Archival Report

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Relationships Between Altered Functional Magnetic Resonance Imaging Activation and Cortical Thickness in Patients With Euthymic Bipolar I Disorder

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ABSTRACT

BACKGROUND: Performance during cognitive control functional magnetic resonance imaging (fMRI) tasks are associated with frontal lobe hypoactivation in patients with bipolar disorder, even while euthymic. We examine the structural underpinnings for this functional abnormality simultaneously with brain activation data.

METHODS: In a sample of 90 adults (45 with interepisode bipolar I disorder and 45 healthy controls), we explored abnormal functional activation patterns in euthymic patients with bipolar disorder during a Go/NoGo fMRI task and their associations with regional deficits in cortical gray matter thickness. Cross-sectional differences in fMRI activation were used to form a priori hypotheses for region of interest cortical gray matter thickness analyses. Blood oxygen level–dependent fMRI to structural magnetic resonance imaging thickness correlations were conducted across the sample and within patients and controls separately.

RESULTS: During response inhibition (NoGo − Go), patients with bipolar I disorder showed significant hypoactivation and reduced thickness in the inferior frontal cortex, superior frontal gyrus, and cingulate compared to controls. Cingulate hypoactivation corresponded with reduced regional thickness. A significant activation by disease state interaction was observed with thickness in left prefrontal areas.

CONCLUSIONS: Reduced cingulate fMRI activation is associated with reduced cortical thickness. In the left frontal lobe, a thinner cortex was associated with increased fMRI activation in patients but showed a reverse trend in controls. These findings suggest that reduced activation in the inferior frontal cortex and cingulate during a response inhibition task may have an underlying structural etiology, which may explain task-related functional hypoactivation that persists even when patients are euthymic.

Keywords: Bipolar I disorder, Bipolar euthymia, fMRI, Go/NoGo task, Cortical thickness, Structure–function correlation

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Bipolar disorder affects approximately 3% of the U.S. adult population each year (1) and is characterized by dramatic shifts of mood between euthymia, mania, and depression. Converging evidence suggests that dysfunction in anteriorly oriented frontolimbic network(s), including specific prefrontal regions (e.g., the inferior frontal cortex [IFC] and anterior cingulate cortex [ACC]) that project to specific subcortical areas (e.g., the amygdala and striatum) (2,3), may contribute to mood dysregulation in patients with bipolar disorder (2,4–9). Functional magnetic resonance imaging (fMRI) studies of patients with bipolar disorder have consistently revealed a functional deficit in IFC that is seen during both mania (10–15) and euthymia (4,16–20). The IFC comprises the pars triangularis, pars opercularis, and pars orbitalis in the inferior frontal gyrus (e.g., Brodmann areas [BAs] 44, 45, and 47), and the persistence of a decrease in IFC function in euthymic patients with bipolar disorder suggests its independence from mood state.

The underlying etiology of IFC hypofunction is not known. As changes in the hemodynamic response measured with fMRI are linked with neural activity, subtle disorganization in underlying gray matter structure may contribute to functional deficits. Structural anatomic studies have reported extensive anatomical connectivity between the IFC and brain regions associated with mood regulation and emotional responses (21–23), including the ACC and the amygdala. A structural abnormality in the IFC could lead to fMRI-related hypofunction and consequently to disconnectivity with other "affective" brain regions.

Structural studies have shown that overall brain volumes appear within the normal range in patients with bipolar disorder (8,24,25). However, regional differences have been observed in prefrontal cortical, subcortical, and medial

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temporal structures (4,26,27). Most studies of the prefrontal cortex (PFC) have examined relatively large frontal lobe regions (28–32). Of the fewer studies segmenting more functionally distinct frontal regions, some (33–43) but not all (44–46) have found differences between patient and control groups.

To our knowledge, no imaging study has simultaneously collected and evaluated structural MRI (sMRI) and fMRI data to assess the relationship between fMRI and sMRI gray matter abnormalities in patients with bipolar disorder. The current study was designed to 1) assess disease-specific alterations in neural function in the IFC using an fMRI task that activates this region; 2) explore structural contributions to IFC hypofunction using sophisticated techniques to measure regional variations in brain morphology; and 3) relate gray matter alterations to neural function. Specifically, we tested whether regionally specific differences in gray matter thickness measured with sMRI may be associated with the functional deficits seen in this region in our (19) and others' (16) previous fMRI studies of patients with bipolar disorder.

