

## Neuroticism and Individual Differences in Neural Function in Unmedicated Major Depression: Findings From the EMBARC Study

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### ABSTRACT

**BACKGROUND:** Personality dysfunction represents one of the only predictors of differential response between active treatments for depression to have replicated. We examine whether depressed patients with higher neuroticism scores, a marker of personality dysfunction, show differences compared with depressed patients with lower scores in the functioning of two brain regions associated with treatment response, the anterior cingulate and anterior insula cortices.

**METHODS:** Functional magnetic resonance imaging data during an emotional Stroop task were collected from 135 adults with major depressive disorder at four academic medical centers participating in the EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care) study. Secondary analyses were conducted including a sample of 28 healthy subjects.

**RESULTS:** In whole-brain analyses, higher neuroticism among adults with depression was associated with increased activity in and connectivity with the right anterior insula cortex to incongruent compared with congruent emotional stimuli (all  $k \geq 281$ , all  $p < .05$  familywise error corrected), covarying for concurrent psychiatric distress. We also observed an unanticipated relationship between neuroticism and reduced activity in the precuneus ( $k = 269$ ,  $p < .05$  familywise error corrected). Exploratory analyses including healthy subjects suggested that associations between neuroticism and brain function may be nonlinear over the full range of neuroticism scores.

**CONCLUSIONS:** This study provides convergent evidence for the importance of the right anterior insula cortex as a brain-based marker of clinically meaningful individual differences in neuroticism among adults with depression. This is a critical next step in linking personality dysfunction, a replicated clinical predictor of differential antidepressant treatment response, with differences in underlying brain function.

**Keywords:** Emotion regulation, fMRI, Major depressive disorder, Neuroticism, Precuneus, Right anterior insula

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Neuroticism reflects the tendency to experience negative emotions and to cope poorly with affective states (1). High levels of neuroticism have enormous public health consequences, including impairments in work functioning (2), increased medical treatment utilization (2), and reduced longevity (3). Neuroticism is a strong vulnerability marker for the development of depression (4–9), but, critically, the clinical effects of neuroticism do not stop once an episode of depression emerges. To the contrary, markers of dysfunctional personality, including high levels of neuroticism, represent one of the only replicated prescriptive indicators of differential response between active treatments for depression (10–12). That is, among individuals with depression, individual differences in neuroticism and personality functioning exist, and these

differences have consequences for the likelihood that a given treatment will be effective. Specifically, higher levels of neuroticism (12) and frank comorbid personality disorder (11) have each been associated with superior response to selective serotonin reuptake inhibitors compared with cognitive therapy, two generally effective treatments for depression (13). These patterns are reinforced by evidence that selective serotonin reuptake inhibitors may have strong specific effects, compared with placebo, in reducing levels of neuroticism itself, over and above changes in symptoms (14,15). Although personality dysfunction does not invariably predict differential response across all forms of treatment [see (16,17)], no other patient characteristic in the depression treatment outcome literature has so often been related to differential response

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across active treatments. However, the neural mechanisms driving these effects are unknown.

Neuroticism was initially conceptualized as a genetically based, biologically driven trait associated with heightened reactivity in limbic systems to stressors in the environment (18,19). More recent work has revealed associations between neuroticism and the functioning of the subgenual anterior cingulate cortex (sgACC) and right anterior insula (rAI), regions implicated in the processing and regulation of emotionally relevant information (20–23). Haas *et al.* (24), for example, observed increased activity in the sgACC in healthy adults as a function of neuroticism during an emotional Stroop task. There are several reasons why individuals with higher levels of neuroticism may perform differently on such a task. The incongruent condition of an emotional Stroop task requires participants to manage competing, emotionally salient elements of the stimulus, control attentional resources in the presence of a distractor, and select the appropriate response while suppressing a competing response. Even with nonemotional stimuli, neuroticism is associated with general difficulties in the control of attentional resources, which manifests in tasks involving attention capture, selective attention, and disengagement of attention from distracting information (25–27). These effects may be further exacerbated when stimuli are negative (27) or emotionally relevant, given the salience of such information (28,29). Furthermore, there is mounting evidence suggesting that neuroticism may also be associated with individual differences in neural activity in a key part of the salience network. Together with more dorsal portions of the ACC, the rAI is believed to be a critical region involved in salience detection (22,23). Increased activity in the rAI has been associated with neuroticism in healthy samples across a wide variety of emotionally relevant tasks for which salience detection is a key feature, including loss anticipation (30), emotion processing (31), pain perception (32), and decision making (33,34).

Converging evidence from treatment trials examining patterns of brain activity associated with response to treatments for depression suggests key roles for individual differences in the functioning of the sgACC and rAI in predicting differential treatment outcomes. Specifically, several observational treatment studies suggest that higher activity in the sgACC (both at rest and during tasks) is associated with better response to antidepressant medications [see (35)], whereas lower sustained activity during emotion processing is associated with better response to cognitive therapy (36,37). By contrast, the sole randomized controlled trial examining neural predictors of treatment outcome did not observe that the sgACC differentiated response to antidepressant and cognitive therapy treatments. Rather, the rAI was the region that most clearly predicted differential response: subjects with higher metabolism in this region at rest were more likely to remit with drug treatment and less likely to remit with cognitive therapy, and vice versa (38).

