Published in final edited form as:

Psychiatry Res. 2011 June 30; 192(3): 188–194. doi:10.1016/j.psychres.2010.12.007.

Rostral anterior cingulate cortex activity and early symptom improvement during treatment for major depressive disorder

Alexander S. Korb^{*}, Aimee M. Hunter, Ian A. Cook, and Andrew F. Leuchter

Laboratory of Brain, Behavior, and Pharmacology, and the UCLA Depression Research & Clinic Program, Semel Institute for Neuroscience and Human Behavior at UCLA; Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA

Abstract

In treatment trials for Major Depressive Disorder (MDD), early symptom improvement is predictive of eventual clinical response. Clinical response may also be predicted by elevated pretreatment theta (4-7 Hz) current density in the rostral anterior cingulate (rACC) and medial orbitofrontal cortex (mOFC). We investigated the relationship between pretreatment EEG and early improvement in predicting clinical outcome in 72 MDD subjects across three placebo-controlled treatment trials. Subjects were randomized to receive fluoxetine, venlafaxine, or placebo. Theta current density in the rACC and mOFC was computed with Low-Resolution Brain Electromagnetic Tomography (LORETA). An ANCOVA, examining week 8 Hamilton Depression Rating Scale (HamD) percent change, showed a significant effect of week-2-HamD-percent-change, and a significant three-way interaction of week-2-HamD-percent-change $\times$ Treatment $\times$ rACC. Medication subjects with robust early improvement showed almost no relationship between rACC theta current density and final clinical outcome. However, in subjects with little early improvement, rACC activity showed a strong relationship with clinical outcome. The model examining mOFC showed a trend in the three-way interaction. A combination of pretreatment rACC activity and early symptom improvement may be useful for predicting treatment response.

Keywords

Depression; EEG; LORETA; Placebo; Orbitofrontal; rostral anterior cingulate

1. Introduction

Major Depressive Disorder (MDD) is difficult to treat because there is no accepted method to predict which treatment will benefit a particular patient. The current trial-and-error strategy for medication selection (Fochtmann and Gelenberg, 2005) eventually leads to response for the majority of patients, but patients may have less than a 30% chance of recovery with an initial trial of an antidepressant medication (Trivedi et al., 2006). Recovery from depression would be hastened by development of predictors that could be measured

© 2010 Elsevier Ireland Ltd. All rights reserved.

Correspondence to: Alexander S. Korb, Ph.D., 760 Westwood Plaza, Rm. 37-461, Los Angeles, CA 90024-1759, alexkorb@ucla.edu, Phone: (310) 825-0248, Fax : (310) 825-7642.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

prior to treatment or early in the course of treatment (Leuchter et al., 2009b). Such predictors include pretreatment regional brain activity, as well as early improvement in symptoms (Leuchter et al., 2009b).

Prior reports, using various neuroimaging techniques, have shown that subjects who ultimately respond to antidepressant treatment typically have elevated pretreatment metabolic activity in the rACC and mOFC, as demonstrated with positron emission tomography (PET) (Mayberg et al., 1997; Saxena et al., 2003), or increased theta current density as measured using quantitative electroencephalography (QEEG) (Pizzagalli et al., 2001; Mulert et al., 2007; Korb et al., 2009). Theta current density studies have utilized Low-Resolution Brain Electromagnetic Tomography (LORETA), which is a widely used and well-validated QEEG source localization algorithm (Seeck et al., 1998; Worrell et al., 2000; Oakes et al., 2004). It is not surprising that responders differ from non-responders in both glucose metabolism and theta current density, given that rACC theta current density has been shown to correlate with rACC metabolism (Oakes et al., 2004).

In addition to the predictions of pretreatment brain activity, numerous reports also have demonstrated a strong relationship between eventual response and symptom improvement in the first two weeks of treatment (Szegedi et al., 2003; Katz et al., 2004; Papakostas et al., 2007; Stassen et al., 2007; Szegedi et al., 2009). Conversely, the absence of early improvement during pharmacotherapy is associated with poor eight week outcome (Nierenberg et al., 1995; Szegedi et al., 2009), although the lack of specificity of these changes limits the usefulness of this measure as a sole predictor (Leuchter et al., 2009b; Szegedi et al., 2009). Whereas distinct lines of research have identified brain function and early symptom improvement as predictors of response, the relationship between these predictors is unknown. Understanding whether early improvement in symptoms is linked to, or independent of, rACC or mOFC activity is important in determining how these predictors could potentially be employed in clinical practice.

While elevated baseline rACC and mOFC activity have been associated with greater likelihood of clinical response, the relationship between pretreatment rACC/mOFC activity and early improvement regarding ultimate clinical outcome has not been examined¹. It is not known whether baseline theta current density predicts symptom improvement early or at other time points during eight weeks of treatment. Similarly, it is not known whether the relationship between baseline activity and eight-week outcome is dependent on (or independent of) early clinical improvement.

This study investigated relationships among early improvement, rACC and mOFC activity, and clinical outcome. We hypothesized that early improvement in symptoms would be predictive of final clinical outcomes. Exploratory analyses examined the relationship of pretreatment theta current density to clinical improvement at various time points during the first eight weeks of treatment, and also examined the combination and interaction of early improvement and pretreatment theta current density in the prediction of final clinical outcomes.

