Brain Electrical Tomography in Depression: The Importance of Symptom Severity, Anxiety, and Melancholic Features

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Background: *The frontal lobe has been crucially involved in the neurobiology of major depression, but inconsistencies among studies exist, in part due to a failure of considering modulatory variables such as symptom severity, comorbidity with anxiety, and distinct subtypes, as codeterminants for patterns of brain activation in depression.*

Methods: *Resting electroencephalogram was recorded in 38 unmedicated subjects with major depressive disorder and 18 normal comparison subjects, and analyzed with a tomographic source localization method that computes the cortical three-dimensional distribution of current density for standard electroencephalogram frequency bands. Symptom severity and anxiety were measured via self-report and melancholic features via clinical interview.*

Results: *Depressed subjects showed more excitatory (beta3, 21.5–30.0 Hz) activity in the right superior and inferior frontal lobe (Brodmann's area 9/10/11) than comparison subjects. In melancholic subjects, this effect was particularly pronounced for severe depression, and right frontal activity correlated positively with anxiety. Depressed subjects showed posterior cingulate and precuneus hypoactivity.*

Conclusions: *While confirming prior results implicating right frontal and posterior cingulate regions, this study highlights the importance of depression severity, anxiety, and melancholic features in patterns of brain activity accompanying depression.* Biol Psychiatry 2002;52: 73–85 © *2002 Society of Biological Psychiatry*

Key Words: Melancholic depression, anxiety, frontal asymmetry, cingulate cortex, affect, source localization

Introduction

The region most frequently found to be dysfunctional in major depressive disorder (MDD) is the prefrontal cortex (PFC) (Brody et al 2001a; Davidson and Henriques, 2000). Distinct PFC subdivisions likely play different roles in the pathophysiology of depression: decreased activation in the dorsolateral PFC (DLPFC) (Baxter et al 1989; Biver et al 1994; Bench et al 1992), but increases in the ventrolateral PFC (VLPFC) (Biver et al 1994; Brody et al 1999, 2001b; Drevets et al 1992; Mayberg et al 1999) are among the most replicated findings. Consistent with these patterns, remission from depression has been associated with increased DLPFC activation (Baxter et al 1989; Martinot et al 1990; Mayberg et al 1999) and VLPFC decreases (Brody et al 1999, 2001b; Mayberg et al 1999).

In electroencephalographic (EEG) studies of depression, an abnormal pattern of asymmetric activity in the frontal regions due to relative hyperactivity over the right and/or relative hypoactivity over the left frontal regions has been frequently observed (Davidson and Henriques 2000). This pattern has been reported in individuals with subclinical depression (Schaffer et al 1983; but see Reid et al 1998), MDD (Bell et al 1998; Gotlib et al 1998; Henriques and Davidson 1991; Kano et al 1992; see also Reid et al 1998), remitted depression (Henriques and Davidson 1990), MDD with comorbid anxiety disorders (Bruder et al 1997), seasonal affective disorder (Allen et al 1993), and unselected subjects (Pauli et al 1999). Although these asymmetric findings concur with Positron Emission Tomography (PET)/Single-Photon Emission Computed Tomography (SPECT) results of increased right activation (Reischies et al 1989; Brody et al 2001b) and serotonergic uptake (D'haenen et al 1992), as well as

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decreased left frontal activation (e.g., Bench et al 1992, 1993; Drevets et al 1997; Martinot et al 1990), conclusive statements about the intracerebral generating sources cannot be drawn from scalp-recorded data.

In recent years, the assumption that unipolar depression is clinically, etiologically, and most likely pathophysiologically heterogeneous has attracted considerable interest (Davidson and Henriques 2000; Drevets 2000; Heller and Nitschke 1998). Numerous factors may contribute to this heterogeneity including symptom severity, comorbidity with anxiety, distinct subtypes characterized by specific clusters of symptoms, and prior history of psychopathology. The impact of these sources of heterogeneity on patterns of brain function in depression is unclear. Depression severity has been associated with reduced left (e.g., Baxter et al 1989; Bench et al 1993; Drevets et al 1992; Kato et al 1995) or increased right (Galynker et al 1998; Osuch et al 2000) frontal metabolism and blood flow. Anxiety-depression comorbidity has been characterized by more right than left anterior activity in MDD subjects (Bruder et al 1997), consistent with a key role of the right PFC in anxiety and anxiety disorders (Bremner et al 1999; Davidson et al 2000c; Lucey et al 1995; Nitschke et al 1999; Rauch et al 1997; Stapleton et al 1997; Stewart et al 1988; Wiedemann et al 1999). Finally, specific symptoms of depression may be accompanied by different dysfunctional patterns of activation. Psychomotor retardation, anhedonia, and flat affect, for example, have been associated with decreased left (but not right) DLPFC activation (Bench et al 1993; Galynker et al 1998).

The present study was undertaken to extend this literature by examining in a single sample three factors known to have substantial variability across depressed patients: depression severity, anxiety, and melancholic features (e.g., anhedonia, lack of mood reactivity). Given that depression severity, anxiety, and melancholic features likely covary in depression, analytic strategies tested the unique contributions of each in modulating patterns of brain activity. A novel source localization technique that combines improved spatial specificity with the high time resolution of EEG data were employed to examine intracerebral generating sources for standard EEG frequency bands. Conventional scalp power spectra were also computed for the sake of comparison and in an attempt to directly replicate previous asymmetry findings in depression (Davidson and Henriques 2000). Based on prior findings reviewed above, we hypothesized that depression severity would be associated with decreased left and/or increased right PFC activity, and that increased levels of anxiety would additionally modulate frontal asymmetry in favor of the right hemisphere. Analyses examining melancholic and nonmelancholic subjects separately were conducted to test for differences between those two forms of depression, with no specific hypotheses advanced due to the absence of previous research contrasting them.

