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

Supplemental Information

The Low Field Magnetic Stimulation (LFMS) Device

The LFMS device was designed and constructed at McLean Hospital and consists of a coil with housing, an amplifier, a control board, and a computer for blinding and control. The device is equipped with an audio system to provide faint 'beeps' to mimic system operation during sham operation, as well as with an emergency cutoff switch. The operator's console controls operation in a blinded fashion and uses program links that were randomized prior to the study in order to select active or sham treatment, based on the order of subject acceptance. Both the blind and a post-treatment confirmation file are protected files on the system. The device was reviewed by the FDA and was declared to be a "non-significant risk device".

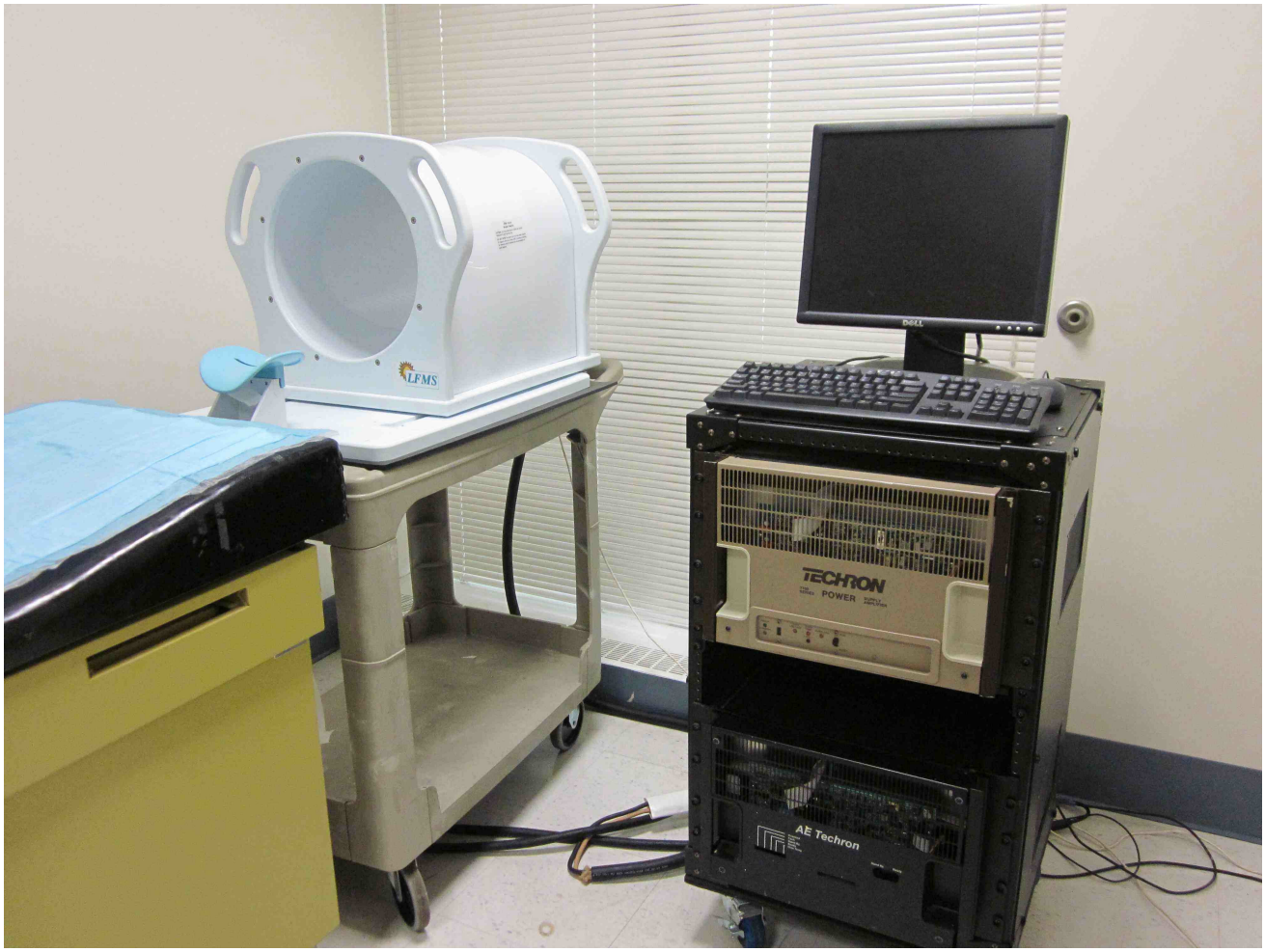

Figure S1. LFMS Device. The LFMS includes a coil, power source and computer with control card. The treatment volume is at the end of the coil, so the patient's head is not inserted far into the device. Fields inside the device were calculated and measured to be on the order of 0.7 V/m and 20 Gauss. These fields replicate the features first observed to produce an antidepressant effect in a magnetic resonance imaging (MRI) setting, using a magnetic resonance spectroscopic imaging procedure, as previously reported (1).

Hamilton Depression Rating Scale, 17-Item (HDRS-17) Itemized Response

The clinician-rated HDRS-17 is used as a standard measure of antidepressant response, and was chosen for this study to facilitate a comparison of these results to those of other studies of antidepressants. However, the HDRS-17 contains items that assess symptoms over several days or weeks in addition to items that assess symptoms that may change on an immediate timescale. Therefore, to help evaluate the utility of the HDRS-17 in our study we have provided detailed responses to the individual items of the HDRS-17. It is instructive to note the responses of both the active and sham-treated groups because the typical timescale of each item will be relevant to either a treatment response or a placebo response. Responses showing the most change were concentrated in the more immediate items (depressed mood, guilt, work and interest, anxiety, both psychic and somatic). Responses showing the least change (either with active or sham treatment) were concentrated in the items that would not be expected to show immediate response, including insomnia and weight loss. Although not adequately powered for statistical comparisons, these itemized responses provide a basis for interpreting the total HDRS-17 response to LFMS.

