Midline and right frontal brain function as a physiologic biomarker of remission in major depression

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Abstract

Prior investigations have reported that changes in the prefrontal electroencephalogram (EEG) precede symptom improvement from antidepressant medications, and could serve as a biomarker of treatment outcome in major depressive disorder (MDD). A new physiologically-defined region of interest, overlying the midline and right frontal (MRF) cortical area, was examined here for a relationship between early decreases in theta-band cordance and remission. Subjects were 72 adults with unipolar MDD who had completed placebo-controlled antidepressant treatment trials, with 37 randomized to medication and 35 to placebo. We assessed changes in cordance and absolute and relative power in the MRF region at 48 hours, 1 week, and 2 weeks after start of drug, as potential predictors of remission (final Ham-D$_{17}$ ≤5). Eleven of 37 medication subjects (30%) remitted vs 6 of 35 placebo subjects (17%). Change in MRF cordance one and two weeks after start of drug was significantly associated with remission in medication subjects (*P*=0.02 at 1 week), with Receiver Operating Characteristic (ROC) analysis yielding 0.76 area under the curve. Decreases in MRF cordance at 1 week predicted remission with medication with 69% overall accuracy (90% sensitivity; 60% specificity). MRF cordance changes were not associated with remission with placebo. Absolute and relative power did not differentiate groups. These results suggest that remission may be predictable from physiologic measurements after 1 week of treatment, and that this region merits further investigation in the neurobiology of treatment response.

Additional Keywords

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1. Introduction

Achievement of remission has been identified as the key objective of treatment for major depressive disorder (MDD) (cf. Nierenberg and Wright, 1999; cf. Keller, 2004). Although some 85–90% of patients can eventually experience symptomatic improvement with antidepressant medications, attaining this objective remains elusive. In the STAR*D effectiveness study of "real world" patients with MDD ("Sequenced Treatment Alternative to Relieve Depression" http://star-d.org), less than a third achieved remission with the first antidepressant trial, despite aggressive dosing, close measurement-based monitoring, and a 12-week period to exhibit improvement (Trivedi et al., 2006a); at the end of a second level of randomized treatment, the total fraction of remitted subjects was approximately 50%, leaving almost half of subjects with incomplete responses (Rush et al., 2006; Trivedi et al., 2006b). Ominously, patients who do not achieve remission suffer not only ongoing symptoms, but also persistent impairments in psychosocial function (Miller et al., 1998; Papakostas et al., 2004), functional disability at work and home (Mojtabai, 2001; Ormel et al., 2004; Vos et al., 2004), and increased rates of relapse (Paykel et al., 1995; Judd et al., 1998; Nierenberg and Wright, 1999). In a comparison of long-term outcomes for individuals who entered follow-up after an acute course of treatment either with or without residual symptoms, Paykel and colleagues (1995) found that 76% of subjects who entered follow-up with residual symptoms (i.e., response but not remission) had relapsed by 15 months vs only 25% of those who had experienced an initial remission, giving added clinical significance to this distinction in outcome threshold. Means to achieve remission have been the focus of large-scale investigations. Algorithm-based approaches, such as studied in the TMAP ("Texas Medication Algorithm Project", Rush et al., 1999; Trivedi et al., 2000) and STAR*D trials, provide an evidence base for selecting subsequent treatments, but these decisions are made for individual patients only *after* a remission has failed to occur despite an adequate trial of a particular intervention, a process which takes weeks to months for each sequential trial. The duration of algorithm-based treatment could be shortened if practitioners could identify, early in a treatment phase, those individuals who are unlikely to remit, and institute different, augmented, and/or more complex treatments sooner for those patients who need them.