Methods and Materials

Participants

Subjects were recruited through advertisements in local media, and those potentially meeting study criteria based on a phone screen were invited for a diagnostic interview. Depressed subjects met DSM-IV criteria for MDD (American Psychiatric Association 1994), as determined by the Structured Clinical Interview for DSM (SCID) (Spitzer et al 1992), modified to make DSM-IV diagnoses. Twenty melancholic (13 female) and 18 nonmelancholic (10 female) subjects were distinguished depending on the presence of DSM-IV melancholic features. Individuals with any history of mania, psychosis or other Axis I disorders were excluded, with the exception of specific phobias and social phobia secondary to MDD. Dysthymia was allowed only if occurring with MDD. Additionally, subjects had no first-degree relatives with a history of mania or psychosis. Screened with the SCID, Nonpatient Edition, 18 normal comparison participants (10 female) had no current or past Axis I pathology in themselves or first-degree relatives. Diagnostic reliability was assessed by independent ratings of 10 randomly selected audio-taped SCID interviews (kappa = 0.80). All participants were right-handed (score on the Chapmans' Handedness Inventory between 13 and 17) (Chapman and Chapman 1987) and were unmedicated upon study entry. The length of time since any past medication use exceeded washout period recommendations (e.g., 4 weeks for antidepressants). Data for six additional subjects were lost due to technical problems. The three subject groups did not differ in age, gender ratio, or sociodemographic variables (Table 1).

Procedure

After written informed consent was obtained following complete description of the study (approved by the University of Wisconsin Human Subjects Committee), subjects were administered the SCID and the 17-item version of the Hamilton Rating Scale of Depression (HRSD) (Hamilton 1960) in separate sessions. At the SCID session, participants completed the Beck Depression Inventory (BDI) (Beck et al 1961) and the trait form of the State-Trait Anxiety Inventory (STAI) (Spielberger et al 1970), which was not initially included in the study protocol resulting in reduced sample available for STAI analyses. On another day, participants underwent [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) PET (Abercrombie et al 1998; Larson et al 1998; Lindgren et al 1999) and EEG recording. After an overview of the procedures, electrodes were applied, and two intravenous lines (right arm and left hand) were inserted per PET protocol. EEG recording began simultaneously with the FDG injection and consisted of 10 contiguous 3-min trials covering the 30 min necessary for radiotracer uptake. Before every trial, subjects were verbally instructed to open or close their eyes according to a counterbalanced order across subjects. Two laboratory assistants seated to the left of the participant drew blood samples from the left hand,

Table 1. Sociodemographic and Mood Data in Comparison, Melancholic, and Nonmelancholic Depressed Subjects

	Comparison Subjects		Melancholic Depressed		Nonmelancholic Depressed	
Female/Male[a]	10/8		13/7		10/8	
	Mean	SD	Mean	SD	Mean	SD
Age (y)	38.6	13.6	36.5	12.9	33.1	8.8
Education[b]	2.3	1.1	2.6	0.8	2.9	1.0
BDI	2.9	3.1	33.8[c]	6.4	29.5[d]	8.1
HRSD	N/A	N/A	18.2	5.1	20.1	5.5
STAI	30.5	7.0	64.9[c]	4.3	56.7[d]	11.2

BDI, Beck Depression Inventory (Beck et al 1961); HRSD, Hamilton Rating Scale for Depression (Hamilton 1960); STAI, State-Trait Anxiety Inventory (trait form; Spielberger et al 1970). Comparison subjects: $n = 18$. Melancholic depressed subjects: $n = 20$ ($n = 16$ for BDI, $n = 17$ for HRSD, $n = 9$ for STAI). Nonmelancholic depressed subjects: $n = 18$ ($n = 15$ for HRSD, $n = 11$ for STAI).

[a]Chi-square test ($df = 2$), $p > .75$.

[b]Possible range (Hollingshead 1957): 1–7.

[c]$p < .0001$ (t tests, $df = 36$): Melancholic depressed subjects differ from comparison subjects.

[d]$p < .0001$ (t tests, $df = 34$): Nonmelancholic depressed subjects differ from comparison subjects.

as required by PET procedures. Upon completion of EEG recording, electrodes and intravenous lines were removed.

Apparatus and Physiologic Recording

Electroencephalogram was recorded from 28 scalp sites (10/20 system plus FC3/4, FC7/8, CP5/6, PO3/4 and FPz; reference: left ear) using a modified lycra electrode cap (Electro-Cap International, Inc.). Two additional channels recorded horizontal and vertical electro-oculogram (EOG). Impedances for EEG and EOG electrodes were under 5 KΩ and 20 KΩ, respectively. Electroencephalogram and EOG data were amplified with a Grass Model 12 Neurodata system using Model 12C preamplifiers with a bandpass of 1–300 Hz and a 60-Hz Notch filter. The signal was also filtered with MF6 digital antialiasing low-pass filters set at 100 Hz, and subsequently digitized online at 250 Hz.

Data Reduction and Analysis

Nonoverlapping, artifact-free 2048-msec EEG epochs were extracted for each trial. To minimize artifacts caused by blinks, only EEG epochs during eyes-closed trials were analyzed. The resultant 7876 epochs were distributed similarly among melancholic (mean: 134.2, SD: 66.0), nonmelancholic (136.7 ± 69.9), and comparison (151.7 ± 99.6) subjects.

Using average reference, spectral analyses were performed for the 2048-msec epochs via Discrete Fourier Transform (DFT) (boxcar windowing; Brillinger 1981), resulting in a frequency resolution of 0.5 Hz. In light of the observation that EEG frequency bands reflect different functions and behave statistically independently (Kubicki et al 1979), Low Resolution Electromagnetic Tomography (LORETA) (Pascual-Marqui et al 1994, 1999) was used to estimate the three-dimensional intracerebral current density distribution for the following bands: delta (1.5–6.0 Hz), theta (6.5–8.0 Hz), alpha1 (8.5–10.0 Hz), alpha2 (10.5–12.0 Hz), beta1 (12.5–18.0 Hz), beta2 (18.5–21.0 Hz), and beta3 (21.5–30.0 Hz).

Instead of assuming a specific number of sources for solving the inverse problem as other source localization methods do (e.g., dipole modeling), LORETA assumes that neighboring neuronal sources are similarly active (i.e., have similar orientations and strengths), consistent with animal data using single-unit recordings (Llinas 1988). This core assumption is implemented by computing the "smoothest" of all possible activity distributions and seems particularly appropriate when differences in brain electrical activity are expected to be spatially distributed, as might be the case when comparing resting EEG data of depressed and comparison subjects. Recently, the algorithm received important cross-modal validity, as LORETA localization was consistent with MRI (magnetic resonance imaging) (Worrell et al 2000) and functional MRI (Seeck et al 1998) results as well as electrocorticography from subdural electrodes (Seeck et al 1998).

