



Effects of lithium on cortical thickness and hippocampal subfield volumes in psychotic bipolar disorder



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ABSTRACT

Relative to healthy controls, lithium free bipolar patients exhibit significant gray matter abnormalities. Lithium, the long-time reference standard medication treatment for bipolar disorder, has been proposed to be neuro-protective against these abnormalities. However, its effects on cortical thickness and hippocampal subfield (HSF) volumes remain unstudied and unclear, respectively, in bipolar disorder. This study included 342 healthy controls (HC), 51 lithium free PBD patients (NoLi), and 51 PBD patients taking lithium (Li). Regional gray matter thickness and HSF volume values were extracted from 3T MRI images. After matching NoLi and Li samples, regions where HC differed from either Li or NoLi were identified. In regions of significant or trending HC–NoLi difference, Li–NoLi comparisons were made. No significant HC–Li thickness or HSF volume differences were found. Significantly thinner occipital cortices were observed in NoLi compared to HC. In these regions, Li consistently exhibited non-significant trends for greater cortical thickness relative to NoLi. Significantly less volume was observed in NoLi compared to both HC and Li in right HSFs. Our results suggest that PBD in patients not treated with Li is associated with thinner occipital cortices and reduced HSF volumes compared with HC. Patients treated with Li exhibited significantly larger HSF volumes than NoLi, and those treated with Li were no different from HC in cortical thickness or hippocampal volumes. This evidence directly supports the hypothesis that Li may counteract the locally thinner and smaller gray matter structure found in PBD.

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1. Introduction

Bipolar mood disorder is a common psychiatric illness, whose pathophysiology is still largely unknown. It affects approximately

5.7 million American adults, or about 2.6 percent of the U.S. population age 18 and older in a given year (Kessler et al., 2005). Lithium has been the reference standard psychopharmacological treatment for bipolar mood disorder for much of the past 50 years (Brambilla et al., 2001) and is one of only two medications known to reduce risk of suicide (Goodwin et al., 2003). After decades of intensive research, the mechanisms of lithium's action in bipolar disorder have proven to be complex and diverse and they still remain unclear (Jope, 1999; Marmol, 2008; Toker et al., 2012).

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Lithium has been suggested to be neuro-protective in the context of other psychiatric disorders, as studies have indicated that lithium may change disease progress in Alzheimer's patients with early symptoms (Forlenza et al., 2012; Diniz et al., 2013). It has also been suggested that lithium may stimulate increases in gray matter volume and density in bipolar patients (Moore et al., 2000, 2009; Sassi et al., 2002; Bearden et al., 2007), particularly hippocampal volume increases (Yücel et al., 2007; Hallahan et al., 2011; Hajek et al., 2012a, 2012b, 2014). However, research into the effects of lithium on the brain in bipolar disorder, particularly psychotic bipolar disorder (PBD), remains unclear and inconsistent (Kato et al., 1996; Davanzo et al., 2001; Brambilla et al., 2004; Friedman et al., 2004; Patel et al., 2008; Dickstein et al., 2009; Seleke et al., 2013).

Several lines of evidence implicate brain structural abnormalities, particularly thinner cortex, in patients with bipolar disorder, and it has been suggested that these abnormalities may parallel phases of illness (Benedetti et al., 2011). Findings, however, have been largely inconsistent across studies. Some studies with samples consisting of bipolar patients with mixed lithium usage show significantly thinner cortices in the left rostral and right dorsal paracingulate cortex (Fornito et al., 2008) and other studies demonstrate more widespread differences in cortical thickness when compared to healthy controls (Lyoo et al., 2006). It has also been found that relative to healthy control subjects, currently euthymic lithium-free patients with bipolar disorder have significantly thinner gray matter in bilateral prefrontal cortex and the left anterior cingulate cortex, a finding that was more pronounced in patients with a history of psychosis (Foland-Ross, 2011). Thus far, the effect of lithium on this phenomenon of thinner cortex has not been studied.

The hippocampus has been implicated in affective and cognitive abnormalities in mood disorders and is routinely observed as smaller in major depressive disorder patients (Kempton et al., 2011). In previous research on bipolar disorder, patients have largely been found to exhibit hippocampal volumes similar to controls (Strakowski et al., 1999; Altshuler et al., 2000; Brambilla et al., 2003; Delaloye et al., 2009; Foland-Ross et al., 2013). However, in meta-analysis of a series of relatively small studies grouping patients according to presence and absence of lithium treatment, structural hippocampal differences were noted between controls and bipolar patients with minimal lithium exposure (Hajek et al., 2012b, 2014), raising the possibility that disease effects may be masked by medication effects in the current body of bipolar disorder literature. These disease effects may be magnified in PBD, as studies have suggested an association between psychosis and smaller hippocampi in bipolar disorder (Strasser et al., 2005).

