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Rostral Anterior Cingulate Cortex Theta Current Density and Response to Antidepressants and Placebo in Major Depression

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Abstract

Objective—To assess whether pretreatment theta current density in the rostral anterior cingulate (rACC) and medial orbitofrontal cortex (mOFC) differentiates responders from non-responders to antidepressant medication or placebo in a double-blinded study.

Methods—Pretreatment EEGs were collected from 72 subjects with Major Depressive Disorder (MDD) who participated in one of three placebo-controlled trials. Subjects were randomized to receive treatment with fluoxetine, venlafaxine, or placebo. Low-resolution brain electromagnetic tomography (LORETA) was used to assess theta current density in the rACC and mOFC.

Results—Medication responders showed elevated rACC and mOFC theta current density compared to medication non-responders (rACC: $p=0.042$; mOFC: $p=0.039$). There was no significant difference in either brain region between placebo responders and placebo non-responders.

Conclusions—Theta current density in the rACC and mOFC may be useful as a biomarker for prediction of response to antidepressant medication.

Significance—This is the first double-blinded treatment study to examine pretreatment rACC and mOFC theta current density in relation to antidepressant response and placebo response. Results support the potential clinical utility of this approach for predicting clinical outcome to antidepressant treatments in MDD.

Keywords

Depression; EEG; LORETA; Placebo; Anterior Cingulate

1. Introduction

Major Depressive Disorder (MDD) is difficult to treat, as fewer than 50% of patients respond to an initial 8-week trial of an antidepressant medication (Papakostas et al., 2007; Quitkin et al., 2000). Treatment of MDD would be improved by biomarkers that predicted response to a particular treatment so that those at greatest risk of non-response could receive alternate

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treatments. EEG biomarkers would be particularly practical to help direct treatment of MDD due to the inexpensive and non-invasive nature of the method. One such potential biomarker of treatment response is theta current density in the rostral anterior cingulate cortex (rACC) and medial orbitofrontal cortex (mOFC), a subregion of prefrontal cortex (PFC), as there is evidence to suggest that response is associated with pretreatment neurophysiologic activity in these areas (Mayberg et al., 1997; Mulert et al., 2007b; Pizzagalli et al., 2001; Saxena et al., 2003; Wu et al., 1999).

Neuroimaging studies of brain metabolism in MDD have shown that responders to antidepressant medication have elevated pretreatment resting metabolism in the rACC and medial PFC compared to non-responders (Mayberg et al., 1997; Saxena et al., 2003). This finding is not limited to pharmacotherapy interventions, as responders to sleep deprivation have also been shown to have elevated rACC and mOFC metabolism compared to non-responders (Wu et al., 1999), as well as elevated OFC perfusion (Volk et al., 1997).

Brain function and treatment response in MDD also have been studied using quantitative electroencephalographic (QEEG) imaging with low resolution electromagnetic tomography (LORETA) (Pascual-Marqui et al., 1999). LORETA is a widely used EEG source localization tool that computes sources of brain electrical activity from a linear weighted sum of scalp electrical potentials. The LORETA solution space is constrained to cortical gray matter, as cortical pyramidal cells are assumed to be the source of the EEG signal (Gloor, 1985). LORETA's ability to localize EEG sources has been validated against magnetic resonance imaging (MRI) (Worrell et al., 2000), functional MRI (fMRI) (Seeck et al., 1998), positron emission tomography (PET) (Oakes et al., 2004; Pizzagalli et al., 2003) and subdural electrocorticography (Seeck et al., 1998). The findings from PET studies may be especially applicable to the current study as theta band current density in the rACC has been shown to correlate positively with glucose metabolism (Pizzagalli et al., 2003).