The LORETA version utilized in the current study (Pascual-Marqui et al 1999; Pizzagalli et al 2001) employs a three-shell spherical head model registered to the Talairach brain atlas (Talairach and Tournoux 1988) and EEG electrode coordinates derived from cross-registrations between spherical and realistic head geometry (Towle et al 1993). The LORETA solution space (2394 voxels; spatial resolution: 7 mm) was restricted to cortical gray matter and hippocampi, according to the digitized Talairach and probability atlases of the Brain Imaging Center, Montreal Neurologic Institute (MNI305). For analyses in the frequency domain, at each voxel, LORETA values represent the power (i.e., squared magnitude) of the computed intracerebral current density (unit: amperes per square meter, $Å/m^2$). Before statistical analyses, the LORETA solution for every subject and every band was normalized to a total power of 1, and then log-transformed.

Statistical Analyses

A randomization procedure was implemented for controlling Type I errors arising from multiple comparisons (Holmes et al 1996). At every iteration, two randomly selected groups, Group1 and Group2 containing n1 and n2 subjects, respectively, were tested at each of the 2394 voxels (where n1 and n2 are the numbers of subjects of two actual groups under investigation). After each iteration, the largest absolute t value was stored in a histogram. After 5000 iterations, the t value associated with the

most extreme 5% of the distribution was identified for each frequency band (i.e., two-tailed $p < .050$). Finally, a mean t value was computed across the seven bands for thresholding statistical maps (comparison vs. depressed subjects: mean t value: $t_{54} = 2.63$; comparison vs. melancholic subjects: $t_{36} = 2.64$; comparison vs. nonmelancholic subjects: $t_{34} = 2.59$), which consisted of voxel-by-voxel t tests comparing two groups. The Structure-Probability Maps atlas (Lancaster et al 1997) was used to determine the brain region(s), Brodmann area(s) (BA), and Talairach coordinates closest to significant results.

Scalp Power Spectrum Analyses

For any effects found in the LORETA analyses, conventional scalp power analyses were conducted for the corresponding bands using the same nonoverlapping EEG epochs. For these analyses, the analytic procedure typically employed in our laboratory (Fast Hartley Transform, Hamming window) was employed for maximizing the comparison with previous scalp findings (Davidson and Henriques 2000). After re-referencing the data to the average reference, power density (μV^2/Hz) was computed by summing power values across each 0.5-Hz bin and dividing by the number of bins. Subsequently, for each channel, mean power density was computed (weighted by the number of artifact-free epochs), log-transformed, and finally whole-head residualized using the mean band power across the 28 electrodes (Davidson et al 2000b). Based on an extensive literature implicating alpha in depression, the same scalp power analyses were run for the alpha1 (8.5–10.0 Hz) and alpha2 (10.5–12.0 Hz) bands, irrespective of the LORETA results.

Results

Self-Report Measures of Affect

Melancholic and nonmelancholic depressed subjects showed significantly more depression and anxiety than comparison subjects, with no statistical differences between the depression subtypes (Table 1). The melancholic subjects showed a trend for higher STAI scores (trait form) than nonmelancholic subjects ($t_{18} = 2.07$, $p = .053$).

Analyses Comparing Depressed and Comparison Subjects

WHOLE-BRAIN LORETA. Contrary to extant EEG literature in depression, no effects emerged for alpha bands in frontal regions. Instead, depressed subjects showed more beta3 (21.5–30.0 Hz) than comparison subjects in two spatially distinct clusters—one inferior (BA 11) and one superior (BAs 9/10)—of the right frontal lobe and less beta3 within a medial posterior cluster including the posterior cingulate gyrus (BAs 23/31) and precuneus (BA 7) (Figure 1). As shown in Table 2, the only other significant results to emerge for any band were a virtually identical posterior cluster for beta2 (18.5–21.0 Hz) and a much smaller but overlapping cluster for alpha1 (8.5–10.0 Hz). To examine whether these effects were differentially present in melancholic or nonmelancholic subjects, follow-up whole-brain LORETA analyses for alpha1, beta2, and beta3 were conducted separately contrasting each depression group to comparison subjects. Melancholic subjects had more activity than comparison subjects in the right inferior frontal gyrus (BA 11) (beta3: $t_{36} = -2.64$) and less in the posterior cluster (BAs 7/23/31) (beta2: $t_{36} = 2.91$; beta3: $t_{36} = 3.76$; all ps $< .05$, corrected). Nonmelancholic subjects showed more activity than comparison subjects in the right superior frontal gyrus (BA 10) (beta3: $t_{36} = -2.64$) and less in the same posterior cluster (BAs 7/31) (beta3: $t_{36} = -2.86$; all ps $< .05$, corrected). No significant results emerged for alpha1.

ANOVAS. To test *a priori* predictions about asymmetrical frontal activity, a four-way ANOVA was run with *Group* (comparison subjects, depressed subjects) and *Gender* as between-subject factors, and *Hemisphere* (right, left) and *Cluster* (inferior, superior) as within-subject factors. Left frontal clusters homologous to the LORETA-implicated right frontal clusters were defined by reversing the sign of the X coordinates. The main effect of *Group* [$F(2,52) = 7.89$, $p < .008$] indicated more bilateral beta3 activity for depressed than comparison subjects. The only other effects to emerge were *Cluster* [$F(1,52) = 15894.68$, $p < .0001$; superior > inferior] and *Hemisphere* × *Cluster* [$F(1,52) = 128.81$, $p < .0001$]. Although the predicted *Group* × *Hemisphere* interaction was not significant ($p > .20$), separate ANOVAs were conducted for the left and right frontal clusters (collapsing across *Gender* and *Cluster*) to further interrogate hypothesized frontal differences between groups. For the right [$F(1,54) = 8.41$, $p < .006$] but not the left [$F(1,54) = 1.50$, $p > .20$] frontal clusters, the main effect of *Group* was significant, indicating that the bilateral frontal hyperactivity was driven by the right hemisphere. The same ANOVA conducted with a three-level *Group* factor contrasting comparison, melancholic, and nonmelancholic subjects on beta3 activity within the right frontal cluster resulted in identical effects. Posthoc (Newman-Keuls) tests showed that both melancholic ($p < .035$) and nonmelancholic ($p < .020$) depressed subjects exhibited higher activity in the right frontal clusters than comparison subjects (Figure 2A), whereas the two depression groups did not differ ($p > .45$).

