EDITORIAL

Repetitive Transcranial Magnetic Stimulation: What Are the Next Steps?

In a priority communication in this issue, George et al (2000) present a carefully conducted small-sample, sham-controlled, masked study of the antidepressant efficacy of repetitive transcranial magnetic stimulation (rTMS). Using two active stimulation conditions (5 Hz vs. 20 Hz rTMS), they found that the percentage of patients who achieved at least a 50% reduction in scores on the Hamilton Rating Scale for Depression (HRSD) was greater among the combined active rTMS conditions (45%) than in the sham condition (0%). Significant advantages for active rTMS were also observed in self-ratings of depressive symptomatology and clinician ratings of anxiety. With justification, George et al (2000) conclude that rTMS delivered to the left dorsolateral prefrontal cortex (DLPFC) has antidepressant properties.

This study is one of several controlled (Berman et al 2000; George et al 1997; Grunhaus et al 2000; Klein et al 1999; Pascual-Leone et al 1996) and open (Figiel et al 1998; George et al 1995) investigations that have similarly shown that nonconvulsive magnetic stimulation of prefrontal cortical regions exerts antidepressant effects. These demonstrations are of more than academic interest. Presently, the Food and Drug Administration (FDA) is considering an application for approval of an rTMS device for routine clinical use in the treatment of major depression. If granted, such approval would result in widespread availability of rTMS, no longer requiring an institutional review board– and FDA-approved research protocol for its use. The American Medical Association is considering recommending a Current Procedural Terminology (CPT) code for rTMS, which, if enacted, may lead to third-party reimbursement for the procedure. The American Psychiatric Association is considering expanding the mandate of the Committee on Electroconvulsive Therapy (formerly the APA Task Force on ECT) to include the new physical interventions of rTMS and vagus nerve stimulation (Rush et al 2000). Thus, the enthusiasm about the initial findings with these new somatic treatments may be on the verge of altering practice and reimbursement patterns and policies.

Sufficient evidence has accrued that it is safe to conclude that rTMS (to the left DLPFC) exerts antidepressant effects, over and beyond placebo contributions (George et al 1999; Lisanby and Sackeim 2000). Nonetheless, like sleep deprivation, interventions may exert antidepressant effects and have doubtful clinical utility. The study by George et al (2000) is a case in point. Response was defined by a weak criterion, a 50% reduction in HRSD scores, without report on the number of patients who achieved remission (e.g., HRSD scores < 8). The active and sham groups did not significantly differ in the percentage reduction in HRSD scores, and on average the active treatment groups showed marked symptomatology following the end of rTMS (average HRSD = 18.3). In other words, although statistically significant, the antidepressant effects in the George and colleagues study were modest.

With few exceptions (Grunhaus et al 2000; Pascual-Leone et al 1996), this pattern has characterized virtually all controlled and uncontrolled studies of rTMS in major depression. There are reports of essentially no antidepressant effect (Loo et al 1999) and several reports of small to moderate effect size (Berman et al 2000; George et al 1997, 2000; Klein et al 1999). No controlled study of rTMS has shown that a substantial percentage of patients achieve remission following rTMS, and no rTMS study in major depression has included a controlled follow-up. Thus, the persistence of any benefit is unknown—that is, patients who improve with rTMS may relapse within days, weeks, or months. The efficacy of rTMS as a continuation treatment is unexplored.

Given the state of the evidence, it is premature for rTMS to be approved for routine clinical use. The fundamental issue is that establishing statistically significant differences relative to a sham control in quantitative measures does not guarantee clinical significance. The research to date has not shown that a substantial number of patients who receive rTMS show marked symptomatic improvement that is maintained for any meaningful period of time.

In this circumstance, one route in research will be to "purify" rTMS so that the antidepressant effects are more clinically robust. Essentially, there are two directions to be pursued: isolation of individual difference factors predictive of response and optimization of rTMS delivery. Some work has suggested that the presence of psychotic depression (Grunhaus et al 2000) and older age (Figiel et al 1998) are linked to inferior rTMS outcome. George et al (2000) suggest that patients with greater distance of the coil from the target site of stimulation, lower orbitofrontal (anterior cingulate) activity, and longer duration of current episode may be less likely to respond. At a practical level, of particular importance is the issue of treatment resistance. Patients usually consider rTMS only after disappointing results with pharmacologic treatment, and rTMS has often been presented as an alternative to ECT (Figiel et al 1998; Grunhaus et al 2000). Episode duration may serve as a surrogate (albeit poor) for measures of treatment

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resistance (Prudic et al 1996), and George et al (2000) suggest that longer episode duration was associated with poorer rTMS outcome. It is possible that the patients most likely to improve with rTMS are also those most likely to improve with standard pharmacologic treatment. Were this the case, much of the attraction of rTMS would be undone. Although the side effect burden of rTMS is slight, acute pharmacologic treatment has the advantage of a built-in mechanism for continuation/maintenance treatment (maintaining the same regimen) and is far less labor intensive than rTMS.

The second avenue for purifying the antidepressant effects of rTMS will focus on treatment parameters. The hope is that the initial demonstrations of antidepressant properties are only the tip of the iceberg. We have little, if any, certainty about where to stimulate, how to stimulate (intensity, frequency, waveform, train duration, intertrain interval), how frequently to stimulate (treatment schedule and duration), etc. Here, the parallel to ECT may be instructive. Despite producing a generalized seizure, it is well established that the efficacy and cognitive side effects of ECT are highly contingent on current paths and current density and electrical waveform (i.e., electrode positioning, stimulus dosage, and type of electrical stimulus) (McCall et al 2000; Sackeim et al 1987, 1993, 2000). Similarly, optimization of rTMS treatment parameters could conceivably result in the emergence of a clinically meaningful treatment modality. The findings of George et al (2000) that slow rTMS (5 Hz) tended to exert greater antidepressant effects than fast rTMS (20 Hz) underscore this possibility.

The isolation of key individual difference prognosticators requires large-sample studies. The parameter space for rTMS is extraordinarily large, and will also require large-scale studies to derive optimization of technique. In addition, presently all rTMS treatment studies have based the intensity (percent device output) of repetitive pulses to the prefrontal cortex on the threshold for eliciting a motor response to a single pulse delivered to the representation of a muscle in the primary motor strip. The validity of this approach is questionable, and it is used only because behavioral or physiologic markers of the adequacy/safety of repetitive stimulation to the prefrontal cortex have not been identified. Unfortunately, the industry supporting rTMS studies is small, limiting the possibility of large-scale research to refine indications and technical enhancement.

Whether or not rTMS finds a role in the routine treatment of major depression, the fact that it exerts antidepressant properties is extraordinary and presents novel opportunities to investigate the brain circuitry and physiology underlying antidepressant effects. Though far from established, it appears that very slow stimulation of the right DLPFC (Klein et al 1999) or fast stimulation of the left DLPFC (Berman et al 2000; George et al 1997, 2000; Grunhaus et al 2000; Pascual-Leone et al 1996) exerts antidepressant effects. There is some evidence that slow stimulation (<1 Hz) has a net inhibitory effect, whereas fast stimulation (>1 Hz) is excitatory. The supposition, yet to be rigorously tested, is that slow stimulation of the left DLPFC or fast stimulation of the right DLPFC lacks antidepressant properties (Pascual-Leone et al 1996). Were this the case, it would have major implications for theories regarding the role of functional brain asymmetry in the regulation of mood and antidepressant effects. More broadly, rTMS can be used as a probe to identify the circuitry of cortical regions involved in the regulation of mood and that subserve the relief of major depression.

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