¹Our lab has previously examined response and baseline theta current density in these subjects (Korb et al., 2009). We have also examined data from these subjects to address other research questions (Cook et al., 2002; Leuchter et al., 2002; Leuchter et al., 2004; Hunter et al., 2006; Korb et al., 2008; Cook et al., 2009; Hunter et al., 2010).

2. Methods

2.1 Study design

We analyzed resting EEG data collected from three placebo-controlled treatment trials of MDD as described previously (Korb et al., 2009). The trials used identical inclusion and exclusion criteria, and included an initial week of single-blinded placebo treatment, followed by eight weeks of double-blinded treatment with placebo or medication. In the medication arm, two of the trials used venlafaxine (150 mg. daily), and the third used fluoxetine (20 mg. daily). Data were analyzed for all 72 subjects who completed the eight weeks of treatment (fluoxetine $n=13$, venlafaxine $n=24$, placebo $n=35$).

2.2 Subjects

The UCLA Institutional Review Board approved all experimental procedures. Experimental procedures were explained fully to each subject, and written informed consent was obtained. Subjects were recruited from outpatient clinics of the UCLA Neuropsychiatric Hospital and through community advertisements. At entry, all subjects had 17-item Hamilton Depression Rating Scale (HamD) scores ≥ 16 (Hamilton, 1960) and met DSM-IV criteria for a major depressive episode diagnosed using the Structured Clinical Interview for DSM-IV (First et al., 1995). Demographics of the sample are shown in Table 1. Subjects were excluded if they suffered from any medical illness or received any medication known to significantly affect brain function, if they had a history of suicide attempt, or if they had previously failed to benefit from treatment with the antidepressant being studied. All subjects were free of any psychotropic medication for at least two weeks prior to enrollment.

2.3 EEG procedures

EEG recordings methods have been described previously (Cook et al., 2002), and utilized an extended International 10-20 System with an electrode cap of 36 tin recording electrodes (ElectroCap, Inc.; Eaton, OH) referenced to Pz. Electrode impedances were balanced and under 5k Ω for all channels. While subjects rested in the eyes-closed, maximally alert state in a sound-attenuated room with subdued lighting, up to twenty minutes of EEG data were collected using the QND system (Neurodata, Inc.; Pasadena, CA). Patients were frequently and vigorously re-alerted at the first sign of drowsiness. EEG data were digitized on line at 256 samples/channel/sec with a high-frequency filter of 70 Hz and a low-frequency filter of 0.3 Hz, as well as a notch filter at 60 Hz. Only EEG that was free of eye movement, drowsiness, excess muscle, or other artifacts was considered for further processing; an EEG technologist selected for processing the first 10 to 16 two-second epochs of data that met this criteria. Twenty to thirty-two seconds of EEG has been shown to be sufficient for characterizing clinically relevant differences in depression (Cook et al., 2002; Mientus et al., 2002; Bares et al., 2007; Korb et al., 2008). Prior to processing, a second EEG technologist, blinded to subject identity and treatment condition, independently confirmed that only artifact-free data were selected. The average number of epochs selected per subject was 14.1 ± 2.2 . These epochs were then transformed to three-dimensional current density maps using LORETA.

2.4 LORETA analysis

The LORETA-KEY package (<http://www.unizh.ch/keyinst/loreta>) (Pascual-Marqui et al., 1999) was used to compute theta-band (4-7 Hz) current density for each subject. Our LORETA methods have been described previously (Korb et al., 2009) and are summarized here. A cross-spectral matrix was used to compute current density in each of 2394 cortical voxels. For each subject, theta band current density was normalized to a total power of 1.0.

Based on previous studies, regions of interest (ROIs) were created for the rACC and mOFC (Fig 1A and 1B). The rACC ROI consisted of 14 voxels and was taken from the results of a previous study on current density and treatment response (Pizzagalli et al., 2001) (Fig. 1A). The mOFC ROI consisted of 34 voxels and was based on anatomical classifications (Fig. 1B). Voxels in each ROI were averaged and log-transformed, resulting in a single current density value for that ROI.

2.5 Statistical analysis

To examine the effect of week 2 HamD percent change on week 8 HamD percent change, a simple linear regression was run for both the placebo-treated group and the medication-treated group.

To examine the effect of pretreatment theta current density on HamD percent change at all available time points, we conducted a multilevel mixed-effects regression analysis. The multilevel regression included the factors of Visit (5 levels: 48 hours, Week 1, Week 2, Week 4 and Week 8) and Treatment (2 levels: medication and placebo). It also included baseline-theta-current-density as a continuous variable. In order to avoid co-linearity, baseline-theta-current-density was centered by subtracting the mean. All 2-way interactions and the 3-way interaction were included. A separate regression was run for each ROI (rACC, mOFC).

