Functional Imaging

Another method of evaluating TMS neurobiological effects for efficient therapeutic application is to combine TMS with functional neuroimaging. Combining imaging with TMS allows the physician to directly monitor TMS effects on the brain and to understand the varying effects of different TMS use parameters on brain function. Studies discussed elsewhere in this book suggest that TMS at different frequencies has divergent effects on brain activity.[8–12] Combining TMS with functional brain imaging promises to better delineate the behavioral neuropsychology of various psychiatric syndromes and some of the pathophysiologic circuits in the brain.

Several studies combining TMS with other neurophysiological and neuroimaging techniques have helped to elucidate how TMS achieves its effects in general and in psychiatric patients. Our group at MUSC developed and perfected the technique of interleaving TMS with blood oxygen level–dependent (BOLD) functional magnetic resonance imaging (fMRI), allowing for direct imaging of TMS effects with high spatial (1 to 2 mm) and temporal (2 to 3 seconds) resolution.[15–20] Another group in Germany has succeeded in interleaving TMS and fMRI in this manner, partially replicating the earlier work.[9,21] Work with this technology has demonstrated an intensity dose effect of TMS over the prefrontal cortex.[22,23] This had earlier been shown with TMS over motor cortex and is replicated each time a motor threshold is identified. An initial TMS/fMRI study found

that prefrontal TMS at 80% motor threshold (MT) produced significantly less local and remote blood flow change than did 120% MT TMS.[24] Strafella and Paus used PET to show that prefrontal cortex TMS causes dopamine release in the caudate nucleus[25] and has reciprocal activity with the anterior cingulate gyrus.[26] Our group at MUSC[22,27] and groups in Scotland[28] and Australia[29] have all shown that lateral prefrontal TMS can cause changes in the anterior cingulate gyrus and other limbic regions in depressed patients. Imaging studies have consistently demonstrated that TMS delivered over the prefrontal cortex has immediate effects in important subcortical limbic regions. The exciting work in the field over the next decade is to determine whether the initial TMS effect on cortex and the secondary synaptic changes in other regions differs as a function of mood state, cortical excitability, and other factors that may change resting brain activity.

Paired-pulse TMS is a useful tool for evaluating cortical excitability, and there are several exciting findings regarding excitability in psychiatric disorders.[30] A fundamental limitation with paired-pulse TMS is that it measures excitability within the motor cortex, because it uses motor evoked potentials (MEPs) as the neurobiological end point. Psychiatric uses of TMS would be greatly enhanced if the clinician could directly assess the cortical excitability of other brain regions. Bohning and colleagues[31] have shown the feasibility of performing paired-pulse TMS within an fMRI scanner, using the regional BOLD response as the dependent variable. This paired-pulse TMS/fMRI technique involves a paired-pulse TMS setup as in a clinical neurophysiological laboratory, with a TMS positioner for holding the coil against the scalp within the scanner. The investigator also must interleave the paired-pulse TMS with fMRI scanner acquisition in a single event or block design. Pilot work has involved extracting the blood flow changes beneath the coil and comparing these TMS-induced changes with a theoretical model. Figure 21–1 demonstrates the initial results with this technique. These preliminary data demonstrate the feasibility of interleaved paired-pulse TMS/fMRI. They also demonstrate that it may be possible to use the modulation of the BOLD response by pairs of TMS pulses to test intracortical inhibition and facilitation and to investigate brain communication at time resolutions greater than that of the 3-second lag hemodynamic response.[9]

Extending the more theoretical imaging work described previously, several studies have used imaging to try and understand the therapeutic behavioral effects seen over time with TMS, particularly in depression. In contrast to imaging studies with ECT, which have found that ECT shuts off global and regional activity,[32,33] most studies using serial scans in depressed patients undergoing TMS have found increased activity in the cingulate and other limbic regions.[27,28] However, two studies have found divergent effects of TMS on regional activity in depressed patients, as determined by the frequency of stimulation and the baseline state of the patient.[29,34] 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 reduced activity over time after chronic daily low-frequency stimulation. However, these two small sample studies have numerous flaws. 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 with ECT, for which the net effect of the ECT seizure is to decrease prefrontal and global activity.[32]

