Rapid Mood-Elevating Effects of Low Field Magnetic Stimulation in Depression

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Background: We previously reported rapid mood elevation following an experimental magnetic resonance imaging procedure in depressed patients with bipolar disorder (BPD). This prompted the design, construction, and testing of a portable electromagnetic device that reproduces only the rapidly oscillating (1 kHz, <1 V/m) electromagnetic field of the experimental procedure, called low field magnetic stimulation (LFMS).

Methods: We used a randomized, double blind, sham controlled treatment protocol to study the effects of LFMS in a large group of stably medicated, depressed patients with either BPD ($n = 41$) or major depressive disorder ($n = 22$). Subjects received a single, 20-minute treatment. Change in mood was assessed immediately afterward using a visual analog scale (VAS), the 17-item Hamilton Depression Rating Scale (HDRS-17), and the Positive and Negative Affect Schedule scales.

Results: Substantial improvement (>10% of baseline) in mood was observed following LFMS treatment relative to sham treatment for both diagnostic subgroups for our primary outcomes, the VAS and the HDRS-17. These differences were not statistically significant in primary analyses stratifying by diagnosis but were significant in secondary analyses combining data across the two diagnostic groups ($p = .01$ VAS, $p = .02$ HDRS-17). Rapid improvement in mood was also observed using the Positive and Negative Affect Schedule scales as secondary measures (positive affect scale $p = .02$ BPD, $p = .002$ combined group). A finite element method calculation indicates a broad penetration of the LFMS electric field throughout the cerebral cortex.

Conclusions: Low field magnetic stimulation may produce rapid changes in mood using a previously unexplored range of electromagnetic fields.

Key Words: Bipolar depression, depression, field, electromagnetic field, rapid antidepressant, therapy

Depression is a common and often recurrent disease, with a lifetime prevalence rate in the United States of over 20% (1,2), and is estimated by the World Health Organization to be the leading cause of disease-associated disability in developed countries worldwide (3). Bipolar disorder (BPD) is distinguished from major depressive disorder (MDD) by the presence of episodes of abnormally elevated mood (4). However, it is the depression that is the primary cause of disability and death in both these disorders (5).

Antidepressant drugs are effective in relieving depression in many patients (6) but have limited efficacy overall (7,8); fewer than 40% of patients with MDD in controlled clinical trials have complete remissions (9–11). Even in depressed patients who do experience remissions, relapse rates are very high (37% to 70% within the first year) (12). Many depressed patients are considered treatment resistant, with 33% failing to remit after 3 or more treatment trials (13,14). Patients with BPD often have treatment-resistant depression and risk the induction of mania with treatment (15). There are few effective treatments for these treatment-resistant patients (5,16).

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Received Apr 1, 2013; revised Sep 18, 2013; accepted Oct 12, 2013.

A limitation of currently available antidepressant therapies, including antidepressant drugs, electroconvulsive therapy (ECT), or repetitive transcranial magnetic stimulation, is that they have little immediate therapeutic effect. Typically, antidepressant drugs require a minimum of 4 to 6 weeks to exert a clinically meaningful improvement in mood (17). Even ECT, which has remission rates ≥65% in many studies, requires two to three treatments per week for 3 to 4 weeks to achieve its full effect (18–20). This time lag to clinical response leaves patients vulnerable to the often disabling symptoms of depression, including a high risk of suicidal behavior during the first weeks of treatment (21). Rapid relief from depression has been reported following intravenous infusion of ketamine (22,23) or scopolamine (24,25), deep brain stimulation (26–29), or sleep deprivation (30). In most cases, these rapid responses are transient, and durable responses have a delay that is more typical of standard antidepressant medications. Few rapid antidepressant treatments have been studied in BPD. These findings of rapid antidepressant responses, even in treatment-resistant patients, have stimulated considerable interest in the potential to develop rapidly acting treatments without the delayed onset of currently available treatments.

Low field magnetic stimulation (LFMS) uses time-varying magnetic fields that are within clinical magnetic resonance imaging (MRI) guidelines but that differ from those used in structural or functional MRI (fMRI) in their waveform, frequency, and strength (31). Low field magnetic stimulation delivers a magnetic field waveform that induces a low, pulsed electric field (≤1 V/m, 1 kHz) in the brain. Following the serendipitous observation of rapid mood improvement in bipolar depressed patients undergoing an experimental magnetic resonance spectroscopic imaging procedure (MRSI) (32), a small sham-controlled study in BPD patients suggested that these dynamic, relatively weak electromagnetic fields could induce rapid improvements in mood (31).

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2013.10.024

One of the dynamic components of the gradient field in the MRSI protocol was postulated to mediate this rapid antidepressant effect (see Methods and Materials). A prototype system containing a small MRI-style coil was subsequently used to reproduce these electromagnetic pulses for preclinical studies. Antidepressant-like behavioral effects of LFMS were demonstrated in the forced swim test (33), an animal model sensitive to antidepressant treatments (34).

