

Neural Correlates of Three Promising Endophenotypes of Depression: Evidence from the EMBARC Study

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Major depressive disorder (MDD) is clinically, and likely pathophysiologically, heterogeneous. A potentially fruitful approach to parsing this heterogeneity is to focus on promising endophenotypes. Guided by the NIMH Research Domain Criteria initiative, we used source localization of scalp-recorded EEG resting data to examine the neural correlates of three emerging endophenotypes of depression: neuroticism, blunted reward learning, and cognitive control deficits. Data were drawn from the ongoing multi-site EMBARC study. We estimated intracranial current density for standard EEG frequency bands in 82 unmedicated adults with MDD, using Low-Resolution Brain Electromagnetic Tomography. Region-of-interest and whole-brain analyses tested associations between resting state EEG current density and endophenotypes of interest. Neuroticism was associated with increased resting gamma (36.5–44 Hz) current density in the ventral (subgenual) anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC). In contrast, reduced cognitive control correlated with decreased gamma activity in the left dorsolateral prefrontal cortex (dlPFC), decreased theta (6.5–8 Hz) and alpha2 (10.5–12 Hz) activity in the dorsal ACC, and increased alpha2 activity in the right dlPFC. Finally, blunted reward learning correlated with lower OFC and left dlPFC gamma activity. Computational modeling of trial-by-trial reinforcement learning further indicated that lower OFC gamma activity was linked to reduced reward sensitivity. Three putative endophenotypes of depression were found to have partially dissociable resting intracranial EEG correlates, reflecting different underlying neural dysfunctions. Overall, these findings highlight the need to parse the heterogeneity of MDD by focusing on promising endophenotypes linked to specific pathophysiological abnormalities.

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INTRODUCTION

Major depressive disorder (MDD), as currently defined, represents a highly heterogeneous disorder that is etiologically and pathophysiologically complex. One potentially promising approach to parsing this heterogeneity is the investigation of endophenotypes (Chan and Gottesman, 2008; Gottesman and Gould, 2003). Endophenotypes are assumed to lie on the pathway between genotype and disease, and be less complex than the downstream symptom clusters that currently define psychiatric diagnoses. Gottesman and

colleagues proposed that endophenotypes must meet the following criteria: (1) be associated with the disease; (2) be heritable; (3) be primarily state-independent; (4) cosegregate within families; (5) be more common in non-affected family members of individuals with the disease compared with the general population; and (6) be measured reliably.

Neuroticism, blunted reward learning and cognitive control deficits have emerged as among the most promising behavioral endophenotypes of depression (Goldstein and Klein, 2014; Pizzagalli, 2014; Snyder, 2013), and map well onto central Research Domain Criteria (RDoC) domains, particularly negative valence systems (neuroticism), positive valence systems (reward learning), and cognitive systems (cognitive control). First, neuroticism—the propensity to experience negative emotions—is elevated in current and remitted depression (De Fruyt *et al*, 2006; Klein *et al*, 2011), and predicts first onset of MDD (Kendler *et al*, 2006). Twin

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studies indicate that neuroticism shares significant genetic variance with depression, and is moderately heritable (eg, Birley *et al*, 2006; Kendler *et al*, 2006). Moreover, neuroticism cosegregates within families (Farmer *et al*, 2002; Ouimette *et al*, 1996), and non-depressed family members of those with MDD have higher levels of neuroticism than the general population (Modell *et al*, 2003). Finally, measures of neuroticism (eg, NEO Personality Inventory) have relatively strong psychometric properties (Costa *et al*, 2005).

Second, blunted reward learning—defined as a diminished ability to modulate behavior as a function of rewards—has been observed in both individuals with current and remitted MDD (Goldstein and Klein, 2014; Pechtel *et al*, 2013; Pizzagalli, 2014). A twin study estimated the heritability of reward learning to be 0.46 (Bogdan and Pizzagalli, 2009), as assessed by a commonly used Probabilistic Reward Task (PRT; Pizzagalli *et al*, 2005a). In addition, the same study reported a moderate ($r=0.29$) genetic correlation between depression and reward learning. Data related to the reliability of reward learning is limited, with one study finding significant test–retest reliability ($r=0.57$) over 38 days (Pizzagalli *et al*, 2005a). To our knowledge, no study has evaluated whether reward learning fulfills the cosegregation or familial association endophenotype criteria.

Finally, MDD is characterized by broad impairments in cognitive control, which often persist following remission (Snyder, 2013) and exhibit trait-like stability (Sarapas *et al*, 2012). Moderate-to-high heritability (Friedman *et al*, 2008; Stins *et al*, 2004), as well as strong test–retest reliability and internal consistency (Wöstmann *et al*, 2013) have been reported for commonly used cognitive control paradigms (eg, Stroop, Eriksen Flanker). In addition, there is evidence of cognitive control impairments in healthy, unaffected twins discordant for MDD (Christensen *et al*, 2006). Evidence for cosegregation and familial association is lacking.

With regards to neural substrates, neuroticism has been associated with increased amygdala and anterior cingulate cortex (ACC) activity (Haas *et al*, 2007; Servaas *et al*, 2013), both in the ‘affective’ (ie, rostral (rACC) and subgenual (sgACC)) and ‘cognitive’ subdivisions (ie, dorsal (dACC)). In contrast, tasks tapping reward learning have been shown to recruit the striatum, orbitofrontal cortex (OFC; Hornak *et al*, 2004; O’Doherty, 2004), dACC (Rushworth *et al*, 2007; Santesso *et al*, 2008), and left dorsolateral prefrontal cortex (dlPFC; BA 9/46; Ahn *et al*, 2013; Pizzagalli *et al*, 2005b), especially in tasks requiring integration of reinforcements over time (eg, PRT). Finally, cognitive control has been reliably linked to the dlPFC and dACC (Pizzagalli, 2011; Ridderinkhof *et al*, 2004).

