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Research paper

Lithium monotherapy associated clinical improvement effects on amygdala-ventromedial prefrontal cortex resting state connectivity in bipolar disorder

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A B S T R A C T

Background: This study, for the first time, investigated lithium monotherapy associated effects on amygdala-ventromedial prefrontal cortex (vMPFC) resting-state functional connectivity and correlation with clinical improvement in bipolar disorder (BP)

Methods: Thirty-six medication-free subjects − 24 BP (12 hypomanic BPM) and 12 depressed (BPD)) and 12 closely matched healthy controls (HC), were included. BP subjects were treated with lithium and scanned at baseline, after 2 weeks and 8 weeks. HC were scanned at same time points but were not treated. The effect of lithium was studied for the BP group as a whole using two way (group, time) ANOVA while regressing out effects of state. Next, correlation between changes in amygdala-vMPFC resting-state connectivity and clinical global impression (CGI) of severity and improvement scale scores for overall BP illness was calculated. An exploratory analysis was also conducted for the BPD and BPM subgroups separately.

Results: Group by time interaction revealed that lithium monotherapy in patients was associated with increase in amygdala-medial OFC connectivity after 8 weeks of treatment ($p = 0.05$ (cluster-wise corrected)) compared to repeat testing in healthy controls. Increased amygdala-vMPFC connectivity correlated with clinical improvement at week 2 and week 8 as measured with the CGI-I scale.

Limitations: The results pertain to open-label treatment and do not account for non-treatment related improvement effects. Only functional connectivity was measured which does not give information regarding one regions effect on the other.

Conclusions: Lithium monotherapy in BP is associated with modulation of amygdala-vMPFC connectivity which correlates with state-independent global clinical improvement.

1. Background

Bipolar disorder (BP) is a severe mood disorder characterized by periods of depression (BPD) and (hypo)mania (BPM). Mood generating subcortical areas such as the amygdala and mood regulating cortical areas such as the ventromedial prefrontal cortex (vMPFC) play an important role in mood regulation and understanding the pathophysiology of BP.

Within the vMPFC region, the anterior cingulate cortex (ACC)–particularly ventral ACC (vACC), has been shown to be activated with emotional processes involved in reward and motivation and is thought to be the affective subdivision of the ACC (Bush et al., 2002; Critchley, 2004; Devinsky et al., 1995; Vogt et al., 1992). The vACC has also been shown to be more active in baseline resting states and is more strongly linked to autonomic control centers, which are activated in emotional states (Raichle et al., 2001). Moreover, vACC has been shown to have extensive reciprocal connections with the amygdala (Anand and Charney, 2000; Barbas and De Olmos, 1990; McDonald et al., 1999; Morgan et al., 1993; Paus, 2001; Sotres-Bayon et al., 2004), which suggests that these areas are functionally coupled (Ghashghaei and Barbas, 2002; McDonald, 1991, 1998) and that these connections play an integral role in the regulation of mood states (Amaral and Price, 1984; Damasio, 1997; Price, 2005; Sotres-Bayon et al., 2004). The medial orbitofrontal cortex (mOFC) is another area, which has been shown to have abnormal activation and connectivity in BP (Strakowski et al., 2004).

The importance of amygdala in generating emotional responses was shown in numerous studies (Adolphs et al., 2002; Amaral, 2003; Davis, 1992a; Davis and Myers, 2002; Hilton SM, 1963; Kaada, 1972; Kapp BS, 1992; LeDoux, 1992; Sanders and Shekhar, 1995). The amygdala has been identified as a key limbic region, which integrates sensory information particularly in relation to fear and anxiety and promotes appropriate visceral and behavioral responses (Amaral, 2003; Davis, 1992b; LeDoux, 2000). Functional magnetic resonance imaging (fMRI)

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studies report that increased amygdala activation is associated with several affective states including fear response to negative social stimuli (Adolphs et al., 2001; Baxter and Murray, 2002; Hariri et al., 2002; Phillips and Swartz, 2014). In addition to activation, amygdala and frontal brain regions were also shown to be involved in abnormalities in functional connectivity in patients with BP. In their 2009 paper, Almeida and colleagues showed that patients with BP had abnormal amygdala- medial orbito-frontal cortex connectivity (Almeida et al., 2009). Similarly, Anticevic and colleagues showed that compared to healthy controls, patients with bipolar-1 disorders showed decreased amygdala-dorsolateral prefrontal cortex (DLPFC) connectivity. Therefore, vMPFC and amygdala activation and connectivity may play an integral role in the pathophysiology of BP (Almeida et al., 2009) and pharmacological treatments, which are effective in BP, would be expected to have a significant effect on vMPFC-amygdala activation and connectivity (Almeida et al., 2009; Altshuler et al., 1998; Anticevic et al., 2013)

Lithium has been used in the treatment of bipolar disorder (BP) for nearly six decades at present and remains as one of the most effective and specific treatments for this disorder (Manji et al., 1999; Soares and Gershon, 1998). Lithium is effective for both the depressed and manic phases of BP (Price and Heninger, 1994). Furthermore, lithium has been shown in many studies to be prophylactic against future mood episodes and maintenance of stable mood.(Dunner et al., 1976; Fieve et al., 1976; Goodwin et al., 2016; Kane et al., 1982; Tondo et al., 1998). Lithium is a life-saving medication as it has consistently been shown to decrease the rate of suicides as well as overall mortality in subjects who take it (Cipriani et al., 2013). However, despite decades of clinical use and research, the neural and molecular mechanisms of action of lithium remain unclear. Elucidating these mechanisms will tremendously increase our knowledge regarding the etiology of BP and how to treat it.