We have previously reported data with the quantitative electroencephalography (QEEG) measure cordance that showed a relationship between changes in prefrontal brain activity in the first one-to-two weeks of treatment and later clinical outcome, considering a response threshold of 10 on the 17-item Hamilton Depression Rating Scale (Cook and Leuchter, 2001; Cook et al., 2002; 2005). Cordance is a continuous numerical measure of regional brain activity, described in a series of publications from our group and other independent, international researchers (e.g., Leuchter et al., 1999, 2002, 2004; Cook and Leuchter 2001; Cook et al., 2002, [2005]; Stubbeman et al., 2004; Hunter et al., 2005, [2006], 2008; Bareš et al., 2007, [2008]; Kopeček 2006, 2007, 2008; Morgan et al., 2007); it combines complementary information from absolute and relative power EEG spectral measures to yield a metric which had a stronger correlation with regional cerebral perfusion than either component alone (Leuchter et al., 1999), providing a physiologic framework for the interpretation of findings. These earlier studies examined an empirically-predefined region of interest (ROI) that included prefrontal EEG channels bilaterally and at the midline (FP1, FP2, and FPZ electrodes, figure 1a). This association between early prefrontal changes and later clinical outcome was independently replicated and extended by Bareš and colleagues (2007, 2008), expanding the evidence for use of cordance as a predictive biomarker in treatment for MDD. None of these trials, however, used remission as the clinical endpoint criterion.

In addition to our prior studies of cordance during treatment in patients with MDD, we also have examined cordance in non-depressed individuals. In a separate investigation, a sample of psychiatrically-well adults were studied to determine the behavior of cordance during exposure

to an antidepressant or placebo in never-depressed brains (Leuchter et al., 2008). In that study, we reported that cordance values in the prefrontal region did *not* change differently in the medication and placebo groups; however, a different region was identified via hierarchical cluster analysis (Milligan and Cooper, 1987; Mirkin, 1996; Mojena, 1977) that exhibited differential changes under medication vs placebo exposure. The cluster analysis method identifies groups of locations (e.g., voxels for positron emission tomography (PET) studies or electrodes for QEEG experiments) which exhibit a common trait, such as being characterized by significantly intercorrelated cordance values. Electrodes overlying a midline and right frontal cortical area were found uniquely to form such a cluster (figure 1b). In comparisons of medication and placebo exposure, this ROI exhibited significant differences at 48 hours and 1 week: healthy subjects receiving medication exhibited a decrease in cordance in that area, whereas the placebo-exposed subjects did not. This was the only identified region observed to exhibit this property (Leuchter et al., 2008).

Given the physiologically-determined basis of this new ROI (figure 1b), the present analysis was undertaken to examine the predictive properties of a midline and right frontal (MRF) cordance regional measure; we hypothesized that early decreases in cordance in this ROI would be associated with remission of symptoms from medication, but not placebo.

2. Methods

2.1 Subjects and trial design

Subjects were 72 adult outpatients with unipolar MDD, who had completed one of three 8-week, placebo-controlled antidepressant treatment trials conducted in our lab. All protocols had been reviewed and approved by the UCLA Institutional Review Board and subjects had given informed consent to participate in research, as per the provisions of the Declaration of Helsinki.

All three trials shared the same fundamental design and entry criteria, described fully in Cook et al. (2002), and summarized briefly here. After giving consent and enrolling, subjects were assessed clinically with a structured interview (including SCID-P (First et al., 1994)) to determine that they met criteria for the presence of unipolar MDD with a score 16 or greater on the 17-item Hamilton Depression Rating Scale (Ham-D$_{17}$), and were without other psychiatric comorbidities except for anxiety-spectrum disorders. Exclusionary criteria included the presence of any poorly controlled medical illness that could affect brain function (e.g., untreated hypothyroidism), concurrent use of medications that could interfere with EEG activity (e.g., benzodiazepines), or any history of head trauma, brain surgery, or skull defect. These entry criteria had been established to allow enrollment of subjects with moderate to severe levels of depressive symptomatology (cf. Rush et al., 2003) who were seeking treatment, and excluding subjects for whom the EEG assessments of brain function would be compromised by extraneous factors. The average Ham-D$_{17}$ score in our sample was a 21.9 (s.d. 3.4), which is similar to the severity of depression of subjects in the STAR*D project (21.8 (s.d. 5.2)) (Trivedi et al., 2006a). Demographically, the medication group was 62.2% female with a mean age of 42.7 (s.d. 12.3) years; the placebo group (n=35) was 51.7% female with a mean age of 40.6 (s.d. 11.9) years. Age, gender, and intake symptom severity did not different significantly among trial groups.