Inspired by the RDoC initiative, the goal of this study was to examine the association between these three candidate endophenotypes and intracranial estimates of resting brain electrical activity (EEG) in an unmedicated depressed sample. We employed a region-of-interest (ROI) approach, followed by an exploratory whole-brain analysis to test the specificity of ROI findings. ROIs were selected based on the literature reviewed above, and within the constraints of EEG source localization techniques, which cannot probe sub-cortical structures (eg, amygdala, caudate). Based on prior studies, we hypothesized that: (1) neuroticism would be associated with greater resting activity in the affective (rACC/sgACC) and cognitive (dACC) subdivisions of the ACC; (2) blunted reward learning would be linked to lower

activity in the OFC, dACC, and left dlPFC; and (3) reduced cognitive control would correlate with lower activity in the dlPFC and cognitive (dACC)—but not affective—ACC subdivision. Finally, a cluster analysis was conducted in an effort to empirically derive subgroups of depressed patients on the basis of endophenotype profiles.

MATERIALS AND METHODS

Data were collected in a multi-site clinical trial entitled ‘Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression’ (EMBARC). Recruiting sites are Columbia University (CU), Massachusetts General Hospital (MGH), the University of Texas Southwestern Medical Center (UT), and the University of Michigan (UM). Participants completed several behavioral, self-report, and physiological assessments before enrolling in the double-blind, placebo-controlled clinical trial of sertraline and bupropion. Data collection for the treatment phase is ongoing and the blind remains unbroken. Accordingly, the current study only considers baseline resting EEG, behavioral (Flanker and PRT), and self-report (NEO) data for the first 100 MDD subjects. Participants provided informed consent following procedures approved by site IRBs.

Participants

Eligible participants (aged 18–65 years) met DSM-IV criteria for a current MDD episode (SCID-I/P), scored 14 or above on the 16-item Quick Inventory of Depression Symptomatology (Rush *et al*, 2003), and were medication free for >3 weeks before completing any study measures. Exclusion criteria included: history of psychosis or bipolar disorder; substance dependence in the past 6 months (excluding nicotine) or substance abuse in the past 2 months; active suicidality; or unstable medical conditions (for more information about the sample, see Supplementary Materials). Data from 82 MDD subjects who passed quality control criteria for both Flanker and PRT (see Supplementary Materials) and had NEO scores were analyzed.

Measures

NEO Five-Factor Inventory: 3 (NEO-FFI-3). The NEO-FFI is a 60-item self-report questionnaire assessing Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness (12 items/factor; McCrae and Costa, 2010).

Probabilistic Reward Task (PRT). The PRT uses a differential reinforcement schedule to probe reward learning (ie, the ability to modulate behavior as a function of rewards), and has been described in detail (Pizzagalli *et al*, 2005a, 2008; see Supplementary Materials). Participants performed two blocks of 100 trials.

Flanker Task. A modified version of the Eriksen Flanker Task with an individually titrated response window was used (Eriksen and Eriksen, 1974; Holmes *et al*, 2010). Participants first completed a practice session followed by five blocks consisting of 70 trials each (46 congruent and 24 incongruent), for a total of 350 trials. On each trial, participants

pressed a button to indicate whether a center arrow pointed left or right. The central arrow was presented with adjacent flankers, which either pointed in the same direction (congruent condition) or the opposite direction (incongruent condition) as the central arrow (see Supplementary Materials). Both accuracy and reaction time (RT) were recorded.

Hamilton Rating Scale for Depression (HRSD). The 32-item HRSD is a clinician-administered measure of depressive symptom severity (Hamilton, 1960). It was administered by trained clinical evaluators.

Data Acquisition and Reduction

Resting EEG recording consisted of four contiguous 2-min trials (two eyes open, two eyes closed), for a total of 8 min. Site certification, intersite standardization, quality assurance, and preprocessing of resting EEG for all sites were performed at the Columbia site (see Supplementary Materials for details). McLean Hospital was responsible for site training and certification, quality assurance, and analysis of Flanker and PRT data as well as Low-Resolution Brain Electromagnetic Tomography (LORETA) analyses. Hypotheses were tested for the theta (6.5–8 Hz), alpha1 (8.5–10 Hz), alpha2 (10.5–12 Hz), and gamma (36.5–44 Hz) frequency bands (for rationale, see Supplementary Materials). LORETA (Pascual-Marqui *et al*, 1999) was used to estimate the three-dimensional intracerebral current density distribution for each frequency band. With respect to the ACC, to test the specificity of findings, LORETA voxels corresponding to the affective (BA25 (sgACC); BA24/32 (rACC)) and cognitive (BA24'/32' (dACC)) subdivisions were identified (Pizzagalli, 2011). Similarly, anatomical considerations were used to identify the dlPFC (lateral BA9 and BA46) and OFC (BA11/13/47/12; Kringelbach and Rolls, 2004; see Supplementary Material, Supplementary Figure 1, for ROI definitions). For each ROI, intensity-normalized current density was averaged across voxels.