EEG studies of treatment response utilizing LORETA are consistent with other neuroimaging methods. Responders to antidepressant medication have been shown to have elevated pretreatment theta band current density in the ACC (Mulert et al., 2007b; Pizzagalli et al., 2001) and mOFC (Mulert et al., 2007b) relative to non-responders. These open-label studies examined response to a tricyclic agent with serotonin-norepinephrine reuptake inhibition (SNRI) nortriptyline (Pizzagalli et al., 2001), the selective norepinephrine compound reboxetine (Mulert et al., 2007b), and the selective serotonin reuptake inhibitor (SSRI) citalopram (Mulert et al., 2007b). While theta current density and treatment response have not yet been studied in a double-blind trial, these reports suggest that rACC and mOFC current density may be robust predictors of clinical response across classes of antidepressant medication.

One challenge shared by all studies of treatment response in depression is the fact that many patients show clinical response to placebo treatment. While many depressed patients respond to treatment with placebo, and brain function has been shown to change with treatment in these subjects (Leuchter et al., 2002; Mayberg et al., 2002), no studies have yet assessed the usefulness of ACC and mOFC theta current density in predicting response to treatment with placebo.

We examined pretreatment levels of theta current density in rACC and mOFC in patients treated in double-blind placebo-controlled studies with either an SSRI (fluoxetine) or SNRI (venlafaxine). We hypothesized that when comparing responders versus non-responders to medication, responders would show elevated pretreatment theta current density in rACC and mOFC. We examined whether this relationship differed between the two medications.

Furthermore, we investigated whether pretreatment rACC and mOFC theta activity would be associated with response to placebo.

2. Methods

2.1 Study Design

We analyzed resting EEG collected from three placebo-controlled, double-blinded treatment trials that utilized identical inclusion and exclusion criteria. The studies included an initial week of single blinded placebo treatment, followed by eight weeks of double-blinded treatment with placebo or medication. Two of the studies used venlafaxine (150 mg. daily) for the medication arm, and the other used fluoxetine (20 mg. daily). We analyzed the data from all 72 subjects that completed treatment (fluoxetine n=13, venlafaxine n=24, placebo n=35).

2.2 Subjects

Subjects were adults ages 18-75 enrolled in one of three double-blinded placebo controlled treatment studies of MDD (n = 72) (Table 1). Subjects were recruited through community advertisements, and from outpatient clinics of the UCLA Neuropsychiatric Hospital. All subjects had been free of all psychotropic medications for at least two weeks prior to QEEG recording, which along with the week of single-blind placebo treatment helped ensure the elimination of antecedent drug effects.

The UCLA Institutional Review Board approved all experimental procedures, and written informed consent was obtained after experimental procedures were explained fully to the subjects. All subjects met DSM-IV criteria for MDD diagnosed using the Structured Clinical Interview for DSM-IV (First et al., 1995), and had 17-item Hamilton Depression Rating Scale (HAM-D-17) scores ≥ 16 (Hamilton, 1960). Subjects were excluded if they previously had failed to benefit from treatment with the antidepressant being studied, if they had a history of suicide attempt, or if they suffered from any medical illness or received any medication known to significantly affect brain function.

2.3 Clinical Assessment

After eight weeks of treatment subjects were classified as responders if they had a 50% or more reduction in HAM-D-17. Subjects were classified as remitters if they had a week 8 HAM-D-17 ≤ 7 .

2.4 EEG Procedures

EEG recordings were performed using methods described previously (Cook et al., 2002), using 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 under 5k Ω for all channels. Up to twenty minutes of EEG were collected using the QND system (Neurodata, Inc.; Pasadena, CA) while subjects rested in the eyes-closed, maximally alert state in a sound-attenuated room with subdued lighting. Patients were frequently and vigorously reminded to stay alert at the first sign of drowsiness. Data were digitized online 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. An EEG technologist selected for processing the first 10 to 16 two-second epochs of data that were free of eye movement, drowsiness, excess muscle, or other artifacts. Epochs were untapered and non-overlapping. Twenty to thirty-two seconds of EEG has been shown to be sufficient in characterizing clinically relevant differences in depression (Bares et al., 2007; Cook et al., 2002; Hunter et al., 2006; Korb et al., 2008; Mientus et al., 2002). A second technologist blinded to subject identity and treatment condition confirmed

independently that only artifact-free data were selected prior to processing. Average number of epochs used per subject was 14.1 ± 2.2 (s.d.).