To predict final clinical outcome (week 8 HamD percent change) using a combination of baseline rACC theta current density (continuous) and early improvement (continuous), we applied an ANCOVA model. The ANCOVA included variables for week-2-HamD-percent-change (continuous) and baseline-theta-current-density (continuous) as covariates of interest, as well as a factor of Treatment (2 levels). The continuous variables were centered to avoid co-linearity. The ANCOVA also included all 2-way interactions and the 3-way interaction. A separate ANCOVA was conducted for each ROI.

3. Results

3.1 Week 2 HamD percent change

At week 2 the medication group ($n = 37$) showed a mean percent change in HamD of 35.6% (*S.D.* 27.1%). The placebo group ($n = 35$) showed a mean week 2 HamD percent change of 31.1% (*S.D.* 27.2%). Percent change in HamD at week 2 was a highly significant predictor of week 8 HamD percent change in both the medication group ($\beta = 0.711$, $P < 0.001$) and the placebo group ($\beta = 0.605$, $P = 0.004$).

3.2 Theta current density and HamD percent change at multiple time points

The multilevel mixed-effects regression showed a significant effect of baseline rACC theta current density by Visit ($\chi^2_5 = 11.30$, $P = 0.046$). The marginal effects of rACC by visit are listed in Table 2. rACC was significantly related to HamD percent change only at week 2 and week 8. At both time points, elevated baseline rACC theta current density was associated with greater decrease in symptoms. There was no significant difference by treatment group on the effect of rACC theta current density by Visit ($\chi^2_4 = 2.81$, $P = 0.590$).

In the mOFC region, the multilevel mixed-effects regression the effect of baseline theta current density by Visit approached significance ($\chi^2_5 = 10.70$, $P = 0.058$). For comparison to rACC the marginal effects of mOFC by visit are listed in Table 2, even though the interaction by Visit was not significant. There was no significant difference by treatment group on the effect of mOFC theta current density by visit ($\chi^2_4 = 3.91$, $P = 0.418$).

3.3 Combining early improvement and baseline theta current density

The full results of the ANCOVA are shown in Table 3. In ANCOVA including the rACC, the overall model was significant ($F_{7, 64} = 5.64, P < 0.001$), and explained 38.2% of the variance in week 8 HamD percent change. There was a highly significant main effect of week-2-HamD-percent-change on week-8-HamD-percent-change ($F_{1, 64} = 18.18, P < 0.001$). The factor Treatment also had a significant effect ($F_{1, 64} = 5.05, P = 0.028$). The three-way interaction of week-2-HamD-percent-change $\times$ Treatment $\times$ rACC was also significant ($F_{1, 64} = 4.24, P = 0.044$).

Figure 2 illustrates the relationship, by treatment, among baseline rACC theta current density, early improvement, and percent change in HamD at eight weeks. Medication subjects with robust early improvement showed almost no relationship between rACC theta current density and final clinical outcome. However, subjects with little to no early improvement showed a strong relationship between theta current density and final clinical outcome. In placebo-treated subjects, rACC theta current density and week-8-HamD-percent-change showed a different relationship. Placebo subjects with robust early improvement show a slight positive relationship between rACC theta current density and week-8-HamD-percent-change. However, placebo subjects with little to no early improvement show a slight negative relationship between rACC theta current density and week-8-HamD-percent-change.

In the ANCOVA including the mOFC, the overall model was significant ($F_{7, 64} = 5.64, P < 0.001$), and explained 37.7% of the variance in week-8-HamD-percent-change. There was also a highly significant main effect of week-2-HamD-percent-change on week-8-HamD-percent-change ($F_{1, 64} = 16.10, P < 0.001$). The factor of Treatment was significant ($F_{1, 64} = 4.82, P = 0.032$). The three-way interaction of week-2-HamD-percent-change $\times$ Treatment $\times$ mOFC showed a similar overall pattern as seen in the rACC but did not reach significance ($F_{1, 64} = 3.22, P = 0.077$).

4. Discussion

As hypothesized, the present study showed that across treatments early improvement in symptoms was significantly correlated with final clinical outcome, agreeing with numerous previous reports (Szegeedi et al., 2003; Katz et al., 2004; Papakostas et al., 2007; Stassen et al., 2007; Szegeedi et al., 2009). Further results demonstrated, for the first time, relationships among early improvement in depressive symptoms, pretreatment rACC/mOFC activity, and clinical outcome. Higher pretreatment rACC theta current density was associated with greater symptom improvement at both week 2 and week 8. A similar trend was seen in the mOFC. Finally, combining early improvement and baseline rACC theta current density in a single analysis revealed a significant interaction of these variables in predicting week 8 outcomes. The interaction showed a differential effect of rACC/mOFC theta current density depending on type of treatment and the degree of early improvement.

The present study is the first to show a relationship between pre-treatment rACC theta current density and medication or placebo response over time intervals shorter than four weeks. In prior work, pretreatment activity in these same regions has been evaluated in relationship to acute response to sleep deprivation. Whereas we did not see a significant relationship over our shortest time interval (48 hours), previous reports have found elevated pretreatment rACC and mOFC perfusion and metabolism in next-day responders to sleep deprivation (Volk et al., 1997; Wu et al., 1999). Differences between our results and those from sleep deprivation studies may be due to differences in the mechanisms underlying these interventions.

