Reduced Amygdala Volumes in First-Episode Bipolar Disorder and Correlation with Cerebral White Matter

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Background: Previous magnetic resonance imaging (MRI) findings on amygdala volume abnormalities in bipolar disorder have been inconsistent, which may partly reflect clinical heterogeneity. It is unclear whether amygdala abnormalities are present early in the course of illness and/or are the consequence of disease progression.

Methods: Twenty patients with first-episode bipolar disorder and 23 matched healthy comparison subjects were included. Magnetic resonance images were used to measure amygdala volumes, as well as whole brain measures of gray and white matter volume.

Results: First-episode bipolar patients had significant reductions in amygdala volume relative to healthy subjects in an analysis of covariance that accounted for the effects of age, sex, and whole brain volume. First-episode patients also showed a trend reduction in cerebral white matter volume, and there was a significant correlation between cerebral white matter volume and total amygdala volume in patients but not control subjects.

Conclusions: These findings indicate that amygdala volume deficits are present early in the course of bipolar disorder and may occur within a neuroanatomical context of reduced cerebral white matter. Additional research should examine whether the nature of regional white matter deficits, particularly in frontal-temporal tracts, may help parse the pathophysiology of amygdala volume abnormalities in bipolar disorder.

Key Words: Amygdala, bipolar disorder, first episode, white matter

A number of lines of research point to a key role of the amygdala in the pathophysiology of bipolar affective disorder. Functional imaging studies of healthy subjects have shown that the amygdala is critical for identifying the emotional significance of social stimuli, such as facial expressions of negative and positive affect (Adolphs et al 1998; Anderson and Phelps 2000; Phan et al 2002) and that it also participates in the generation of emotional responses to social-emotional cues (Phillips et al 2003). There is growing evidence that patients with bipolar disorder exhibit facial affect recognition biases (Getz et al 2003; Harmer et al 2002; Lembke and Ketter 2002; Lennox et al 2004; McClure et al 2003; Addington and Addington 1998) and that these are associated with abnormal activation of the amygdala during functional imaging (Lennox et al 2004; Yurgelun-Todd et al 2000). In addition, lesions or damage to the amygdala can produce both symptoms of mania and deficits in identifying emotions in facial expressions (Adolphs et al 1998; Starkstein et al 1988). Thus, amygdala abnormalities may play an important role in the expression of bipolar illness.

Although clinical and functional imaging studies point to amygdala dysfunction in bipolar disorder, its structural underpinnings are unclear. Morphometric magnetic resonance imaging (MRI) studies that have specifically examined amygdala volumes in individuals diagnosed with bipolar disorder have produced mixed results (Drevets 2003). There have been similar numbers of findings of increased (Altshuler et al 1998, 2000; Brambilla et al 2003; Strakowski et al 1999) and decreased (Blumberg et al 2003; Chen et al 2004; Pearlson et al 1997; Swayze et al 1992) volume of the amygdala in adult bipolar disorder. In pediatric bipolar disorder, there is more consistent evidence of smaller amygdalae (Blumberg et al 2003, 2005; Chang et al 2005; DelBello et al 2004), with one report of unaltered amygdala volumes in this population (Frazier et al 2005). Differences in imaging methodologies are very likely contributors to these variable findings. For instance, early studies had insufficient image resolution to reliably delineate small subcortical structures (Soares and Mann 1997), and some measured the amygdala in only one or two slices (Swayze et al 1992), precluding comparison with more recent investigations. Other potential moderating variables are medication effects, and there is preliminary evidence that lithium is associated with increased amygdala volume (Chang et al 2005), while paroxetine treatment may lead to amygdala volume reduction (Szeszko et al 2004). The presence of comorbid Axis I diagnoses has been found to predict greater abnormality (reduction) of amygdala volumes in one study (Chen et al 2004). Further, most studies to date represent cross-sectional snapshots of patients at different ages, leaving open the possibility of age-related changes in amygdala abnormalities. In fact, Chen et al (2004) found age-related increases in amygdala volume among bipolar but not healthy adolescents, which may help explain findings of larger amygdala in some adult patient samples.

Another potential contributor to variable morphometric findings is clinical heterogeneity across and within study samples, which may reflect underlying pathophysiological heterogeneity. For instance, it has been proposed that repeated or prolonged episodes of affective dysregulation may have cumulative toxic effects on the central nervous system, particularly through the release of stress-related hormones such as glucocorticoids (Altshuler 1993). If this perspective is correct, then patients with a longer duration of illness may demonstrate neuroanatomical changes on MRI that reflect this disease progression. In contrast,

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neuropathological abnormalities detected early in the course of the illness, before the potentially neurotoxic effects of repeated episodes, may represent developmental abnormalities or candidate vulnerability markers for the development of the disorder. In fact, recent neurodevelopmental models of bipolar disorder posit that abnormalities in subcortical structures such as the amygdala are an early feature of bipolar disorder, because the maturation of these regions culminates early in the temporal sequence of structural brain development relative to the maturation of prefrontal cortical brain regions (Blumberg et al 2004). To examine this issue, we studied amygdala volumes in a sample of 20 bipolar patients from the McLean-Harvard First-Episode Psychosis Project (Tohen et al 1992, 2000, 2003). Patients were presenting for their first psychiatric hospitalization and first episode of psychotic bipolar disorder. We hypothesized that abnormalities in amygdala volume would be apparent in these first-episode bipolar patients, consistent with a neurodevelopmental origin of these abnormalities.