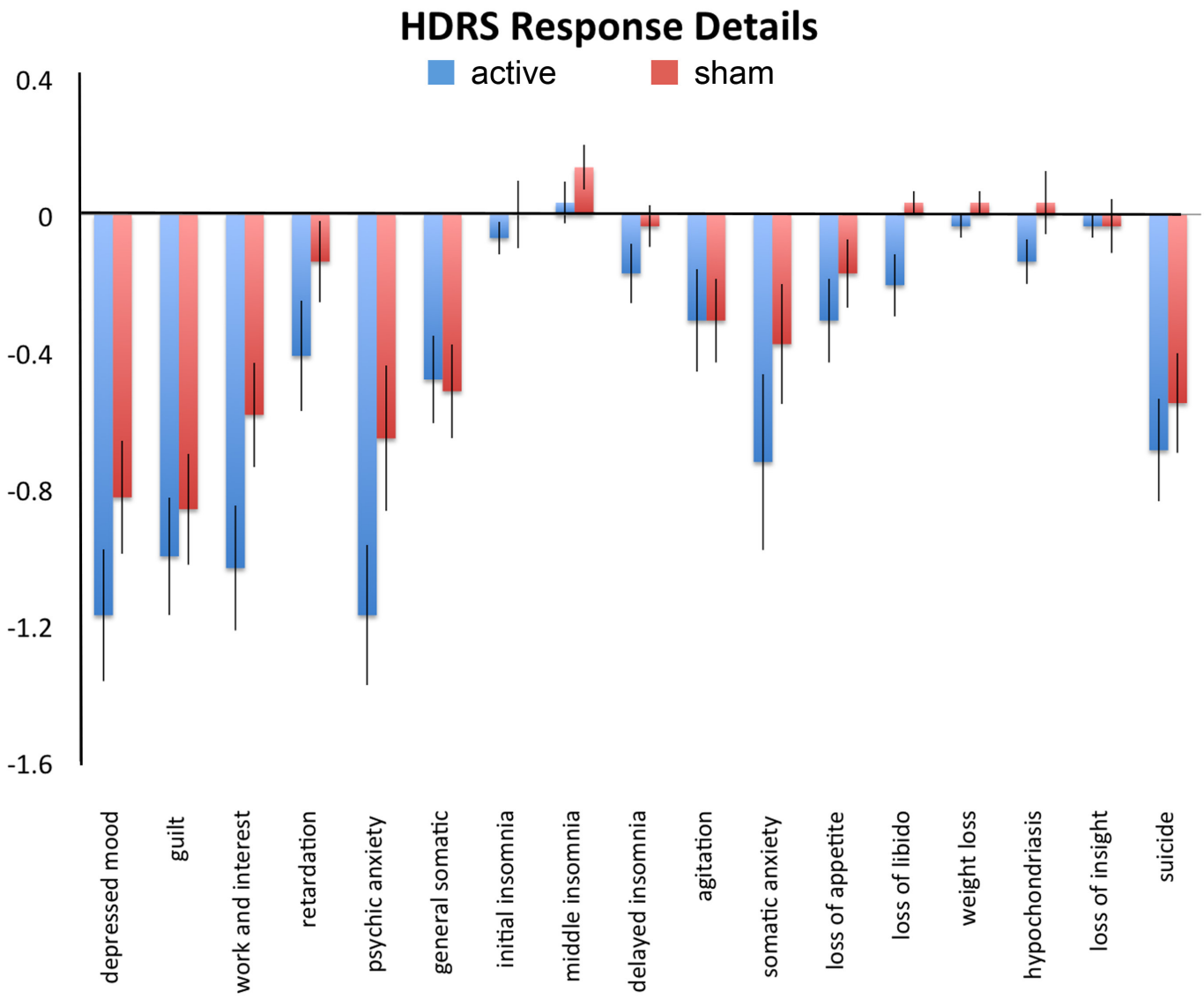

Figure S2. Itemized HDRS-17 (2) responses for subjects treated with active or sham LFMS. Immediate (post – pre) change in response to the individual items in the HDRS-17 following a 20 minute treatment with either active or sham LFMS in a randomized double blind study of patients with bipolar disorder (BPD) or major depression (MDD), currently depressed, as described in Figure 1 and the text. Results are shown for the combined group of BPD and MDD patients (n = 63). Values represent raw group means (with standard errors). The HDRS-17 measures symptoms expected to change over a range of typical time-scales. Note that the scores for both active and sham-treated LFMS groups are greatest for those items that can change rapidly, and not those that require longer time frames.

Positive And Negative Affect Schedule (PANAS) Itemized Response

We used the self-rated PANAS scales as secondary measures to better characterize and qualitatively assess the observed mood altering effects of LFMS and found the Positive Affect (PA) scale to be the most sensitive measure of changes in depressed mood following LFMS treatment. We examined the treatment-associated changes in the individual items of the PA and Negative Affect (NA) scales of the PANAS. Raw mean rating changes for these individual items are presented in Figure S3. For the PA scale, which yielded a significant difference in response between active and sham LFMS for BPD and the combined sample (Figure 2, Table 2), we observed improvement (increased PA score) across most items during active LFMS with a low sham response. For the NA scale, for which no statistically significant relative improvement (decreased scores) was observed (Figure 2, Table 2), most items (notably "distressed, upset and scared") showed a numerical improvement for LFMS and sham, although improvement was more pronounced for LFMS-treated patients. Because the study was not powered to compare item-level responses, no statistical comparisons were made for these individual items.

Previous studies have consistently shown that high PA reflects elevated mood-related affect, such as "high energy, elation and enthusiasm", whereas low PA is characterized by "sadness, lethargy and anhedonia" and has been reported to be significantly related only to depressive symptoms (3-5). The NA scale, on the other hand, reflects subjective distress and is not specific for depressed mood or affect per se but is also high in patients with anxiety and other psychiatric disorders. It is noteworthy that the PA score reflecting depressed mood substantially improved following LFMS treatment whereas no significant change was observed for the NA scale of the PANAS (Figure 2, Figure S3). The improvement in the PA scale of the PANAS confirms and extends the data from the Visual Analogue Scale (VAS) and HDRS-17 and

suggests that depressed mood and not other non-specific affective domains (e.g. anxiety or psychic distress) is most prominently affected by LFMS.