2.5 LORETA Analyses

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 using a cross spectral matrix. LORETA computes current density as a linear weighted sum of scalp electrical potentials. It does not assume a specific number of sources for solving the “inverse problem,” but assumes that neighboring voxels are similarly active. Based on this assumption, LORETA finds the smoothest possible distribution of sources.

The LORETA version used in this study implemented a three-shell spherical head model registered to the Talairach and Tournoux (Talairach and Tournoux, 1988) anatomical brain atlas, and electrode coordinates derived from cross-registration between spherical and realistic head geometry (Towle et al., 1993). The LORETA solution space is constrained to cortical grey matter (including hippocampus and amygdala) using the digitized probability atlas of the Montreal Neurological Institute Brain Imaging Center. The solution space is divided into 2394 7 mm-wide cubic voxels. For each subject the theta band LORETA solution was normalized to total power of 1.

Regions of interest (ROIs) were created for the rACC and mOFC (Fig 1A and 1B). To test for regional specificity of the result a third ROI was created for the posterior cingulate cortex (PCC) as a control region (Mulert et al., 2007a). The rACC ROI was a 14 voxel region taken from the results of a previous study on current density and treatment response (Pizzagalli et al., 2001). The rACC ROI included 7 voxels in Brodmann Area (BA) 10, 1 voxel in BA 24, and 6 voxels in BA 32 resulting in a total volume of 4.80cm^3 (Fig. 1A)

The mOFC ROI was created based on anatomical classifications in LORETA. This ROI included 9 voxels in BA 10, 1 voxel in BA 11, 5 voxels in BA 25 and 19 voxels in BA 47, resulting in a total volume of 11.66cm^3 (Fig. 1B).

The PCC ROI was also created based on anatomical classifications (Mulert et al., 2007a). The PCC ROI included 6 voxels in BA23, 6 voxels in BA29, 25 voxels in BA30, and 9 voxels in BA31, resulting in a total volume of 15.78cm^3 . Voxels in an ROI were averaged and log-transformed to give one value for that ROI.

2.6 Statistical Analyses

In order to test for theta current density differences between responders and non-responders while controlling for baseline HAMD-17 differences, we ran an ANCOVA for each area of interest. The ANCOVA contained the factors Treatment (3 levels: placebo, fluoxetine and venlafaxine) and Response (2 levels: responders and non-responders), as well as baseline HAMD-17 as a covariate. A separate ANCOVA was run for each ROI. The threshold of significance was set at $p < 0.05$. In order to study the clinical outcome of remission, we repeated the ANCOVA analyses, but replaced the factor of Response with Remission. In addition, we calculated the correlation coefficient between the rACC and mOFC theta current density.

To directly compare our results with previous non-placebo controlled studies we examined the medication group in a separate ANOVA with the factors Medication (2 levels: fluoxetine and venlafaxine) and Response (2 levels: responders and non-responders). We also examined the predictive power of rACC and mOFC theta in medication treatment by conducting logistic regressions on theta activity with Response as the dependent variable, and we repeated the regressions while controlling for baseline illness severity. Because of the directionality of previous results, and thus our hypotheses, for the logistic regression we set a one-tailed

threshold of significance at $p < 0.05$ using a Wald test. To assess the potential clinical usefulness of this biomarker, we performed Receiver Operating Characteristic (ROC) analyses (Zweig and Campbell, 1993) and calculated specificity and sensitivity for an optimal cut-point.

As an exploratory analysis we also examined the placebo group separately. Current density differences were assessed with a one-way ANOVA with the factor Response.