Combining TMS with functional imaging will likely continue to be an important method for understanding TMS psychiatric behavioral effects. Combination TMS and imaging will likely also evolve to be an important neuroscience tool for researching brain connectivity.[9,11,35–39]

Therapeutic Psychiatric Uses of Transcranial Magnetic Stimulation

Despite the lack of complete understanding of the pathophysiology of psychiatric disorders and with only limited knowledge of

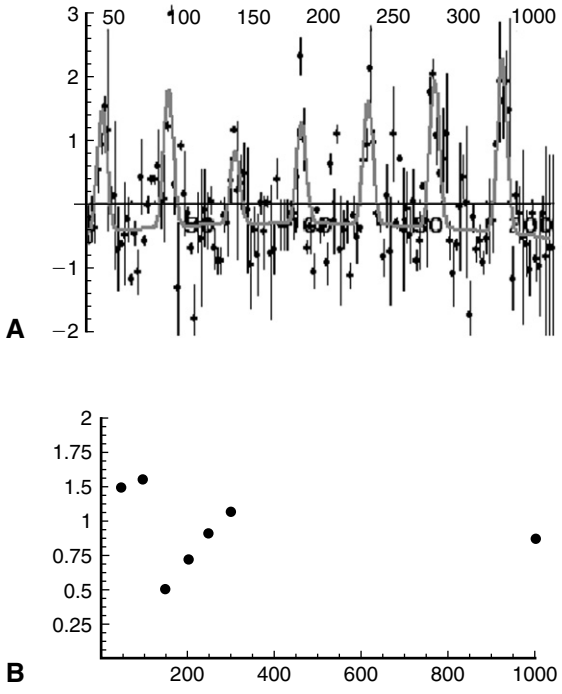

Figure 21–1 The paired-pulse transcranial magnetic stimulation/functional magnetic resonance imaging (ppTMS/fMRI) technique. These are blood oxygen level–dependent (BOLD) response data from directly underneath the TMS coil in motor cortex in two subjects. A mathematical model made of a hemodynamic response function multiplied by an exponential recovery function with independent amplitude scaling factors (relative to an inter-stimulus interval [ISI] = 1,000 amplitude) for the different ISI has been fit to the data and superimposed on the plots as a *thick line*. Further work is ongoing at shorter ISIs and using TMS over nonmotor regions. Although this is technically challenging and much work remains, ppTMS/fMRI could prove to be a useful tool in understanding the neurobiological effects of TMS and the pathophysiology of different neuropsychiatric disorders. The therapeutic uses of TMS in psychiatry have suffered because of inadequate understanding of disease pathophysiology and the neurobiological effects of TMS. Techniques such as this should improve future TMS therapeutic trials in psychiatry, making them more informed and focused in their hypotheses.

the translational neurobiologic effects of TMS, there has been much enthusiasm and controversy regarding TMS as a psychiatric treatment. The rapid launch of TMS in clinical trials was no doubt aided by the long history and widespread use of ECT. Although there has been much progress, no one understands how ECT works to treat depression,[40–44] although it remains clearly the most effective treatment for resistant depression. TMS was immediately adopted within psychiatry as a potentially more focal, nonconvulsive, and less-invasive method of ECT. With this background, it becomes clear why TMS was used initially in depression, despite there being other psychiatric disorders with a better defined and more regionally focused pathophysiology, such as obsessive-compulsive disorder (OCD).