Prompted by our preliminary clinical findings in depressed BPD patients, as well as the forced swim test data in rats, we hypothesized that an LFMS device that produced this waveform would rapidly improve depressed mood in patients with either BPD or MDD. We designed and constructed this LFMS device and calculated the estimated distribution and penetration of the LFMS-induced electromagnetic fields in the brain using the finite element method (FEM). We then conducted a randomized, double blind, sham-controlled study of LFMS using this new device in a large group of stably medicated, but still symptomatically depressed, BPD and MDD patients and observed rapid (within 20 minutes) elevation of mood.

Methods and Materials

Subjects

Sixty-three patients ages 18 to 65 who met DSM-IV criteria for either BPD or MDD (35) and who were in a current episode of depression, defined as having a score greater than or equal to 17 on the 17-item Hamilton Depression Rating Scale (HDRS-17) (36), contributed data to the analysis. All patients contributing data (mean baseline HDRS-17 score = 22.4 $\pm$ 4.2) were on a stable regimen of antidepressant or mood-stabilizing medications for at least 6 weeks before randomization. Eligible patients were randomly assigned in a 1:1 ratio to either active LFMS or sham treatment in permuted blocks of 10 within diagnostic strata (MDD and BPD). All procedures were reviewed and approved by the McLean Hospital Institutional Review Board, and all subjects provided informed consent before enrollment.

Potentially qualifying subjects participated in a screening visit. They provided informed consent, had their diagnosis confirmed, and were interviewed by a physician to determine eligibility, including ability to give consent. Eligible subjects received a physical exam and had their mood rated using the HDRS-17 and Young Mania Rating Scale (for BPD subjects). Qualified subjects then had a treatment visit scheduled. During their treatment visit, subjects had their pretreatment mood assessed with the HDRS-17, visual analog scale (VAS), and Positive and Negative Affect Schedule (PANAS), followed by either 20 minutes of active or sham LFMS. Following the treatment, subjects were observed for 10 to 15 minutes, after which the HDRS-17, VAS, and PANAS were administered again for posttreatment mood ratings. Subjects were asked about any sensation or discomfort after treatment and were contacted 1 week after the treatment visit by telephone, for safety purposes only, not for clinical ratings. Detailed clinical procedures are presented in Supplement 1.

Characteristics of the sample at baseline, including medication details, are presented in Table 1 and were compared using the Wilcoxon rank-sum tests (ordinal and continuous variables) and Fisher's exact tests (categorical variables). There were no significant differences in demographic characteristics, medication usage, or baseline clinical ratings between the active and sham groups, either for BPD, MDD, or the combined sample. Most subjects were taking multiple medications during the study. Safety data, including reported adverse events, were collected on all subjects. There was one report of hypomania the day following treatment in a BPD subject that was determined to be unlikely to be related to treatment because this subject received a sham treatment. There were two reports of dizziness during the venipuncture at the initial physical exam. Forty-four additional patients were treated with LFMS in an exploratory group. These subjects did not satisfy the study enrollment criteria, due to either subthreshold HDRS-17 scores (less than 17) or comorbid psychiatric conditions such as posttraumatic stress disorder or obsessive-compulsive disorder. As these additional patients were treated for exploratory, primarily safety, purposes and fell under separate institutional review board approval, they were excluded from the data analysis of this report.

Table 1. Subject Demographics, Medication Profiles, and Baseline Clinical Ratings for the Patients Entered in the LFMS Trial

	Bipolar Disorder			Major Depression			Combined Sample		
	Active	Sham	*p*	Active	Sham	*p*	Active	Sham	*p*
n	21	20		13	9		34	29	
Demographics									
Female	15	10	.21	9	4	.38	24	14	.12
Age	42.5 (12.1)	43.6 (12.6)	.64	47.1 (13.5)	48.8 (10.0)	.97	44.2 (12.7)	45.3 (11.9)	.68
Medication									
Antidepressants	14	14	.74	12	9	1.00	26	23	.76
Antipsychotics	13	11	1.00	6	5	1.00	19	16	1.00
Anticonvulsants	16	15	1.00	5	3	1.00	21	18	1.00
Benzodiazepines	11	8	.55	7	6	.67	18	14	1.00
Baseline Clinical Ratings									
HDRS-17	23.8 (5.1)	22.2 (3.7)	.36	20.6 (2.6)	22.4 (4.2)	.33	22.6 (4.5)	22.3 (3.8)	.93
VAS	6.3 (1.6)	6.3 (1.7)	.98	5.1 (2.0)	6.9 (2.3)	.07	5.8 (1.9)	6.4 (1.9)	.22
PA (PANAS)	18.9 (4.7)	21.1 (7.0)	.41	21.4 (10.1)	19.6 (6.1)	1.00	19.8 (7.3)	20.6 (6.6)	.52
NA (PANAS)	26.4 (9.1)	22.7 (7.8)	.30	21.7 (8.8)	22.6 (6.0)	.48	24.6 (9.2)	22.6 (7.2)	.67

Values are mean (SD) or *n*. Medications are reported according to current prescription; many subjects had multiple prescriptions. *p* values are from Wilcoxon rank-sum test (continuous and ordinal variables) or Fisher's exact test (categorical variables) comparing active treatment with sham treatment. Age and medication data are missing for one patient with BPD.