Further studies are needed to examine the structural impact of lithium in PBD. Specifically, the medication's effects in PBD on cortical thickness should be assessed for the first time, and its effects on hippocampal volumes should be confirmed and localized in a large-scale study. This study investigated these effects of lithium in patients with PBD recruited as part of the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) study. These subjects were separated into groups of patients either treated or not treated with lithium. A previous study using the B-SNIP database did not identify lithium effects on gray matter, but used voxel-based rather than surface-based analysis and was conducted on an interim study sample which was 50% of the total study sample (Ivleva et al., 2013). We hypothesized that patients not on lithium would exhibit thinner cortices and smaller hippocampal subfields (HSFs) compared to healthy controls while patients on lithium would not. We also examined the potential confounding effect of cognitive, demographic (age, gender, race), clinical (anti-psychotic use), and social measures (socioeconomic status) on these comparisons.

2. Methods and materials

We compared MRI-derived cortical thickness data between healthy controls (HC), lithium taking probands with PBD (Li) and probands with PBD currently not on lithium (NoLi). Data were derived from B-SNIP, which represents a 6-site study (Wayne State University, Harvard University, Maryland Psychiatric Research Center, University of Chicago/University of Illinois at Chicago, University of Texas Southwestern, and the Institute of Living/Yale University).

2.1. Study participants

The study included 342 HC, 51 Li, and 135 NoLi from the B-SNIP database for whom 3.0 T MRI data, clinical measures, and demographic information were available. 19 participants (10 controls and 9 probands) were excluded due to motion and scanner artifacts. A chi-square test showed that proportion of images with artifacts did not differ significantly between groups.

All participants met the following inclusion criteria: (1) ages 15–65; (2) sufficient proficiency in English to understand task instructions; (3) no known history of neurologic disorders including head injury; (4) no history of substance abuse within the last month or substance dependence within the last 6 months; (5) negative urine toxicology screen on day of testing. Control subjects met the following additional criteria: (1) no personal or family history (first degree) of psychotic or bipolar disorders; (2) no personal history of recurrent mood disorder; (3) no lifetime history of substance dependence; (4) no history of any significant cluster A axis II personality features defined by meeting full or minus-one criteria of a Cluster A diagnosis using the Structured Interview for DSM-IV-TR Personality (SID-P) (Pfohl et al., 1997). Institutional review boards at each site approved the study and all sites used identical diagnostic, clinical, and recruitment techniques (Tammimga et al., 2013).

At the time of enrollment and assessments, patients were known to be clinically stable on current treatments. A structured medication history was administered by research staff to ascertain all medications currently taken by participants. In this study, the presence or absence of psychotropic medications was considered.

All participants underwent a diagnostic interview using the Structured Clinical Interview for DSM-IV-TR (SCID-IV) (First and Gibbon, 1997) and were categorized by diagnosis. Interviews were performed by trained clinicians who established reliability at regular intervals and met for weekly conferences to discuss difficult cases. Controls were also administered the SID-P. Diagnoses were made at each site by a consensus process led by a senior clinician that included reviews of results from clinical interviews, psychiatric and medical histories, and medical records when available. Healthy controls and patients meeting criteria for Bipolar Disorder Type I who also endorsed psychotic symptoms (with mood component more significant) were included for this analysis.

2.2. MRI-structural imaging

Subjects were scanned at six sites: Boston, MA (3.0 T, GE Signa, Pewaukee, WI); Detroit, MI (3.0 T, Siemens Allegra, Malvern, PA); Baltimore (3.0 T, Siemens Trio Tim, Erlangen, Germany); Hartford (3.0 T, Siemens Allegra, Malvern, PA); Dallas, TX (3.0 T, Philips Achieva, Andover, MA); and Chicago, IL (3.0 T, GE Signa, Pewaukee, WI). High-resolution isotropic T1-weighted MPRAGE scans (TR = 6.7 ms, TE = 3.1 ms, 8° flip angle, 256 × 240 matrix size, total scan duration = 10:52.6 min, 170 sagittal slices, 1 mm slice thickness, 1 × 1 × 1.2 mm³ voxel resolution) were obtained following the

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