Depression

Although there is controversy and much more work is needed, certain brain regions have consistently been implicated in the pathogenesis of depression and mood regulation.[45–52,53] These include the medial and dorsolateral prefrontal cortex, the cingulate gyrus, and other regions commonly referred to as limbic (e.g., amygdala, hippocampus, parahippocampus, septum, hypothalamus, limbic thalamus, insula) and paralimbic (e.g., anterior temporal pole, orbitofrontal cortex). A widely held

theory during the past decade has been that depression results from a dysregulation of prefrontal cortical and limbic regions.[50,51,54,55]

In the modern era, the first few attempts to use TMS as an antidepressant were not influenced by this regional neuroanatomic literature, and stimulation was applied over the vertex.[56–58] However, working within the prefrontal cortical limbic dysregulation framework outlined previously and realizing that theories of ECT action emphasize the role of prefrontal cortex effects,[59] one of us (MSG) performed the first open trial of prefrontal TMS as an antidepressant in 1995,[60] followed immediately by a crossover double-blind study.[61] 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 and in connected limbic regions, thereby alleviating depression symptoms.[62] Functional imaging studies performed after these initial clinical trials suggest that this hunch was correct.[63] Prefrontal TMS sends direct information to important mood-regulating regions like the cingulate gyrus, orbitofrontal cortex, insula, and hippocampus. 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 bridge from functional neuroimaging advances in circuit knowledge to the bedside as a focal, noninvasive treatment. Unfortunately, inadequate knowledge of the pathophysiologic circuit and of TMS effects has limited its use in this manner and much more work is needed in terms of the optimal anatomic location, TMS use parameters, and dosing regimen.

Since the initial studies, there has been continued interest in TMS as an antidepressant treatment. Multiple trials have been conducted from researchers around the world.[64,65] 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 sample sizes in these antidepressant trials are small (in all, less than 100 per trial) compared with industry-sponsored pharmaceutical trials of antidepressants. A thorough review of all of these trials is beyond the scope of this update. However, most of the more than 20 double-blind, randomized studies have found modest antidepressant effects that take several weeks to build. Not all TMS antidepressant treatment studies have been positive.[66]

Meta-analyses of Transcranial Magnetic Stimulation Antidepressant Effect

One way of succinctly reviewing the field of TMS as an antidepressant is to perform meta-analyses on the published trials. There have been five independent meta-analyses of the published or public TMS antidepressant literature, each varying slightly in the articles included and the statistics used.[67–71] Despite the differences in their methods, the results of all five meta-analyses are the same. Daily prefrontal TMS delivered over several weeks has antidepressant effects greater than sham treatment. For example, Burt and colleagues[67] 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 the studies directly comparing TMS to ECT. The effect size for TMS in these studies was greater than in the studies comparing TMS to sham, perhaps reflecting subject selection bias. The investigators suggested that perhaps TMS works best in patients who are also clinical candidates for ECT. The meta-analysis conducted by Kozel and George[69] was confined to published double-blind studies with individual data using TMS over the left prefrontal cortex. The summary analysis using all 12 studies that met criteria revealed a cumulative effect size of 0.53 (Hedge's d; range, 0.24 to 0.82), and the total number of subjects studied was 230. Kozel and George[69] then used a funnel plot technique to assess whether there is a publication bias in the literature, 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,

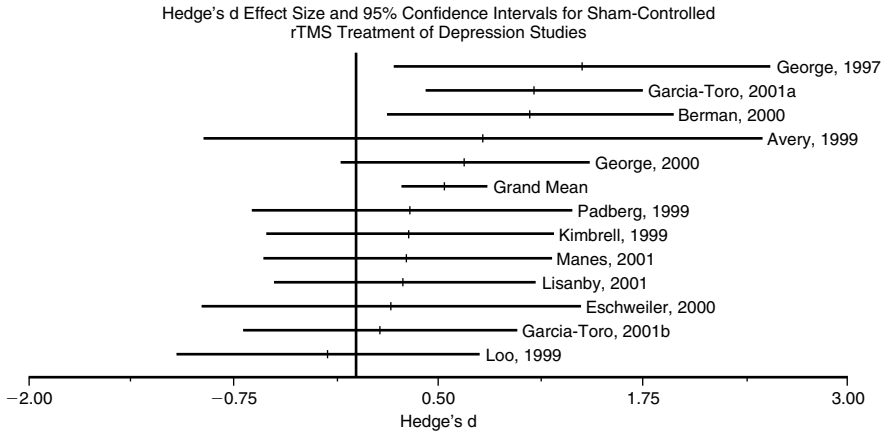

Figure 21–2 Size plot of the effect of prefrontal transcranial magnetic stimulation (TMS) as an antidepressant. This is a Forrest plot of the effect sizes of the sham-controlled studies of repeated (at least 2 weeks), daily left prefrontal TMS to treat depression. The effect sizes have varied widely, with all but one finding the effects significantly greater than the sham. The mean effect size is consistent with other antidepressant treatments. (From Kozel FA, George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation [rTMS] to treat depression. J Psychiatr Pract 2002;8:270–275.)