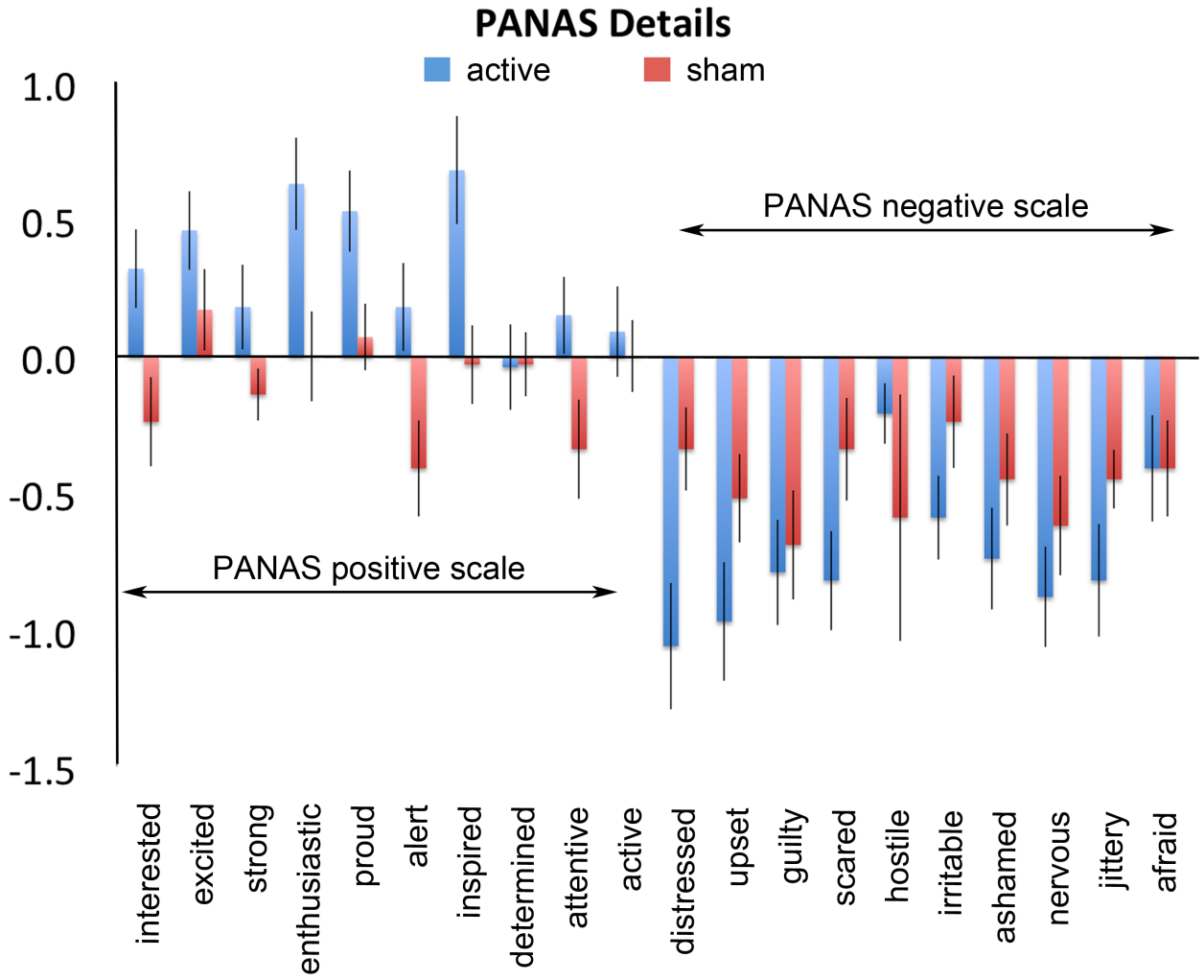

Figure S3. Itemized PANAS responses for patients treated with active or sham LFMS. Immediate (post – pre) change in response to the individual positive and negative affect scales in the PANAS occurring over a 20 minute treatment with active or sham LFMS in a randomized double blind study of patients with bipolar disorder (BPD) or major depression (MDD), currently depressed, as described in Figure 1 and the text. Results are shown for the combined group of BPD and MDD patients (n = 63). Values represent raw group mean (with standard error). The PA scale has been shown to assess change in mood, including depressed mood, while the NA scale has been shown to assess symptoms of stress and anxiety (4, 5). PA data were significantly different (active vs sham LFMS) for the BPD patients (see text and Table 2) and for the combined group of BPD and MDD patients (shown here and Table 2). There was no consistent sham response observed for the PA items.