In this study, we used functional magnetic resonance imaging (fMRI) to examine whether depressed individuals with high levels of neuroticism (vs. depressed individuals with lower levels of neuroticism) displayed increased activity in the sgACC and rAI during a variant of the face-word emotional Stroop task. Activity in both brain regions has been associated

with neuroticism and separately with differential treatment response in depression. Tasks such as the emotional Stroop task that require cognitive and attentional control in the context of emotional processing reliably elicit activity in anterior insula and sgACC regions (39). Thus, the emotional Stroop task provides a promising probe of the role of neuroticism in brain function in depression. This study is a first step to determine whether activity in these two brain regions might represent core neural markers of clinically meaningful individual differences in depression that may help to explain the association between personality dysfunction and differential treatment response. In secondary analyses, we incorporate data from a small sample of healthy control (HC) subjects to examine associations with neuroticism across the full range of neuroticism scores.

## METHODS AND MATERIALS

### Participants

Study participants were recruited as part of the EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care) study, a multisite randomized controlled trial examining medication treatment of depression (40,41). All data came from baseline assessments before treatment. The initial sample comprised 190 individuals with a current diagnosis of major depressive disorder (MDD) who were not currently receiving treatment and who completed the fMRI task at one of the four scanning sites: Columbia University, Massachusetts General Hospital, the University of Michigan, and the University of Texas Southwestern Medical Center. In secondary analyses, data from 40 HC subjects were incorporated to determine the effects of neuroticism across the full range of scores. Psychiatric diagnoses were made using the Structured Clinical Interview for DSM-IV Axis I Disorders (42). Full inclusion and exclusion criteria have been reported elsewhere (41) and are described in the [Supplement](#). The study was approved by the institutional review boards at each site. All participants provided written informed consent.

Of the original sample, data from 49 MDD subjects and 9 HC subjects were excluded owing to excessive motion (>4 mm), low signal-to-noise ratio (<80), technical issues, or artifacts in fMRI data. Three additional MDD subjects were excluded owing to poor behavioral performance (accuracy <70%), and three participants from each group were excluded owing to missing data on core clinical measures. This yielded a final sample of 135 MDD subjects and 28 HC subjects, representing data loss of 28.9% and 30.0%, respectively,  $\chi^2_1 = 0.02$ ,  $p = .89$ , consistent with other neuroimaging data sets (38).

### Clinical Measures

Neuroticism was assessed using the NEO Five-Factor Inventory-3 (43). Because neuroticism scores can be highly correlated with symptom measures (44), we covaried for psychiatric symptoms (see below). Depressive symptoms were assessed using the 24-item Hamilton Depression Rating Scale (45). Subscales of the Mood and Anxiety Symptom Questionnaire were used to assess anhedonia and anxious arousal (46,47).

## Paradigm

The Emotional Conflict Task (48) was used as an emotional Stroop task to probe implicit emotion reactivity and regulation processes during the presentation of conflicting emotional information. Stimuli consisted of 148 pictures of emotional faces (happy or fearful), and participants were asked to label the expression while ignoring an emotion word (“happy” or “fear”) that overlaid the image. The emotion words either matched the emotional faces (congruent trials) or conflicted with them (incongruent trials). Stimuli were presented for 1000 ms, with a variable interstimulus interval (3000–5000 ms, mean 4000 ms), in a pseudorandom order, counterbalanced as a function of expression, word, gender, and response button. Before the scan, participants practiced the task and were required to achieve >85% accuracy.

## Neuroimaging Data Acquisition

Structural and functional MRI data were collected at each site using 3T MRI scanners. See the Supplement for detailed acquisition parameters.

## Functional Neuroimaging Data Preprocessing

Preprocessing of functional images was implemented using Nipype software (<http://nipype.org/nipype>), using a combination of modules from different software packages. The first five volumes of the run were discarded. Functional images were realigned using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>), coregistered to the participant’s structural image, and normalized to Montreal Neurological Institute space using a linear affine transformation implemented in FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). Montreal Neurological Institute space was defined using the OASIS template (<http://www.oasis-brains.org>), with a resolution of 2 mm isotropic. AFNI 3dDespike (<http://afni.nimh.nih.gov/afni>) was used to address spikes in signal intensity (using 3 SD and 5 SD cutoffs for spikes and deviations from the curve, respectively). Finally, data were spatially smoothed using an 8-mm adaptive kernel (FSL).

## Functional Neuroimaging Data Analyses

First-level models were estimated using SPM8. Models were fit separately for each participant and included regressors for each trial type, along with nuisance regressors representing the first trial of the block, error trials, and posterror trials. Regressors were convolved with the canonical hemodynamic response function. Temporal derivatives of the hemodynamic response function and the six movement parameters were included as variables of no interest. A high-pass filter (60 seconds) was used. For the current study, the contrast between incongruent and congruent trials served as the comparison of interest (additional details in the Supplement).