BPD, bipolar disorder; HDRS-17, 17-item Hamilton Depression Rating Scale; LFMS, low field magnetic stimulation; NA, negative affect; PA, positive affect; PANAS, Positive And Negative Affect Schedule; VAS, visual analog scale.

Outcome Measures

The primary outcome measures were a self-rated VAS, designed to be responsive to an immediate change in mood, and the observer-rated HDRS-17 (36), commonly used in clinical studies of antidepressant treatments. Both scales were completed just before and following active or sham LFMS treatment. The HDRS-17 was chosen to allow comparison with standard antidepressant treatments, even though several of its items would not be expected to change rapidly. Nonetheless, all items in the HDRS-17 were administered each time. Changes in the two self-rated PANAS scales, the positive affect (PA) and negative affect (NA), were used as secondary outcome measures to further assess rapid changes in specific aspects of mood and affect (37).

LFMS Device

This study employed a portable tabletop LFMS device that generated the time-varying electromagnetic fields of LFMS as discovered in studies in a magnetic resonance scanner. The LFMS device consists of a magnetic coil, an amplifier, waveform generator, and computer for control and for enforcement of the blind. It is designed to deliver the target fields at the end of the device, not in its center, allowing patients' heads to be less enclosed. The LFMS device has been designated a nonsignificant risk device by the Food and Drug Administration. The LFMS device is shown in Supplement 1.

The magnetic field generated by the LFMS device was adapted from the readout component of the MRI protocol in the original study, which resembles the readout in an fMRI acquisition. This component was chosen as the most likely to mediate the observed effect on mood because the electric field pulses that it induces have millisecond time scales that are compatible with neuronal activity (38) and because of the comparatively large number of these pulses that are produced during the treatment. The similarity of the LFMS waveform to fMRI readout waveforms, which are known to produce peripheral nerve stimulation, was also a factor in the selection. The static and radiofrequency magnetic fields in the MRI system were not considered as sources for the antidepressant effect, in part because they were also present in the original study in the sham treatment, which had no effect.

The LFMS magnetic field waveform is a train of alternating trapezoids with ramp times of 256 microseconds and peak dwell times of 768 microseconds. These magnetic field pulses are produced in .5 second bursts every 2 seconds for 20 minutes. The electric field, which is described by the time derivative of the magnetic field, is a series of 256 microsecond square pulses of alternating sign, delivered each 1024 microseconds with the same burst pattern and is shown in Figure 1. The electromagnetic field distribution is similar to that of a transverse gradient coil in an MRI system. A representative description of the field distribution based on the device design in the target region can be made using the lowest order of a quasistatic approximation:

$$\vec{B}(\vec{r},t) = G(t)(\hat{x}z+\hat{z}x)$$

$$\vec{E}(\vec{r},t) = E_0(t)\hat{y}+E_2(t)(\hat{x}2xy+\hat{y}2(z^2-x^2)-\hat{z}2yz)$$

The coefficients of this expansion were calculated from a grid of field values that were evaluated from the LFMS device design. The values for the coefficients for the LFMS device are G = .95 G/cm, E_0 = .72 V/m, E_2 = 14.1 V/m^3, and the gradient slew rate is dG/dt = 74.2 T/m/s. Magnetic fields in the LFMS device are less than 20G.

The coil in the LFMS device produces a faint sound during operation, but there is no physical sensation associated with its use. The coil sound is readily duplicated during sham treatment but no electromagnetic fields are produced, assuring an adequate sham control and maintenance of the double blind.

Data Analysis

Because our preliminary study investigated the mood-elevating effects of LFMS in BPD patients only, we did not have a strong basis for choosing a priori between a statistical analysis stratified by diagnosis and a statistical analysis combining data across diagnostic groups. Recognizing that BPD and MDD have some unique pathophysiologic and etiologic features and that treatment response can differ between BPD and MDD, our primary statistical analysis tested for treatment effects separately in BPD and MDD. A secondary analysis combined data across the