A two-way ANOVA with *Group* (melancholic, nonmelancholic, comparison subjects) and *Gender* examined whether beta3 activity within the medial posterior cluster was differentially affected by the presence of melancholic features. The only significant result was the main effect of *Group* [$F(2,50) = 8.05$, $p < .001$]. Posthoc tests revealed

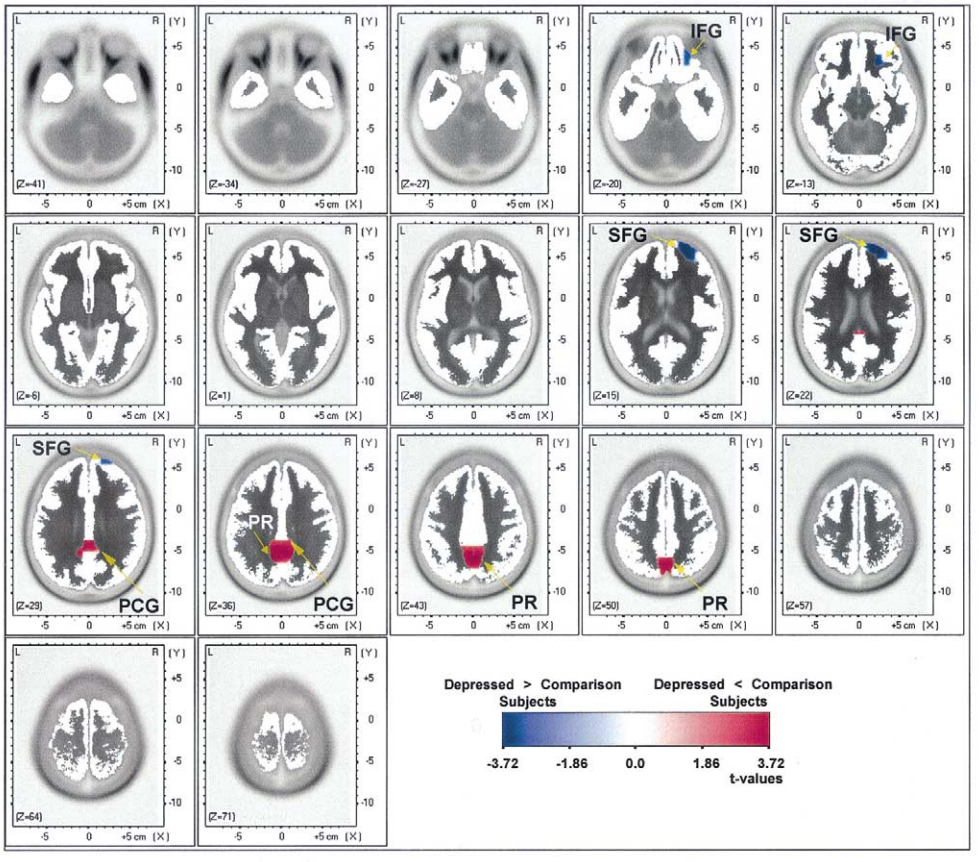

Figure 1. Results of voxel-by-voxel *t* tests contrasting comparison ($n = 18$) and depressed ($n = 38$) subjects for beta3 (21.5–30.0 Hz). Red: less beta3 for depressed subjects (PCG, posterior cingulate gyrus; PR, precuneus). Blue: more beta3 for depressed subjects (IFG, inferior frontal gyrus; SFG, superior frontal gyrus). Coordinates in mm (Talairach and Tournoux 1988), origin at anterior commissure.

that both depressed groups had less activity than comparison subjects (melancholic: $p < .002$, nonmelancholic: $p < .003$), but did not differ from one another ($p > .50$) (Figure 2B).

Analyses Examining Depression Severity and Anxiety

ANOVAS. To test if depression severity modulated activity within the different clusters, 21 individuals (12 melancholic, 9 nonmelancholic) with BDI ≥ 30 were defined as "severely depressed," and 13 individuals (4 melancholic, 9 nonmelancholic) with BDI scores between 13 and 29 were defined as "mild/moderately depressed" (Beck and Steer 1987). The first four depressed subjects enrolled in the study were not administered the BDI and thus not included in these analyses. The BDI was used instead of the HRSD because of the substantial variability across depressed subjects in when

Table 2. Summary of Significant Results Emerging from Whole-Brain LORETA Analyses

	X	Y	Z	Hemisphere	Region	BA	Voxels	*t* value
Comparison > Depressed								
Alpha1 (8.5–10.0 Hz)	−3	−25	36	Bilateral	Posterior Cingulate Gyrus	31	8	2.79
Beta2 (18.5–21.0 Hz)	4	−32	29	Bilateral	Posterior Cingulate Gyrus	23	38	2.99
Beta3 (21.5–30.0 Hz)	4	−60	43	Bilateral	Precuneus	7	40	3.72
Comparison < Depressed								
Beta3 (21.5–30.0 Hz)	18	59	22	Right	Superior Frontal Gyrus	10	15	−2.90
Beta3 (21.5–30.0 Hz)	25	31	−13	Right	Inferior Frontal Gyrus	11	5	−2.87

For all *t* values, $p < .05$ (corrected). Positive *t* values indicate decreased current density, and negative *t* values indicate increased current density in depressed subjects. The coordinates (Talairach and Tournoux 1988), anatomical regions, and Brodmann areas (BA) are listed for the extreme *t* values within a band. X = left(−) to right(+); Y = posterior(−) to anterior(+); Z = inferior(−) to superior(+).