Whole-brain voxelwise analyses were conducted at the second level to examine between-persons effects. Consistent with prior EMBARC reports, all models covaried for scanning site, gender, and age. The primary aim of the study was to examine differences between MDD as a function of neuroticism. As such, the best control participants for examining neural function of individuals with MDD and high levels of neuroticism are individuals with MDD and lower levels of neuroticism. Thus,

the primary whole-brain analyses focused exclusively on the effects of neuroticism in MDD. Because measures of neuroticism can be contaminated with current distress, we additionally covaried for current levels of depression, anhedonia, and anxiety. Secondary whole-brain analyses incorporated data from the HC group. The lack of overlap in neuroticism scores between the groups (Supplemental Figure S2) precluded us from examining the group-by-neuroticism interaction effect to determine whether the effect of neuroticism differed between the groups. To ascertain whether the effect of neuroticism was similar at the lower (HC) and higher (MDD) ends of the range, we included both linear and curvilinear (neuroticism<sup>2</sup>) terms in the model (additional details in the Supplement).

Voxelwise regression analyses were implemented using the GLM Flex suite of software tools ([http://mrtools.mgh.harvard.edu/index.php/Main\\_Page](http://mrtools.mgh.harvard.edu/index.php/Main_Page)). This software uses all available data to estimate the model in a given voxel. See Supplemental Figure S1 for a map of sample sizes per voxel (minimum  $n = 32$ ). Statistical inferences were made on the basis of cluster level statistics (cluster forming threshold  $p < .005$ , uncorrected, extent threshold  $p < .05$  familywise error [FWE] corrected). Given that the size of the effect of neuroticism on neural function in depression is currently unknown, these thresholds were chosen a priori as a way of balancing protection from both type I and II errors (49).

To explore whether neuroticism was also associated with differences in connectivity between brain regions, we conducted exploratory generalized psychophysiological interaction analyses (50). Given the findings reported below, we used as the seed region a mask of the dorsal rAI derived from a relevant parcellation study of the insula (51). First-level and second-level models were the same as those described above.

## Clinical, Demographic, and Behavioral Data Analyses

Associations with clinical, demographic, and behavioral data were examined with SAS version 9.4 (SAS Institute Inc., Cary, NC). Associations with neuroimaging data were examined using parameter estimates extracted from significant clusters of activity. Reaction time data were log-transformed when examined as the dependent variable. Differences in accuracy were examined using Poisson regression models of error rates, with robust standard errors where appropriate (52).

## RESULTS

### Primary Analyses: Neuroticism in MDD

**Clinical Features and Behavioral Results.** Table 1 displays demographic and clinical characteristics. The distribution of neuroticism scores in the MDD group (Supplemental Figure S2) was centered (mean = 68.85, SD = 7.86) nearly 2 SD higher than published population norms (mean = 50, SD = 10) (43), consistent with the level and variability of neuroticism scores observed in previous samples of patients with depression (53). Depression severity was the only variable significantly associated with neuroticism in the MDD group. As expected, Wilcoxon signed rank tests of within-subject effects revealed that accuracy for the incongruent condition was lower than accuracy for the congruent condition ( $p < .001$ ),

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**Table 1. Demographic and Clinical Characteristics**

Variable	MDD Group (n = 135)	HC Group (n = 28)	Effect of Group	Association With Neuroticism	
				MDD Group	Full Sample
<b>Demographic</b>					
Female, %	67.41	60.71	$\chi^2_1 = 0.46$	$r_{pb} = -.02$	$r_{pb} = .03$
Married, %	20.90 <sup>a</sup>	17.86	$\chi^2_1 = 0.13$	$r_{pb} = -.17$	$r_{pb} = -.06$
Unemployed, % <sup>b</sup>	48.06	23.08	$\chi^2_2 = 6.39^c$	$\rho = .09$	$\rho = .20^c$
Age, mean (SD)	36.51 (12.56)	37.39 (16.08)	$t_{161} = -0.32$	$r = -.11$	$r = -.10$
Years of education, mean (SD) <sup>d</sup>	14.84 (2.46)	15.82 (5.04)	$t_{29.71} = -1.01$	$r = .002$	$r = -.09$
IQ, mean (SD) <sup>e</sup>	114.85 (12.07)	118.42 (13.07)	$t_{137} = -1.30$	$r = .003$	$r = -.08$
<b>Behavioral Performance</b>					
Correct, incongruent (%) <sup>f</sup>	93.88 (5.15%)	93.49 (5.17%)	$z = -0.37$	$z = -0.08$	$z = 0.22$
Correct, congruent (%) <sup>f</sup>	96.91 (3.86%)	97.38 (2.76%)	$z = 0.74$	$z = -0.15$	$z = 0.94$
Reaction time, incongruent, mean (SD) <sup>g</sup>	782.59 (138.81)	794.23 (186.48)	$t_{161} = -0.16$	$r = .07$	$r = .03$
Reaction time, congruent, mean (SD) <sup>g</sup>	718.36 (123.10)	729.84 (164.55)	$t_{161} = -0.23$	$r = .05$	$r = .02$
<b>Clinical Measures</b>					
Neuroticism, mean (SD)	68.85 (7.86)	36.39 (7.24)	$t_{161} = 20.15^h$	—	—
HDRS, mean (SD) <sup>d</sup>	26.61 (5.50)	0.71 (1.01)	$t_{160.17} = 50.74^h$	$r = .18^c$	$r = .79^h$
MASQ-Anhedonia, mean (SD) <sup>d</sup>	43.77 (5.22)	26.04 (7.95)	$t_{31.98} = 11.31^h$	$r = .14$	$r = .71^h$
MASQ-Anxiety, mean (SD) <sup>d</sup>	17.67 (5.90)	10.79 (0.99)	$t_{158.49} = 12.73^h$	$r = .13$	$r = .43^h$
<b>Clinical Features</b>					
Duration of episode, months, mean (SD) <sup>i</sup>	36.75 (60.90)	—	—	$r = .01$	—
Age of onset, years, mean (SD)	16.13 (5.90)	—	—	$r = -.10$	—
Recurrent, % <sup>j</sup>	86.36	—	—	$r_{pb} = -.04$	—
Melancholic, %	38.52	—	—	$r_{pb} = -.06$	—
Atypical, %	30.37	—	—	$r_{pb} = .06$	—
Current anxiety disorder, %	37.04	—	—	$r_{pb} = .01$	—
Current eating disorder, %	1.48	—	—	$r_{pb} = .17$	—
Lifetime alcohol/substance disorder, %	22.22	7.14	Fisher's exact: $p = .07$	$r_{pb} = .08$	$r_{pb} = .16^c$