In the past few decades, exciting data has become available regarding the effect of lithium on neuronal plasticity, regional gray matter density and neuronal viability pointing to neurotrophic effects of lithium (McDonald, 2015). Lithium effects on neuronal plasticity could restore the integrity of the corticolimbic circuit involved in mood regulation (Anand and Shekhar, 2003; Gray et al., 2003; Soares, 2002). In this regard, a number of studies to date have reported structural changes associated with lithium therapy. Meta-analyses (Kempton et al., 2008; McDonald et al., 2004), as well an analysis of data from an international consortium (Hallahan et al., 2011) have provided further evidence in support of this finding, however a number of studies have also reported no changes with lithium treatment (McDonald, 2015). One major methodological issue has been that most studies to date have used a cross-sectional design to compare structural volumetric differences between subjects on lithium for a variable period of time versus subjects who are not on lithium. In many of these studies, subjects were also on other mood-stabilizing medications. Only very few studies have used a rigorous longitudinal design to study lithium effects, however all of these studies have investigated the effects of lithium on brain structure and no study has been done to date has examined the effect of lithium monotherapy on brain activation and connectivity.

In addition to the abovementioned lithium-associated structural and neuronal changes, lithium effects were also shown to be associated with changes in electroencephalography (EEG) oscillations. In his 2016 review, Atagun demonstrated that lithium enhances the magnitudes of oscillations in delta and theta waves, which were found to be of lower magnitudes in patients with BP at baseline (Atagun, 2016). One other important finding in that paper was that there was a correlation found between lithium levels and the brain oscillations. These findings suggest that lithium effects on brain neurophysiological function may underlie its efficacy in BP. In this regard, we have previously reported that cortico-limbic connectivity is reduced in major depression and bipolar disorder (Anand et al., 2009, 2005). We have also shown that antidepressant treatment with selective serotonin reuptake inhibitors (SSRI) increases cortico-limbic connectivity in depressed patients.

In this study, we investigated lithium monotherapy associated effects on amygdala-vMPFC resting-state functional connectivity in medication-free BP using resting state low-frequency BOLD (blood oxygen level dependence) fluctuations (LFBF) correlation. Keeping in mind the integral role of vMPFC and amygdala in mood regulation we *a priori* confined our a priori hypothesis to amygdala-vMPFC connectivity. Furthermore, both the early effects (2 weeks) and late (8 weeks) effects of treatment were measured. Closely matched healthy controls (HC) were scanned at the same time points but did not receive any treatment. The hypothesis tested was that lithium treatment would be associated with increase in amygdala-vMPFC connectivity, that these effects would be cumulative over time and that the increase in connectivity will correlate with clinical improvement.

2. Methods

2.1. Participants

Thirty-six medication-free subjects − 24 BP (12 BPM and 12 BPD) and 12 HC closely matched for age and gender were recruited from the outpatient clinic at University Hospital, Indiana University School of Medicine and by advertisement from the community. All subjects took part in the study after signing an informed consent form approved by the Investigational Review Board (IRB) at Indiana University School of Medicine. Both patients and HC were paid $50 for screening and $50 for each MRI scan. All subjects underwent a detailed structured diagnostic interview – Mini Neuropsychiatric Interview (MINI) that generated a DSM-IV diagnosis. Inclusion criteria for were: ages 18–60 years (inclusive) and able to give voluntary informed consent; 2) Satisfy criteria for Diagnostic and Statistical Manual 4th edition (DSM-IV) for Bipolar Disorder Depressive Episode or for (hypo)manic episode; 3) Satisfy criteria to undergo an MRI scan based on MRI screening questionnaire; 4) Able to be managed as outpatients during the study as ascertained by the following – i. Clinical Global Severity Scale < 5 i.e. moderately ill ii. No significant suicidal or homicidal ideation or grossly disabled; 5) Satisfy criteria for DSM-IV depressive episode-current; 17-item Hamilton Depression Rating Scale (HDRS) score $\geq$ 12 but < 30 and Young Mania Rating Scale (YMRS) score $\leq$ 8 or for manic or hypomanic episode with HDRS $\leq$ 13 and YMRS $\geq$13.

Exclusion criteria for all patients were: 1) meeting DSM-IV criteria for schizophrenia, schizoaffective disorder, or an anxiety disorder as a primary diagnosis; 2) use of psychotropics in the past 2 weeks; use of fluoxetine in the past 4 weeks; 3) acutely suicidal or homicidal or requiring inpatient treatment; 4) meeting DSM-IV criteria for substance dependence within the past year, except caffeine or nicotine; 5) positive urinary toxicology screening at baseline; 6) use of alcohol in the past 1 week; serious medical or neurological illness; 7) current pregnancy or breast feeding; 8) metallic implants or other contraindications to MRI. Inclusion criteria for healthy subjects were: 1) ages 18–60 years and ability to give voluntary informed consent; 2) no history of psychiatric illness or substance abuse or dependence; 3) no significant family history of psychiatric or neurological illness; 4) not currently taking any prescription or centrally acting medications; 5) no use of alcohol in the past 1 week; and no serious medical or neurological illness. Exclusion criteria for healthy subjects were: 1) under 18 years of age; 2) pregnant or breast-feeding; 3) metallic implants or other contraindication to MRI.

2.1.1. Lithium treatment

Immediately after the baseline scan, BP subjects were started on lithium treatment 300 mg p.o. BID. Levels were checked after one week and when necessary lithium was increased to achieve trough levels between 0.5 – 1.0/L meq depending on efficacy and tolerance. Lithium levels were also checked near the time of the second and third scans. Patients were educated in detail about the side effects of lithium, ways to avoid these side effects, and how to contact the research team in case of uncomfortable side effects.