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Brain GABA levels in patients with bipolar disorder

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ABSTRACT

Purpose: A growing body of research supports an important role for GABA in the pathophysiology of bipolar and other mood disorders. The purpose of the current study was to directly examine brain GABA levels in a clinical sample of bipolar patients.
General methods: We used magnetic resonance spectroscopy (MRS) to examine whole brain and regional GABA, glutamate and glutamine in 13 patients with bipolar disorder compared to a matched group of 11 healthy controls.
Findings: There were no significant differences in GABA, glutamate or glutamine between patients and controls.
Conclusions: Further research is needed to better characterize the GABAergic and glutamatergic effects of pharmacotherapy, anxiety comorbidity and clinical state in bipolar disorder.

1. Introduction

Converging lines of evidence suggest that dysfunction in brain gamma-aminobutyric acid (GABA) system activity contributes to vulnerability to bipolar disorder as well as other mood and anxiety states. For instance, Benes and Berretta (2001) have highlighted the critical role of GABAergic interneurons in corticolimbic circuitry and hypothesized, based on data from post-mortem studies, that abnormalities in GABAergic neurotransmission may be important in the development of bipolar illness (and schizophrenia) through disturbances in early CNS development. Disturbances in GABAergic activity may, for instance, result in abnormal modulation of dopaminergic and other neurotransmitter activity in the amygdala, hippocampus and other pertinent brain regions. Cortical and subcortical regions of interest (ROI) that have been identified as abnormal in previous studies of bipolar disorder include the temporal lobes, amygdala, hippocampus, basal ganglia, putamen, anterior cingulate, caudate and prefrontal cortex (Bearden et al., 2001; DelBello et al., 2004; Woo et al., 2007).

Various alterations in GABAergic neurons have been found in different brain areas. For example, reductions in the density of GABAergic neurons have been demonstrated in the anterior cingulate cortex of patients with bipolar disorder utilizing immunocytochemistry (Cotter et al., 2002). Similarly, reductions in the levels of GABA regulating proteins glutamic acid decarboxylase (GAD) and reelin have been documented in the cerebella of bipolar patients using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and Western blotting (Fatemi et al., 2005). Further, decreases in overall reelin, parvalbumin, and GAD have been reported using immunocytochemistry and Western blotting (Torrey et al., 2005).

The opposite trend has been found in some studies of GABAergic activity in frontal regions. One recent immunocytochemistry study showed preliminary evidence for greater density of prefrontal cortex GABA interneurons in bipolar patients, as measured by the density of neurons immunoreactive to calcium-binding proteins found on cortical GABAergic interneurons (Sakai et al., 2008). Similarly, Bielau et al. (2007) found increased levels of GAD in the orbitofrontal cortex of bipolar patients.

Polymorphisms have also been found in genes coding for the GABA receptor. Data from a case–control sample examining allele and genotype frequency implicated an alpha3 subunit GABA receptor (GABRA3) polymorphism in conferring susceptibility to bipolar disorder (Massat et al., 2002). Further studies have identified alterations in GABRA1 (Horiuchi

Abbreviations: AG, agoraphobia; CSF, cerebrospinal fluid; Cho, choline; Cr, creatine; DSM, Diagnostic and Statistical Manual of Mental Disorders; FOV, field-of-view; GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase or generalized anxiety disorder; Glu, glutamate; GLX, glutamate, glutamine and GABA; GM, gray matter; MADRS, Montgomery Asberg Depression Rating Scale; MINI, Mini International Neuropsychiatric Interview; mpFLASH3D, magnetization-prepared Fast Low-Angle SHot in 3-Dimensions; MRS, magnetic resonance spectroscopy; Myo, Myo-inositol; NAA, N-acetyl-aspartate; NAAG, N-acetyl-aspartyl-glutamate; OCD, obsessive compulsive disorder; PD, panic disorder; PTSD, posttraumatic stress disorder; RF, radio-frequency; ROI, region of interest; SAD, social anxiety disorder; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; SUB, sub-cortical structures; TEM, transverse electromagnetic; WM, white matter.

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et al., 2004) and GABRA5 polymorphisms (Otani et al., 2005) associated with bipolar disorder.

In further support of the role of alterations in GABAergic function in the neurophysiology of bipolar disorder, Dean et al. (2001) reported increased binding of the benzodiazepine antagonist flumazenil to the benzodiazepine binding site on the GABA(A) receptor in bipolar subjects. In a follow-up study (Dean et al., 2005), they reported an insensitivity to the hypnotic zolpidem in the hippocampi of bipolar patients, leading them to hypothesize an increase in regional GABA(A) receptors containing the alpha5 subunit, a subunit to which zolpidem does not bind.

Clinical studies, despite some inconsistencies, on the whole also support an important role for GABA in the pathophysiology of bipolar and other mood disorders. One study reported that patients with mood disorders ($n = 133$) had lower plasma GABA levels than controls (Petty et al., 1990), and that levels of GABA in plasma were similarly decreased in the patients with unipolar depression, bipolar depression, and mania. Another study demonstrated no significant differences in cerebrospinal fluid (CSF) GABA levels between euthymic bipolar patients and normal controls, consistent with the hypothesis that changes in GABA levels may be state dependent (Berrettini et al., 1986). One study reported that GABA levels were significantly lower in the CSF of unipolar and bipolar depressed patients compared to manic, schizophrenic, or control groups (Gerner et al., 1984) whereas another found comparable CSF GABA levels in patients ($n = 25$) with depression (bipolar and unipolar) compared to normal controls (Roy et al., 1991). In contrast, a recent Magnetic Resonance Imaging (MRS) study found significantly increased occipital GABA levels in bipolar patients (Wang et al., 2006).