HC, healthy control; HDRS, Hamilton Depression Rating Scale; MASQ, Mood and Anxiety Symptoms Questionnaire; MDD, major depressive disorder;  $r_{pb}$ , point biserial correlation.

<sup>a</sup>Data were missing from 1 participant.

<sup>b</sup>Data were missing from 2 participants (MDD group) and considered not classifiable as employed vs. unemployed for 6 others (4 in the MDD group, 2 in the HC group).

<sup>c</sup> $p < .05$ .

<sup>d</sup>The Satterthwaite method was used owing to inequality of variances.

<sup>e</sup>Data were missing from 20 MDD and 4 HC participants.

<sup>f</sup>Owing to the shape of the distributions, data were examined using Poisson regression models of error rates using robust standard errors.

<sup>g</sup>Reaction time data were log-transformed for analyses.

<sup>h</sup> $p < .001$ .

<sup>i</sup>Data were missing from 2 participants.

<sup>j</sup>Data were missing from 3 participants.

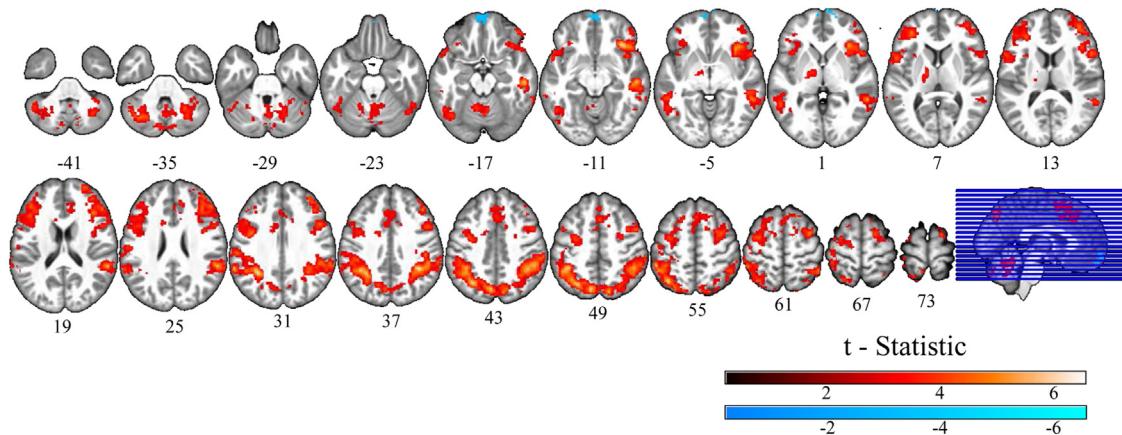
and dependent  $t$  tests revealed significantly slower reaction times to the incongruent compared with the congruent conditions ( $t_{134} = 20.25$ ,  $p < .001$ ). Neuroticism was not significantly associated with behavior (Table 1).

**Task Effects.** As expected, significantly greater blood oxygen level-dependent (BOLD) response to incongruent, compared with congruent, stimuli was observed for the MDD group in the anterior insula cortex, cingulate, dorsolateral prefrontal cortex (PFC), lateral parietal cortex, precuneus, and thalamus, along with activity in motor regions, fusiform gyrus, cerebellum, and right middle temporal gyrus (Figure 1 and Table 2). We also observed a significant negative effect (which represented greater negative relative BOLD signal

during the incongruent compared with the congruent condition) (Table 2) in the frontal pole.