resembling a funnel.] The funnel plot indicated 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 (Fig. 21–2). These investigators then employed 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 (i.e., 55 studies with Rosenthal's method and 20 with Orwin's method). The most critical meta-analysis of the TMS antidepressant field was conducted using the guidelines put forth in the Cochrane library.[70] However, even this stringent meta-analysis included 14 trials suitable for their analysis and found that left prefrontal TMS at 2 weeks produced significantly greater improvements in the Hamilton Rating Scale than did sham.[70] For reasons that are not clear, despite finding a statistically significant antidepressant effect at 2 weeks, they conclude that there is no strong evidence of a TMS effect.

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 sham.

Transcranial Magnetic Stimulation Compared with Electroconvulsive Therapy

Although there is consensus that TMS has statistically significant antidepressant effects, a more important question is whether these effects are clinically significant. The meta-analyses previously discussed 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 to 0.40) are common in randomized controlled trials of novel antidepressants.[72] 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 ECT or rTMS. In an initial study, Grunhaus and colleagues[73] compared 40 patients who presented for ECT treatment and were randomized to receive 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. The same group replicated

this finding in a larger and independent cohort with an improved design.[74] Janicak and colleagues[75] 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), the length of treatment (3 to 4 weeks), the lack of a blind, and the lack of a sham control.[76] 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[77] reported a study comparing the antidepressant effects of standard ECT (three times per week), and one ECT per week followed by TMS on the other 4 weekdays. At 3 weeks, they found that both regimens produced similar antidepressant effects. Unfortunately, detailed neuropsychological testing was not performed, but one would assume that the TMS and ECT group had less cognitive side effects than the pure ECT group. The Israeli group found that relapse rates in the 6 months after ECT or rTMS were similar.[78] In sum, studies suggest that TMS clinical antidepressant effects are in the range of other antidepressants and persist as long as the clinical effects after ECT.

Transcranial Magnetic Stimulation and Sleep Deprivation Response

Psychiatrists have known for years that it is possible to transiently improve depression symptoms in depressed patients by keeping them awake all night. About one half of all depressed patients who are sleep deprived (SD) for one night report a substantial improvement in mood the following morning.[79] Unfortunately, more than one half of these subjects immediately relapse into depression when they next are allowed to sleep. This SD effect is remarkable for its speed of response (most other antidepressants, including ECT, take 2 to 3 weeks to improve mood) and because it is possible to predict who will respond to SD based on functional brain imaging assessing the resting activity in the cingulate gyrus.[80–82] Two studies have examined the relationship between sleep deprivation and TMS in depression. Padberg and colleagues[83] studied in an open trial whether the response to partial sleep deprivation might predict the clinical outcome of rTMS treatment. Thirty-three drug-free patients suffering from a major depressive episode underwent a partial sleep deprivation at least 5 days before rTMS and subsequently received 10 sessions of 10-Hz rTMS of the left prefrontal cortex. After rTMS, a significant overall improvement of 32% on the Hamilton Rating Scale for Depression was observed. Amelioration of depression after partial sleep deprivation was inversely correlated with improvement after rTMS, softly suggesting that those who responded to TMS were not those who responded to sleep deprivation. With this sample size, this was not significantly predictive. If these results were to replicate, an investigator could perhaps use a pre-TMS SD response to refine those getting TMS. Approaching this topic from a different perspective, another group used a controlled, balanced, parallel design to study whether rTMS, applied in the morning after partial sleep deprivation (PSD), is able to prevent depression relapse.[84] Twenty PSD responders were randomly assigned to receive active or sham stimulation for 4 days after sleep deprivation. Active stimulation prolonged significantly ($P < .001$) the antidepressant effect of PSD up to 4 days. This study suggests that rTMS may be an effective method to prevent relapse after depression improvement after partial SD or other antidepressant treatments[85] Further studies like these are needed, particularly given the role of pre-SD cingulate hyperactivity in predicting SD response and the multiple imaging studies showing that prefrontal TMS affects the cingulate acutely[22,24,26,86,87] and over the longer term.[88]

