Adding Low-Field Magnetic Stimulation to Noninvasive Electromagnetic Neuromodulatory Therapies

Mouhsin Shafi, Adam Philip Stern, and Alvaro Pascual-Leone

Driven by the limitations of traditional approaches to treating depression, there has recently been a surge of studies examining the utility of various noninvasive neuromodulation technologies in the treatment of depression. In this issue, Rohan *et al.* (1) report substantial improvement in mood immediately following one 20-minute treatment application of low-field magnetic stimulation (LFMS), performed with a novel portable tabletop device Figure 1. The stimulation paradigm they utilized consists of a 1-kHz oscillating magnetic field, adapted from the component of the magnetic resonance imaging protocol that they previously serendipitously found to have beneficial mood effects (2). In the current study, LFMS was applied in a double-blind, sham-controlled design to a heterogeneous group of 63 patients with either bipolar depression or major depressive disorder, and effects on mood were assessed primarily using a self-rated visual analog scale and observer-rated 17-item Hamilton Depression Rating Scale (HDRS-17). The authors found that real LFMS produced an immediate improvement on several scales across the combined population of depressed patients as compared with sham. Although they must be interpreted with caution and much additional work is necessary before the clinical utility of the approach can be determined, these results are highly intriguing.

A particularly striking aspect of the LFMS effect is that a mood elevation was found immediately after one brief treatment. Psychiatric treatments, including the neuromodulatory gold standard of electroconvulsive therapy (3), generally show much slower onset of effect, typically requiring weeks before separating from placebo in sham-controlled clinical trials. While ketamine has been shown to have a rapid antidepressant effect within 24 hours (4), durability and clinical utility need further elucidation. Rohan *et al.* (1) were able to demonstrate improvement in mood 10 to 15 minutes after completion of the intervention, although whether these effects had any durability could not be determined by their study design. Rapidity of onset can be an essential factor in the clinical realm, where there are few effective treatment options available to rapidly assist the high-risk acutely suicidal patient. The LFMS approach features other notable strengths, including a completely noninvasive approach with no known adverse effects. The absence of any physical sensation with stimulation enables fairly robust blinding, which is a benefit for future trials. The device is also small and portable, thus enabling potential future home use, and utilizes technology and physical properties that are relatively well known.

From the Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.

Authors MS and APS contributed equally to this work.

Address correspondence to Adam Philip Stern, M.D., Beth Israel Deaconess Medical Center, 330 Brookline Avenue, KS-158, Boston, MA 02215; E-mail: AStern2@bidmc.harvard.edu.

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However, there are a number of unanswered questions that cloud an assessment of the clinical significance of the present results. Most importantly, the study was not designed to measure the durability of mood improvement. Mood effects were evaluated immediately (10 to 15 minutes) after the intervention, but there were no subsequent assessments to see if the effects persisted for any meaningful period of time. A related concern is the unclear validity and reliability of the outcome measures over such short periods of time. For example, one of the two primary outcome measures, the HDRS-17, requires the clinician to assess the patient's symptoms of depression over the past week; it is difficult to know what reported changes in these measures mean when they are assessed less than an hour apart.

Another concern is the relatively small size and heterogeneity of the tested population. The authors included patients with bipolar disorder, as well as major depressive disorder. Given that the underlying psychopathologies and the pharmacologic treatments in these two populations are distinct, combining these populations into a single sample may confound the data in unclear ways. A related concern is the heterogeneity of the results between the different subpopulations; a significant benefit over sham was seen in the visual analog scale in the major depressive disorder but not the bipolar disorder subjects, whereas the opposite was observed on the Positive and Negative Affect Scale-Positive Affect, and significant effects were not present in either subpopulation (but were present across all subjects) in the HDRS-17. This variability underscores the need for reliable assessments in larger, more homogenous populations.

Neuromodulation based on electromagnetic induction has become broadly accepted in psychiatric therapeutics thanks to the approval by the Food and Drug Administration in 2008 of the Neuronetics device and more recently in 2013 of the Brainsway device for the treatment of medication-resistant depression. In the meantime, over 500 transcranial magnetic stimulation (TMS) devices are in operation in the United States alone. Alternative approaches are also being explored including electroencephalogram-synchronized TMS (sTMS). A pilot study of this intervention showed that subjects with either fixed or random frequency sTMS had significantly greater reductions in depression severity than those receiving sham (5). Like LFMS, sTMS is delivered with a portable device and the tolerability was outstanding. In addition, TMS is being actively investigated for a growing number of neurologic disorders (6).