**Effect of Neuroticism on BOLD Response.** We observed a significant positive relationship in whole-brain analyses between neuroticism and activity in the dorsal rAI in MDD ( $k = 281$ , FWE corrected  $p = .03$ ; peak,  $t = 3.76$   $x = 32$ ,  $y = 22$ ,  $z = -2$ ) (Figure 2A) to the incongruent compared with the congruent conditions, covarying for current depression, anhedonia, and anxiety symptoms. We also observed a significant negative relationship in the left precuneus ( $k = 269$ , FWE corrected  $p = .04$ ; peak,  $t = -4.27$   $x = 0$ ,  $y = -64$ ,  $z = 30$ ) (Figure 2B), owing to a weaker positive relationship between neuroticism and BOLD response to the incongruent compared





**Figure 1.** Neural correlates of the incongruence effect in major depressive disorder. Significant clusters ( $p < .05$  familywise error corrected) of blood oxygen level-dependent response to the incongruent-minus-congruent contrast across the depressed group.

with the congruent conditions in this region (Figure 2B, inset). Secondary analyses of extracted data revealed that the effect of neuroticism remained significant in both the rAI and the precuneus regions (all  $F \geq 5.51$ , all  $p \leq .03$ ) when covarying for demographic and clinical variables (see the Supplement for additional details). Furthermore, we repeated the primary whole-brain models examining neuroticism on its own [see (54,55)] and observed two similar clusters: a significant cluster in the dorsal rAI that extended in the frontal operculum ( $k = 419$ , FWE corrected  $p = .004$ ) and a cluster that was just shy of significance in the left precuneus ( $k = 233$ , FWE corrected  $p = .09$ ).

**Effect of Neuroticism on Functional Connectivity.**

Given the findings in the dorsal rAI noted above and given this region’s association with other large-scale cortical networks, we used a dorsal rAI mask from a recent parcellation study of the insula as the seed region for whole-brain generalized psychophysiological interaction analyses (51), and we overlaid significant results on a map generated by a recent parcellation

of large-scale cortical networks (56). We observed three significant clusters (Figure 3) demonstrating reduced connectivity with the dorsal rAI as a function of neuroticism to incongruent versus congruent stimuli: a cluster in the lateral PFC (lateral Brodmann area 10) localized in a region associated with the frontoparietal control network ( $k = 287$ , FWE corrected  $p = .03$ ; peak,  $t = -4.08$   $x = 42$ ,  $y = 50$ ,  $z = -2$ ); a cluster in a thin strip of cortex in the inferior middle and posterior cingulate, also associated with the frontoparietal control network ( $k = 448$ , FWE corrected  $p = .002$ ; peak,  $t = -5.01$   $x = 4$ ,  $y = -12$ ,  $z = 26$ ); and a cluster in the occipital lobe, associated with the visual network and extending ventrally into the cerebellum ( $k = 1048$ , FWE corrected  $p < .001$ ; peak,  $t = -4.45$   $x = -6$ ,  $y = -78$ ,  $z = -8$ ). In each cluster, the negative association was due to reduced connectivity during incongruent and increased connectivity during congruent stimuli (Figure 3, inset). As above, the effect of neuroticism in each cluster remained significant when demographic and clinical variables were covaried (all  $F \geq 13.80$ , all  $p \leq .001$ ) (details in the Supplement along with an analysis of the effects of scanner site).

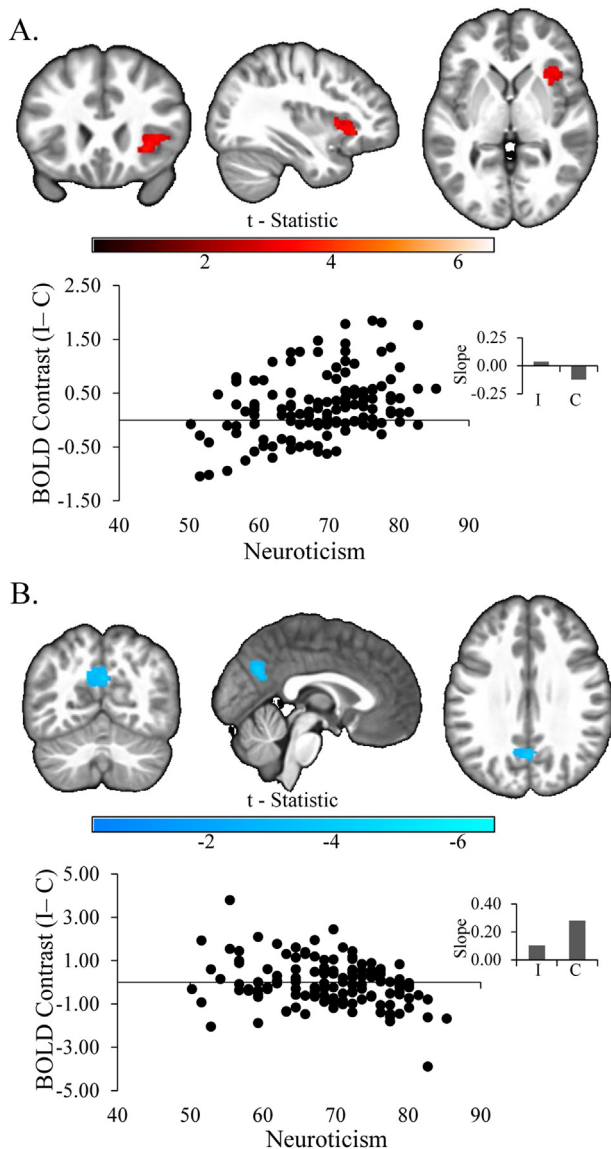
**Table 2. Coordinates of Clusters Showing Significant Task Effects Among Patients With MDD (Incongruent–Congruent)**