Transcranial Magnetic Stimulation as a Potential Adjunct to Other Antidepressant Therapies

Because of its noninvasiveness, some have wondered whether TMS might ultimately evolve into a treatment that would be given in addition to medications to speed their onset of action. This notion was particularly popular after an initial report of TMS antidepressant effects that occurred after just 1 week.[89]

These rapid responses have not been replicated despite many attempts, and it appears that TMS takes at least 2 weeks and probably longer to achieve maximum clinical effects.[76] There has never been a study showing faster onset of action of any two combined antidepressants, including ECT.[90] This is why it is not general clinical practice to start with combinations of antidepressant treatments. The sample sizes needed to demonstrate an additive or synergistic effect of TMS on top of a traditional antidepressant is unknown, but it would likely be more than 300. Nevertheless, at least two groups have used TMS as an adjunct treatment, with both failing to find an additive effect of TMS.[91,92] Both studies were underpowered to detect even a large and potentially clinically significant effect.

Other Thorny Issues

Although the literature suggests that prefrontal TMS has an antidepressant effect greater than sham and that the magnitude of this effect is at least as large as other antidepressants, many issues are not resolved. For example, it is unclear how best to deliver TMS to treat depression. Most, but not all,[65,93] studies have used focal coils positioned over the left prefrontal cortex. It is still not known whether TMS over one hemisphere is better than another 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.[60] However, 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.[94] An electroencephalographic montage, taking into account different skull sizes, would seem a better approach. However, it is unclear what scalp position to chose, resulting in the TMS coil being placed over which underlying cortical structure.

Most studies have stimulated with the intensity needed to cause movement in the thumb (i.e., MT). There is increasing recognition that higher intensities of stimulation are needed to reach the prefrontal cortex, especially in elderly patients, where prefrontal atrophy may outpace that of motor cortex, where the motor threshold is measured.[95–98] 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. There are virtually no data on using TMS as a maintenance treatment in depression.[85,99]

Transcranial Magnetic Stimulation to Treat Mania

Grisaru and colleagues in Israel delivered right or left prefrontal TMS to a series of bipolar affective disorder (BPAD) patients admitted to their hospital for mania.[100] 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 investigators concluded that TMS might be useful as an antimanic agent. However, 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. The investigators failed to replicate this antimanic effect in a follow-up study[101] and offered the suggestion that the antimanic effect of right prefrontal stimulation was a worsening (or antidepressant) effect of the group stimulated with left prefrontal stimulation.

Current State of Transcranial Magnetic Stimulation for Depression in Clinical Practice

TMS is a promising tool for treating depression acutely. It probably 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 an antidepressant treatment, it is still considered investigational in the United States by the Food and Drug Administration (FDA). Despite the body of work showing antidepressant efficacy, prefrontal TMS is not an approved treatment from the standpoint of the FDA. The FDA treats the data from each TMS manufacturer separately,

precluding consideration of the meta-analyses described earlier. A large-scale industry sponsored clinical trial designed for FDA approval is underway in the United States. The National Institutes of Mental Health (NIMH) is also funding a multisite trial. A small number of US, Canadian, and European psychiatrists are using TMS in clinical practice to treat depression under their general license to practice.

Review of Potential Antidepressant Mechanisms

How does TMS act to improve depression? The work done has provided evidence that prefrontal TMS produces immediate[24–26,102,103] and longer-term[27,104,105] changes in mood-regulating circuits. The original hypothesis about its antidepressant mechanism of action is still the most likely explanation.[22] What remains unclear is which specific prefrontal or other brain locations might be the best for treating depression and whether this can be determined with a group algorithm or requires individual imaging guidance. Much work remains to understand the optimum dosing strategy for the antidepressant effect of TMS. It is unlikely that the combinations of intensity, frequency, coil shape, scalp location, number of stimuli, or dosing strategy (e.g., daily, twice daily) used in the first decade of TMS as an antidepressant are the most effective for treating depression.[76] It is not understood how electrical stimulation of these circuits over time results in improvement of depression symptoms. The translational cascade of events remains undefined. Determining these answers using clinical trials alone would be a slow and expensive process. We hope that the work with TMS in animal models and functional imaging reviewed earlier will soon streamline this research area.