The current finding that higher pretreatment rACC activity is related to greater degree of response at week 8 endpoint is consistent with an independent LORETA report, which found that higher pretreatment rACC theta current density was associated with response following six months of open label antidepressant treatment (Pizzagalli et al., 2001). Prior studies utilizing PET have reported mixed results regarding the direction of the relationship between pretreatment rACC activity and response. Whereas Mayberg and colleagues (Mayberg et al., 1997) and Saxena and co-workers (Saxena et al., 2003) found higher pretreatment rACC metabolism associated with medication response after six to twelve weeks of treatment, respectively, groups led by Brody (Brody et al., 1999) and Konarski (Konarski et al., 2009) showed *lower* pretreatment rACC metabolism in responders. Given the interaction seen in our results, it is possible that discrepancies among the PET study findings may be explained by differences in subjects' early improvement across studies. Alternatively, since neither of these studies was placebo controlled, placebo response may play a role.

In contrast to our present findings, Mulert and colleagues showed that pretreatment rACC and mOFC theta current density differed between responders and non-responders in a four-week open label study (Mulert et al., 2007). Our analysis did not show a significant relationship between rACC or mOFC theta current density and degree of response at four weeks. Methodological differences may explain the discrepancies. For example, the Mulert study was conducted on an inpatient population with open-label treatment. Perhaps more puzzling, however, is the observation from our data that that rACC and mOFC theta current density related significantly to HamD percent change at week 2 and week 8 but not week 4. This may be explained by research from our lab that has identified, using growth mixture modeling in this same subject population, a class of patients who show symptom volatility in response to medication (Hunter et al., 2010). Patients in the symptom volatility group show little or no early improvement, large improvements around week 4, but ultimately do not respond to medication at later timepoints. Thus the current result may be explained by the fact that these subjects are clinically better off at 4 weeks than they are at 2 or 8 weeks.

Our results illustrate a complex relationship among treatment, theta current density, early improvement, and eight week outcome (Figure 2). Most notably, there was a significant interaction of $rACC \times \text{Week 2 HamD Percent Change} \times \text{Treatment}$. Thus the effect of rACC activity on final clinical outcome depended both on how much subjects improved at week 2 and whether they were treated with medication or placebo. Medication subjects with robust early improvement showed almost no relationship between rACC activity and week 8 HamD percent change. However, subjects who showed little or no early improvement had a strong positive relationship between these two variables. These relationships are further illustrated in figure 3 with individual subject data. This complex relationship of rACC theta current density and week 8 outcome may have clinical relevance for patients who fail to improve early in treatment; if their pretreatment rACC activity is known, then their likelihood of subsequent response may, in part, be determined.

Placebo-treated subjects showed a different relationship from medication treated subjects among theta current density, early improvement and eight week HamD percent change. In placebo subjects with robust early improvement, higher baseline theta current density was associated with better outcome at eight weeks. However, in placebo subjects with little or no early improvement, higher theta was associated with worse outcomes. There is scant relevant literature to assist in interpreting this finding. Despite the relevance to clinical psychiatry, the mechanisms of the placebo antidepressant response remain incompletely understood. Prior work by Mayberg and colleagues (Mayberg et al., 2002) reported changes in subgenual ACC in placebo responders, an area which has extensive connections with both rACC and mOFC. While neither rACC nor mOFC have been directly implicated in the

placebo antidepressant response, they have been shown to play a role in other types of placebo response. For example, research on pain and placebo analgesia has shown that higher activity in both OFC and rACC are related to a stronger placebo response (Kong et al., 2006).

Current research cannot fully explain the variability in time-course and degree to which MDD patients respond to treatment. Therefore, the mechanism of how rACC activity relates to response is also unclear. However, there is evidence that rACC activity may influence or be influenced by the same mechanisms that lead to treatment response. For example, two common targets of antidepressant medications, the serotonin transporter and monoamine oxidase, exist in high concentrations in the rACC in depressed subjects (Varnas et al., 2004; Meyer et al., 2009). In addition, the rACC may also be influenced by the mechanisms that contribute to depression; for example, polymorphisms in genes that control these targets may lead both to increased risk for depression (Hariri et al., 2005; Pezawas et al., 2005; Aklillu et al., 2009; Rivera et al., 2009; Fan et al., 2010; Holmes et al., 2010) as well as to functional and structural abnormalities in the rACC (Pezawas et al., 2005; Passamonti et al., 2008; Holmes et al., 2010).

We interpret elevated rACC theta current density as evidence of elevated neural activity, because rACC theta current density has been shown to correlate positively with rACC glucose metabolism (Pizzagalli et al., 2003). In the mOFC, however, no significant correlation has been demonstrated between theta current density and glucose metabolism (Pizzagalli et al., 2003). Nonetheless, mOFC theta current density may be functionally related to rACC theta current density, as these areas have been shown to be physically and functionally connected (Ongur and Price, 2000; Kringelbach and Rolls, 2004). The rACC and mOFC are both important areas in the limbic-cortical dysregulation model of MDD (Mayberg, 2003). The rACC is thought primarily to process emotion and attention (Lane et al., 1998), while the mOFC primarily processes emotion and reward (O'Doherty et al., 2001; Rolls et al., 2008). Elevated activity in these areas may increase the salience and rewarding aspects of treatment. It has been proposed that this elevated activity may reflect a compensatory neural response to depression that renders a patient more likely to improve in response to treatment with medication (Mayberg et al., 1997; Pizzagalli et al., 2001; Saxena et al., 2003) and sleep deprivation (Volk et al., 1997; Wu et al., 1999). Our results are consistent with this model.

