Published in final edited form as:

Psychiatry Res. 2011 July 30; 193(1): 53–55. doi:10.1016/j.psychres.2010.12.012.

Preliminary evidence of within-subject changes in gray matter density associated with remission of bipolar depression

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Abstract

A preliminary within-subjects MRI study of seven patients with a diagnosis of bipolar I disorder revealed that after remission from depression, gray matter density *increases* were observed in subgenual prefrontal cortex, parahippocampal gyrus, and inferior temporal gyri. *Decreases* were observed in superior and inferior frontal gyri and anterior cingulate.

Keywords

Bipolar Disorder; Depression; Magnetic resonance imaging; MRI; Prefrontal

1. Introduction

The structural neuroimaging literature is rife with studies describing gray matter density abnormalities in patients with bipolar disorder (Lyoo et al., 2004; Lochhead et al., 2004; Adler et al., 2005; Chen et al., 2007; Moorhead et al., 2007; Almeida et al., 2009). Compared to healthy subjects, patients diagnosed with bipolar disorder have been reported to have decreased gray matter density in the anterior cingulate and adjacent medial prefrontal gyrus (Lyoo et al., 2004; Nugent et al., 2006) as well as the left middle temporal gyrus (Chen et al., 2007). Other studies report decreased gray matter density in the dorsolateral/ventrolateral cortex (Nugent et al., 2006). There are also reports of greater gray matter density in bipolar disorder patients in the left parahippocampal gyrus (Chen et al., 2007).

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Disclosure/Conflict of Interest

Dr. Brooks is on the speaker's bureau of Merck and Pfizer. Dr. Altshuler serves on the advisory boards of Forest Laboratories and Sepracor, Inc. Drs. Foland-Ross and Thompson do not report any disclosures.

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Many structural imaging studies of bipolar disorder analyze patients regardless of mood state, reflecting an assumption that cortical structure is impervious to state-related changes. Recent evidence, including data from our group, suggests that gray matter density may be associated with mood state. Brooks et al. (Brooks et al., 2009a) compared groups of depressed or euthymic bipolar disorder patients and found depressed patients exhibited significantly lower gray matter density bilaterally in the medial and superior frontal gyri (BA 10) and significantly greater gray matter density in the dorsolateral prefrontal cortex (BA 10/46), the temporal lobe (BA 20), and the parahippocampal gyrus compared to euthymic patients. A simultaneous report by Nery et al. (Nery et al., 2009) revealed that manually traced orbitofrontal volumes (primarily BA 10 and 11) were significantly lower in depressed than in euthymic bipolar disorder patients, and that decreases in orbitofrontal volume correlated with more severe depression.

Although compelling, relations between mood and brain structure rely on cross-sectional data. Finding structural differences using a within-subjects design would control for confounding between-subjects factors and provide stronger evidence of neural plasticity associated with mood states in bipolar disorder. For the current study, we obtained MRI scans from patients scanned initially in the depressed state, and again during the remitted state.

2. Methods

The UCLA Institutional Review Board approved this study; all participants provided verbal and written informed consent before enrollment.

2.1 Participants

Patients were required to meet criteria for bipolar disorder type I currently in the depressed phase according to the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, and Williams 2002). To enter the study, patients were further to score greater than 18 on the Hamilton Depression (HAM-D) 21-item scale (Hamilton, 1960) and score less than 7 on the Young Mania Rating scale (Young et al., 1978). Exclusion criteria included left-handedness, hypertension, neurological illness, metal implants, substance abuse within the past six months, and a history of skull fracture or head trauma with loss of consciousness of more than five minutes. Subjects with other active Axis I co-morbidities were excluded.

Seven subjects were included in the study (3 female; 42.4 ± 14.9 years) who met criteria for bipolar disorder type I depressed phase. Three patients had a diagnosis of alcohol abuse in remission and one patient had history of polysubstance dependence, in remission. When depressed, the mean HAM-D score, at the time of the MRI scan was 20.4 (SD = 3.1) and the Young Mania Rating Scale Score (YMRS) was 2.9 (SD = 2.4). The mean age at onset of illness was 21.6 (SD = 7.3) years.