Electromagnetic Fields Analysis

This section of the Supplemental Materials describes the details of the electromagnetic calculation. This calculation was performed using standard software and methods and is described here for completeness. The finite element method (FEM) implemented in COMSOL software (COMSOL Inc, Burlington, MA) was used to evaluate the electromagnetic fields within the head of a subject. The source of the fields was a continuous current distribution based on the LFMS coil, and a standard MRI based model of the human head was used to represent the patient. The purpose of this calculation was to determine the likely penetration and distribution of the electric fields induced by LFMS in a patient's brain, given the effects of conductive tissue and shielding charge density. It was expected that the head, a weakly conducting object, would screen a significant portion of the free-air electric field of the device.

An anatomic MR image (T1 contrast, 1 mm resolution) of a 26-year old woman was used as a model for the head in this calculation. This model, which was truncated at the neck, was segmented into 7 tissue types that were used to construct an electrical conductivity map using published conductivity values, as listed in Table S1 (6-8). The boundary surface of the head was approximated by a 552 plane surface that was obtained by using the MATLAB software package (The MathWorks, Inc, Natick, MA). The volume within the head was represented as a mesh of nodes, obtained by using the standard geometric meshing algorithms of the FEM program; a conductivity value was assigned to each node to form a continuous electrical conductivity distribution. The boundaries between different tissue types in the brain were not modeled as boundary surfaces. Figure S4 shows the MRI image, the tissue segmentation and the mesh for the model.

The continuous current distribution that was used to model the coil is shown below and was modulated by with a sinusoidal waveform at a frequency of 1 kHz:

$$\vec{K}(R,\varphi,z,t) = K\left[\hat{\varphi}\cos\varphi + \hat{z}\frac{z}{R}\sin\varphi\right]\sin 2\pi f t$$

This coil has a radius R = 18 cm, current density K = 3685 A/m, and frequency f = 1 kHz.

The FEM solution for the fields that penetrated the head was performed in two stages. At this first stage the steady state electromagnetic fields of the coil in free space, expressed primarily as the vector potential A_1 produced by a current distribution J_c at a frequency ω, were solved using the equation:

$$(i\omega\sigma - \omega^2\epsilon)\vec{A}_1(\vec{r}) + \vec{\nabla}\times\left(\mu^{-1}\vec{\nabla}\times\vec{A}_1(\vec{r})\right) = \vec{J}_c(\vec{r})$$

with a boundary condition at infinity, $\vec{n}\times\vec{A}(\vec{r}) = 0$. This first stage FEM employed a direct linear solver (SPOOLES) followed by a linear system solver with geometric multi-grid pre-conditioning (GMRES) and smoothing (Vanka).

In the second stage of the calculation the weakly conducting head was added to the model, and the fields and induced current density from the first stage were used as an external condition to find the scalar potential from the shielding charge of the head V_2. The fields in the head were solved using the steady state electromagnetic equation:

$$-\vec{\nabla}\cdot\left((\sigma + i\omega\epsilon)\vec{\nabla}V_2(\vec{r}) - \vec{J}_1(\vec{r})\right) = 0$$

with a boundary condition V = 0 at infinity. The inclusion of the conductivity within the divergence operand accommodated the description of shielding charges that accumulate on the surface of the head. At this second stage of the calculation we employed the PARDISO solver while the same preconditioning and smoothing as were used in stage one (9).