Probabilistic Reward Task. The primary variable of interest was change in *response bias* (RB) scores from the first to the second block ($RB_{\text{Block2}} - RB_{\text{Block1}}$), which reflects reward learning. In addition, *discriminability* scores, indexing the ability to differentiate between stimuli, were included as a covariate in specificity analyses (for formulas, see Supplementary Materials). The development of a RB depends both on the sensitivity to individual rewarding feedback and the ability to incrementally associate stimuli/actions with rewards over the course of the task. To discriminate between these components of reward learning, we fitted a series of reinforcement learning models to trial-by-trial behavioral data as described previously (Huys *et al*, 2013). These contained two key parameters: *reward sensitivity*, which indexes the reinforcing strength of the individual reward outcomes, and *learning rate*, which measures the ability to progressively associate outcomes with antecedent stimuli/actions (see Supplementary Materials).

Flanker task. The primary variables of interest were the *interference effects*: lower accuracy and longer RTs on incongruent than congruent trials. These effects were com-

puted as $(\text{Accuracy}_{\text{Compatible trials}} - \text{Accuracy}_{\text{Incompatible trials}})$ and $(\text{RT}_{\text{Incompatible trials}} - \text{RT}_{\text{Compatible trials}})$.

Statistical Analyses

For ROI-based analyses, four separate sets of multiple regressions were run to examine the association between LORETA-derived EEG current density and (1) neuroticism, (2) reward learning, and the Flanker interference effects on both (3) accuracy and (4) RT. For neuroticism, current density in the affective (sgACC and rACC) and cognitive (dACC) subdivisions of the ACC were entered as predictors. For reward learning, current density in the OFC, left and right dlPFC, and dACC were entered as predictors. Finally, for Flanker interference effects, separate multiple regressions were run for accuracy and RT, with current density in the rACC, dACC, and left/right dlPFC serving as predictors. Regressions were run separately for each frequency band. All predictor variables were entered simultaneously in multiple regression models, and all models included site (CU/MGH/UT/UM) as a covariate. For significant findings, specificity analyses were performed to test whether associations remained when accounting for (1) depression severity (by entering HRSD scores as an additional predictor) and (2) the other endophenotypes. In addition, to the extent that significant findings emerged in the reward learning analyses, we followed-up with two multiple regressions testing whether significant ROIs also predicted the *reward sensitivity* and *learning rate* parameters extracted from the computational models. Regression analyses were carried out using SAS version 9.2 PROC GLM. [Several univariate outliers (absolute value $z > 3.0$) were identified. Specifically, gamma, theta, alpha1, and alpha2 current density values in BA24/32 (rACC) for 1 subject; theta, alpha1 and alpha2 in BA24'/32' (dACC) for 1 subject; gamma and alpha1 left dlPFC values for 1 subject. These data were omitted from the relevant analyses.]

To evaluate regional specificity, exploratory whole-brain correlational analyses were conducted between (1) neuroticism, reward learning and Flanker interference effects, and (2) current density in the theta, alpha1, alpha2, and gamma bands separately. To control for multiple comparisons, analyses were carried out using the 'Randomise' permutation-based inference tool in FSL for nonparametric statistical thresholding (5000 permutations, $p < 0.05$, FWE corrected; Winkler *et al*, 2014). Finally, in an effort to empirically derive subgroups of depressed patients on the basis of endophenotype measures, a two-step cluster analysis was conducted in SPSS (Version 20) using the Log-likelihood distance measure and Schwarz's Bayesian Information Criterion as clustering criteria (Chiu *et al*, 2001; Fava *et al*, 2012), and without pre-specifying the desired number of clusters.

RESULTS

Supplementary Table 1 provides a summary of significant ROI findings.

Neuroticism

The first regression predicted neuroticism scores, with gamma current density in the cognitive (dACC) and affective (sgACC) ACC subdivisions entered as predictors. As