After clinical assessment, subjects began a 1-week single-blind placebo lead-in period. Subjects who still fulfilled entry criteria at the end of the lead-in period were then randomized to receive 8 weeks of placebo or antidepressant medication, administered under double-blind conditions. For the present analysis, we examined those subjects who completed the trial. Among the 37 medication subjects, 13 were assigned to fluoxetine (20 mg/d), and 24 to venlafaxine (150 mg/d). In the study with fluoxetine, doses were constant throughout the entire

treatment period; in the venlafaxine studies, dosing began at 37.5 mg/d and was escalated to 150 mg/d by the end of week 2, and remained constant at that dose for the remaining weeks (with a matching increase in the number of placebo pills to maintain blinding).

2.2 EEG Methods

2.2.1 Data acquisition—Using procedures employed in our previous reports and summarized here, recordings were made with the QND System (Neurodata, Inc., Pasadena, CA). During recordings, subjects rested in the eyes-closed, maximally alert state, in a quiet room with subdued lighting. To avoid subject drowsiness, the technologists monitored the EEG data during the recording and re-alerted the subjects every 30–45 seconds as needed. Electrodes were placed with an electrode cap (ElectroCap, Eaton, OH) using 35 recording electrodes distributed across the head according to an extension of the International 10–20 System montage. Data were collected using a Pz referential montage and were digitized at 256 samples/channel/sec by the QND system (bandpass filtered 0.3 – 70 Hz). Each EEG recording was reviewed by a technologist who was blinded to subject identity, treatment condition, and clinical status; the first 20–32 seconds of artifact-free data were selected to be processed. These selections were confirmed by a second technologist.

2.2.2 Cordance calculations—Cordance values were calculated using an algorithm that has been detailed elsewhere (Leuchter et al., 1999) and may be summarized as follows. Cordance is computed by a normalization and integration of absolute and relative power values from all electrode sites for a given EEG recording; cordance values are calculated in three steps. First, EEG power values are computed using a re-attributional electrode montage in which power values from pairs of electrodes that share a common electrode are averaged together to yield the re-attributed power (Cook et al., 1998). This is similar to the single source method of Hjorth (1970, 1975), in which voltage signals are recombined, but the re-attributional montage approach has been shown to provide a higher association between QEEG measures and regional cortical perfusion than the Hjorth method (Cook et al., 1998). These absolute power values are used to derive relative power (percentage of power in each frequency band) for each electrode.

Second, these absolute and relative power values for each individual EEG recording are normalized across electrode sites, using a z-transformation statistic for each electrode site s in each frequency band f (yielding $A_{norm}(s,f)$ and $R_{norm}(s,f)$ respectively). This normalization process places absolute and relative power values into a common unit (standard deviation or z-score units) which allows them to be combined. These z-scores are based on the average power values in each band for all electrodes within a given EEG recording (i.e., these are not z-scores referenced to a normative population).

Third, the cordance values are formed by summing the z-scores for normalized absolute and relative power ($Z(s,f) = A_{norm}(s,f) + R_{norm}(s,f)$, for each electrode site and in each frequency band). Cordance values have been shown to have higher correlations with regional cerebral blood flow than absolute or relative power alone (Leuchter et al., 1999), and thus this combination measure can be placed in context with prior work in depression that employed functional measures of brain activity such as PET scan data.