2.7 Topographic maps

In order to provide a context for connecting our results with surface EEG measures we computed relative surface theta power (4-7Hz). Maps of relative power were generated to illustrate the distribution of surface theta band differences between responders and non-responders (Fig 2).

3. Results

3.1 Medication and Placebo Groups

Thirty-seven subjects (51%) responded to treatment with medication or placebo. Responders did not differ from non-responders in age, sex, number of prior depressive episodes, or in power spectra (see supplementary material, Figure S1). However, responders had significantly lower baseline HAMD-17 scores than non-responders ($F_{(1,66)} = 5.83$, $p = 0.019$).

The ANCOVA on theta current density, which controlled for baseline HAMD-17, showed a significant main effect of Response in the rACC ($F_{(1,65)} = 4.40$, $p = 0.040$). The factor of Treatment did not show a significant effect (Treatment: $F_{(2,65)} = 1.26$, $p = 0.290$), and neither did the interaction term (Response $\times$ Treatment: $F_{(2,65)} = 0.80$, $p = 0.455$). In the mOFC the main effect of Response approached significance but did not reach it ($F_{(1,65)} = 3.95$, $p = 0.051$) and neither the factor of Treatment nor the interaction term reached significance (Treatment: $F_{(2,65)} = 1.19$, $p = 0.312$; Response $\times$ Treatment: $F_{(2,65)} = 0.78$, $p = 0.465$). We also found that theta current density in rACC and mOFC were highly correlated ($r^2 = 0.95$, $p < 0.0001$). In the PCC no factors reached significance or showed a trend. The relative surface power maps showed elevated midline frontal theta relative power in responders compared to non-responders, although this did not reach significance. (Fig 2).

Twenty-one subjects remitted (29%). We found no theta current density differences between remitters and non-remitters in the rACC, mOFC or PCC. None of the treatment factors or interaction terms reached significance or trend levels.

3.2 Medication Group

Twenty-two subjects (59%) responded to medication. Medication responders did not differ significantly from non-responders in age, sex, pretreatment symptom severity or number of prior episodes (Table 1A). The two-way ANOVAs for rACC and mOFC theta current density both revealed a significant main effect of Response (rACC: $F_{(1,33)} = 4.46$, $p = 0.042$; mOFC: $F_{(1,33)} = 4.61$, $p = 0.039$), agreeing with our hypothesis that medication responders would show significantly higher pretreatment theta current density than non-responders in these areas (Fig. 3A,3B). The factor of Medication was not significant (rACC: $F_{(1,33)} = 2.37$, $p = 0.133$; mOFC: $F_{(1,33)} = 2.16$, $p = 0.151$), nor was the interaction term (rACC: $F_{(1,33)} = 0.64$, $p = 0.431$; mOFC: $F_{(1,33)} = 0.73$, $p = 0.400$). There was no significant difference between groups in the PCC ($F_{(1,33)} = 0.20$, $p = 0.65$) (Fig. 3C).

The logistic regression found that both rACC theta and mOFC theta significantly predicted response to medication (rACC: $\beta = 2.98 \pm 1.55$, $p = 0.027$; mOFC: $\beta = 3.27 \pm 1.68$, $p = 0.026$). The effect of higher theta current density predicting response remained significant after controlling

for baseline illness severity (rACC: $\beta=2.76\pm1.58$, $p=0.040$; mOFC: $\beta=2.99\pm1.72$, $p=0.042$). An ROC analysis of rACC theta current density yielded 71.2% area under the curve (95% C.I. = 54.4% – 88.0%, sensitivity=64%, specificity=67%); the mOFC biomarker yielded 68.8% area under the curve (95% C.I. = 51.4% – 86.1%, sensitivity=73%, specificity=60%).