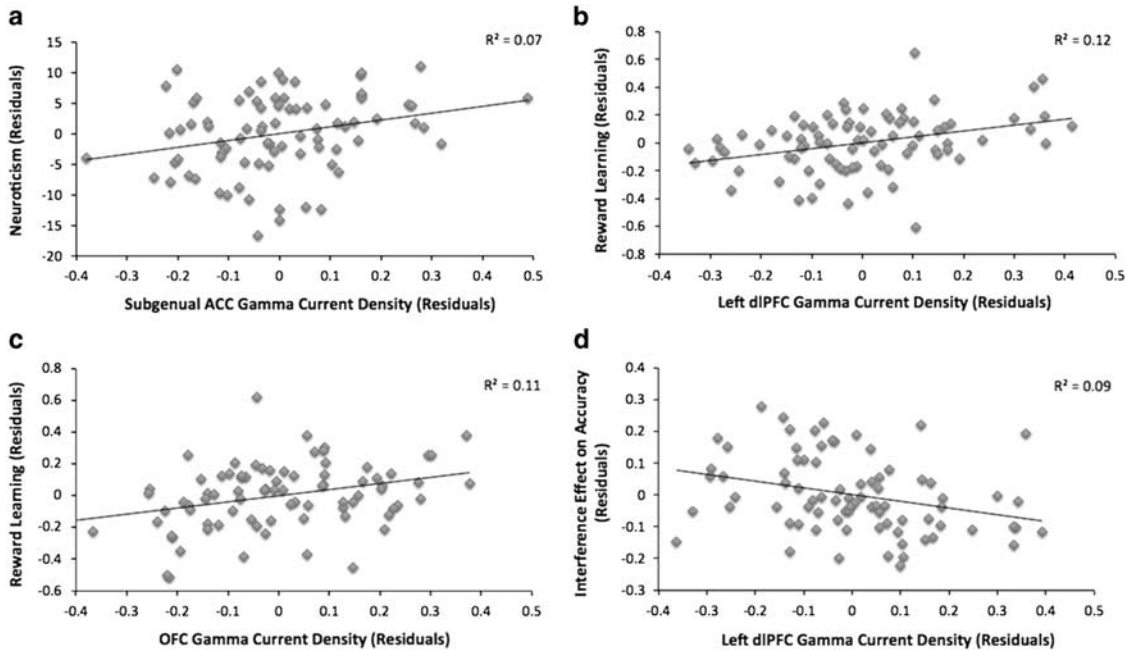


Figure 1 Partial regression plots displaying the association between (a) neuroticism and gamma current density in the subgenual anterior cingulate cortex (sgACC; BA25), after controlling for the model covariates (site and gamma activity in BA 24/32' (dACC)); (b) reward learning and gamma activity in the left dorsolateral prefrontal cortex (dlPFC), after controlling for the model covariates (site and gamma activity in the right dlPFC, dACC, and orbitofrontal cortex (OFC)); (c) reward learning and gamma activity in the OFC, after controlling for the model covariates (site and gamma activity in the left and right dlPFC, and dACC); (d) Flanker interference effect on accuracy and gamma activity in the left dlPFC, after controlling for the model covariates (site and gamma activity in the right dlPFC, dACC, and BA 24/32 (rACC)). The association in panel a remains significant ($\beta = 0.29$, $p = 0.030$) after removing the sgACC residual value at the far right of panel.

expected, when controlling for dACC, gamma activity in sgACC was associated with neuroticism ($\beta = 0.31$, $p = 0.018$; Figure 1a). In contrast, gamma activity in dACC did not predict neuroticism ($\beta = -0.01$, $p = 0.965$). An analogous model entering gamma current density in the dACC and rACC yielded a nonsignificant trend between rACC and neuroticism ($\beta = 0.24$, $p = 0.054$; dACC: $\beta = -0.07$, $p = 0.646$). [Given the very high correlation between current density in BA25 (sgACC) and neighboring BA24/32 (rACC) (for gamma, $r = 0.74$), these variables were included as predictors in separate regression models to minimize multicollinearity.] No significant predictors emerged for the theta or alpha bands (p 's > 0.15).

Specificity analyses. The relationship between sgACC gamma activity and neuroticism remained when accounting for (1) current depressive symptoms (HRSD) and the other NEO personality factors ($\beta = 0.27$, $p = 0.024$); and (2) Flanker interference effects and reward learning ($\beta = 0.29$, $p = 0.025$).

Reward Learning

Greater gamma activity in the OFC ($\beta = 0.33$, $p = 0.004$) and left dlPFC ($\beta = 0.34$, $p = 0.002$)—but not right dlPFC ($\beta = -0.11$, $p = 0.358$) or dACC ($\beta = -0.05$, $p = 0.682$)—predicted reward learning (Figure 1b and c). Importantly, the correlations between reward learning and gamma activity in the left ($r = 0.31$, $p = 0.005$) and right dlPFC ($r = -0.04$, $p = 0.711$) were significantly different ($z = 2.36$, $p = 0.018$; Meng et al, 1992). Models considering theta and alpha current density yielded no significant associations (p 's > 0.06).

Specificity analysis. The relationships between gamma activity in the OFC/left dlPFC and reward learning remained significant when accounting for (1) current depressive symptoms and PRT discriminability (both β 's $= 0.34$, $p < 0.005$); and (2) neuroticism and the Flanker interference effects (OFC: $\beta = 0.33$, $p = 0.008$; left dlPFC: $\beta = 0.41$, $p < 0.001$).

Computational modeling. A multiple regression indicated that gamma activity in the OFC ($\beta = 0.27$, $p = 0.043$)—but not the left dlPFC ($\beta = 0.11$, $p = 0.378$)—positively predicted reward sensitivity. No significant findings emerged in the prediction of learning rate (p 's > 0.20).

Cognitive Control

Flanker interference effect (accuracy). The regression revealed that gamma activity in the left dlPFC ($\beta = -0.31$, $p = 0.009$)—but not right dlPFC ($\beta = 0.03$), dACC ($\beta = 0.20$), or rACC ($\beta = -0.05$) (all p 's > 0.15)—was a significant negative predictor of the Flanker interference accuracy effect (Figure 1d). The correlations involving the left ($r = -0.30$, $p = 0.007$) and right ($r = -0.04$, $p = 0.71$) dlPFC gamma activity were different only at a trend level ($z = -1.72$, $p = 0.085$). Models for theta and alpha yielded no effects (p 's > 0.05).

Specificity analysis. The relationship between gamma current density in the left dlPFC and the Flanker interference effect was confirmed when accounting for (1) current depressive symptoms ($\beta = -0.32$, $p < 0.009$) and (2) neuroticism and reward learning ($\beta = -0.30$, $p = 0.020$).