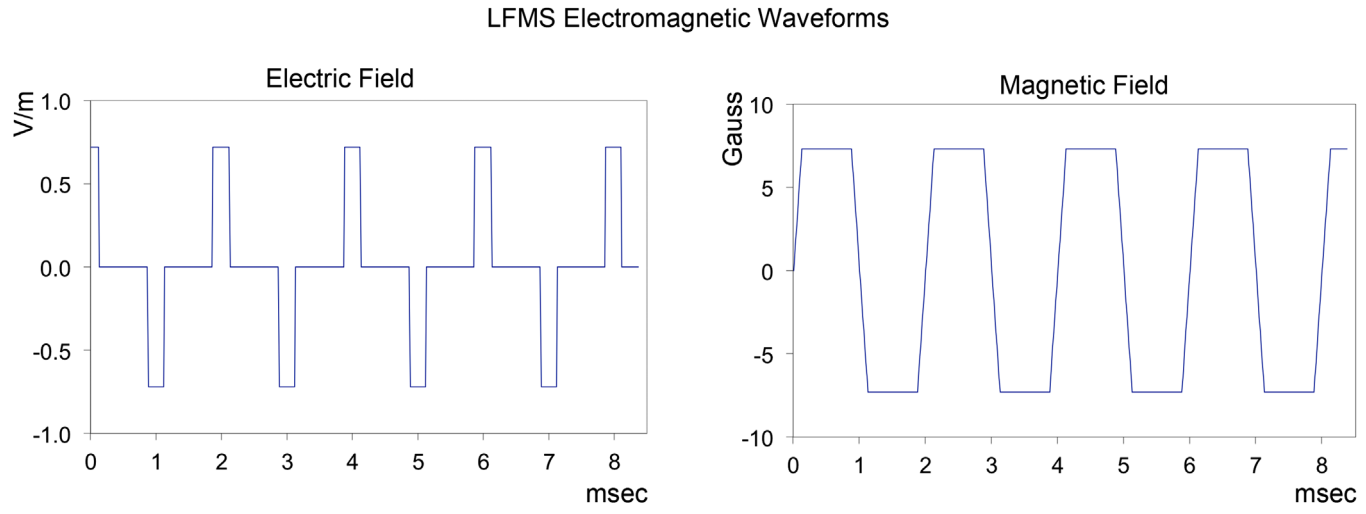

Figure 1. The magnetic and electric field waveforms produced by the low field magnetic stimulation (LFMS) device. Electric fields are produced in 256 microsecond pulses separated by 1 millisecond by the tabletop LFMS device. Magnetic fields are sustained for 1 msec with 256 microsecond ramps between peak values. The simple, regular electric field pulses are made possible by the fast transitions of the sustained magnetic field pulses. These plots represent time courses of the free-space fields at a representative point on the surface of the head; field strengths within the device vary spatially and are changed by the presence of a patient's head, as illustrated in Figure 3.

diagnostic groups, conditional on observing comparable effect sizes in our primary analysis.

For our primary statistical analysis, linear regression with baseline score and treatment as covariates compared mean rating changes between LFMS and sham exposure for each primary (VAS, HDRS-17) and secondary (PANAS scales) outcome measure. Robust heteroscedastistic-consistent (type HC3) standard errors were used in place of ordinary least squares regression standard errors to guard against biased standard error estimation (39,40). Our analytic approach was otherwise equivalent to analysis of covariance. Models for our secondary analysis combining data across diagnostic groups were identical to those for the primary analysis except that diagnosis and diagnosis × treatment interaction (if significant at the $p = .10$ level after multiple testing correction) were included as additional predictors. Bonferroni multiple testing corrections were applied separately to results for our primary and secondary outcomes (that is, statistical significance required uncorrected $p < .0125$ for stratified analysis, $p < .025$ for combined analysis). Confidence intervals and p values reported in the text reflect Bonferroni multiple testing adjustments; nominal p values are presented in the tables. Analyses were conducted using Stata software, version 11 (StataCorp, Plano, Texas). All statistical tests were two-sided.

Electromagnetic Field Analysis Methods

To estimate the probable magnitude, degree of penetration, and anatomic location of the LFMS-induced electromagnetic fields, we used a finite element method calculation (COMSOL; Comsol, Inc., Burlington, Massachusetts) to estimate these fields in the presence of a weakly conducting head. An anatomic magnetic resonance image (T1 contrast, 1 mm resolution) of a 26-year-old woman was used as a model and its interior was represented as a mesh of nodes within the FEM program. A conductivity value was assigned to each node to form a continuous conductivity map. The electromagnetic fields were calculated using a current distribution on a 35 cm diameter cylindrical surface with periodic longitudinal boundary conditions to model the coil. This mathematical model differed from the