Methods and Materials

Subjects

Participants were 20 patients with first-episode bipolar disorder with psychotic features and 23 matched healthy comparison subjects. Detailed recruitment methods and other study procedures have been described in previous reports on the McLean-Harvard First-Episode Psychosis Project initiative (Tohen et al 1992, 2000, 2003). Briefly, trained clinical evaluators recruited patients from consecutive inpatient admissions over 8 years (1989–1996) at McLean Hospital. Psychiatric diagnoses were updated to DSM-IV criteria after 1994 (American Psychiatric Association 1994). Comparison subjects were recruited via advertisements in local newspapers; they had no history of psychiatric illness and no first-degree relatives with known psychiatric illness. Subjects were included in this study if they were 18 years of age or older and if they provided written informed consent based on McLean Hospital Institutional Review Board approval. Subjects were monetarily compensated for their participation ($50). Exclusionary criteria for all subjects were: 1) presence of acute intoxication or a withdrawal syndrome associated with drug or alcohol abuse or delirium of any cause; 2) intelligence quotient (IQ) less than 70 or DSM-IV organic mental disorder; and 3) contraindications for MRI scanning (metal implants, pacemaker, aneurysm clips, pregnancy, or claustrophobia).

All subjects were interviewed using the Structured Clinical Interview for DSM-III-R - Patient Version (SCID-P) (Spitzer 1988) by masters-level raters with greater than 5 years clinical experience (Tohen et al 2003). First-episode bipolar patients were included in the study if they met the following criteria: 1) a first lifetime episode of clinically defined psychotic mood disorder without symptomatic remission since onset; and 2) meeting DSM-IV criteria for a principal diagnosis of bipolar disorder with psychotic features. In addition to the exclusionary criteria listed previously, reasons for exclusion of bipolar patients were: 1) previous psychiatric hospitalizations, unless for alcohol or substance abuse detoxification; 2) ill for more than 1 year; or 3) previous antipsychotic or mood stabilizer treatment for more than 3 months total. Six of the bipolar patients reported a family history of bipolar disorder. Table 1 summarizes subjects' demographic characteristics and clinical features for the patients. Subjects were matched in terms of age, sex, and handedness; bipolar patients had a trend toward fewer years of education than healthy control subjects. Finally, we should note that although two of the first-episode patients were initially hospitalized for depression, they both switched into a manic or mixed episode shortly after their admission to the inpatient unit.

Table 1. Demographic Characteristics for Bipolar Patients and Healthy Comparison Subjects and Clinical Features of Illness and Discharge Medications of the Bipolar Patients

	First-Episode Bipolar Patients (n = 20)	Healthy Comparison Subjects (n = 23)	p
Age, Years	23 (3)	25 (3)	.15
Sex, Male	13 (65)	16 (70)	.75
Handedness, Right	20 (100)	23 (100)	—
Education, Years	15 (2)	16 (2)	.06
Affective State, *n* (%)			
Manic	14 (70)		
Mixed	4 (20)		
Depressed	2 (10)		
Age at Onset, Mean (SD), Years	23 (3)		
Hospitalizations, Mean (SD)	1 (0)		
History of Substance Dependence, *n* (%)	8 (40)		
History of Psychosis, *n* (%)	20 (100)		
Lithium Carbonate, *n* (%)	8 (40)		
Anticonvulsant, *n* (%)	5 (25)		
Conventional Antipsychotic, *n* (%)	13 (65)		
Atypical Antipsychotic, *n* (%)	5 (25)		
Antidepressant, *n* (%)	2 (10)		

Mean (SD) or *n* (%).

MRI Protocol

Structural MRI images were obtained on a 1.5 Tesla GE Signa whole-body scanner (General Electric Medical Systems, Milwaukee, Wisconsin). Sagittal localizing images were acquired, followed by high-resolution T1-weighted coronal images of the whole brain (3-mm spoiled gradient-recalled acquisition). The acquisition parameters were: repetition time (TR) = 35 milliseconds, echo time (TE) = 5 milliseconds, flip angle = 45°, 256 x 256 matrix, voxel dimensions = .976 x .976 x 3 mm.

Images were reconstructed off-line on a SUN Microsystems Sparc2 workstation (Sun Microsystems, Inc., Mountainview, California) using a semiautomated segmentation software package (Kikinis et al 1992), as described in previous reports (e.g., Loeber et al 2001; Vakili et al 2000). Briefly, coronal volumetric images were segmented into gray and white matter using a semiautomated algorithm in MRX (General Electric, Schenectady, New York) (Kikinis et al 1992). The full series of coronal images was restored by an experienced image analyst (C.M.C.) with established intrarater reliability of .94 for classifying background (nonbrain tissue), .97 for gray matter, .92 for white matter, and .91 for cerebrospinal fluid. A single rater, who was blind to diagnosis and all other subject identifying information, manually traced the boundaries of the amygdala and cerebrum (supratentorial tissue) on each coronal slice for each subject with reference to an anatomical atlas (Yuh et al 1994). The anterior boundary of the amygdala region of interest (ROI) was defined as the first slice showing the temporal stem connecting the temporal lobe with the rest of the brain. The posterior boundary was defined as the last slice before the appearance of the mammillary bodies. Lateral borders consisted of the inferior horn of the lateral ventricles and the joining of the four main branches of the