This study has several limitations. First, it should be noted that the LORETA method is not a direct measure of rACC or mOFC activity, but rather a low-resolution estimate of current density. Second, we do not have information to allow for clinical subtyping of depression (e.g., melancholic depression), and it is possible that such subtypes may demonstrate different neurophysiologic characteristics. In addition, there are limitations on applying the results of this study to clinical practice. While rACC activity measures may one day be employed clinically, the research is not yet sophisticated enough to predict individual responses.

These findings may be viewed within the framework of recent results indicating that prefrontal QEEG monitoring may be particularly useful in the management of MDD (Cook et al., 2009; Leuchter et al., 2009a; Leuchter et al., 2009c; Hunter et al., 2010). For example, early changes in the theta band in the QEEG measure cordance may differentiate between eventual responders, non-responders and patients exhibiting symptom volatility (Hunter et al., 2010). Similarly the QEEG Antidepressant Treatment Response (ATR) index, which combines baseline and week 1 change measurements, may predict remission on medication (Leuchter et al., 2009a; Leuchter et al., 2009c).

Results of this study add to our understanding of the factors that contribute to early improvement, as well as to the relationships between pretreatment brain function and early improvement in predicting clinical outcome. Early improvement is clinically relevant not only because expedited symptom improvement is desirable, but also because prior work has shown that symptom improvement in the first two weeks is predictive of subsequent response (Szegedi et al., 2003; Katz et al., 2004; Papakostas et al., 2007; Stassen et al., 2007). Further study of the relationships between brain function and early improvement may help point to mechanisms of clinical response in MDD, and improve prediction of treatment outcomes.

Acknowledgments

The authors thank Barbara Siegman R.EEG.T., and Suzie Hodgkin, R.EEG.T., (recording EEG data); Michelle Abrams, R.N., (subject recruitment and evaluation); David Schairer (EEG data processing); and UCLA Academic Technology Services (ATS) Statistical Consulting. This work was supported by NIMH-NRSA training fellowship (NIMH T32 MH17140), by a grant from the National Center for Complementary and Alternative Medicine (R01 AT002479), and by an endowment in depression research from Joanne and George Miller and Family. We also acknowledge the grant support of Eli Lilly and Company, Wyeth-Ayerst Laboratories, and Aspect Medical Systems, Inc. LORETA-KEY software was provided by Roberto D. Pascual-Marqui, KEY Institute for Brain-Mind Research, University of Zurich.

References

- Aklillu E, Karlsson S, Zachrisson OO, Ozdemir V, Agren H. Association of MAOA gene functional promoter polymorphism with CSF dopamine turnover and atypical depression. *Pharmacogenetics and Genomics*. 2009; 19:267–275. [PubMed: 19214141]
- Bares M, Brunovsky M, Kopecek M, Stopkova P, Novak T, Kozeny J, Hoschl C. Changes in QEEG prefrontal cordance as a predictor of response to antidepressants in patients with treatment resistant depressive disorder: a pilot study. *Journal of Psychiatric Research*. 2007; 41:319–325. [PubMed: 16889798]
- Brody AL, Saxena S, Silverman DH, Alborzian S, Fairbanks LA, Phelps ME, Huang SC, Wu HM, Maidment K, Baxter LR Jr. Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine. *Psychiatry Research*. 1999; 91:127–139. [PubMed: 10641577]
- Cook IA, Hunter AM, Abrams M, Siegman B, Leuchter AF. Midline and right frontal brain function as a physiologic biomarker of remission in major depression. *Psychiatry Research: Neuroimaging*. 2009; 174:152–157.
- Cook IA, Leuchter AF, Morgan M, Witte E, Stubbeman WF, Abrams M, Rosenberg S, Uijtdehaage SH. Early changes in prefrontal activity characterize clinical responders to antidepressants. *Neuropsychopharmacology*. 2002; 27:120–131. [PubMed: 12062912]
- Fan M, Liu B, Jiang T, Jiang X, Zhao H, Zhang J. Meta-analysis of the association between the monoamine oxidase-A gene and mood disorders. *Psychiatric Genetics*. 2010; 20:1–7. [PubMed: 20010318]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, J. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P, version 2.0). New York State Psychiatric Institute, Biometrics Research Department; New York: 1995.
- Fochtman, L.J.; Gelenberg, A.J. Guideline Watch: Practice Guideline for the Treatment of Patients with Major Depressive Disorder. 2005.
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960; 23:56–62. [PubMed: 14399272]
- Hariri AR, Drabant EM, Munoz KE, Kolachana BS, Mattay VS, Egan MF, Weinberger DR. A susceptibility gene for affective disorders and the response of the human amygdala. *Archives of General Psychiatry*. 2005; 62:146–152. [PubMed: 15699291]
- Holmes AJ, Bogdan R, Pizzagalli DA. Serotonin transporter genotype and action monitoring dysfunction: a possible substrate underlying increased vulnerability to depression. *Neuropsychopharmacology*. 2010; 35:1186–1197. [PubMed: 20090673]