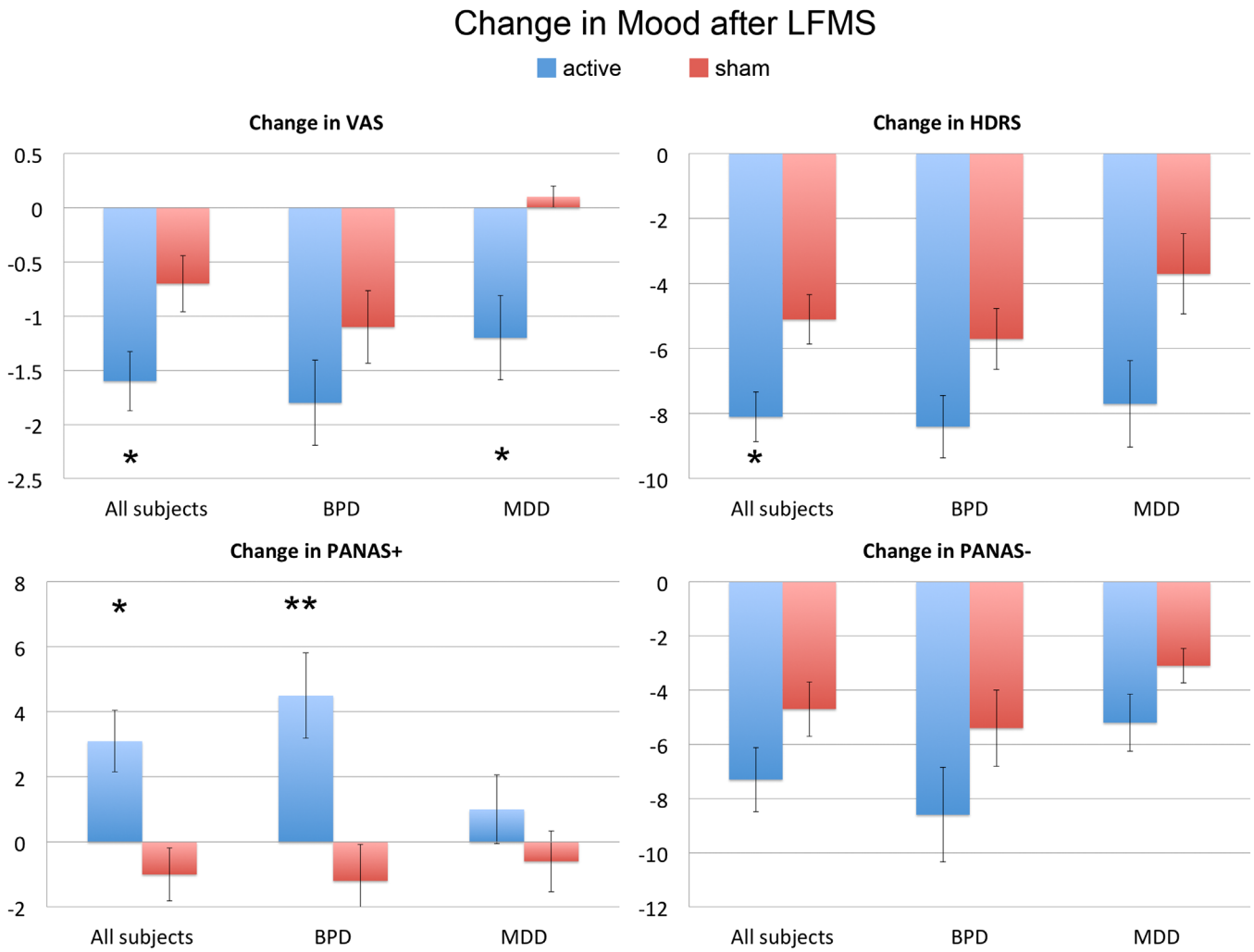

Figure 2. Change in mood after a single 20-minute application of low field magnetic stimulation (LFMS). Subjects had either bipolar disorder (BPD) or major depressive disorder (MDD) by DSM-IV criteria and were currently depressed (17-item Hamilton Depression Rating Scale [HDRS-17] ≥17). All subjects were administered active or sham LFMS treatment for 20 minutes in a randomized double blind protocol. Results are shown for the primary outcome measures (visual analog scale [VAS] and HDRS-17) and the secondary outcome measures (Positive and Negative Affect Schedule [PANAS]), and for the diagnostic subgroups of BPD ($n = 41$) and MDD ($n = 22$) patients as well as for the combined group ($n = 63$). A negative change indicates improvement in mood in the VAS, HDRS-17, and negative affect scale; a positive change indicates improvement in mood in the positive affect scale. Statistical analyses were carried out as described in the text and are presented in Table 2. Statistical significance after Bonferroni correction: *$p < .05$; **$p < .01$.

physical coil with respect to its longitudinal symmetry; to accommodate this difference, the FEM results presented here have been scaled so that the source magnetic field gradient values in the FEM matched the values calculated from the device design (.95 G/cm). Further details of the FEM calculation are presented in Supplement 1.

Results

Rapid, Mood-Elevating Effects of LFMS

Raw mean changes in mood rating scores by diagnosis and treatment condition are presented in Figure 2, with corresponding model-estimated changes presented in Table 2. Improvements in both self-rated (VAS) and observer-rated (HDRS-17) mood were greater for active than sham treatment for all outcome measures and patient subgroups. These differences were not statistically significant in the stratified analyses, in which the treatment subgroups were relatively modest in size. However, they reached significance when the data were combined across diagnostic groups. Mean improvements in VAS score were greater for active than sham by .8 points for BPD (95% confidence interval [CI] −.6:2.1, $p = .60$), 1.6 points for MDD (95% CI −.4:3.6, $p = .17$), and 1.1 points (95% CI .2:1.9, $p = .01$) for the combined sample. Mean improvements in HDRS-17 score were greater for LFMS than sham by 2.5 points for BPD (95% CI −1.2:6.2, $p = .34$), 3.2 points for MDD (95% CI −3.3:9.6, $p = .74$), and 3.1 points (95% CI .5:5.8, $p = .02$) for the combined sample. The HDRS-17 is typically used for mood assessment over longer timescales and some of its items require responses that summarize symptoms over multiple days. Thus, the change in mood rating observed was not surprisingly concentrated in the short timescale response items. Details of the HDRS-17 response by individual item are presented in Supplement 1.