METHODS AND MATERIALS

Participants

Ninety adult subjects participated in this study. Forty-five currently euthymic patients (24 men) with bipolar I disorder (BDI) diagnosed using the DSM-IV and ranging in age from 20 to 61 years (mean ± SD, 39.9 ± 12.1 years) were recruited through the University of California, Los Angeles (UCLA) Mood Disorders Clinic and advertisements. An additional 45 healthy controls (23 men) ranging in age from 20 to 63 years (mean ± SD, 37.7 ± 10.5) were recruited using local advertising.

In bipolar subjects, the Structured Clinical Interview for DSM-IV (SCID) Axis I Disorders, Research Version (47) was used to confirm a diagnosis of BDI. Patients with BDI and a history of alcohol or drug use disorder could participate if they were sober for >3 months, as confirmed by self-report, and had no mood episode within 30 days of the scan per SCID assessment. At the time of scanning, all patients with BDI were euthymic, operationally defined as a score < 7 on both the Young Mania Rating Scale (48) and the Hamilton Depression Rating Scale (49). The SCID was used to confirm that control participants were free of any current or past Axis I psychiatric illness. Exclusion criteria for all subjects included left-handedness, head injury with a loss of consciousness >5 minutes, ferrous metal implants, neurologic illness, and pregnancy. All participants provided written informed consent in accordance with the UCLA Institutional Review Board.

fMRI Paradigm

A well-validated response inhibition task (Go/NoGo) (50) was used to probe brain regions involved in cognitive control, including the IFC, other orbitofrontal cortex (OFC) regions (i.e., BAs 10, 11, and 47), and the ACC (i.e., BA 24/32). Task details have been published previously (50) and are shown in Figure 1A and presented in the Supplement.

fMRI Behavioral Analysis

Means and SDs were computed for accuracy and response times for the Go and NoGo conditions. The distribution for accuracy was nonnormal because most subjects made few or no errors. Consequently, accuracy was dichotomized (i.e., high and low performance) and differences were assessed nonparametrically. Differences in accuracy and response time were tested independently using two-tailed Fisher's exact and Mann-Whitney *U* tests, respectively.

fMRI Acquisition

Imaging data were collected on a Trio 3T scanner (Siemens, Munich, Germany) at the UCLA Ahmanson-Lovelace Brain Mapping Center. An echo planar image gradient-echo pulse sequence (repetition time/echo time = 2500/25 ms; flip angle = 78°; field of view = 192 mm; 64 × 64 matrix; 3 × 3 mm in-plane resolution; slice thickness = 3 mm; 0.75-mm gap; 30 total interleaved slices) using an integrated parallel acquisition technique was acquired covering the entire brain. Scan time was 4 minutes and 48 seconds, or 112 volumes. Echo planar images with T2-weighted sequences for intra- and intersubject registration were acquired with the following parameters: repetition time/echo time = 5000/34 ms; flip angle = 90°; field of view = 192 mm; 128 × 128 matrix; in-plane voxel size 1.5 × 1.5 mm, slice thickness = 3 mm, and 30 total slices.

sMRI Acquisition

To evaluate brain structure, high-resolution T1-weighted magnetization-prepared rapid acquisition gradient-echo scans were acquired (repetition time/echo time = 1900/2.26 ms; flip angle = 9°; field of view = 250 mm × 250 mm; 256 × 256 matrix; voxel size 1 × 1 × 1mm; and total sequence time 6 minutes and 50 seconds) in the same imaging session.

Neuroimaging Data Analysis

Figure 1 summarizes the analysis procedures. Briefly, fMRI data were first analyzed separately to determine group differences in brain activation during the NoGo − Go contrast (Figure 1A). A priori structural regions of interest (ROIs) were then chosen based on significant between-group differences and analyzed for differences in cortical thickness (Figure 1B). Structure–function relationships were subsequently determined by assessing whether regions that showed abnormalities in cortical thickness between diagnostic groups overlapped with those showing abnormalities in task-dependent fMRI activation (Figure 1C).

fMRI Preprocessing and Analyses

Functional data were processed using FEAT software (version 6.0), which is part of the Oxford Centre for Functional MRI of the Brain's (FMRIB's) Software Library (FSL) (available at www.fmrib.ox.ac.uk/fsl). FSL's Brain Extraction Tool (53), was used to skull strip the structural images. Motion correction was performed using Motion Correction in FMRIB's Linear Image Registration Tool (FLIRT) (54). Spatial smoothing used a Gaussian kernel of 5 mm full width at half maximum (FWHM). Grand-mean intensity normalization (by a single multiplicative factor) and high-pass temporal filtering (using a Gaussian-weighted least-squares straight line fitting, with sigma = 45.0 s) were conducted on the 4-dimensional datasets. Using FMRIB's Improved Linear Model, time series statistical