Patients were re-evaluated longitudinally and remission was achieved when patients no longer met criteria for a depressive episode for at least two weeks and had a HAM-D score less than 7. After patients had achieved remission, repeat MRI scans were obtained. The mean time in a euthymic state before the second scan was 4.7 (SD = 2.8) weeks. When

patients were euthymic, the mean HAM-D score at the time of the MRI scan was 2.7 (SD = 3.8) and YMRS score was 2.9 (SD = 1.9).

During their depressed states, two patients were unmedicated, the remaining five were taking citalopram (n=3), bupropion (n=2), olanzapine (n=1), divalproex (n=2), and/or venlafaxine (n=1). In the euthymic state, all patients were medicated; relative to the depressed state, two had no changes in medication, one patient had lithium added, one had bupropion added, one changed from citalopram to sertraline, and two had divalproex discontinued.

2.2 Imaging

Scans were acquired on a 3T MRI scanner using a spoiled-gradient echo pulse sequence, with a slice thickness of 1.2 mm (TE = 3.7 ms, TR = 25 ms, FOV = 20°, NEX = 1). Image processing was performed using the Statistical Parametric Mapping (SPM8, Update 3164) software (www.fil.ion.ucl.ac.uk/spm) and to test for differences in gray matter density over time using a within-subjects paired t-test. For the SPM analyses, an intensity threshold of $P < 0.005$ (uncorrected) with a corresponding $t > 3.7$ was applied. The spatial extent (k) threshold was set to 25 voxels (200 mm³).

3. Results

Results from the statistical parametric map are provided in the Supplementary Table and illustrated in Figure 1. Compared to the euthymic state, when depressed subjects exhibited significant decreases in gray matter density in the superior (BA 10), medial (BA 4), and inferior frontal gyri (BA 46), anterior cingulate (BA 32), and lingual gyrus. Significant increases in gray matter density were observed in the subgenual prefrontal cortex (BA 25), inferior temporal gyrus (BA 20), and the parahippocampal gyrus.

We also performed an exploratory analysis of the relation between change in gray matter density in the region located in BA 10 and demographic/clinical variables. The change in density was not significantly related to age, illness duration, number of affective episodes, or change in HAM-D score.

4. Discussion

These preliminary data of within-subject changes in gray matter density provide evidence that mood state may influence gray matter density changes as measured with VBM. The present within-subject findings are consistent with the between-subjects findings reported previously (Brooks et al., 2009a; Nery et al., 2009) where depressed patients exhibited lower gray matter density in portions of the dorsolateral (BA 9 & 46) and inferior portions of prefrontal cortex (BA10) and greater density in the parahippocampal gyrus compared to euthymic subjects. These regions have been implicated in cerebral metabolic studies of bipolar depression (Ketter et al., 2001; Brooks et al., 2009b), and are known components of emotion and behavior regulatory networks (Mega, and Cummings, 1994). This congruence is striking, as our previous study (Brooks et al., 2009a) involved unmedicated patients (whereas our current findings were obtained in medicated patients).

Our findings highlight an important methodological issue in structural neuroimaging studies that could account for variable findings: Prior studies of gray matter density have compared patients with bipolar disorder to healthy controls and have not accounted for mood state. For example, Lyoo et al. (Lyoo et al., 2004) found differences in the density of the anterior cingulate and medial prefrontal gyrus in a study that included 22 of depressed bipolar patients and 17 were hypomanic/manic ones. A subsequent study (Nugent et al., 2006) found similar decreases in gray matter density that also included dorsolateral and ventrolateral prefrontal cortex in 36 patients with unreported mood states (7 type I, 29 type II). Stanfield (Stanfield et al., 2009) analyzed gray matter density in a sample of 66 bipolar type I patients, who were on average euthymic (exclusion criteria for mood state were not provided), and reported lower gray matter density in the left and right lateral orbital gyri and right inferior frontal gyrus relative to healthy comparison subjects. Lower gray matter density in the subgenual prefrontal cortex was found in a study of subjects with bipolar disorder that included 17 euthymic 10 depressed patients, with no attempt to account for mood (Almeida et al., 2009). Chen et al.'s (Chen et al., 2007) finding of gray matter differences between 24 bipolar disorder patients and controls in unspecified mood states. Finally, a meta-analysis (Bora et al., 2010) of gray matter differences associated with bipolar disorder included 24 studies of patients in various mood states compared to healthy subjects and suggested that bipolar disorder was associated with lower gray matter density in anterior cingulate and prefrontal cortices and greater density in the subgenual prefrontal cortex and amygdala. Comparisons based on mood state were not reported.