- Hunter AM, Leuchter AF, Morgan ML, Cook IA. Changes in brain function (quantitative EEG cordance) during placebo lead-in and treatment outcomes in clinical trials for major depression. *American Journal of Psychiatry*. 2006; 163:1426–1432. [PubMed: 16877657]
- Hunter AM, Muthen BO, Cook IA, Leuchter AF. Antidepressant response trajectories and quantitative electroencephalography (QEEG) biomarkers in major depressive disorder. *Journal of Psychiatric Research*. 2010; 44:90–98. [PubMed: 19631948]
- Katz MM, Tekell JL, Bowden CL, Brannan S, Houston JP, Berman N, Frazer A. Onset and early behavioral effects of pharmacologically different antidepressants and placebo in depression. *Neuropsychopharmacology*. 2004; 29:566–579. [PubMed: 14627997]
- Konarski JZ, Kennedy SH, Segal ZV, Lau MA, Bieling PJ, McIntyre RS, Mayberg HS. Predictors of nonresponse to cognitive behavioural therapy or venlafaxine using glucose metabolism in major depressive disorder. *Journal of Psychiatry and Neuroscience*. 2009; 34:175–180. [PubMed: 19448846]
- Kong J, Gollub RL, Rosman IS, Webb JM, Vangel MG, Kirsch I, Kaptchuk TJ. Brain activity associated with expectancy-enhanced placebo analgesia as measured by functional magnetic resonance imaging. *Journal of Neuroscience*. 2006; 26:381–388. [PubMed: 16407533]
- Korb AS, Cook IA, Hunter AM, Leuchter AF. Brain electrical source differences between depressed subjects and healthy controls. *Brain Topography*. 2008; 21:138–146. [PubMed: 18958615]
- Korb AS, Hunter AM, Cook IA, Leuchter AF. Rostral anterior cingulate cortex theta current density and response to antidepressants and placebo in major depression. *Clinical Neurophysiology*. 2009; 120:1313–1319. [PubMed: 19539524]
- Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Progress in Neurobiology*. 2004; 72:341–372. [PubMed: 15157726]
- Lane RD, Reiman EM, Axelrod B, Yun LS, Holmes A, Schwartz GE. Neural correlates of levels of emotional awareness. Evidence of an interaction between emotion and attention in the anterior cingulate cortex. *Journal of Cognitive Neuroscience*. 1998; 10:525–535. [PubMed: 9712681]
- Leuchter AF, Cook IA, Gilmer WS, Marangell LB, Burgoyne KS, Howland RH, Trivedi MH, Zisook S, Jain R, McCracken JT, Fava M, Iosifescu D, Greenwald S. Effectiveness of a quantitative electroencephalographic biomarker for predicting differential response or remission with escitalopram and bupropion in Major Depressive Disorder. *Psychiatry Research*. 2009a; 169:132–138. [PubMed: 19709754]
- Leuchter AF, Cook IA, Hunter AM, Korb AS. A new paradigm for the prediction of antidepressant treatment response. *Dialogues in Clinical Neuroscience*. 2009b; 11:435–446. [PubMed: 20135901]
- Leuchter AF, Cook IA, Marangell LB, Gilmer WS, Burgoyne KS, Howland RH, Trivedi MH, Zisook S, Jain R, McCracken JT, Fava M, Iosifescu D, Greenwald S. Comparative effectiveness of biomarkers and clinical indicators for predicting outcomes of SSRI treatment in Major Depressive Disorder: results of the BRITE-MD study. *Psychiatry Research*. 2009c; 169:124–131. [PubMed: 19712979]
- Leuchter AF, Cook IA, Witte EA, Morgan M, Abrams M. Changes in brain function of depressed subjects during treatment with placebo. *American Journal of Psychiatry*. 2002; 159:122–129. [PubMed: 11772700]
- Leuchter AF, Morgan M, Cook IA, Dunkin J, Abrams M, Witte E. Pretreatment neurophysiological and clinical characteristics of placebo responders in treatment trials for major depression. *Psychopharmacology (Berl)*. 2004; 177:15–22. [PubMed: 15252704]
- Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *British Medical Bulletin*. 2003; 65:193–207. [PubMed: 12697626]
- Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, Silva JA, McGinnis S, Glass TG, Martin CC, Fox PT. Cingulate function in depression: a potential predictor of treatment response. *Neuroreport*. 1997; 8:1057–1061. [PubMed: 9141092]
- Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S, Jerabek PA. The functional neuroanatomy of the placebo effect. *American Journal of Psychiatry*. 2002; 159:728–737. [PubMed: 11986125]