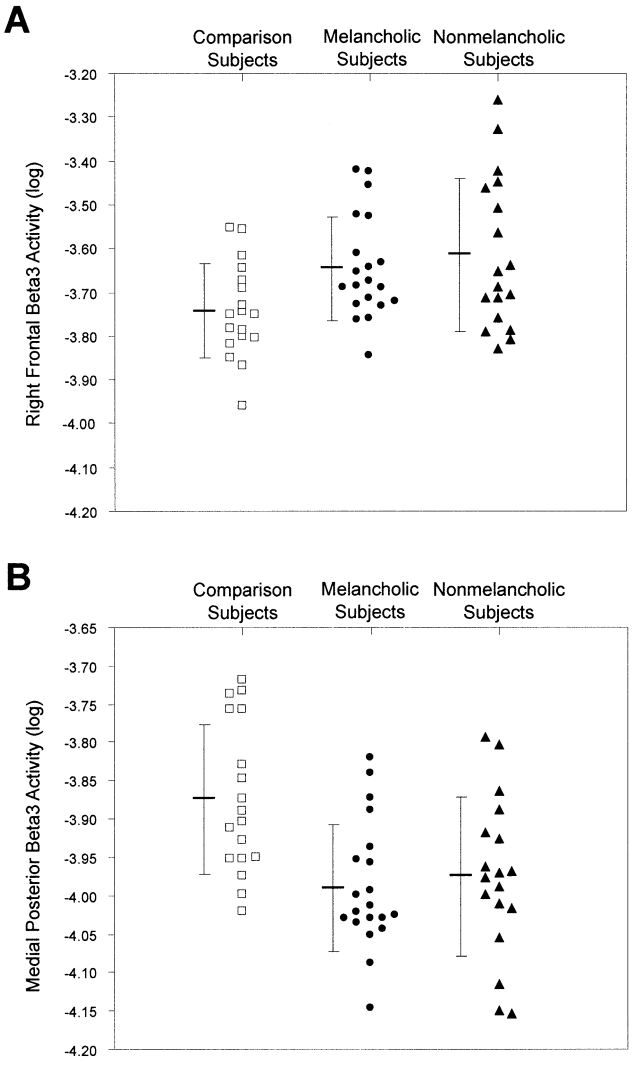

Figure 2. Mean beta3 for comparison (n = 18), melancholic (n = 20), and nonmelancholic (n = 18) subjects in the (**A**) right frontal clusters and (**B**) medial posterior cluster. Group means (±1 SD) are also shown. Less negative beta3 values (log Å/m^2) reflect higher activity.

the HRSD was administered in relation to both the SCID and physiology sessions.

For nonmelancholic subjects, a four-way ANOVA on beta3 activity for the frontal clusters with *Group* (comparison, mild/moderately, severely depressed), *Gender*, *Hemisphere*, and *Cluster* as factors revealed no effects involving *Group*. For melancholic subjects, the ANOVA contrasting severely depressed and comparison subjects (melancholic subjects with BDI scores in the mild/moderate range were excluded because of their small sample size) resulted in *Group* [$F(1,26) = 5.15$, $p < .040$] and *Group* × *Hemisphere* [$F(1,26) = 4.73$, $p < .040$] effects. As illustrated in Figure 3A, severely depressed melancholic subjects had significantly more activity than comparison subjects in the right ($p < .005$), but not the left ($p > .50$), frontal cluster.

For the medial posterior cluster, a *Group* effect emerged for both ANOVAs [nonmelancholic: $F(2,30) = 4.88$, $p < .015$; melancholic: $F(1,26) = 12.76$, $p < .002$], due to less activity for severely depressed than comparison subjects in both cases ($ps < .010$) (Figure 3B).

CORRELATIONS. Pearson's correlations were computed to test the impact of depression severity (BDI) and anxiety (STAI) on beta3 activity within the LORETA clusters implicated. No significant correlations were ob-

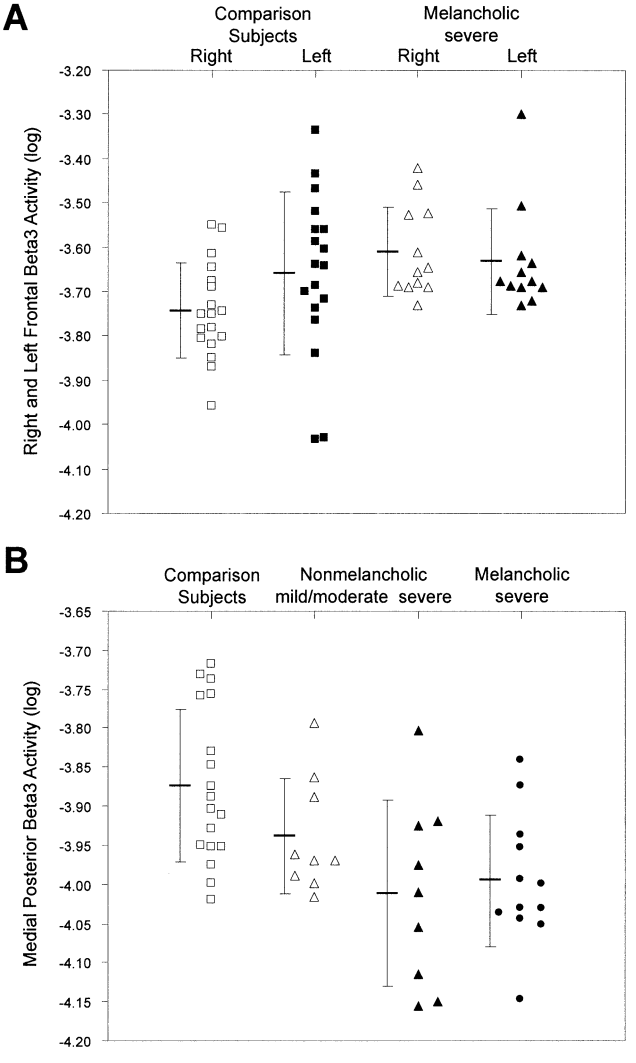

Figure 3. Mean beta3 in the (**A**) right and left frontal clusters for comparison (n = 18) and severely depressed melancholic (n = 12) subjects and (**B**) medial posterior cluster for comparison (n = 18), mild/moderately depressed nonmelancholic (n = 9), severely depressed nonmelancholic (n = 9), and severely depressed melancholic (n = 12) subjects. Group means (±1 SD) are also shown. Less negative beta3 values (log Å/m^2) reflect higher activity.

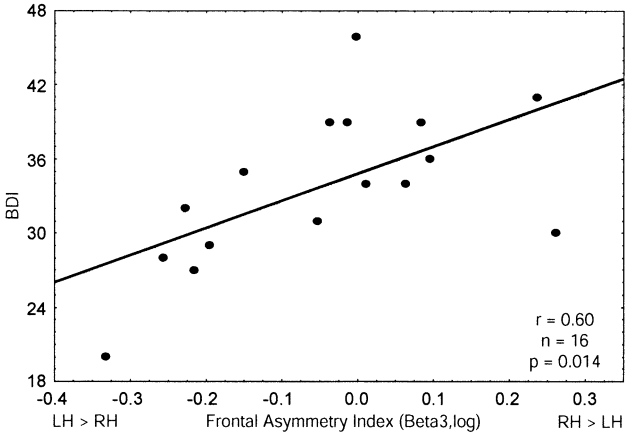

Figure 4. Scatterplot and Pearson's correlations for BDI scores and mean frontal LORETA beta3 asymmetry index (right–left). Less negative beta3 values (log Å/m^2) reflect higher right than left activity. Melancholic subjects only (n = 16). BDI, Beck depression inventory; RH, right hemisphere; LH, left hemisphere.