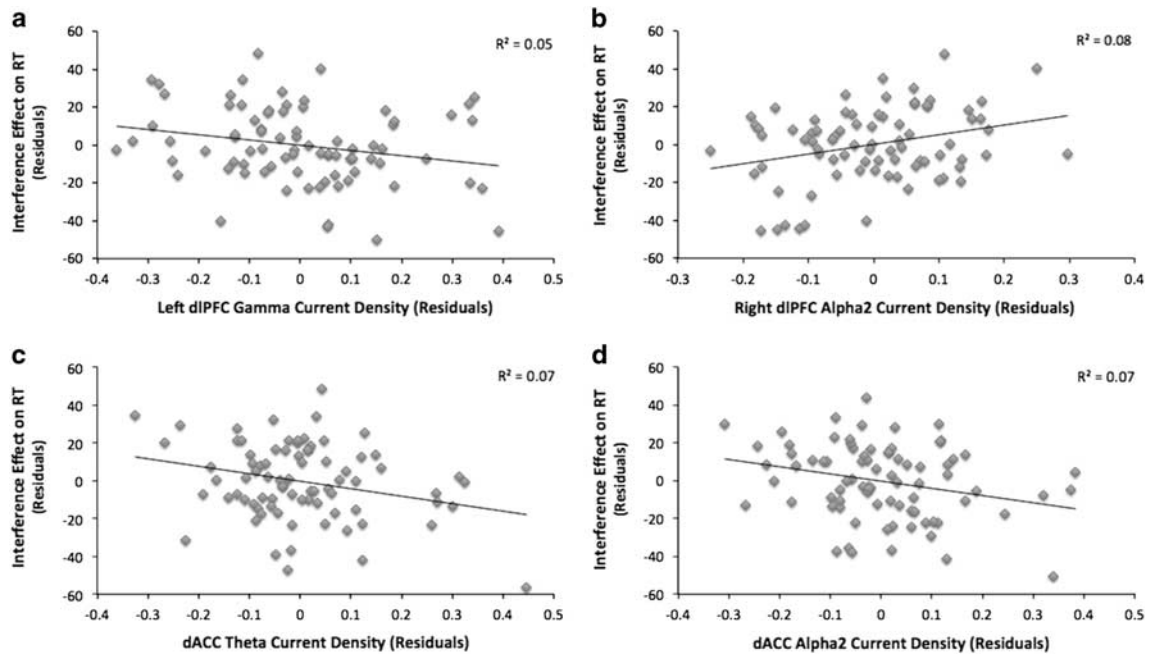


Figure 2 Partial regression plots displaying the association between Flanker interference effect on reaction time (RT) and (a) gamma current density in left dlPFC, after controlling for model covariates (site and gamma activity in the right dlPFC, BA 24/32' (dACC) and BA 24/32 (rACC), (b) alpha2 current density in the right dlPFC, controlling for site and alpha2 activity in the left dlPFC, dACC, and rACC, (c) theta current density in dACC, controlling for theta activity in rACC, and left and right dlPFC, and (d) alpha2 current density in dACC, controlling for alpha2 activity in rACC, and left and right dlPFC. The theta dACC effect is reduced to a trend level ($\beta = -0.29$, $p = 0.060$) in the model after removing the residual value at the bottom right corner of panel c. It should be noted that the zero-order correlation (ie, excluding model covariates) between theta dACC and interference effect on RT is significant ($r = -0.25$; $p = 0.026$).

Table 1 Whole-Brain Correlations between Candidate Endophenotypes and LORETA-Estimated Current Density

Covariate	Region (frequency band)	Number of voxels	Peak-r MNI coordinates			Mean r
			x	y	z	
Neuroticism	Bilateral OFC/sgACC (γ)	36	11	31	-27	0.27*
Reward learning	L dlPFC/OFC (γ)	51	-38	52	8	0.38***
Flanker ACC	L dlPFC (γ)	4	-38	38	36	-0.38***

Abbreviations: dlPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; sgACC, subgenual anterior cingulate cortex; γ , Gamma (36.5–44 Hz).

For each cluster, the number of voxels exceeding the statistical threshold is reported (using the 'Randomise' permutation-based inference tool in FSL for nonparametric statistical thresholding, with 5000 permutations, $p < 0.05$, FWE corrected for multiple comparisons; Winkler et al, 2014); Neuroticism = NEO Five-Factor Inventory (Neuroticism total score); Reward Learning = Change in response bias scores from block 1 to block 2 in the Probabilistic Reward Task; Flanker ACC = Flanker interference effect on accuracy. Peak-r MNI coordinates = MNI coordinates for the voxel associated with the largest Pearson's correlation between the covariate and current density (unit: amperes per square meter, A/m^2); Mean r = the mean Pearson's r averaged across all voxels belonging to the cluster. Similar to the analyses above, site is included as a covariate.

* $p < 0.05$, *** $p < 0.001$ (uncorrected).

Flanker interference effect (RT). When considering gamma, only current density in the left dlPFC was a negative predictor of interference RT effects ($\beta = -0.23$, $p = 0.045$; Figure 2a). For theta, only dACC activity was negatively associated with the interference RT effect ($\beta = -0.33$, $p = 0.019$; Figure 2c). For alpha2, dACC activity was negatively associated ($\beta = -0.31$, $p = 0.020$) and right dlPFC activity positively associated ($\beta = 0.51$, $p = 0.012$), with the interference effect (Figure 2b and d). All other predictors were nonsignificant (p 's > 0.05).

Specificity analysis. The above relationships were confirmed when accounting for (1) current depressive

symptoms (theta dACC: $\beta = -0.34$, $p = 0.018$; alpha2 dACC: $\beta = -0.34$, $p = 0.012$; alpha2 right dlPFC: $\beta = 0.58$, $p = 0.005$), with the exception of gamma activity in the left dlPFC ($\beta = -0.22$, $p = 0.054$), and (2) neuroticism and reward learning (theta dACC: $\beta = -0.32$; gamma left dlPFC: $\beta = -0.32$; alpha2 right dlPFC: $\beta = 0.58$; alpha2 dACC: $\beta = -0.34$, p 's < 0.020).