How can we think about the LFMS findings in the larger context of the expanding field of noninvasive neuromodulation? LFMS induces electric fields that are of significantly lower strength (<1 V/m) as compared with more established forms of electromagnetic stimulation (≥ 100 V/m in electroconvulsive therapy, deep brain stimulation, and repetitive TMS), in which the electric field at the target site is of sufficient magnitude to directly induce neuronal depolarization (7). In contrast to LFMS, deep brain stimulation and TMS have a more focal field of stimulation and aim to target specific neural networks. As a result, the mechanism

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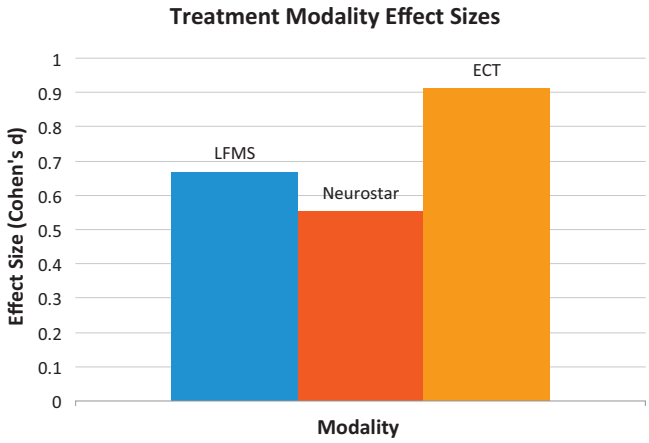

Figure 1. Low-field magnetic stimulation calculated from [1]; Neurostar [10]; electroconvulsive therapy [3].

by which LFMS could be exerting a behaviorally relevant effect is highly undefined. The authors suggest that the effect seen from LFMS may stem from changes in membrane potential in the dendritic cortex in layers 5 and 6, which project to limbic and other subcortical regions. What is evident, however, is that the device produces a global electric field that is likely affecting a wide array of cortical brain structures. With this widespread approach, it is also unclear if specific neuroanatomical structures or functional neural networks may be implicated in the observed behavioral effect. In the absence of a putative neural substrate for the observed effect, moving directly to large-scale clinical trials may be risky and in conflict with recent National Institute of Mental Health directives calling for assessments of engagement of a defined neurobiologic target or mediator. Further investigation into the potential mechanisms of action of this modality could better inform the approach and also potentially allow for experimental optimization of parameters to maximize any potential behavioral effect.

The consideration of low-strength magnetic fields for modulation of biological activity is not new. A recent review in *Cochrane Database of Systematic Review* of electromagnetic fields used in the treatment of osteoarthritis showed that electromagnetic field treatment may provide moderate benefit with regard to pain relief (8). Low-frequency electromagnetic fields have also been shown to have anti-inflammatory and neoangiogenic effects that can contribute to wound healing (9). The biological effects of magnetic fields are diverse, and the potential applications for this approach are therefore quite broad and largely undefined.

Despite all of the uncertainties, the results described by Rohan *et al*. (1)—in particular the rapidity of the response—are highly intriguing and add a novel paradigm to the repertoire of neuromodulation techniques that may have therapeutic utility in neuropsychiatric diseases. It is unclear at this time if these approaches achieve their antidepressant effects through a common mechanism or whether their approaches may in some ways be complementary. The benefit from combining neuromodulation techniques with conventional behavioral and/or pharmacologic therapy is also an area that needs further exploration. Future research should also be directed toward an evaluation of the neural substrates and functional networks modulated by these different techniques, optimization of the stimulation parameters to maximize the clinical effect, and an assessment of how these various therapeutic modalities can be integrated together.

If the results described in this study are replicated in larger studies and the effects are shown to be durable, LFMS would be a welcome addition to the clinical armamentarium in the treatment of depression, may find application in other psychiatric and neurologic diseases, and may help to inform and guide us toward future directions in neuromodulation.

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