Our study has several limitations. First, the number of patients in our scanning sample was small. The power afforded by within-subjects comparisons was sufficient to detect prefrontal differences, but our small sample size may have limited the power to detect more subtle changes elsewhere. Second, patients in the present study were medicated which may have affected brain structure. Lithium treatment has been associated with increases in anterior cingulate gray matter density (Moore et al., 2000; Bearden et al., 2007), but only one patient in our study was prescribed this medication. A systematic effect of medication is less likely, as our within-subject findings agree with prior between-subject findings in unmedicated subjects (Brooks et al., 2009a; Nery et al., 2009). Third, we did not have a control group that had scans repeated longitudinally. This will be considered in future studies.

In conclusion, our preliminary data suggest mood state can alter gray matter structure. The lack of consensus among prior structural neuroimaging studies of bipolar disorder could reflect, in part, the varied mood states of the patients. It is unclear whether these changes presage functional changes observed in studies of cerebral blood flow and metabolism. What is clear, however, is that the mood state of patients cannot be ignored in neuroimaging studies of bipolar disorder.

Acknowledgments

This work was supported in part by Supported by the NIMH (K24 MH-01848 to Dr. Altshuler. The authors gratefully acknowledge the National Institute of Mental Health (NIMH; MH078556 to LCFR, and MH075944 and MH01848 to LLA). PT is supported, in part, by NIH grants EB008432, EB008281, EB007813, HD050735, AG036535, RR021813 and RR013642.

For their generous support, the authors also thank the National Association for Research on Schizophrenia and Affective Disorders (NARSAD), Brain Mapping Medical Research Organization, Brain Mapping Support Foundation, Pierson-Lovelace Foundation, The Ahmanson Foundation, William M. and Linda R. Dietel Philanthropic Fund at the Northern Piedmont Community Foundation, Tamkin Foundation, Jennifer Jones-Simon Foundation, Capital Group Companies Charitable Foundation, Robson Family and Northstar Fund.

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Figure 1. Regions of decreased gray matter density in depression are shown in blue/green and regions of increased density during depression are shown in red/yellow.

Table 1

Coordinates for regions with statistically significant differences in gray matter density between depressed and euthymic states.

Region	BA	Hemisphere	Talairach Coordinates					Cluster size	t	
			x	y	z					
Decreased density during depression										
Superior frontal gyrus	10	Right	26	53	5	144	17.84			
Cuneus/lingual gyrus		Right	22	-73	15	420	9.97			
Cingulate gyrus/Medial frontal	4	Right	20	-21	40	319	8.42			
Superior temporal gyrus	41	Left	-48	-28	8	86	7.07			
Culmen		Left	-18	-40	-25	40	5.78			
Precuneus		Right	12	-56	38	73	5.53			
Anterior cingulate	32	Left	-12	49	-1	43	4.87			
Inferior frontal gyrus	46	Left	-38	32	10	42	4.77			
Increased density during depression										
Superior frontal gyrus	22	Right	64	32	-11	111	11.47			
Fusiform/inferior temporal gyrus	20	Right	55	-21	-26	66	11.36			
Subgenual prefrontal	25	Right	4	-3	9	169	8.49			
Parahippocampal gyrus/inferior temporal		Right	40	-17	-28	37	6.60			
Middle frontal gyrus	6	Right	40	18	24	31	5.89			
Parahippocampal gyrus		Right	18	-21	-21	29	5.89			
Superior temporal gyrus	22	Right	57	-46	21	30	5.17			

Note: n = 7. BA = Brodmann's Area. Cluster size is expressed as number of voxels. For all *t*'s, $P < 0.005$.