Exploratory Whole-Brain Analyses to Examine Specificity of Findings

For the whole-brain correlations with neuroticism, 36 voxels spanning the bilateral OFC and sgACC/rACC (BA11/47, BA25, BA24) correlated positively with gamma activity

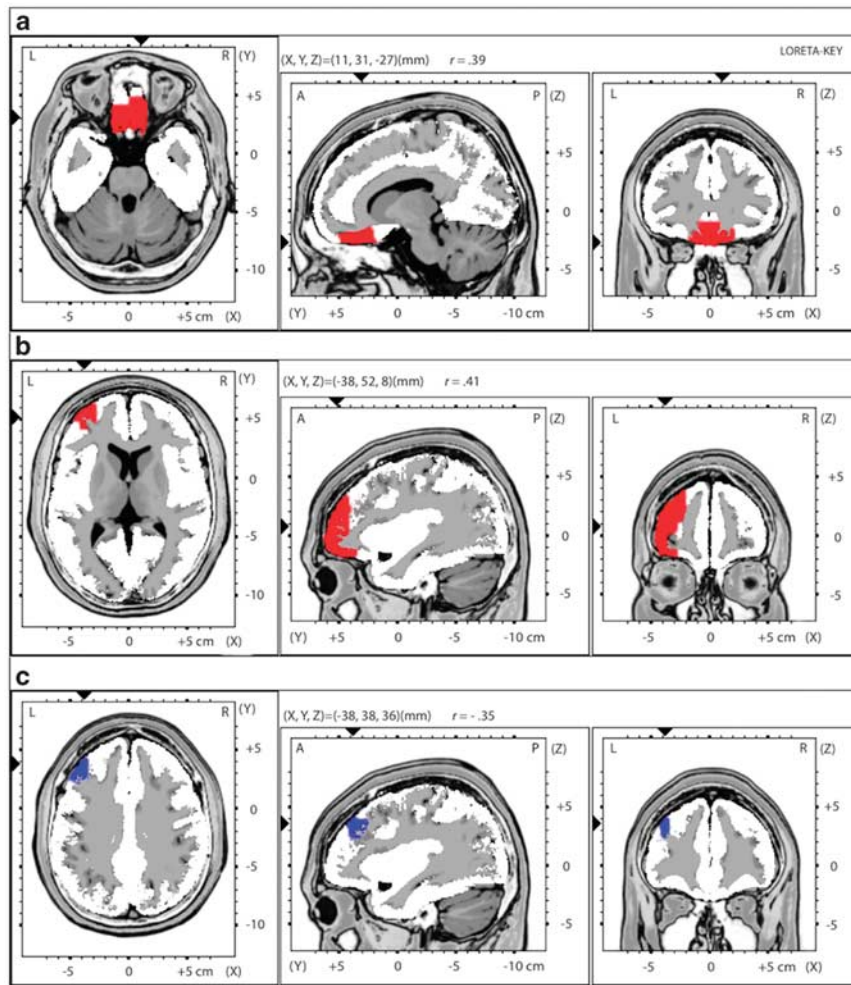


Figure 3 Whole-brain analysis displaying voxel-by-voxel correlations between (a) gamma (36.5–44 Hz) current density and neuroticism (displaying axial/sagittal/coronal views of the bilateral OFC/subgenual ACC cluster (36 voxels) that was significantly positively correlated with neuroticism); (b) gamma current density and reward learning (displaying axial/sagittal/coronal views of the left dlPFC/OFC cluster (51 voxels) that was significantly positively correlated with reward learning); (c) gamma current density and Flanker interference effect on accuracy (displaying axial/sagittal/coronal views of the left dlPFC cluster (4 voxels) that was significantly negatively correlated with the compatibility effect on accuracy).

(Table 1 and Figure 3a). For reward learning, 51 voxels encompassing the left OFC to the dlPFC (including lateral BA10, BA11, BA47, BA9 and BA46) correlated positively with gamma activity (Table 1 and Figure 3b). For the Flanker accuracy interference effect, 4 voxels were significantly negatively correlated with gamma activity (left dlPFC; BA9/10; Table 1 and Figure 3c). For the interference RT effect, no significant effects emerged.

Intercorrelations between Neuroticism, Reward Learning, and Flanker Performance

The three endophenotypes were not significantly intercorrelated (see Supplementary Material).

Cluster Analysis

In an effort to delineate subgroups of depressed patients on the basis of endophenotype profiles, we entered the following standardized variables into a two-step cluster analysis: neuroticism, PRT reward learning scores, and the Flanker

accuracy interference effect. A three-cluster solution yielded the best fit (Bayesian Information Criterion = 180.69 and LL = 1.21). The first cluster included 41% ($N = 34$) of the sample, the second cluster 29% ($N = 24$), and the third cluster 28% ($N = 23$). ANOVAs revealed significant differences across clusters in neuroticism ($F(2,78) = 52.39$, $p < 0.001$), reward learning ($F(2,78) = 75.41$, $p < 0.001$), and the interference effect ($F(2,78) = 11.46$, $p < 0.001$). Notably, there were no significant differences across clusters in total HRSD depression scores ($F(2,78) = 1.32$, $p = 0.27$; see Figure 4 for additional details).