Some behavioral evidence from treatment trials is consistent with the functional imaging data showing repeated subtle changes in mood-regulating circuits. Szuba and colleagues[106,107] initially discovered that there is a subtle but statistically significant improvement in self-rated mood within each day over the 20 minutes of a daily TMS session (and that this is greater than with sham TMS). We found a nonstatistically significant trend confirming this in an independent study in bipolar depression.[108] A later clinical trial found this as well[109] and suggested that these subtle within-subject, within-session effects might predict eventual response. These three studies suggest that during each treatment session, the mood regulating circuit is being activated and slightly normalized. This gradual daily improvement then sums over several weeks when genuine clinical antidepressant effects emerge. Moreover, if they are important in eventual clinical response, one could consider dose-finding studies of different use parameters designed to find the parameters that maximally produced within-day changes. The parameters that produced the greatest within-day changes would be hypothesized to also be the most potent for eventual full treatment.

There are fewer data to suggest that TMS works to improve depression through activating normal anticonvulsant regulating systems—a widely held theory about the antidepressant mechanisms of action of ECT.[110] An appealing notion is that the brain "interprets" TMS-induced currents as potential seizures, with resultant activation of anticonvulsant cascades, which are tied to antidepressant efficacy. In support of this hypothesis, several animal studies have found that TMS has electroconvulsive shock (ECS)–like anticonvulsant effects.[111–113] However, there is only scant evidence to suggest that TMS has anticonvulsant effects in depressed patients. An initial open study found that the MT slightly increased during 2 weeks of TMS.[114] However, the MT does not always correlate with seizure threshold, and this was an open study with only small effects. Operator bias can influence MT determination, particularly with respect to coil location and angle. In a double-blind study, we examined for—and failed to find—a significant change in MT over the course of a TMS treatment trial.[108] Moreover, if TMS antidepressant efficacy were linked to its ability to initiate anticonvulsant cascades, the TMS use parameters closest to producing seizures would be predicted to be the most efficacious. However, there is no clear advantage of higher-frequency TMS,[115,116] even though it is clearly more likely to provoke seizures. Further work,

perhaps using surrogate markers such as MR spectroscopy–measured γ-aminobutyric acid (GABA), are needed to explore this hypothesized antidepressant mechanism of action.

Transcranial Magnetic Stimulation as a Treatment for Other Psychiatric Conditions

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

Schizophrenia

Several studies have used TMS to investigate schizophrenia without consistent replications of early findings, which were compounded by medication issues.[117–120] The syndrome of schizophrenia involves many different symptoms ranging from auditory hallucinations to paranoid thoughts to blunted and restricted affect. The functional neuroanatomy of these different symptoms appears different. TMS treatment studies in schizophrenia have tended to enroll schizophrenia subjects with one particular symptom and then apply TMS to a brain region based on group functional imaging studies. The best example of this is the work of Hoffman and colleagues,[121] who have studied schizophrenia patients with auditory hallucinations and have stimulated them daily for several weeks over the temporal lobe at low frequencies, hypothesizing that they might inhibit a pathologically active region. An initial open study found that two of the three patients reported almost a total cessation of hallucinations for 2 weeks after their treatment.[121] A follow-up study by the same group using a sham condition found improvement of hallucinations after TMS over the left auditory cortex for 10 days.[122] Although an independent group has found similar results,[123] these exciting results need replication in larger studies before final acceptance. The idea of focally using TMS to modify symptoms is attractive.[124] TMS studies on the negative symptoms of schizophrenia have not been as positive. A 1-day prefrontal TMS challenge study by Nahas and colleagues[125] at MUSC failed to find significant effects on negative symptoms. Similarly, a well-conducted sham controlled clinical trial failed to find a treatment effect greater than sham.[126]