2.2.3 Midline and Right Frontal (MRF) Theta Cordance Measure—Cordance values at the FPz, Fz, FP2, AF2, F4, and F8 electrodes were averaged to form MRF regional measure for each subject at each assessment. In healthy adults receiving antidepressant medication (Leuchter et al., 2008), these electrodes uniquely had exhibited a significant intercorrelation in their change in cordance during medication exposure which was not present in subjects receiving placebo.

In this project we focused on theta-band cordance values because activity in the theta band has been consistently associated with depression and antidepressant medication effects in studies from our group and from others (Knott and Lapierre, 1987; Knott et al., 1996, 2000, 2001, [2002]; Pizzagalli et al., 2001; Anderer et al., 2000; Ulrich et al., 1988a, 1988b, [1994]; Bareš et al., 2007, 2008; Kopeček et al., 2007, 2008).

2.2.4 Power spectral measures—To allow *post hoc* comparisons of this work with prior studies employing traditional spectral power measures, absolute and relative power values were computed with a linked-ears montage, using the internal re-referencing of the QND system.

2.3 Data analysis

We used repeated measures ANOVA (SPSS version 15, SPSS Inc., Chicago IL) and logistic regression (LogXact 4.1, Cytel Software Corp, Cambridge MA) to assess changes in theta-band cordance in the MRFC region at 48 hours, 1 week, and 2 weeks after start of drug, as predictors of remission (final Ham-D$_{17}$ ≤ 5). Though a threshold of 7 is commonly employed (cf Frank et al., 1991), a more stringent threshold of 5 was employed here because of work indicating that lower thresholds are associated with better functional outcomes (Zimmerman et al., 2007). Receiver operating characteristic (ROC) analyses were performed (with SPSS) to evaluate the classification accuracy of the MRF cordance measure.

3. Results

3.1 Clinical outcomes

Clinically, 11 of the 37 medication subjects (30%) met criteria for remission after 8 weeks of medication. Of the 35 subjects randomized to placebo, 6 (17%) remitted. Remission rate was not statistically different between treatment groups (Chi square 1.58, *P* = 0.21, 2-tailed). Group average Ham-D$_{17}$ scores are plotted over time for the four groups (i.e., remitters and non-remitters, receiving medication or placebo) in Figure 2. The four outcome groups did not differ significantly on age ($F_{(3,68)}$=1.50, *P* = 0.22) or gender (Chi square 1.25, *P* = 0.74, 2-tailed).

3.2 MRF cordance, MRF power, and symptom severity prior to treatment

The baseline values of cordance, absolute power, and relative power in the MRF ROI were compared for remitters vs non-remitters for medication subjects and for placebo subjects via ANOVA; no significant differences among the four groups were found (data not presented). Baseline severity on the Ham-D$_{17}$ was similarly evaluated via ANOVA and no group differences were found.

3.3 MRF cordance and power changes with medication

The change in MRF cordance was significant in a repeated measures ANOVA with treatment outcome group (remission vs non-remission) as the between-subjects variable and time-point as a within-subjects variable. The model yielded a significant main effect of group ($F_{(1,33)}$ = 6.77, *P* = 0.014) and no significant effect of time or group-by-time interaction. Change in MRF cordance after one week of medication (*n* = 35) was significantly associated with remission (logistic regression coefficient = −1.10, SE = 0.49, exact *P* = 0.017). After two weeks of medication (*n* = 36), change in MRF cordance also showed a statistical significance in the same, decreasing direction (coefficient = −1.08, SE = 0.62, exact *P* = 0.049). Differences at 48 hours were not statistically different between groups. The time course of these MRF cordance changes in shown in Figure 3 and values are presented in the Table. A repeated measures ANOVA was then used to examine absolute and relative power in the MRF region. For absolute power, there was not a significant effect of group ($F_{(1,19)}$ = 0.58, *P* = 0.46) or time ($F_{(2,19)}$ = 2.12, *P* = 0.13), or group × time interaction ($F_{(2,19)}$ = 3.06, *P* = 0.059). In the

analysis of relative power we again did not find a significant effect of group ($F_{(1,19)} = 3.48$, $P = 0.078$) or time ($F_{(2,19)} = 0.46$, $P = 0.63$), or group × time interaction ($F_{(2,19)} = 0.63$, $P = 0.54$).