DISCUSSION

MDD is increasingly recognized as a highly heterogeneous disorder both in terms of symptom presentation and etiology/pathophysiology. To parse this heterogeneity, there has been increased interest in examining relatively less complex and more tractable endophenotypes. The present study examined whether three promising endophenotypes of

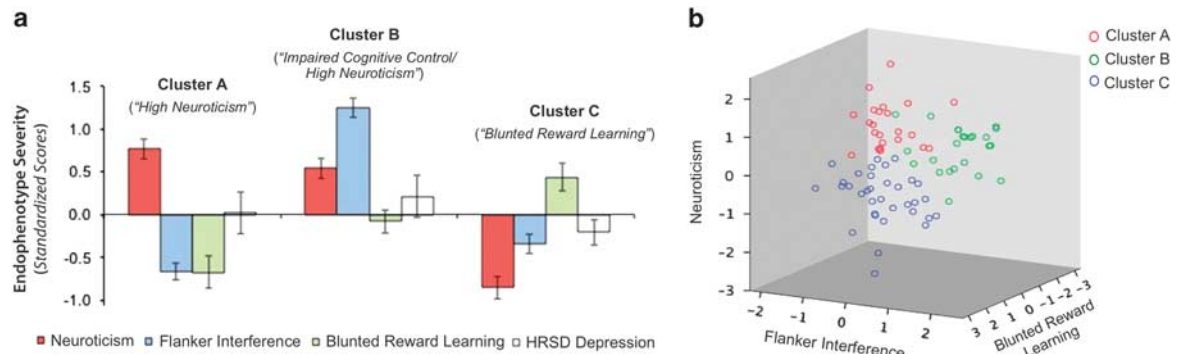


Figure 4 (a) Standardized means (with standard error bars) are displayed for neuroticism (NEO), Flanker interference effect on accuracy, blunted reward learning (PRT), and total depression (HRSD) scores for each of three groups derived from the two-step cluster analysis. (b) Three-dimensional scatterplot displaying association between the three endophenotype variables by cluster group. For consistency across measures, the PRT reward learning variable was reverse scored such that higher scores on each of the displayed measures represent greater severity/impairment.

depression were associated with partially dissociable resting intracranial EEG correlates. To this end, well-validated measures of neuroticism (NEO), reward learning (PRT), and cognitive control (Eriksen Flanker Task) were administered to a sample of depressed adults and correlated with source-localized estimates of resting EEG activity.

Interestingly, the majority of findings emerged in the gamma band. Of note, a combined EEG/FDG-PET study (Oakes *et al*, 2004) revealed that, of all the classic EEG bands, positive correlations between LORETA estimates and resting brain metabolic activity were strongest for gamma. Accordingly, we interpret increased levels of gamma current density as reflecting increased resting brain activity. Here, neuroticism was associated with increased resting gamma current density in a single cluster localized to the OFC and ventral portions of the ACC (ie, subgenual BA25 and rostral BA24). The latter ACC finding partially confirmed our hypotheses. These ventral ACC regions correspond to the 'affective' subdivision of the ACC, which is densely interconnected with limbic and paralimbic structures (eg, amygdala, nucleus accumbens), has been implicated in emotion expression/regulation, and is a critical hub in the default mode network linked to self-referential processing (Buckner *et al*, 2008; Etkin *et al*, 2011). Previous fMRI studies have associated elevated neuroticism with ACC activity (Haas *et al*, 2007; Servaas *et al*, 2013). One study (Haas *et al*, 2007) observed that greater neuroticism correlated with elevated subgenual ACC activation in a nonclinical sample engaged in an emotional conflict task. Our findings extend these reports by showing that neuroticism was associated with elevated subgenual and ventral ACC gamma activity during rest among an unmedicated MDD sample, suggesting that depressed subjects with elevated neuroticism might engage in maladaptive self-referential processing.

Studies probing the neural substrates of neuroticism must contend with potential confounding variables, including current depressive symptoms and related personality variables. Indeed, neuroticism has been repeatedly shown to covary with current depressive symptoms (Klein *et al*, 2011), which, in turn, have been associated with hyperactivity in ventral ACC regions (Gotlib *et al*, 2005; Siegle *et al*, 2007). In an effort to disentangle trait neuroticism effects from the latter confounds, we controlled for current depressive symptoms and the other four NEO factors. Notably, the

neuroticism-ACC gamma association remained significant, suggesting that it more likely reflects the trait-like aspects of neuroticism, rather than current depressive symptoms or related personality trait confounds.

The neuroticism-OFC association was not anticipated. However, neuroticism has previously been linked to both reduced cortical thickness (Rauch *et al*, 2005; Wright *et al*, 2006) and gray matter volume (Kringelbach and Rolls, 2004) in the OFC. Moreover, in addition to its role in value encoding, the OFC has been implicated in emotional processing and regulation/expression (Goodkind *et al*, 2012; Rolls and Grabenhorst, 2008). In spite of parallels with prior reports, the current link between OFC function and neuroticism awaits replication.