k	FWE Corrected $p$	Hemisphere	Region	t	x	y	z	Stimulus Effects, Mean (SD) <sup>a</sup>	
								Incongruent	Congruent
Positive Effect									
20,638	<.001	R/L	Parietal (IPL, SMG, SPL, ANG, precuneus)	6.12	40	-46	38	0.58 (1.16)	0.23 (1.14)
		R/L	Frontal (IFG, MFG, SFG, precentral gyrus, postcentral gyrus, operculum)						
		R	Temporal (MTG, STG)						
2315	<.001	R/L	Cerebellum	4.61	-14	-54	-20	2.21 (1.76)	1.86 (1.72)
1129	<.001	L	Fusiform/MTG	5.43	-42	-66	-20	1.22 (1.42)	0.94 (1.37)
270	.04	L	Thalamus	3.91	-14	-12	6	0.61 (1.08)	0.38 (1.03)
Negative Effect									
267	.04	—	Frontal pole	-3.88	8	70	2	-0.99 (2.23)	-0.57 (2.08)

The main effects of scanning site, gender, and age were covaried. Cluster forming threshold  $p < .005$  uncorrected, cluster extent threshold  $p < .05$  FWE corrected.

ANG, angular gyrus; FWE, familywise error; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MDD, major depressive disorder; MFG, middle frontal gyrus; MTG, middle temporal gyrus; R, right; SFG, superior frontal gyrus; SMG, supramarginal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus.

<sup>a</sup> $\beta$  values for each stimulus type were extracted from the clusters and averaged over the MDD sample.



**Figure 2.** Effect of neuroticism on blood oxygen level-dependent (BOLD) response in major depressive disorder. Significant clusters of positive (A) and negative (B) relationships between neuroticism and brain activity among adults with major depressive disorder, covarying for the effects of site, gender, age, depression, anhedonia, and anxiety. Scatterplots are provided for display purposes only. They depict the bivariate relationships between neuroticism (abscissa) and BOLD response in the significant clusters (ordinate), represented by the  $\beta$  coefficient associated with the incongruent-minus-congruent (I–C) contrast. Insets display slope estimates (standardized  $\beta$ s from regression models of extracted data, covarying for the above variables) representing the relationship between neuroticism and BOLD response to each stimulus type.

### Secondary Analyses: Neuroticism in the Combined MDD and HC Samples

As displayed in Table 1, the HC and MDD groups were well matched on demographic variables with the exception of employment rates. Neuroticism levels among HC subjects (mean = 36.39, SD = 7.24) were substantially ( $\approx 1.5$  SD)

lower than population norms, likely owing to strict inclusion criteria. In line with prior reports [e.g., (57,58)], when the full range of clinical scores was considered across the full sample, neuroticism was significantly associated with depression, anhedonia, and anxiety symptoms as well as employment status and past alcohol and substance abuse diagnoses (Table 1).