ROC analysis of the one-week MRF cordance as a predictor of remission in the medication subjects yielded an area under the curve (AUC) of 0.76. Using a threshold ("cutpoint") of 0 to stratify the physiologic changes, decreases in MRF cordance predicted remission with 69% overall accuracy (90% sensitivity; 60% specificity). For medication subjects, for a cordance decrease at 1 week was associated with a positive predictive value of 0.45 (proportion of subjects with a decrease who remitted as predicted), and a negative predictive value of 0.94 (proportion of subjects without the decrease who did not remit).

3.4 Comparison with Placebo Subjects

As a control condition, we also evaluated data on the 35 subjects from these trials who had been assigned to receive placebo. Changes in MRF cordance at 48 hours, 1 week, or 2 weeks were not significantly associated with remission in our logistic regression models.

3.5 Post hoc consideration of handedness

Because hemispheric function may be lateralized differently in right-handed vs left-handed individuals, we conducted a *post hoc* analysis to evaluate this potential confound. Self-reported handedness did not differ between medication and placebo groups (MED: 29 right handed (RH) and 8 left handed (LH) subjects; PBO: 28 RH and 7 LH; Chi square 0.029, $P = 0.87$) or between remission and non-remission groups overall (remit: 14 RH and 3 LH, non-remit: 43 RH and 12 LH; Chi square 0.137, $P = 0.71$). There was no difference between remitters and non-remitters in the medication group in particular (remit: 8 RH and 3 LH, non-remit: 21 RH and 5 LH; Chi square 0.295, $P = 0.59$).

4. Discussion

Our primary finding was that changes in EEG cordance after one week of antidepressant medication were predictive of remission after 8 weeks on that medication. This result expands prior findings of EEG changes that precede symptomatic response to antidepressant treatment, by focusing on remission as the salient clinical endpoint and using an *a priori* region of interest derived from physiologic findings in never-depressed adults exposed to antidepressants. Our results suggest that remission with antidepressant medications may be predictable from measurements of brain function after 1 week of treatment.

This finding is consonant with other work about ROIs associated with depression. Prefrontal cortical regions have been implicated in the pathophysiology of MDD and in treatment response, particularly dorsolateral prefrontal cortex (PFC) (recently reviewed by: Brody et al., 2001; Davidson et al., 2002; Phillips et al., 2003; Rogers et al., 2004; Fitzgerald et al., 2006). A role for the anterior cingulate cortex (ACC) region has also been identified in the response to antidepressant treatment (Brody et al., 2001; Mayberg et al., 2000). The ACC is distant from the scalp electrodes used in this project, but studies which integrate EEG and magneto-encephalography (MEG) recordings have revealed correlations between the MEG signals from the ACC and simultaneous EEG activity recorded over PFC in the theta band (Asada et al., 1999; Ishii et al., 1999). We interpret the cordance values recorded from our MRF region of interest as likely reflecting both projected rhythms from ACC sources and intrinsic activity within the PFC.

Functional differences between the left and right cerebral hemispheres have been described by other researchers as well. In the "valence effect" theory of emotional processing by the brain,

it has been suggested that the left hemisphere specializes in processing positively-valenced material, while the right hemisphere is adapted to the processing of negative stimuli (cf. Davidson, 1993, 2003). Our present findings suggest that, much as non-depressed healthy subjects exhibited a right frontal regional change in brain activity during exposure to antidepressant medication (Leuchter et al., 2008), the emergence of remission may be associated with a similar regional brain change. Our group (Cook and Leuchter 2001; Cook et al., 2002, 2005) and other researchers (Bareš et al., 2007, 2008; Kopeček 2006, 2007, 2008) have previously focused on a bilateral ROI involving the EEG electrodes overlying the most anterior portions of the prefrontal cortex, based on prior empiric observations. This new finding with this MRF ROI suggests that additional prospective investigations are needed to compare and refine the biomarkers to optimize potential application in treatment planning. For example, cluster analysis could be undertaken in depressed subjects as a method to identify region(s) of interest associated with outcome; such ROIs could then be evaluated prospectively in future datasets to test their validity.