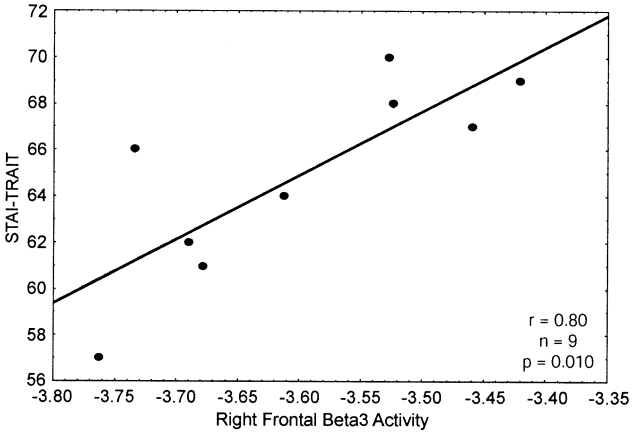

Figure 5. Scatterplot and Pearson's correlation for STAI scores and mean right frontal LORETA beta3. Less negative beta3 values (log Å/m^2) reflect higher activity. Melancholic subjects only (n = 9). STAI, State-Trait Anxiety Inventory.

tained when collapsing across melancholic and nonmelancholic subjects or for the nonmelancholic group alone. However, for melancholic subjects, the BDI was correlated with frontal asymmetry (right-left beta3; r = 0.60, $p < .05$; Figure 4; Table 3), with marginally significant correlations between BDI and right (r = 0.41, p = .11) and left (r = −0.49, p = .054) frontal activity in the expected directions. As shown in Figure 5, they also exhibited a strong correlation between STAI and right frontal activity (r = 0.80, $p < .010$). These correlations for melancholic subjects were significantly different from those for nonmelancholic subjects (STAI: z = 2.61, $p <$ .01; BDI: z = 2.56, $p < .015$), as assessed with Fisher's test for independent correlations (Fisher 1921). For both the BDI and STAI, the discrepant results for the melancholic and nonmelancholic groups were not caused by different variances in the LORETA or self-report data.

To disentangle the effects of depression severity and anxiety on right frontal activity for the melancholic subjects, two hierarchical regression analyses were run. The first analysis predicted STAI, with BDI entered as the first predictor followed by beta3 within the left frontal cluster and then by beta3 in the right frontal cluster. STAI was not significantly predicted by BDI (β = .52, df = 7, $p > .15$) or left frontal beta3 [β = .43, R^2 change = 0.17, F(1,6) = 1.88, $p > .20$]; however, right frontal beta3 was a significant predictor of STAI even after removing the variance associated with the BDI and left prefrontal cluster [β = 0.76; R^2 change = 0.32, F(1,5) = 6.67, $p < .050$]. The second analysis predicted BDI, with the order of predictors being STAI, left frontal beta3, and right frontal beta3. This analysis revealed no significant predictors of BDI (all ps $> .15$).

Scalp Power Analyses

As was done for the LORETA data, scalp power values were analyzed using three-way ANOVAs with *Region*

Table 3. Pearson Correlations between Mood and EEG Features (LORETA beta3 Signals and Scalp beta3 Power)

		STAI	LORETA Right-Left Frontal	LORETA Right Frontal	LORETA Left Frontal	LORETA Medial Posterior	Scalp F3 Power	Scalp F4 Power	Scalp F4-F3 Power
Melancholic	BDI	.52	.60[a]	.41	−.49	.29	−.24	.14	.47
	STAI	—	.35	.80[b]	.26	−.22	.58	.41	−.33
Nonmelancholic	BDI	.36	−.27	−.26	.07	−.26	−.06	−.27	−.28
	STAI	—	−.42	−.30	.39	.23	−.36	−.57	−.45

BDI, Beck Depression Inventory (Beck et al 1961) (melancholic: n = 16; nonmelancholic: n = 18); STAI, State Trait Anxiety Inventory (trait form; Spielberger et al 1970) (melancholic: n = 9; nonmelancholic: n = 11); EEG, electroencephalographic.

LORETA right frontal and medial posterior clusters identified in the whole-brain LORETA analysis comparing depressed and comparison subjects (see Figure 1). Right superior and inferior clusters were averaged together for calculating correlations. Homologous left superior and inferior frontal clusters were derived by reversing the sign of the X coordinate. For correlations involving F3 and F4 scalp sites, residualized power values removing whole-head power were used (Davidson et al 2000b). Higher LORETA beta3 current density and scalp beta3 power indicates more activity.

[a] $p < .050$ (two-tailed).

[b] $p < .010$ (two-tailed).

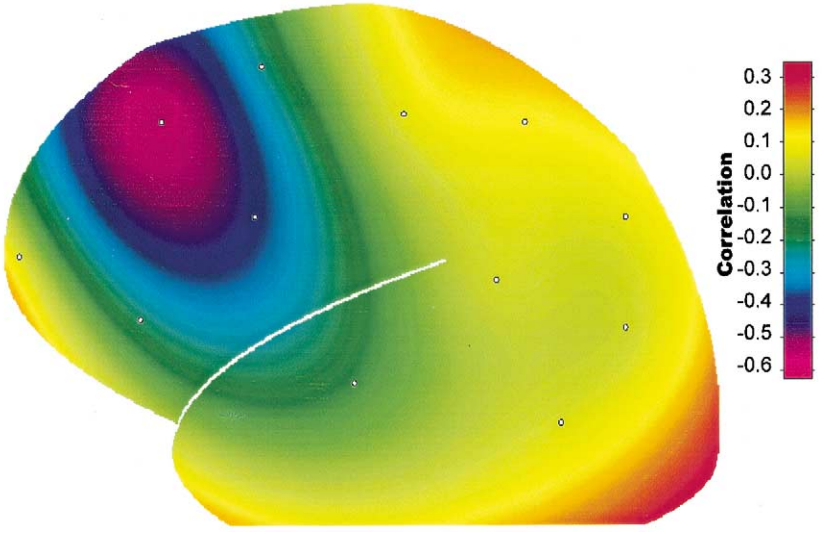

Figure 6. Topographic map of Pearson's correlations between BDI and scalp alpha2 power asymmetry scores (e.g., log F4 –log F3) derived from average-reference data. The map was created by calculating the correlation for each electrode (small circles); these correlations were then used to generate a spline-interpolated map across a lateral view of the head for display purposes only. Negative correlations (cold colors) reflect increasing BDI scores with decreasing alpha2 asymmetry scores, i.e., relatively lower alpha power (more activity) at right-sided electrodes. The only significant correlation was at midfrontal sites. Nonmelancholic subjects only ($n = 11$). BDI, Beck Depression Inventory.