3.3 Placebo Group

Fifteen subjects (43%) responded to placebo. Placebo responders did not differ significantly from non-responders in age, sex, pretreatment symptom severity or number of prior episodes (Table 1B). The one-way ANOVAs showed no significant differences in baseline theta current density between placebo responders and non-responders in rACC ($F_{(1,33)}=0.24$, $p=0.63$), mOFC ($F_{(1,33)}=0.21$, $p=0.65$) or PCC ($F_{(1,33)}=2.43$, $p=0.13$) (Fig. 3D, 3E, 3F).

4. Discussion

This is the first examination of theta current density and treatment response in MDD using a double-blind, placebo-controlled study design. We confirm results from previous unblinded studies showing that responders to treatment have elevated rACC theta current density compared to non-responders. Our results demonstrated some regional specificity as evidenced by the fact that the PCC, used as a control, did not show significant differences between groups.

In the medication group we confirm results from previous unblinded medication studies showing that elevated theta current density in rACC and mOFC predicts response to antidepressant medication, and extend those results to show response prediction using different medications (fluoxetine, venlafaxine) from those previously examined. Our results agree with previous neuroimaging studies of treatment response that used other modalities to evaluate rACC and mOFC activity. For example, elevated rACC and mOFC metabolism have been shown in both medication responders and sleep deprivation responders relative to non-responders (Mayberg et al., 1997; Saxena et al., 2003; Volk et al., 1997; Wu et al., 1999). Our results also agree with prior studies on LORETA and treatment response which reported elevated theta band current density in the rACC (Mulert et al., 2007b; Pizzagalli et al., 2001) and mOFC (Mulert et al., 2007b) in antidepressant medication responders relative to non-responders.

Interestingly, neither rACC nor mOFC showed a significant difference between remitters and non-remitters. This finding appears to be at odds with Pizzagalli's earlier report (2001) that rACC theta predicted degree of response. However, Pizzagalli did not look specifically at remission. In the current study, remitters showed numerically higher theta current density than non-responders, but lower theta current density than subjects who responded but did not remit. This suggests there may be a "window" of rACC activity associated with optimal response. More research is needed to understand the neurobiological differences between response and full remission with treatment.

Previous LORETA studies of MDD examined responders to nortriptyline, reboxetine, and citalopram. Reboxetine primarily affects norepinephrine, citalopram primarily affects serotonin, and nortriptyline exerts effects on both systems. While Mulert and colleagues did study an SSRI (citalopram), as well as reboxetine, their results were driven by the reboxetine group (Mulert et al., 2007b); thus no prior report showed a significant relationship between regional theta current density and response to an SSRI. The present study extends these results to include the SSRI fluoxetine and the SNRI venlafaxine. Because we did not find a significant interaction of medication in our analysis, there was no evidence of a different biomarker effect between the SSRI and SNRI we studied.

In contrast to the present finding in the medication group, Pizzagalli and colleagues did not report mOFC differences between responders and non-responders (Pizzagalli et al., 2001). However, they did not specifically hypothesize differences in this region and thus may have used a different statistical threshold. Other methodological differences also may have contributed to different findings for the mOFC. Pizzagalli and colleagues used the dual-reuptake inhibitor tricyclic antidepressant nortriptyline, which also has anticholinergic and histaminic effects (Taylor and Richelson, 1980). In comparison, the SNRI venlafaxine used in the present study does not have these confounding other actions. Additionally, the prior report assessed response after 4-6 months, whereas our study assessed acute 8-week response. The Mulert group, which first found the mOFC differences, also used a shorter response assessment of 4 weeks.

Because theta current density in both rACC and mOFC predicted treatment response, it is not surprising that theta current density values in these regions were highly correlated. However, this result contrasts with a prior study (Pizzagalli et al., 2001), which found a significant correlation of rACC and OFC theta current density in healthy controls, but did not find this correlation in depressed subjects. This discrepancy between studies may be explained by methodological differences listed above. The other group to show responder/non-responder differences in both rACC and mOFC theta did not report on the correlations in these areas (Mulert et al., 2007b). Correlations between rACC and mOFC theta current density may reflect true correlations of brain activity in these areas, but it could arise as a result of the smoothness constraint of LORETA (Mulert et al., 2007b). Support for this being a true physiologic phenomenon can be found in prior results from PET and single photon emission computed tomography (SPECT) studies of MDD, that showed metabolic and perfusion differences between responders and non-responders to sleep deprivation in both medial prefrontal cortex/OFC and anterior cingulate (Volk et al., 1997; Wu et al., 1999).