As a confirmation of the FEM analysis, the "free-space" fields of the model coil, as evaluated in the first stage, were also expressed using the quasi-static approximation in order to facilitate comparison with the calculated fields of the physical coil presented previously. The coefficients of this expansion are G = 0.95 G/cm, E0 = 0.51 V/m, E2 = 11.8 V/m^3, gradient slew rate dG/dt = 64.8 T/m/s. These coefficients can be compared to those evaluated using the physical coil design, shown in the Methods section.

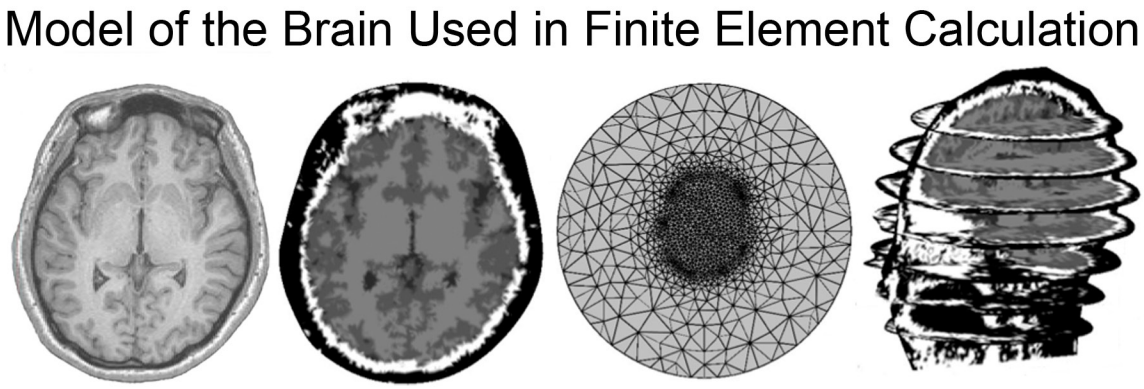

Figure S4. Model of the head used in electric field estimation of LFMS. Different aspects of the model of the head that was used in the finite element method calculation of the electric fields that were induced during LFMS are illustrated. A single slice extracted from the 3D model is shown in three phases of calculation, and in the context of the whole head. Leftmost is the MRI anatomic image, next is the image segmented into 7 tissue types for use in assigning conductivity and permittivity values, next is the geometric mesh that was generated by the FEM software for calculations (mesh is shown for the volume inside the coil). Rightmost is an image in the sagittal orientation showing select slices from the tissue segmentation step, included here to aid in visualization of the model.

Table S1. Tissue parameter values used for the model of the head. The relative permittivity and absolute conductivity values for the 7 tissue segments that were used in the finite element method calculation of the electromagnetic fields of LFMS are listed.

Tissue	**Permittivity ε_r**	**Conductivity σ (S/m)**
Cerebrospinal fluid	5000 (blood)	1.7
Gray Matter	164065	0.0788
White Matter	69811	0.0426
Fat	19287	.00667
Muscle	434932	0.121
Skin	1136	6.50×10^{-8}
Cortical Bone	2702	0.000157

Clinical Procedures

This section of the Supplemental Materials provides a more detailed listing of the clinical procedures and timelines used for the study. Subjects participated in a randomized, double blind, sham controlled trial of LFMS. All procedures were reviewed and approved by the McLean Hospital/Partners HealthCare Institutional Review Board and informed consent was obtained from all subjects prior to enrollment. Sixty-three patients (BPD = 41, MDD = 22) who met inclusion criteria were enrolled and were randomly assigned in a 1:1 ratio to either active LFMS or sham in permuted blocks of 10 within diagnostic strata (BPD and MDD).

Inclusion criteria were:

· Men and women age 18-65

· DSM-IV criteria for either BPD or MDD

· Currently depressed with HDRS ≥ 17; Young Mania Rating Scale <7 for BPD subjects

· Stable medication or therapy regimen, or no treatment, for at least six weeks

· Capable of providing informed consent.

Exclusion criteria were:

- contraindication for MRI due to metal in the eyes or head
- Mixed mood state
- Comorbid axis II personality disorders or anxiety based disorders
- History of brain injury; serious physical illness, neurological disease, or dementia
- Pregnancy
- Current suicidal ideation
- Current drug use, abuse, or dependence; or history of polysubstance use.