(Fp1/2, F3/4, F7/8), *Hemisphere*, and *Group* as factors. Based on the present findings and the extant EEG literature on depression, only the beta3 and alpha bands were examined. In addition, Pearson's correlations assessed the relations between scalp power values at single sites (e.g., F3) or asymmetry indices (e.g., F4-F3) and the BDI and STAI. At the request of a reviewer, the same ANOVAs and correlations were implemented for the theta band, with no significant results.

BETA3 BAND. *Group* (depressed, comparison subjects) was the only effect to emerge for the ANOVA on beta3 [$F(1,52) = 4.34$, $p < .050$], with more frontal activity in depressed than comparison subjects. Paralleling the LORETA analyses, this effect was carried by the right [$F(1,52) = 4.47$, $p < .050$] but not left [$F(1,52) = 2.59$, $p > .10$] frontal sites. An analogous ANOVA for all three groups revealed no *Group* [$F(2,51) = 2.24$, $p > .10$] or other effects. There were no significant correlations between self-reported mood and scalp beta3 power.

ALPHA BANDS. For both the scalp alpha1 (8.5–10.0 Hz) and alpha2 (10.5–12.0 Hz) power values, no ANOVA effects were found; however, the correlation analyses revealed results consistent with previous studies. In nonmelancholic subjects, more right than left frontal activity (F4-F3) derived from the alpha2 band was associated with higher depression and anxiety scores (BDI: $r = -0.61$, $p < .008$; STAI: $r = -0.60$, $p < .050$). The same pattern for anxiety was seen in melancholic subjects, with greater relative right-sided activity at the frontal pole (Fp2-Fp1) associated with higher levels of anxiety on the STAI (alpha1: $r = -0.72$, $p < .050$; alpha2: $r = -0.70$, $p = .053$). No correlations emerged for individual sites using residualized power values removing whole-head power (Davidson et al 2000b), indicative of relatively equal but opposite contributions for both hemispheres. All significant correlations with scalp EEG were specific to frontal sites (see Figure 6).

Correlations Among LORETA Frontal Clusters and Scalp Power Values for the Beta3 Band

Left and right LORETA beta3 were not correlated for comparison, melancholic, or nonmelancholic subjects ($r = -0.20$ to $r = 0.33$, all ps $\geq .15$). In contrast, scalp power values at F3 and F4 were highly correlated for comparison, melancholic, and nonmelancholic subjects ($r = 0.51$ to $r = 0.79$, all ps $< .035$). These results are particularly striking given the high correlations between power values at F3 and activity in the left frontal LORETA cluster and power values at F4 and the right frontal LORETA cluster ($r = 0.54$ to $r = 0.88$, all ps $< .05$).

Discussion

A tomographic source localization method for identifying underlying sources of classical EEG frequency bands was employed to interrogate patterns of brain activity associated with symptom severity, anxiety, and melancholic

features in depression. Depressed subjects showed more beta3 than comparison subjects in distinct right inferior and superior frontal regions and less beta3 than comparison subjects in a medial posterior cluster encompassing the posterior cingulate cortex and the precuneus. As beta rhythm has been shown to increase with attention (Murthy and Fetz 1992), arousal (Bonnet and Arand 2001), vigilance (Bouyer et al 1987), and more recently directly through cortical stimulation via transcranial magnetic stimulation (Paus et al 2001), stronger beta3 current density can be interpreted as reflecting increased excitatory activity. Thus, depressed subjects were characterized by relative hyperactivity in right frontal regions and hypoactivity in the posterior cingulate and precuneus. These effects were present in both melancholic and nonmelancholic subjects, with the abnormal right frontal hyperactivity most conspicuous in melancholic subjects who were severely depressed. Furthermore, right frontal activity was positively correlated with anxiety and depression severity in melancholic subjects only. Regression analyses for the subset of melancholic subjects administered the STAI indicated that the right frontal activity was associated with higher levels of anxiety rather than depression. Notably, no correlations emerged for the depressed sample as a whole or for nonmelancholic subjects, pointing to the importance of considering subtypes in brain research on depression.

Lateralized Patterns of Prefrontal Activity

Adding to the extensive EEG literature suggesting a link between depression and frontal asymmetry (Davidson and Henriques 2000; Heller and Nitschke 1997), melancholic and nonmelancholic depressed subjects showed more right frontal activity than comparison subjects. As a recent PET/EEG study reported a positive correlation between beta activity (13–30 Hz) and regional cerebral blood flow (Nakamura et al 1999), the present findings are consistent with functional neuroimaging reports of increased activity in the right PFC, especially ventrolateral regions, reviewed above, and with Kano et al (1992) who found increased scalp beta power (20.0–29.5 Hz) at right frontal sites. The right-sided focus found here was especially pronounced in melancholic subjects with severe depression, highlighting the importance of considering symptom severity for patterns of brain activity in depression. Notably, posttreatment *decreases* in inferior frontal and VLPFC regions have been found to correlate with improved HRSD scores (Brody et al 1999). Similarly, pharmacological and interpersonal therapy led to normalization (i.e., decrease) of metabolism in the right VLPFC and DLPFC (Brody et al 2001b). Consequently, right prefrontal hyperactivity may be a state marker of depression, which normalizes after remission. A potential contributing factor to the right-sided findings is that the EEG data were recorded during the uptake period of the PET tracer while subjects had two intravenous lines inserted in their arms, a procedure that likely induced negative affect. To the extent that depressed individuals are more susceptible to experience negative affect in response to such adverse circumstances, they would be expected to show the increased right PFC activation consistently reported during induced negative affect (Davidson and Henriques 2000); however, these state-like responses were likely superimposed on trait-like differences in anxiety between depressed and comparison subjects associated with right frontal hyperactivity.