That current density values in these regions are related to treatment response is not surprising, given that both regions have been shown to have abnormal electrophysiological activity in depressed subjects compared to healthy controls (Korb et al., 2008; Mientus et al., 2002; Pizzagalli et al., 2001; Pizzagalli et al., 2002). The rACC is a region that processes emotion and attention (Lane et al., 1998), and the mOFC processes emotion and reward (O'Doherty et al., 2001a; O'Doherty et al., 2001b; Rolls et al., 2008). Prior reports have suggested that increased activity in these areas may point to a compensatory neural response to depression that renders a depressed 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, and we demonstrate that even when subjects are blinded to treatment theta current density predicts response.

To our knowledge, this is the first report to examine the relationship between rACC or mOFC current density and response to placebo. We found no association seen between activity in these two areas and placebo response. Although there was no significant relationship between theta current density and placebo response, we cannot conclude that the rACC and mOFC biomarkers worked differently for subjects treated with medication and those treated with placebo. There was not a significant interaction between type of treatment (active medication vs. placebo) and response indicating that the relationship between theta current density and response was not significantly different between the two groups. Contributing to this lack of differentiation, may be the fact that many patients probably have the capacity to respond either to medication or placebo, and some patients who appear to respond to medication may in fact be "placebo responders" in whom medication is not responsible for the clinical improvement seen. While a previous study demonstrated that subjects treated with placebo and medication showed different patterns of change in surface recorded QEEG (Leuchter et al., 2002), these differences did not emerge until late in the course of treatment. In another study, our group did

detect pretreatment QEEG differences between placebo responders and medication responders (Leuchter et al., 2004), but these differences also did not involve source localization techniques. Current source density prior to, or early in the course of treatment, might not show these same differences. Further examination of the differences in brain function between placebo and medication responders may help elucidate mechanisms of clinical improvement in MDD.

It is interesting to note that both elevated rACC theta current density in the present study, and elevated rACC glucose metabolism as reported in previous studies, are related to improved response. These two measures have been compared directly in depressed and healthy subjects, and it has been shown that rACC theta current density correlates positively with glucose metabolism (Pizzagalli et al., 2003), suggesting an association between elevated theta current density and elevated neural activity in this region. In the mOFC, however, the relationship of theta current density to glucose metabolism is less clear, because a previous report did not find a significant correlation in this region (Pizzagalli et al., 2003). 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 (Kringelbach and Rolls, 2004; Ongur and Price, 2000). The present findings could be consistent with a more complex pattern of interaction between mOFC and rACC activity, such as a cortico-cortical feedback loop. Unfortunately this possibility cannot be determined definitively with LORETA, because it does not directly measure theta activity in the mOFC or rACC, but rather computes a low-resolution estimate from surface measurements. However, patterns of activity could be studied explicitly using activation paradigms or brain imaging methods that facilitate examination of time-dependent interactions between brain regions.

Examination of the distribution of surface theta activity revealed elevated frontal midline relative power in responders relative to non-responders, although this did not reach significance. The distribution of differences has a similar topography to a low-alpha/high-theta spectral component identified by Tenke & Kayser (2005) using an entirely different approach to EEG generators. Because LORETA is a linear algorithm, this low-alpha/high-theta component would likely have been localized by LORETA as theta arising from rACC and mOFC. It is also interesting to note that the midline frontal theta rhythm has been shown to be generated by alternate activity of the ACC and medial prefrontal cortex (Asada et al., 1999). While we did not explicitly study the midline frontal theta rhythm, the similar topographies and brain regions involved may offer a salient context for considering the present findings.