We did not find an association between MRF cordance changes and outcome in subjects receiving placebo. This suggests that these early cordance changes are reflecting neither simply improvement in symptom severity nor exposure to medication, but rather some interplay between those two factors in those subjects who will exhibit a "specific response" (cf. Leuchter et al., 2002) to the administered pharmacotherapy. We interpret our findings as supporting measurement of changes in regional brain activity as a biomarker which is predictive of later attainment of remission with antidepressant treatment.

Limitations of this project include the modest sample size and the use of fluoxetine or venlafaxine as the only interventions. Regarding our clinical sample, subjects with comorbid anxiety were included to improve generalizability of findings to MDD patients seeking care, but we did not have sufficient information to perform a stratified analysis of MRF cordance changes in individuals with or without anxiety; because our ROI has been implicated in anxiety conditions as well as in MDD by some studies (Blackhart et al., 2006; Kline and Allen, 2008; Kim et al., 2008; Gotlib, 1998. Schmidt, 1999) though not by all (e.g., Warwick et al., 2008), future investigations may usefully record the presence and severity of comorbid anxiety-spectrum symptoms and disorders to permit such analyses. Additionally, while the MRF ROI showed encouraging overall accuracy (AUC), other parameters (e.g., positive predictive value) suggest that further refinement to the physiologic biomarker approach is desirable before clinical application could be considered.

The reliability, reproducibility, and generalizability of this potential biomarker of remission need to be tested prospectively, and in comparison to other ROI biomarkers, in a larger sample of "real world" subjects, using other antidepressant medications. If this biomarker's utility is confirmed, algorithm-based treatment approaches could incorporate physiologic guidance so that patients predicted not to remit with a given treatment could to move on to subsequent treatment levels more rapidly than with sequential empirical trials. Additionally, future studies may focus on this ROI to assess its possible role in the neurobiological processes mediating response to treatment for MDD.