A potential confounding factor in these studies is the presence of comorbid anxiety disorders. Recent reports consistently find approximately half of bipolar patients have a significant history of anxiety disorders and that the presence of such comorbidity is associated with more severe bipolar disorder (Altindag et al., 2006; Simon et al., 2004; Simon et al., 2003); anxiety disorders themselves have been associated with altered GABA functioning (Goddard et al., 2001). We recently observed decreased thalamic though not whole brain GABA in a controlled MRS study of individuals with social anxiety disorder (Pollack et al., 2008). And though studies in panic using peripheral measures of GABA (including CSF and plasma) have reported inconsistent findings, direct examination with MRS has revealed decreased brain GABA levels (Goddard et al., 2001). The present study addresses these issues by directly examining central GABA levels in bipolar patients with MRS while also controlling for the influence of anxiety comorbidity.

This study, to our knowledge, is the first to examine the impact of comorbid anxiety on brain GABA levels in a clinical sample of bipolar patients through the use of Magnetic Resonance Spectroscopy (MRS). Because of the high prevalence of anxiety disorders comorbid with bipolar disorder, we examined GABA levels in a representative sample of patients with and without anxiety comorbidity to control for the impact of anxiety on the primary bipolar neuropathology. We also examined subcortical regions of interest (ROI) that have been previously identified as abnormal in bipolar disorder including the thalamus, amygdala, hippocampus, basal ganglia, and caudate (Bearden et al., 2001). We hypothesized that bipolar patients would have decreased levels of brain GABA compared to normal controls, and that the presence of comorbid anxiety disorders would confer an even greater reduction in GABA levels.

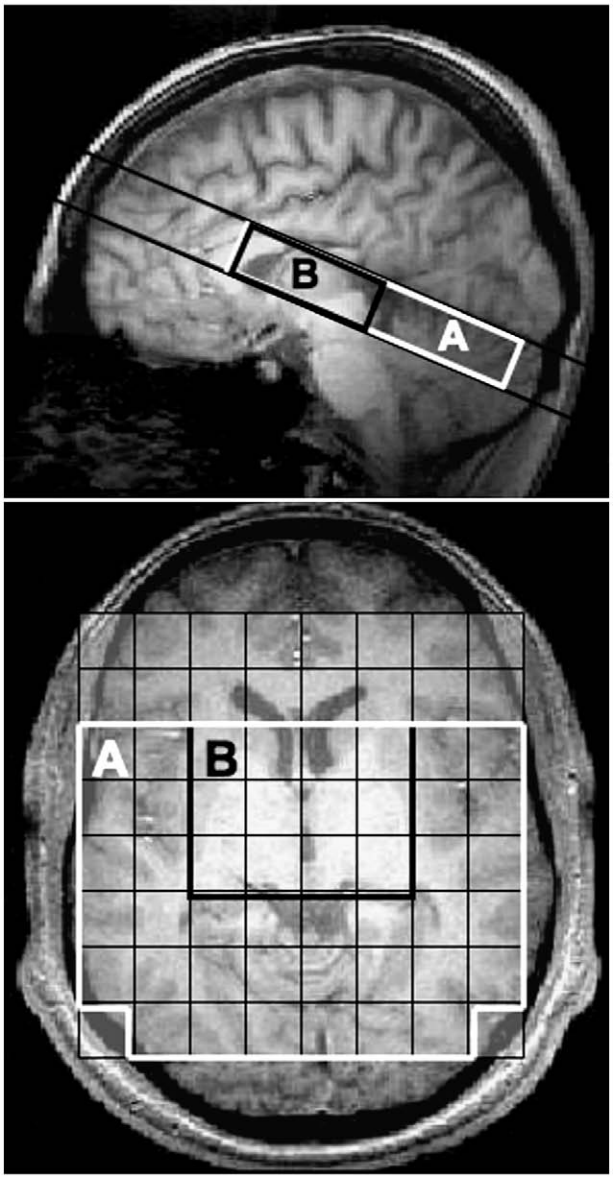

Fig. 1. Sagittal and axial T1-weighted images depicting the placement of the 2 cm thick MRSI slab. Matrix (A) denotes the voxels comprising the "global" measure and matrix (B) denotes those voxels included in the basal-ganglial/thalamic region. Voxels from the frontal regions were not included due to susceptibility artifact from the underlying sinuses.

2. Methods

2.1. Subjects

Participants were 13 patients recruited from the Partners Bipolar Disorder Center at the Massachusetts General Hospital and 11 age and gender-matched healthy control subjects, recruited by advertisement and free of any psychiatric diagnosis. Patients received diagnostic evaluation with the Mini International Neuropsychiatric Interview (MINI Version 4.4; Montgomery and Asberg, 1979), including assessment of the presence or absence of any anxiety disorder including: panic disorder with or without agoraphobia (PD), agoraphobia without panic disorder (AG), social anxiety disorder (SAD), obsessive compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and generalized anxiety disorder (GAD). Patients were assessed as manic, depressed or euthymic, based on the presence or absence of DSM-IV-based criterion for bipolar disorder, and completed the Montgomery Asberg Depression Rating Scale (MADRS; Sheehan et al., 1998). Participants with a neurological or major medical illness, clinically significant head injury, or other major psychiatric disorders including current substance abuse or dependence, as well as those currently on GABAergic agents including valproate and benzodiazepines were excluded from the study. Of the two subjects that qualified for past alcohol abuse, one had been alcohol-free for 12 months and the other had been alcohol-free for 30 years. On the day of the study prior to scanning, subjects provided urine samples to screen for drugs of abuse and pregnancy. Prior to the study, subjects also underwent a breathalyzer test to assess recent consumption of