Anxiety Disorders

In a randomized trial of left and right prefrontal and mid-occipital 20-Hz stimulation in 12 patients with OCD, Greenberg and coworkers[127] 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,[128] which has also been observed in patients with Tourette's disorder.[129] Somewhat surprisingly, OCD patients had a lowered MEP threshold in one study,[130] unrelated to intracortical inhibition, and which appears to replicate (Wassermann EM, personal communication, 2003). 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 sham.[131] In contrast, an open study of a group of 12 OCD patients refractory to standard treatments who were randomly assigned to right or left prefrontal fast rTMS found clinically significant and sustained improvement in a third of patients.[132] Further work is warranted testing TMS as a potential treatment for OCD.

McCann and associates[133] reported that two patients with post-traumatic stress disorder (PTSD) improved during open treatment with 1-Hz rTMS over the right frontal cortex. Grisaru and associates[134] similarly stimulated 10 PTSD patients over motor cortex and found decreased anxiety. Grisaru and colleagues also reported a positive TMS study in PTSD patients (Grisaru N, personal communication, May 2001). Further work is needed.

Chronic Pain

The peripheral and central pathways for pain recognition and regulation are well understood compared with other psychiatric conditions. It is surprising that TMS has not been more widely investigated as a potential treatment for pain. An interesting study hints of potential therapeutic uses of TMS.[135] Lefaucher and colleagues[135] built on neurosurgical studies that found that electrical stimulation of the motor region could alleviate chronic facial pain. They applied a 20-minute session of sub motor threshold rTMS over the motor cortex at 10 Hz using a real or a sham coil in a series of 14 patients with intractable pain due to thalamic stroke or trigeminal neuropathy. They assessed pain levels using a 0 to 10 visual analog scale from day 1 to day 12 after the rTMS session. A significant pain decrease was observed up to 8 days after the "real" rTMS session. It is unclear why stimulation of the motor region would alter sensory pain. Further studies in this area are needed to see if this effect replicates.

Magnetic Seizure Therapy

Another interesting TMS development within psychiatry involves deliberately inducing an ECT-like seizure using TMS coils. The discussion throughout this chapter has focused on using TMS to change brain function without inadvertently causing a seizure. TMS at high frequencies and intensities can cause seizures. ECT produces a seizure through direct electrical 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 one half of treatment-resistant patients. If TMS was used to induce an ECT-like seizure, it might be able to focus on the point of origin of the seizure and spare some brain regions from unnecessary exposure to electrical currents and seizure spread. The direct application of electricity to the scalp with ECT loses focality and power due to the impedance of the overlying tissue. After a proof of concept demonstration in primates,[136] Lisanby and colleagues used an enhanced device with four times the usual number of charging modules to induce seizures in depressed patients referred for ECT.[137] 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, and that their acute cognitive side effects were much less with MST.[138] 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.

Conclusion

TMS is a powerful new brain stimulation tool, with extremely interesting research and one confirmed and several putative therapeutic psychiatric potentials. Although TMS clearly has the ability to engage subcortical-limbic circuits and to produce immediate, intermediate, and long-term effects, its use as a therapy in psychiatry has been limited by incomplete understanding of TMS neurobiological effects and of the underlying pathophysiology of the psychiatric disorders. Further understanding of the ways by which TMS changes neuronal function, especially as a function of its use parameters, will improve its ability both to answer neuroscience questions as well as to treat psychiatric diseases.

Acknowledgments

The authors' work with TMS has been supported in part by research grants from NARSAD, the Stanley Foundation, the Borderline Personality Disorders Research Foundation (BPDRF), the Dana Foundation (Bohning), NINDS grant RO1-AG40956, and the Defense Advanced Research Projects Agency (DARPA). Drs. George, Nahas, Kozel, and Bohning, alone or in combination, hold several TMS-related patents. These are not in the area of TMS therapeutics, but rather are for new TMS machine designs and combining TMS with MRI.