Acknowledgments

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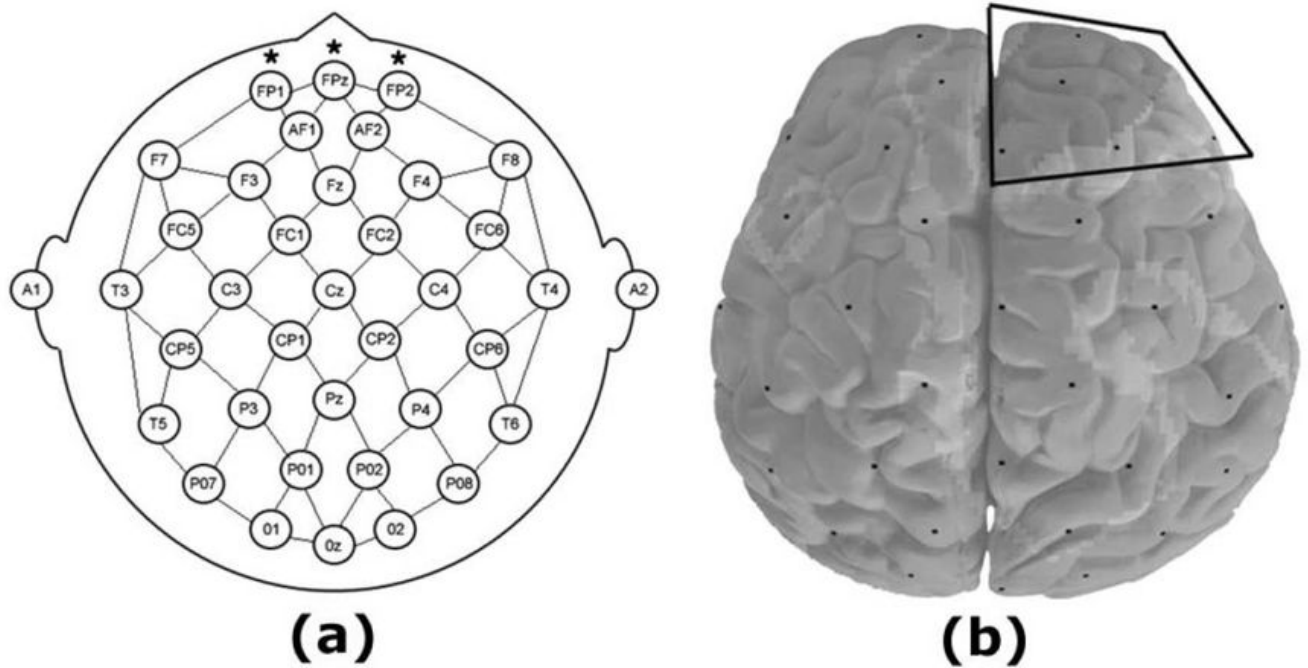
Figure 1. Electrode Placements and Regions of Interest
Panel (a) shows the placement of 35 electrodes in accordance with the International 10–20 system; previously examined Region of Interest (ROI) included FP1, FPz, and FP2 electrodes (marked with asterisks). In Panel (b), the Midline and Right Frontal Cortical (MRFC) ROI includes Fpz, Fz, Fp2, AF2, F4, and F8 electrodes, outlined with black lines. Images depict the head from above.
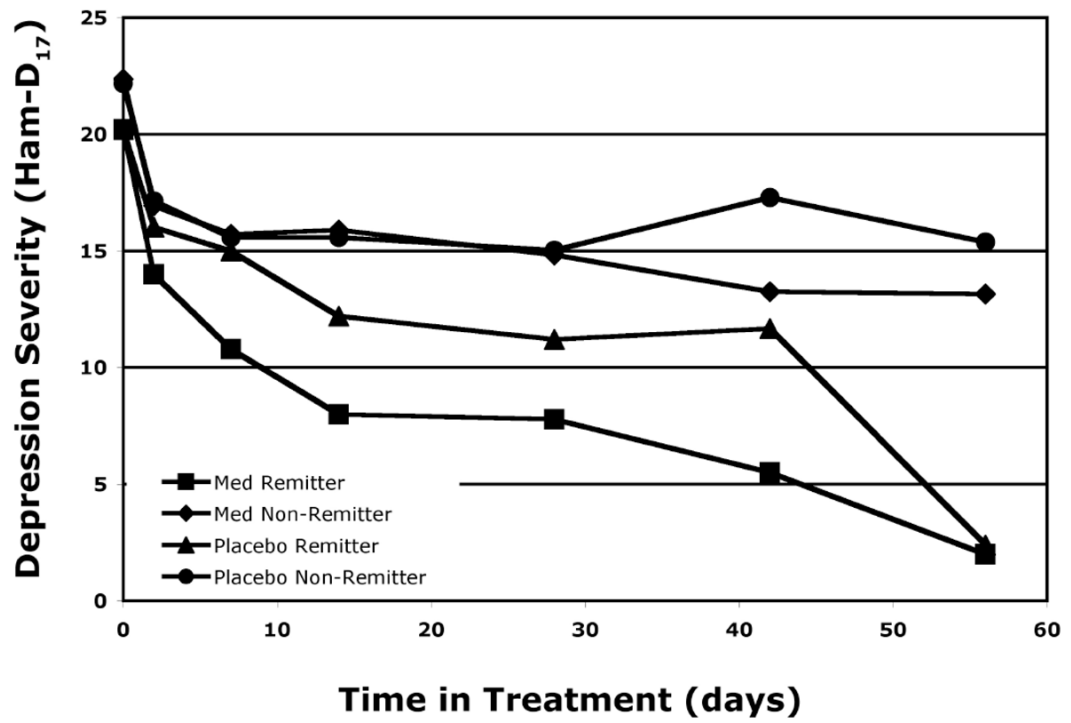
Figure 2. Clinical Symptoms Over Time
Changes in Ham-D17 are plotted for the four groups (remitters and non-remitters on medication or placebo).
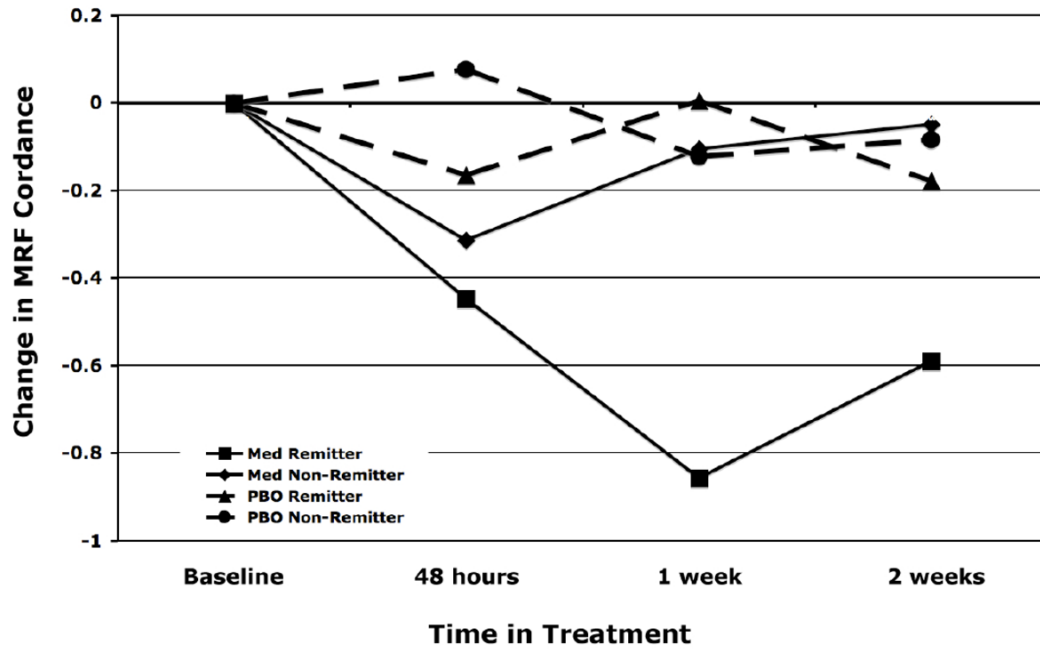
Figure 3. Time Course of MRFC Change
Changes in MRFC at 48 hrs and 1 and 2 weeks of treatment, in subjects in remission (solid
line with circles) and non-remission subjects (dashed line with squares) subjects. Groups show
statistical separation at one and two weeks of exposure to medication. * $p < 0.05$

Table

Cordance Values Over Time. Cordance values at baseline and changes over time are shown for the four groups.

	Baseline Cordance	Change at 48 hrs	Change at 1 week	Change at 2 weeks
Medication Remitters	0.42 (1.29)	− 0.53 (0.60)	−1.14 (0.77)	− 0.49 (0.61)
Medication Non-Remitters	0.34 (1.05)	− 0.24 (0.76)	− 0.03 (0.76)	− 0.10 (0.87)
Placebo Remitters	0.35 (0.99)	− 0.18 (0.89)	0.01 (0.38)	− 0.10 (0.38)
Placebo Non-Remitters	−0.18 (0.96)	0.07 (0.58)	0.09 (0.84)	0.07 (0.91)