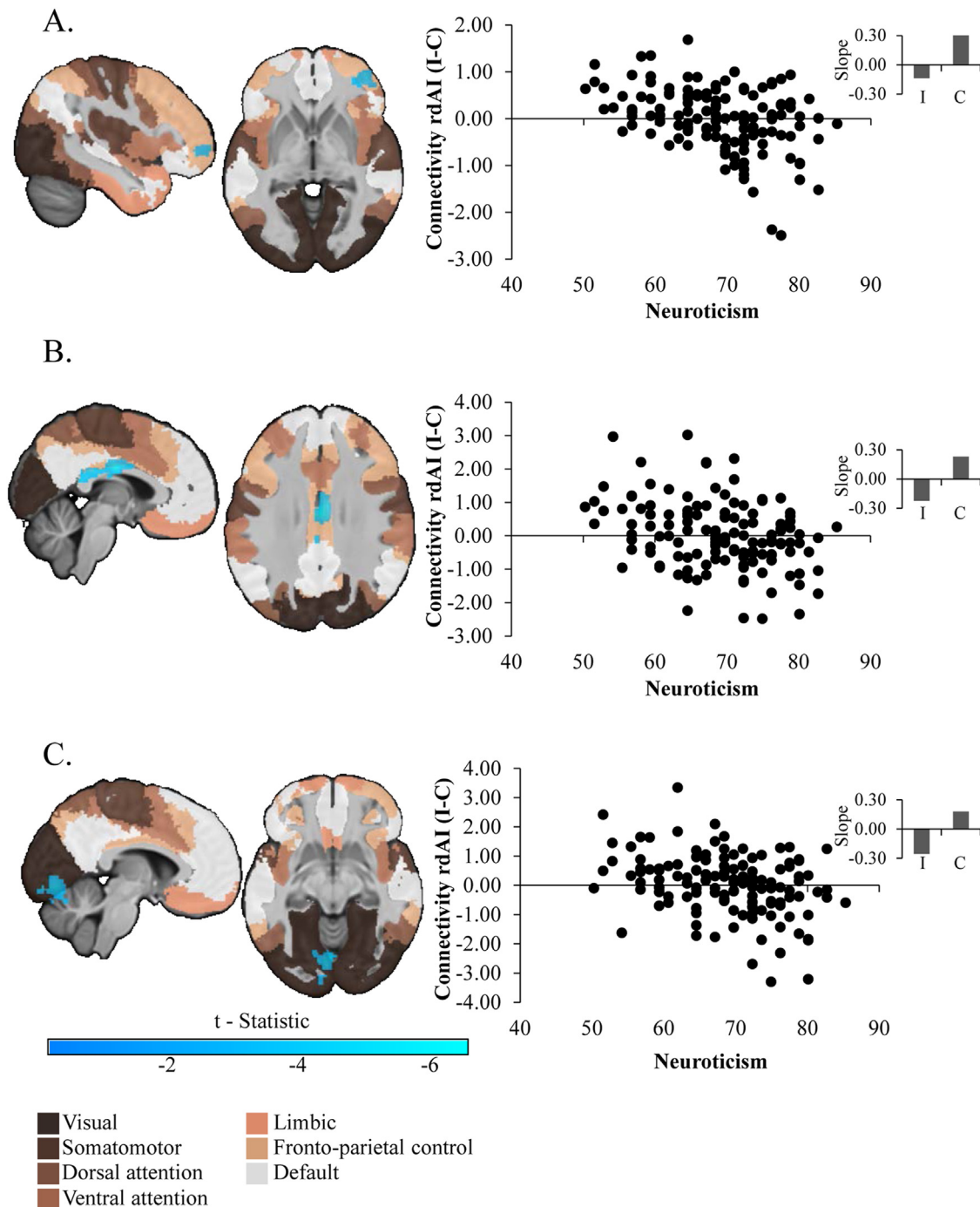
We used repeated measures linear and Poisson regression models to examine the effects of group, condition, and group-by-condition interaction on reaction times and error rates, respectively. Incongruent stimuli were associated with longer reaction times ( $F_{1,161} = 267.90, p < .001$ ) and higher error rates ( $F_{1,161} = 25.40, p < .001$ ) than congruent stimuli. Neither the main effect of group nor the group-by-condition interaction was significant in either analysis (all  $F < 0.53$ , all  $p > .46$ ). Neuroticism was not associated with behavior in any condition, in either group (Table 1).

**Effect of Neuroticism on BOLD Response Across the Sample.** In whole-brain analyses across the full sample, we did not observe a significant effect of group or a linear effect of neuroticism on BOLD response (all  $k < 190$ , FWE corrected  $p > .05$ ). Rather, we observed a significant curvilinear relationship between neuroticism and BOLD response to the incongruent compared with the congruent conditions in a cluster including the rAI and extending into the frontal operculum and laterally to Brodmann area 45 ( $k = 293$ , FWE corrected  $p = .03$ ; peak,  $t = 3.85, x = 28, y = 20, z = 4$ ) (Supplemental Figure S3), whereby subjects with lower and higher levels of neuroticism had the highest BOLD response in this region.

**Effect of Neuroticism on Connectivity Across the Sample.** Using the same dorsal rAI seed described above, we observed a significant effect of group on connectivity between the seed and a cluster in portions of the left superior parietal lobule and precuneus associated with the dorsal attention network, with anterior extension into white matter ( $k = 695$ , FWE corrected  $p < .001$ ; peak,  $t = 3.89, x = -32, y = -20, z = 30$ ) (Supplemental Figure S4). This effect was driven by reduced connectivity to the incongruent compared with the congruent conditions in the HC group compared with the MDD group. Finally, we observed a significant inverse curvilinear effect of neuroticism on connectivity during the incongruent compared with the congruent conditions between the dorsal rAI seed and a cluster in the lateral PFC localized in a region associated with the frontoparietal control network ( $k = 278$ , FWE corrected  $p = .04$ ; peak,  $t = -4.44, x = 38, y = 50, z = 18$ ) (Supplemental Figure S4), such that connectivity was highest for subjects in the middle range of the neuroticism scale.

### DISCUSSION

Adults with depression differ from one another regarding personality features, and these differences have consequences for the likelihood of success of particular treatments (11,12). In this study, we observed that individuals with depression with higher neuroticism had increased activity in the rAI and decreased activity in the left precuneus during an



**Figure 3.** (A–C) Effect of neuroticism on functional connectivity with the right dorsal anterior insula (rdAI) in major depressive disorder. Significant clusters represent results of generalized psychophysiological interaction analyses using an rdAI seed derived from a recent parcellation study (51). To aid interpretation, clusters have been overlaid on the seven-network parcellation of large-scale cortical networks derived by Yeo *et al.* (56). Scatterplots are provided for display purposes only. They depict the bivariate relationships between neuroticism (abscissa) and parameter estimates (ordinate) of the contrast in connectivity during the incongruent (I) vs. congruent (C) conditions. Insets display slope estimates (standardized  $\beta$ s from regression models of extracted data, covarying for the above variables) representing the relationship between neuroticism and connectivity parameter estimates for each stimulus type.

emotional Stroop task. The relationship between neuroticism and rAI activity was hypothesized, given findings linking neuroticism to activity in this region among HC subjects

(30–34,59), findings linking personality dysfunction to antidepressant treatment response (10–12), and findings linking antidepressant treatment response to activity in this region (38,60).