Consistent with the results for our primary outcomes, we observed a greater improvement in the self-rated PANAS PA scores (reflecting decreased ratings of depression) associated with active LFMS for both BPD and MDD patients. The difference was statistically significant for BPD patients alone and for the combined sample but not for MDD patients alone. Mean improvement in the PA scale was greater for LFMS than sham treatment by 5.0 points for BPD (95% CI .8:9.2, $p = .02$), 1.7 points for MDD (95% CI −2.6:6.0, $p = .89$), and 4.1 points (95% CI 1.3:6.9, $p = .002$) for the combined sample. Relative improvement in NA scores (reflecting decreased ratings of anxiety and subjective distress) was more modest than for PA scores for BPD and changes in the NA score observed in the combined sample were not statistically significant. Mean improvement in the NA scale was greater for active than sham treatment by 1.3 points for BPD (95% CI −4.1:6.8, $p = 1.0$), 2.2 points for MDD (95% CI −1.3:5.8, $p = .38$), and 2.0 points (95% CI −1.1:5.1, $p = .29$) for the combined sample. There were no significant interactions between treatment and diagnosis for the four scales used in our study for the combined sample; all results reported are for models without interactions.

Subjects were contacted by phone at 1 week to ascertain patient well-being and safety; there was no attempt to formally assess mood during this call. Thirty-five subjects were successfully contacted and 28 subjects could not be contacted after three calls or messages. No side effects or adverse events of the LFMS protocol were reported.

Electromagnetic Field Results

The electric field distribution within the head during LFMS was found to be substantially reduced compared with the fields calculated in free space, due to shielding charges that arise in the scalp and other surfaces. In the absence of a subject, free space electric fields of .51 V/m were calculated to exist in the center of the device and ranged to .75 V/m at a radius of 8 cm. However, when shielding effects from the subject's head were included, electric fields on the order of .25 V/m were calculated to have penetrated to cortical regions of the brain and fields of less than .05 V/m were calculated to exist in subcortical regions. The electric field amplitude thus decreased sharply away from the scalp, and the primary location for the LFMS electric fields was determined to lie within the cortex. Figure 3 displays the magnitude of the LFMS-induced electric field in the cerebral cortex, visualized in transverse slices of the model embedded within a surface wire mesh.

Discussion

Consistent with our earlier MRI-based study in patients with BPD (31), we observed immediate improvement in mood in a group of 63 stably medicated depressed patients with either BPD or MDD following relatively brief exposure to a rapidly oscillating time-varying low-strength electromagnetic field referred to as LFMS. Using a portable tabletop device to deliver the magnetic pulse train adapted from the previous MRSI protocol and using two self-rated and one observer-rated instrument to measure mood, we demonstrated a very rapid improvement in mood in a double blind sham-controlled study. It is important to underscore that our study

Table 2. Mean Score Changes (Robust Standard Errors) Following Active or Sham Treatment by Diagnosis and for Both Diagnostic Groups Combined

	Bipolar Disorder ($n = 41$)			Major Depression ($n = 22$)			Combined Sample ($n = 63$)		
	LFMS	Sham	*p*	LFMS	Sham	*p*	LFMS	Sham	*p*
Primary									
VAS	−1.81 (.37)	−1.05 (.35)	.15	−1.33 (.53)	.25 (.25)	.04	−1.66 (.29)	−.60 (.23)	.006[a]
HDRS-17	−8.30 (1.00)	−5.79 (1.07)	.09	−7.19 (1.44)	−4.02 (1.54)	.19	−8.13 (.87)	−5.02 (.78)	.009[a]
Secondary									
PA	4.18 (1.37)	−.79 (.93)	.004[a]	1.05 (1.07)	−.63 (1.11)	.30	3.16 (.93)	−.94 (.79)	.001[b]
NA	−7.66 (1.45)	−6.31 (1.39)	.52	−5.28 (1.10)	−3.04 (.63)	.10	−7.00 (1.02)	−5.00 (.91)	.15

Negative changes indicate improvement in mood for all scales except the PA scale (Positive and Negative Affect Schedule). Means are estimated from linear regression models with mean-centered baseline ratings (bipolar disorder, major depression, and combined sample) and diagnosis (combined sample only) as covariates; *p* values are unadjusted for multiple testing; footnotes indicate statistical significance after Bonferroni correction. Due to missing postbaseline HDRS-17 ratings, sample sizes for HDRS-17 changes were 39 for bipolar disorder and 19 for major depressive disorder.