While neither rACC nor mOFC theta current density predicted response to placebo treatment, other neurophysiologic markers might do so. In a prior report, baseline frontocentral QEEG theta cordance was shown to predict response to placebo treatment (Leuchter et al., 2004). The fact that we did not find a relationship between rACC or mOFC theta current density and placebo response suggests that different features of the EEG contain different information about neural activity and how it relates to response. This is supported by the fact that theta current density in the rACC — a relatively deep cortical structure — correlates with glucose metabolism (Pizzagalli et al., 2003), while cordance has stronger correlations with perfusion in more superficial cortices (Leuchter et al., 1999).

This study has several limitations that should be acknowledged. One limitation is that subjects were treated with fixed medication dosage. Subjects who did not respond at this dosage, but who might have responded to a higher dosage, were still classified as non-responders to that agent. Similarly, the outcome measures of response and remission were determined only at 8 weeks. Some non-responders might have responded after a longer period of treatment, and some responders may have remitted, but these subjects' longer-term outcome data were not available. Further research is necessary to examine potential moderators of the relationship between theta current density and response and remission, as well as specificity of the

biomarker for different medications. It should be noted that our methods make use of a cross-spectrum, which results in an un-scaled measure of coherence rather than a direct computation of amplitude. While LORETA has limitations, as do all EEG source localization methods, we nonetheless interpret elevated rACC theta current density as elevated neural activity due to evidence that rACC theta current density correlates with glucose metabolism.

Converging evidence from different methods and modalities suggests that ACC and mOFC activity may predict treatment response in MDD, and that an inexpensive, non-invasive, neurophysiologic method like LORETA may be particularly useful in monitoring these areas. In a clinical setting, low rACC and mOFC theta current density might indicate risk for non-response. The findings to date warrant consideration of directly examining the clinical utility of LORETA methods in treatment of MDD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Regions of Interest

A sagittal view of the ROIs used in our analyses. A) rACC. B) mOFC

Figure 2. Relative Surface Power

Relative surface theta power superimposed on the brain for A) Responders and B) Non-responders.

Figure 3. Theta Current Density

— indicates mean. Medication group theta current density separated by response in A) rACC, B) mOFC, and C) PCC. Placebo group theta current density separated by response in D) rACC, E) mOFC, and F) PCC.

Table 1

Subject Characteristics

A.					
Medication Group	Number of Subjects	Baseline HAMD $\pm$ s.d	Week 8 HAMD $\pm$ s.d	Age (in years) $\pm$ s.d	Median # of Prior Episodes (Range)
All	37 (14 male)	21.8 $\pm$ 3.4	10.4 $\pm$ 7.3	41.6 $\pm$ 12.4	2 (0 - 10+)
Responders	22 (9 male)	21.0 $\pm$ 2.7	5.4 $\pm$ 3.4	42.0 $\pm$ 10.6	2 (0 - 4)
NonResponders	15 (5 male)	23.0 $\pm$ 4.1	17.9 $\pm$ 4.5	41.1 $\pm$ 15.1	2 (0 - 10+)

B.					
Placebo Group	Number of Subjects	Baseline HAMD $\pm$ s.d	Week 8 HAMD $\pm$ s.d	Age $\pm$ s.d in years	Median # of Prior Episodes (Range)
All	35 (15 male)	21.9 $\pm$ 3.5	13.7 $\pm$ 7.6	39.6 $\pm$ 12.2	2 (0 - 10+)
Responders	15 (9 male)	21.1 $\pm$ 3.8	6.9 $\pm$ 3.9	35.5 $\pm$ 13.5	2 (0 - 10+)
NonResponders	20 (6 male)	22.5 $\pm$ 3.2	18.9 $\pm$ 5.3	42.8 $\pm$ 10.4	2 (1 - 10+)