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Thus, this study provides convergent evidence for the importance of activity in the rAI for understanding clinically meaningful individual differences among patients with MDD.

The anterior insula has been implicated in a wide variety of cognitive and emotional regulation processes and is believed to be a central component of the salience network (22,23). One set of theories (23,61) contends that the anterior insula, and particularly the dorsal anterior insula, is pivotal for adaptively switching between the default mode and central executive networks to appropriately process salient stimuli (22,62). One possible interpretation of the present findings is that individuals high in neuroticism may display altered salience processing during the presentation of emotional information. Poorly tuned salience detection could result in faulty cortical network switching. This hypothesis is further supported by the results of exploratory functional connectivity analyses in which we observed reduced connectivity between the dorsal rAI and two regions (one in the lateral PFC and one in the midcingulate and/or posterior cingulate) associated with the frontoparietal cognitive control network.

We did not hypothesize the negative relationship between neuroticism and activity in the precuneus. The ventral precuneus, in which the findings were localized, has been included as a key node of the default mode network (63,64). The negative observed relationship was due to increased activity to the congruent compared with incongruent condition, which could reflect deficits in the switch from default mode processing when responding to the congruent stimuli, the easier of the two conditions (35,65,66). This hypothesis fits well with the possibility that neuroticism may be associated with abnormalities in large-scale cortical network switching; however, these hypotheses require testing in future work with tasks designed specifically to examine these processes.

We did not observe the hypothesized relationship between neuroticism and activity in the sgACC. This stands in contrast to two prior sets of findings. Haas *et al.* (24) observed an association between neuroticism and activity in this region among healthy individuals. Webb *et al.* (67), using scalp recorded electroencephalogram data collected at rest from the same parent study as the data reported herein, observed that increased resting electroencephalogram (gamma current density) signal localized to the sgACC was associated with increased neuroticism scores. In contrast to the study by Haas *et al.* (24), we collected data on relatively few individuals from the middle of the neuroticism range. It is possible that the relationship is strongest over this portion of the range and dissipates at the extremes. In secondary analyses of BOLD response, we observed strong evidence of nonlinear relationships between neuroticism and neural response. Comparison with the findings by Webb *et al.* (67) suggests that there may be a dissociation between task and rest states in the relationship between neuroticism and the functioning of the sgACC in patients with MDD. Future work will need to examine this possibility as well as whether activity in this region in response to different kinds of emotional tasks might be associated with neuroticism.

In secondary analyses, we did not observe mean differences in behavioral performance or BOLD response between the MDD and HC groups. However, we did observe reduced connectivity in the HC group relative to the MDD group

between the dorsal rAI and regions associated with the dorsal attention network. Perhaps the most notable findings from the secondary analyses were the observations of curvilinear relationships between neuroticism and BOLD response in an rAI-frontal-opercular cluster and between neuroticism and measures of functional connectivity between the dorsal-rAI and lateral PFC. These findings suggest that the relationship between neuroticism and brain activity in and connectivity with the rAI may not be simple or linear. Notably, the present findings occur in the context of a broader literature that is mixed regarding the nature, location, and direction of MDD-HC differences in neural function (68–71). We contend that this variability may stem, in part, from the complex relationships between diagnostic status, neuroticism, and brain activity. Whether differences between MDD and HC groups are observed may depend on which parts of the neuroticism spectrum have been sampled in each group.

Many studies, similar to this one, adopt an extreme groups sampling approach to assess the neural correlates of important participant characteristics. Although such approaches have notable strengths, one limitation is that it can be difficult to ascertain the nature of the relationship between the construct in question and brain activity over the middle of the range. It will be important for future work regarding broad dimensions of psychological functioning, conducted in accordance with the Research Domain Criteria initiative (72), to sample across the range of possible scores on dimensional measures and to consider nonlinear relationships with brain function. Additional limitations to the present study include the fact that the sample sizes from the MDD and HC groups were imbalanced, which could have affected power to detect between-group differences. Also, the shorter version of the NEO instruments was used to assess neuroticism. As such, it was not possible to calculate reliable subscales of neuroticism to examine which subscales were driving the observed effects.

## Conclusions

The current findings are among the first to link a clinical characteristic (personality dysfunction) with neural markers (functioning of the rAI)—both of which have been associated with differential response to treatments for depression. This is an important next step for understanding the neural basis of clinically meaningful dimensions on which patients with depression differ, and it provides a target for future work to examine the mechanisms through which alterations in brain function affect treatment outcomes. Once these processes are better understood, it may be possible not only to better tailor existing treatments for specific individuals, but also to develop novel strategies that can more efficiently target an individual's underlying pathology.

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