HDRS-17, 17-item Hamilton Depression Rating Scale; LFMS, low field magnetic stimulation; NA, negative affect; PA, positive affect; VAS, visual analog scale.

[a] $p < .05$.

[b] $p < .01$.

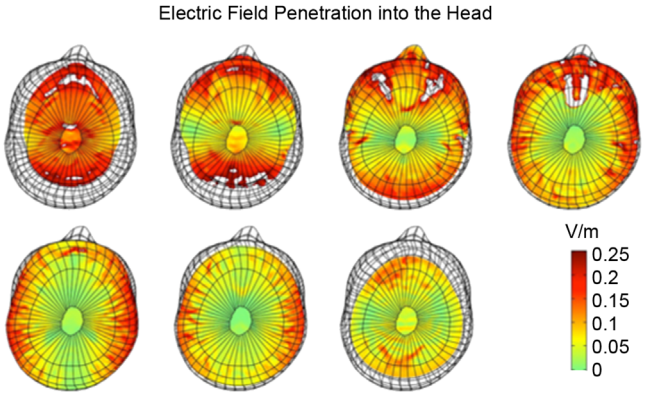

Figure 3. Electric field penetration of low field magnetic stimulation (LFMS) into the cortex. The magnitude of electric fields in seven transverse slices of the brain during LFMS is shown with a wireframe model of the outside surface of the head superimposed to provide context. Fields were calculated using the finite element method (FEM) (62) with a magnetic resonance imaging based model of the human head positioned inside a longitudinally symmetric and periodic model of the LFMS coil. Free space electromagnetic fields were first calculated and then a seven-tissue conductive model of the head was added to the calculation to include shielding effects introduced by the head, especially scalp, muscle, and bone. Finite element method results were calibrated by matching Legendre field coefficients (calculated for both the physical LFMS device and the source in the FEM model) and then scaling the FEM results to match the device-based calculation. While free space electric field values reach .75 V/m at the surface of the head and .51 V/m in the center, shielding by the head reduces the cortical fields to .25 V/m, and the fields in the center of the head are reduced to less than .05 V/m. These calculations suggest that electric field penetration during LFMS treatment can be expected to be strongest in cortical regions such as the prefrontal and orbitofrontal brain regions, as shown.

was not designed to determine whether a single or repeated exposure to LFMS treatment would result in a long-lasting or durable antidepressant response (>60 minutes). Rather, our goals were to isolate the electromagnetic field responsible for our earlier observation of rapid mood elevation in BPD patients (31) and to construct and test a portable device to duplicate the electromagnetic fields achieved previously in the MRI system and associated with that antidepressant response. Use of this device will allow clinical trials of LFMS in larger cohorts of depressed BPD and MDD patients and in studies involving multiple treatments, which are beyond the scope of this study or the capability of our single academic site.

Only the change in the self-rated PANAS PA score for the BPD subgroup was statistically significant in analyses that were limited to diagnostic subgroups. Nonetheless, the comparability of elevation in mood between BPD and MDD patients following LFMS treatment suggests the combined analysis of all subjects is appropriate, and the results from our combined analysis are highly suggestive of rapid effect using any or all three instruments for assessing depressed mood (Table 2).

For the entire group of BPD and MDD patients, we observed a mean reduction in the HDRS-17 score of 8.1 points and 5.0 points for active and sham treatment, respectively (difference of 3.1 points, $p = .02$, Table 2). This reduction reaches the difference of 3 points set as a criterion for clinical significance by the National Institute for Clinical Excellence in the United Kingdom (41). Importantly, the properties of LFMS are still being studied to determine the optimal frequency, spatial distribution, and timing of the electromagnetic field required to produce an antidepressant effect. It is conceivable that the LFMS treatment parameters can be further optimized.

Because there is no physical sensation associated with LFMS, other than the mild operational sounds produced by the magnetic coil that were duplicated during sham treatment, and because subjects were randomized to receive only active or sham treatment (but not both), our findings are unlikely to be due to inadvertent unblinding. A follow-up assessment of the robustness of the blind was made during a separate double-blinded, sham controlled, randomized crossover study of biomarkers in 10 healthy control subjects that received both active and sham LFMS on separate days within 1 week. Subjects were subsequently asked to identify in which order they received active or sham treatment 1 week after their participation. Five subjects were unable to make a guess, while the other five subjects made guesses, with two subjects guessing correctly and three subjects guessing incorrectly. In both the current study and in the follow-up blind evaluation, subjects' responses indicated an inability to discern active from sham LFMS.