The strong association of anxiety with right frontal activity in the melancholic subjects is consistent with EEG (Davidson et al 2000c; Nitschke et al 1999; Wiedemann et al 1999) and PET (Bremner et al 1999; Lucey et al 1995; Rauch et al 1997; Stapleton et al 1997; Stewart et al 1988) studies suggesting a key role of this region in anxiety. The present results underscore the modulating role of anxiety in patterns of frontal activity in major depression. The right prefrontal regions identified here as being strongly associated with symptoms of anxiety are part of a circuit that has been implicated in behavioral inhibition, vigilance and attention (Davidson et al 2000a). The accentuated activity of these prefrontal regions in depressed patients, particularly those with symptoms of anxiety, likely reflects the fact that for these subjects a considerably broader range of stimuli connote threat and capture attention than for comparison subjects, thus producing inhibition of ongoing behavior.

Although melancholic subjects showed evidence of less left frontal activity being associated with increased depression, in line with other studies examining depression severity (e.g., Baxter et al 1989; Bench et al 1993; Drevets et al 1992; Kato et al 1995), the present sample of MDD patients did not as a group display less left frontal activity than comparison subjects, as has been reported elsewhere (Bench et al 1992; Martinot et al 1990). This discrepancy may be partially attributed to differences in subject samples; indeed, decreased left DLPFC activation has been observed in inpatients with MDD (e.g., Baxter et al 1989; Martinot et al 1990), who likely display more psychomotor retardation than depressed samples recruited from the community. Since decreased left DLPFC activation has been associated with increasing degree of psychomotor retardation (Bench et al 1993), differences in symptom profiles between samples may explain these differences. Consistent with this conjecture, the correlational findings indicate that the pattern of decreased left prefrontal activity was most pronounced for those patients with the most severe symptoms of depression.

The frontal LORETA results emerged for the beta3 band and not for alpha, the most investigated EEG frequency band in depression (Davidson and Henriques 2000). The reason for our effects being restricted to the beta3 band and not to the alpha band where most other differences between depressed and comparison subjects have been found is not entirely clear but may be due to methodological differences between this study and other previous studies. It is possible that the absence of group differences in the alpha band was a function of the unusual testing procedure associated with PET (including fasting and intravenous lines) and/or the length of the recording epochs, which were considerably longer than in any of the previous EEG studies.

Posterior Cingulate Hypoactivity

Findings for the medial posterior cluster replicate prior PET results of posterior cingulate hypoactivity (BAs 29/30/31) in depressed patients during rest (Mayberg et al 1999, 2000) and cognitive challenge (Elliott et al 1997). Posterior cingulate hypoactivity may represent a state marker of depression since recent studies reported increased activation in areas 23 and 31 with remission following pharmacological treatment (Mayberg et al 1999, 2000) or interpersonal therapy (Martin et al 2001). Despite emerging evidence suggesting that the posterior cingulate (BAs 23/31) and particularly retrosplenial cortex (BAs 29/30) may be implicated in the regulation of normal and pathologic negative affect, consensus has not been reached (Maddock 1999, 2000; Vogt et al 2000). In unselected subjects, increased posterior cingulate/retrosplenial activation has been reported during trauma-related experiences (Fischer et al 1996) and during tasks involving threat-related words (Maddock and Buonocore 1997), arousing facial expressions (Critchley et al 2000a), and somatic arousal (Critchley et al 2000b). In patients with posttraumatic stress disorders (PTSD), increased posterior cingulate/precuneus activation has been observed during script-driven symptom provocation (Bremner et al 1999; Shin et al 1997). Overall, these results are consistent with animal work implicating the retrosplenial and adjacent posterior cingulate cortex in conditional learning and physiologic arousal (Bussey et al 1996; Devinsky and Luciano 1993). The fact that the depressed patients in this study exhibited increased right-sided prefrontal activity and decreased posterior cingulate activity simultaneously suggests that a state of heightened vigilance in the absence of autonomic/somatic arousal may characterize at least some subtypes of depression.

Strengths, Limitations, and Future Directions

The present results were obtained with a novel tomographic source localization technique based on realistic head geometry and solution space that recently received important cross-modal physiologic validation (Worrell et al 2000; Seeck et al 1998). Although some of the findings uncovered through LORETA were also present in the scalp power data, the former method provided more spatially precise information, and revealed systematic relations with symptom severity that were not present for the scalp beta3 power.

A limitation of the present study is the ubiquitous problem in hemodynamic neuroimaging of testing laterality effects (Davidson and Irwin 1999). Reversing the left-right coordinates is far from optimal because one cannot assume that the identical brain regions can be identified due to anatomical hemispheric differences. Nevertheless, this approach is preferable to the strategy typically employed in neuroimaging research of interpreting "lateralized" findings merely on the basis of thresholded statistical maps. Furthermore, some of the follow-up analyses subdividing the subtypes according to severity or anxiety level were limited by the small sample size resulting in less power to detect effects. A third limitation is that the atypical EEG recording procedure may complicate the interpretations of the results, as it is difficult to determine whether the effects observed are associated with stable, context-independent dysfunctional activity in depression, an interaction between depression and the experimental context, or with both. These alternative interpretations are of clinical import, as depression may be associated with an increased likelihood of experiencing negative affect in slightly aversive situations, including those of daily life.

To further probe the modulatory role of anxiety in brain circuitry accompanying depression, future research would benefit from a more comprehensive assessment of anxiety symptoms using clinician-administered as well as self-report instruments that are more specific to anxiety than the STAI. Previous research has shown that the STAI is a better indicator of general distress and negative affect than anxiety per se and therefore is often highly correlated with measures of depression (Nitschke et al 2001). Statistical procedures, such as the hierarchical regression analyses used here to partial out the variance accounted for by depression, can also be used to extract less contaminated measures of anxiety. In future research, it will also be essential to utilize more objective measures of anxiety as well as other parameters of affective style and emotion regulation that do not rely upon self-reports (Davidson et al 2000a).

In summary, the present results confirm a key role of right frontal regions in the symptoms of major depression, especially when high levels of anxiety are prominent, and provide corroborating evidence implicating the posterior cingulate cortex in the pathophysiology of depression.

Most importantly, our findings underscore the considerable heterogeneity of depression even within melancholic and nonmelancholic subtypes and underscore the need for better, more objective measures of affective dysfunction to systematically characterize the neural circuitry underlying affective processing deficits in depression.

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