- Meyer JH, Wilson AA, Sagrati S, Miler L, Rusjan P, Bloomfield PM, Clark M, Sacher J, Voineskos AN, Houle S. Brain monoamine oxidase A binding in major depressive disorder: relationship to selective serotonin reuptake inhibitor treatment, recovery, and recurrence. *Archives of General Psychiatry*. 2009; 66:1304–1312. [PubMed: 19996035]
- Mientus S, Gallinat J, Wuebben Y, Pascual-Marqui RD, Mulert C, Frick K, Dorn H, Herrmann WM, Winterer G. Cortical hypoactivation during resting EEG in schizophrenics but not in depressives and schizotypal subjects as revealed by low resolution electromagnetic tomography (LORETA). *Psychiatry Res*. 2002; 116:95–111. [PubMed: 12426037]
- Mulert C, Juckel G, Brunnermeier M, Karch S, Leicht G, Mergl R, Moller HJ, Hegerl U, Pogarell O. Rostral anterior cingulate cortex activity in the theta band predicts response to antidepressive medication. *Clinical EEG and Neuroscience*. 2007; 38:78–81. [PubMed: 17515172]
- Nierenberg AA, McLean NE, Alpert JE, Worthington JJ, Rosenbaum JF, Fava M. Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. *American Journal of Psychiatry*. 1995; 152:1500–1503. [PubMed: 7573590]
- Oakes TR, Pizzagalli DA, Hendrick AM, Horras KA, Larson CL, Abercrombie HC, Schaefer SM, Koger JV, Davidson RJ. Functional coupling of simultaneous electrical and metabolic activity in the human brain. *Human Brain Mapping*. 2004; 21:257–270. [PubMed: 15038007]
- O'Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C. Abstract reward and punishment representations in the human orbitofrontal cortex. *Nature Neuroscience*. 2001; 4:95–102.
- Ongur D, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral Cortex*. 2000; 10:206–219. [PubMed: 10731217]
- Papakostas GI, Petersen T, Sklarisky KG, Nierenberg AA, Alpert JE, Fava M. Timing of clinical improvement and symptom resolution in the treatment of major depressive disorder. *Psychiatry Research*. 2007; 149:195–200. [PubMed: 17157390]
- Pascual-Marqui RD, Lehmann D, Koenig T, Kochi K, Merlo MC, Hell D, Koukkou M. Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia. *Psychiatry Res*. 1999; 90:169–179. [PubMed: 10466736]
- Passamonti L, Cerasa A, Gioia MC, Magariello A, Muglia M, Quattrone A, Fera F. Genetically dependent modulation of serotonergic inactivation in the human prefrontal cortex. *Neuroimage*. 2008; 40:1264–1273. [PubMed: 18261931]
- Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nature Neuroscience*. 2005; 8:828–834.
- Pizzagalli D, Pascual-Marqui RD, Nitschke JB, Oakes TR, Larson CL, Abercrombie HC, Schaefer SM, Koger JV, Benca RM, Davidson RJ. Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. *American Journal of Psychiatry*. 2001; 158:405–415. [PubMed: 11229981]
- Pizzagalli DA, Oakes TR, Davidson RJ. Coupling of theta activity and glucose metabolism in the human rostral anterior cingulate cortex: an EEG/PET study of normal and depressed subjects. *Psychophysiology*. 2003; 40:939–949. [PubMed: 14986847]
- Rivera M, Gutierrez B, Molina E, Torres-Gonzalez F, Bellon JA, Moreno-Kustner B, King M, Nazareth I, Martinez-Gonzalez LJ, Martinez-Espin E, Munoz-Garcia MM, Motrico E, Martinez-Canavate T, Lorente JA, Luna JD, Cervilla JA. High-activity variants of the uMAOA polymorphism increase the risk for depression in a large primary care sample. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*. 2009; 150B:395–402.
- Rolls ET, Grabenhorst F, Parris BA. Warm pleasant feelings in the brain. *Neuroimage*. 2008; 41:1504–1513. [PubMed: 18468458]
- Saxena S, Brody AL, Ho ML, Zohrabi N, Maidment KM, Baxter LR Jr. Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression. *American Journal of Psychiatry*. 2003; 160:522–532. [PubMed: 12611834]
- Seeck M, Lazeyras F, Michel CM, Blanke O, Gericke CA, Ives J, Delavelle J, Golay X, Haenggeli CA, de Tribolet N, Landis T. Non-invasive epileptic focus localization using EEG-triggered