How might the LFMS-induced electric field in the brain affect neuronal function? Although the mechanisms responsible for the mood-elevating effects of other electromagnetic therapies such as ECT (18,20), repetitive transcranial magnetic stimulation (42,43), and deep brain stimulation (44,45) (Table 3) are still unknown, the strength, location, and frequency of the pulsed fields that characterize LFMS suggest that its mechanism of action significantly differs from the direct actions of other treatments. These other modalities apply electric fields greater than 50 V/m to various regions of the brain, field strengths that can directly depolarize neurons (46). By contrast, LFMS-induced electric fields are of relatively low strength (≤1 V/m) and are too low to induce depolarization. However, recent work has shown that rapidly fluctuating low strength magnetic fields that are below the threshold for depolarization can still influence neuronal activity. Frohlich *et al.* (47) detected endogenous electric fields of 1 V/m or less in the brain synchronized to neuronal activity and further demonstrated profound changes in local spontaneous neuronal oscillations upon imposing similar exogenous electric fields. Exogenous electric fields on the order of .5 V/m have also been used to entrain and change spiking patterns in brain slice electrophysiology studies (48–50), and a 1 V/m electric field has been calculated to change the membrane potential of a dendrite by up to 10 mV (51). The dendritic network of neurons in the cortex may represent an appropriate location for LFMS to have an effect on mood. Dendrites perform complex calculations on synaptic inputs, and in particular, neurons in layers 5 and 6 of the cortex form a complex network of synapses with inputs

Table 3. Comparison of Electromagnetic Field Parameters Among Various Electromagnetic Treatment Modalities Currently Used for Depression and LFMS

	Method	Field	Pulse	Frequency
ECT	Electrode	>200 V/m	1 msec	60 Hz
DBS	Implant	100 V/m	60 μsec	120 Hz
rTMS	Coil	100 V/m	500 μsec	10 Hz
LFMS	Coil	1 V/m	256 μsec	1 kHz

The delivery method, electric field strength, and pulse characteristics for these electromagnetic therapies are shown. Most treatment modalities feature electric fields well over the 50 V/m threshold required for axonal stimulation. Note that the small voltage used in DBS results in a large electric field when applied over the small distance between electrodes positioned in the brain.

DBS, deep brain stimulation; ECT, electroconvulsive therapy; LFMS, low field magnetic stimulation; rTMS, repetitive transcranial magnetic stimulation.

shown to be active in mood regulation (38,52). These neurons project to limbic and other subcortical regions of the brain (53,54) that also appear to mediate mood. Together, these results suggest a potential cellular mechanism of action for LFMS in depression. Specifically, LFMS has characteristics that should affect the electrical activity of cortical neurons and, by extension, alter neuronal function within distributed neural networks of the brain, even though the electric fields are below the threshold for inducing neuronal depolarization. These possibilities as to mechanism and site of action are speculative until tested.

Could LFMS alter large-scale brain activity in humans? Volkow *et al.* (55) have recently reported significant reductions in the glucose metabolism in several regions of the cerebral cortex measured by 2-fluoro-2-deoxyglucose-positron emission tomography following exposure of healthy volunteers to active compared with sham LFMS treatment. These localized reductions in metabolism were induced by electric field pulses on the order of .1 to .3 V/m at 1 kHz from a purposefully programmed MRI system and were observed in the superior, inferior, and posterior cerebral cortices. The changes were proportional to the magnitude of the induced electric field, suggesting they were causally related. Using the FEM, we calculate that LFMS-induced electric fields on the order of .25 V/m penetrate several wide regions of the cerebral cortex (Figure 3), sufficient to more uniformly alter cerebral cortical function. This broad electrical field penetration in cortical areas, characteristic of LFMS, has recently been independently calculated by Deng *et al.* (56). Altered activity in the cortical regions most strongly penetrated by LFMS fields has been observed in fMRI and positron emission tomography studies of MDD and BPD (57,58) and connectivity between these regions were observed to change following treatment (59–61). These data suggest that LFMS may be altering activity in cortical regions involved in the regulation of mood such as the prefrontal cortices.

Given the rapidity and magnitude of the mood-elevating effects of LFMS reported here, LFMS could serve as a valuable research tool to further define the brain mechanisms and neurocircuits that mediate depressed mood. If durable antidepressant responses are associated with its repeated administration, LFMS could also prove useful as a rapidly acting treatment for depression, either when administered alone or in combination with antidepressant medication.

This study was completed with the support of the Stanley Medical Research Institute 07TGS-1045.

McLean Hospital has filed and been awarded patents for the low field magnetic stimulation treatment and device that have been licensed to Tal Medical. Dr. Rohan is listed as an inventor on these patents. Dr. Rohan, Dr. Yamamoto, and Mr. Cayetano have received consulting fees from Tal Medical, which McLean Hospital approves and limits. Dr. Paul holds an equity interest in Tal Medical. The other authors report no biomedical financial interests or potential conflicts of interest.

ClinicalTrials.gov: Low Field Magnetic Stimulation in Mood Disorders Using the LFMS Device; http://clinicaltrials.gov/show/NCT00578383; NCT00578383.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2013.10.024.

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