Medication

Subjects were enrolled using a criterion of stable medication for 6 weeks as described above; medication and other therapy was not changed or interrupted for this study.

Screening Visit

Subjects signed informed consent prior to the screening interview. Potential subjects were screened by trained clinical interview staff, with physician supervision. A detailed psychiatric and medical history was obtained. The Mini International Neuropsychiatric Interview Plus 6.0 (MINI) (10) was used for confirmation of depressed mood state and either BPD or MDD diagnosis and evaluation of comorbid diagnoses. The VAS, HDRS-17 (2), and PANAS (two self-response scales with 10 positive and 10 negative valenced words) (3) were administered by trained clinical staff.

The study physician conducted a brief interview with each subject to determine potential eligibility. Eligible subjects then received a physical exam and blood draw for laboratory testing (Chem-7, liver function tests, complete blood count with differential, thyroid stimulating hormone, and standard drug screen). A urine pregnancy test was performed for women of

childbearing age. The screening visit for subjects who were McLean patients and had lab results available could be combined with the treatment visit.

Treatment Visit

Subjects received one active or sham LFMS treatment. Treatments were scheduled at McLean Hospital. Treatment visits followed the schedule below:

- Each treatment visit started with a brief interview with the study physician to ascertain changes in mood state or concomitant medications. This interview also included an evaluation of any new-onset suicidal ideation or behavior.
- Because of the unknown effects of LFMS on pregnancy, all women of childbearing age took a urine pregnancy test before treatment, and were excluded from the study if pregnant.
- Upon approval by the study physician the subject proceeded to receive treatment. The VAS, HDRS-17, and PANAS scales were completed immediately preceding treatment.
- LFMS treatment (active or sham) was administered for 20 minutes.
- A 10-15 minute observation and rest period immediately followed treatment.
- After the rest period, the VAS, HDRS-17 and PANAS scales were administered again for post-treatment scores.

Phone Follow-up

Subjects received a follow-up phone contact one week after the first treatment. This phone call was simply to ascertain patient well-being and safety and was not designed to formally assess mood.

Sham Procedure

Strict sham control is possible because the LFMS device produces sound but no physical sensation. Operational sounds are duplicated during sham operation, which occurs with the full

system power on but with no electromagnetic fields produced. Active or sham treatment selection is performed using a randomization schedule that is not apparent to the operator and is executed in treatment order by the clinical user interface. The randomization schedule was generated before the start of the study by the engineering staff. Randomization was performed in blocks of ten subjects stratified by diagnosis (BPD or MDD).

Outcome Measures

The pre-specified primary outcome was change in the VAS following treatment. Change in HDRS-17 score was added as an additional primary outcome after enrollment of the first eight study participants. The pre-specified secondary outcomes were changes in the PA and NA scales (PANAS) following treatment.

Visual Analogue Scale. The VAS is a self-rating scale in which the subject places an "X" on a 0 to 10 linear scale on a sheet of paper. The instruction is "Place an X on the line in a place that represents how your mood is at this moment" and the endpoints of the linear scale are labeled "No Depression" at 0 and "Most Depressed Ever Been" at 10. The VAS is well suited to measure rapid change in mood and has been used for this purpose in previous studies.

Hamilton Depression Rating Scale, 17 item version. The HDRS-17 (2) is a 17 item interviewer rating scale commonly used in assessing severity of symptoms in people suffering from depression and their response to antidepressant medication.

Positive And Negative Affect Schedule. The PANAS (3) is sensitive to rapid changes in mood and has been validated in both psychiatric patients with depression and anxiety disorders (5) as well as non-clinical populations of healthy volunteers (4). The PANAS can be briefly administered and consists of two self-reported 10-item mood scales developed to provide reliable and more detailed measures of positive affect and negative affect.

Safety

Patient safety was addressed by collecting adverse event reports and by coordination with on-call physician support. In a study including a sizeable population of subjects with BPD the possibility of kindling a manic episode was monitored carefully.

Supplemental References

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