- functional MRI and electromagnetic tomography. *Electroencephalography and Clinical Neurophysiology*. 1998; 106:508–512. [PubMed: 9741750]
- Stassen HH, Angst J, Hell D, Scharfetter C, Szegedi A. Is there a common resilience mechanism underlying antidepressant drug response? Evidence from 2848 patients. *Journal of Clinical Psychiatry*. 2007; 68:1195–1205. [PubMed: 17854243]
- Szegedi A, Jansen WT, van Willigenburg AP, van der Meulen E, Stassen HH, Thase ME. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. *Journal of Clinical Psychiatry*. 2009; 70:344–353. [PubMed: 19254516]
- Szegedi A, Muller MJ, Angheliescu I, Klawe C, Kohnen R, Benkert O. Early improvement under mirtazapine and paroxetine predicts later stable response and remission with high sensitivity in patients with major depression. *Journal of Clinical Psychiatry*. 2003; 64:413–420. [PubMed: 12716243]
- Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *American Journal of Psychiatry*. 2006; 163:28–40. [PubMed: 16390886]
- Varnas K, Halldin C, Hall H. Autoradiographic distribution of serotonin transporters and receptor subtypes in human brain. *Human Brain Mapping*. 2004; 22:246–260. [PubMed: 15195291]
- Volk SA, Kaendler SH, Hertel A, Maul FD, Manoocheri R, Weber R, Georgi K, Pflug B, Hor G. Can response to partial sleep deprivation in depressed patients be predicted by regional changes of cerebral blood flow? *Psychiatry Research*. 1997; 75:67–74. [PubMed: 9351489]
- Worrell GA, Lagerlund TD, Sharbrough FW, Brinkmann BH, Busacker NE, Cicora KM, O'Brien TJ. Localization of the epileptic focus by low-resolution electromagnetic tomography in patients with a lesion demonstrated by MRI. *Brain Topography*. 2000; 12:273–282. [PubMed: 10912735]
- Wu J, Buchsbaum MS, Gillin JC, Tang C, Cadwell S, Wiegand M, Najafi A, Klein E, Hazen K, Bunney WE Jr, Fallon JH, Keator D. Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. *American Journal of Psychiatry*. 1999; 156:1149–1158. [PubMed: 10450253]

Figure 1. Regions of Interest

A sagittal view of the ROIs used in our analyses: rACC in red, mOFC in blue.

Figure 2. Pretreatment rACC Theta Current Density and Week Eight HamD Percent Change by Early Improvement

Lines indicate the average marginal effects of rACC theta current density (centered) on Week 8 HamD percent change at different levels of early improvement. That is, the lines reflect the expected relationship between rACC theta current density and outcome at a given degree of early improvement. Medication subjects with robust early improvement (e.g. 50%) show a weak relationship between rACC theta current density and clinical outcome, while medication subjects with little to no early improvement (e.g. 0%) show a strong relationship between rACC theta current density and clinical outcome.

Figure 3. Week 2 response and Wk8HamPctChg by rACC Theta (centered)

Scatter plots show individual subjects' log rACC theta current density (centered) and week 8 HamD percent change. Red dots depict subjects that met response criteria at week 2 (HamD percent change $\geq 50\%$), and are therefore termed Early Responders. Blue dots depict subjects that did not meet response criteria at week 2, and are therefore termed Early NonResponders. Red and blue lines represent the fitted regression lines for the Early Responders and Early NonResponders respectively.

Table 1
Subject Characteristics

Descriptive characteristics of subjects by treatment group.

Treatment	N	Baseline HamD	Age in years	Median # of Prior Episodes (Range)
Medication	37 (14 male)	21.8 ± 3.4	41.6 ± 12.4	2 (0 – 10+)
Placebo	35 (15 male)	21.9 ± 3.5	39.6 ± 12.2	2 (0 – 10+)

Table 2
Marginal Effects of Theta Current Density by Visit

The marginal effects by visit of pretreatment theta current density in the rACC and mOFC. The mOFC values are shown for comparison, even though the overall effect of Visit was not significant.

Visit	rACC		mOFC	
	Marginal Effect	<i>P</i>	Marginal Effect	<i>P</i>
48 Hours	0.046	0.700	0.013	0.920
Week 1	-0.168	0.159	-0.206	0.115
Week 2	-0.266	0.024	-0.313	0.016
Week 4	-0.086	0.466	-0.125	0.333
Week 8	-0.255	0.031	-0.275	0.033

Table 3

ANCOVA Tables

Both A) the rACC model and B) the mOFC model, had $R^2 = 0.38$.

A. rACC model						
Variable	Partial SS	df	MS	F	P	
Model	3.016	7	0.431	5.64	<0.001	
Week 2 HamD % Change	1.389	1	1.389	18.18	<0.001	
rACC	0.058	1	0.058	0.76	0.386	
Treatment	0.386	1	0.386	5.05	0.028	
Week 2 HamD % Change $\times$ rACC	0.02	1	0.02	0.26	0.612	
Treatment $\times$ Week 2 HamD % Change	0.019	1	0.018	0.24	0.624	
Treatment $\times$ rACC	0.028	1	0.028	0.36	0.548	
3-way interaction	0.324	1	0.324	4.24	0.044	
Residual	4.891	64	0.07642			

B. mOFC model						
Variable	Partial SS	df	MS	F	P	
Model	2.98	7	0.426	5.53	<0.001	
Week 2 HamD % Change	1.239	1	1.239	16.1	<0.001	
mOFC	0.035	1	0.035	0.46	0.501	
Treatment	0.371	1	0.371	4.82	0.032	
Week 2 HamD % Change $\times$ mOFC	0.008	1	0.008	0.1	0.752	
Treatment $\times$ Week 2 HamD % Change	0.017	1	0.017	0.22	0.640	
Treatment $\times$ mOFC	0.042	1	0.041	0.54	0.465	
3-way interaction	0.248	1	0.248	3.22	0.077	
Residual	4.926	64	0.077			