Our hypotheses regarding reward learning were partially supported. Specifically, blunted reward learning was associated with reduced gamma activity in the left dlPFC and OFC. Highlighting specificity, these associations remained significant when controlling for current depressive symptoms and discriminability (an index of task difficulty). Interestingly, gamma OFC also emerged as a significant predictor of participants' sensitivity to rewards, as derived from computational modeling of trial-by-trial PRT performance. Prior research has implicated both the OFC (Hornak *et al*, 2004; O'Doherty, 2004) and left dlPFC (Ahn *et al*, 2013; Pizzagalli *et al*, 2005b) in reward learning. In a prior study using a different task, blunted reward responsiveness was associated with reduced resting OFC and left dlPFC activity among healthy controls (Pizzagalli *et al*, 2005b). However, in contrast to the present study, the latter findings emerged in the alpha2, rather than gamma, frequency band. More recent research has implicated gamma activity in reward processing (Marco-Pallarés *et al*, 2015). Contrary to our hypotheses, resting dACC activity was not associated with reward learning across any EEG band examined.

With regards to cognitive control, greater Flanker interference accuracy effects were associated with reduced left dlPFC gamma power. When decomposing this effect, we found that reduced left dlPFC gamma correlated with lower accuracy for incongruent ($r=0.35$, $p=0.001$), but not congruent ($r=0.08$, $p=0.440$), trials. [Although these findings highlight specificity, it is important to emphasize that variance in accuracy was reduced for the congruent ($SD=0.02$), relative to the incongruent ($SD=0.13$), trials, which

may have limited the ability to detect a significant association between LORETA current density and accuracy on congruent trials.] Similarly, left dlPFC gamma activity was negatively associated with interference RT effects. The dlPFC has been strongly implicated in cognitive control (Pizzagalli, 2011; Ridderinkhof *et al*, 2004) and previous studies have linked the left, but not right, dlPFC with cognitive control (MacDonald *et al*, 2000), including studies using the Flanker task (Fassbender *et al*, 2006). In contrast to these findings from task-related fMRI paradigms, the current results indicate that greater *resting* left dlPFC activity predicts performance on a cognitive control task. Within our ROI—but not whole-brain—analyses, increased alpha2 activity in the right dlPFC and decreased theta and alpha2 activity in the dACC were each associated with greater interference RT effects. Because the theta and alpha2 effects were not confirmed in whole-brain analyses, replications are warranted. Importantly, most findings remained significant when controlling for current depressive symptoms and the other endophenotypes.

With regards to our gamma findings, there is evidence that gamma oscillations may facilitate cortical circuit performance and enhance information transmission by increasing signal-to-noise ratio within neocortical circuits (Sohal *et al*, 2009). Although speculative, it is possible that the latter mechanism partially explains the observed findings (eg, greater gamma activity in the left dlPFC reflects relatively enhanced cortical circuit performance in this region, which in turn predicts improved cognitive control performance on the Flanker).

The candidate endophenotypes examined in the current study are themselves complex and multifaceted constructs, which can be parsed into subcomponents. For example, neuroticism has been defined with terms ranging from temperamental, worrying, insecure, and self-conscious (although most, if not all, personality theorists agree that negative emotionality is a defining component; McCrae and Costa, 1987). Similarly, cognitive control is an umbrella term encompassing a range of related abilities, including the ability to *inhibit* automatic or prepotent responses, *shift* in a flexible manner between tasks or mental sets, and *update working memory* in order to retain only relevant information (Friedman *et al*, 2008; Snyder, 2013). Thus, fruitful findings may emerge from studies examining whether different subcomponents of promising endophenotypes have at least partially dissociable neurobiological signatures.

It is also important to highlight that these endophenotypes are not unique to MDD, but rather cut across several DSM diagnostic categories. Thus, it will be important to investigate the transdiagnostic value of candidate endophenotypes by examining their neurobiological and genetic substrates across psychiatrically heterogeneous samples. The current study exclusively focused on MDD given that we were specifically interested in exploring whether the well-documented heterogeneity in this disorder category mapped onto, at least partially, dissociable neural circuitry.

The extent to which these candidate endophenotypes have diagnostic or clinical utility remains an open question. With regards to the present data, an exploratory cluster analysis indicated that three subgroups of depressed patients could be differentiated on the basis of endophenotype profiles, including a subgroup with relatively elevated neuroticism, another with greater impairments in cognitive control, and a

final group with relatively blunted reward learning (Figure 4). Although speculative, knowledge of endophenotype profiles may ultimately help inform optimal treatment selection. For example, depressed individuals with impaired cognitive control may benefit from interventions with pro-cognitive effects (eg, vortioxetine, Mahabeshwarkar *et al*, 2015). Similarly, certain pharmacological (eg, bupropion) and psychotherapeutic (eg, behavioral activation; Dichter *et al*, 2009) interventions may be particularly beneficial for those depressed individuals characterized by blunted reward learning and reward-circuitry deficits.

Limitations

Several limitations of the present study should be noted. First, EEG source localization techniques cannot adequately probe subcortical structures (eg, amygdala, caudate). Although EEG has the benefits of being non-invasive and relatively inexpensive, and thus may be relatively more practical as a diagnostic tool in future clinical settings, it will be important for subsequent studies examining the neural correlates of plausible MDD endophenotypes to employ modalities with greater spatial resolution (eg, fMRI), as well as the ability to probe networks (eg, DMN, salience network). Second, our findings were primarily in the gamma band. There is some evidence suggesting that current density in higher bands (eg, gamma and beta) may be contaminated by muscle or EMG artifacts (Whitham *et al*, 2007). Although the influence of muscle activity cannot be ruled out, we believe it is unlikely that the current gamma findings (which emerged from resting, task-free EEG data) are due to muscle activity owing to their specificity in terms of hypothesized hemispheric laterality and conditions. Finally, nicotine dependence was not exclusionary, which may represent a possible confound (eg, due to nicotine's possible effects on cognitive and reward function).

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