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Short communication

A pilot fMRI study of lithium response in bipolar disorder

Kelly Rootes-Murdy[a,*], Kara Glazer[b], Francis M. Mondimore[c], Fernando S. Goes[b], Pharmacogenomics of Bipolar Disorder (PGBD) Study, Peter P. Zandi[b,d], Arnold Bakker[b], J. Raymond DePaulo Jr.[b], Pamela B. Mahon[b,e,f]

[a] Department of Psychology, Georgia State University, 140 Decatur Street, Atlanta, GA 30303, USA
[b] Department of Psychiatry & Behavioral Science, Johns Hopkins School of Medicine, Baltimore, MD, USA
[c] Johns Hopkins Bayview Medical Center, Community Psychiatry Program, Baltimore, MD, USA
[d] Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
[e] Department of Psychiatry, Brigham & Women's Hospital, Boston, MA, USA
[f] Harvard Medical School, Boston, MA, USA

1. Introduction

Bipolar disorder (BD) is a serious psychiatric disorder with a relapsing and remitting course. Lithium was the first mood stabilizing medication identified for BD and remains the standard of treatment with support for efficacy and reduction of suicide risk (Kessing et al., 2005; Toffol et al., 2015). However, lithium is only effective in approximately 50% of patients and reliable predictors of treatment response that reduce time to mood stabilization are needed (Yildiz et al., 2011). A limited number of clinical factors are consistently associated with lithium response, but have small effect sizes and uncertain predictive value (Tighe et al., 2011). Patients with a family history of lithium-responsive BD tend to also be lithium responders. A history of euphoric, rather than dysphoric or mixed, manic episodes is also associated with a good response to lithium (Rohayem et al., 2008).

Convergent evidence suggests the neuropathology of BD involves dysregulation of a mood network, with disruption of inhibitory cortical modulation of subcortical limbic regions (Langan and McDonald, 2009; Phillips et al., 2008; Phillips and Swartz, 2014). Lithium use has been shown to normalize brain activity in this network and interrogation of the mood network through neuroimaging might also identify brain features correlated with response to lithium treatment (Phillips et al., 2008). Preliminary neuroimaging factors associated with good short-term response to lithium include increased cerebral gray matter volume, increased brain lithium concentration, reduced anterior cingulate myo-inositol levels, increased amygdala-ventromedial prefrontal cortex connectivity, and increased subcortical and amygdala activation to a continuous performance task with emotional distractors (Altinay et al., 2018; Davanzo et al., 2001; Kato et al., 1994; Lyoo et al., 2010; Strakowski et al., 2016). Here we examine the relationship between longer-term response to lithium treatment in BD and brain function during an emotional faces task utilizing functional magnetic resonance imaging (fMRI) after treatment with lithium.

2. Methods

2.1. Participants and procedures

This study includes 12 BD participants recruited through the Pharmacogenomics of Bipolar Disorder (PGBD) Study, a prospective trial of adult BD patients being treated with lithium monotherapy (Oedegaard et al., 2016). An additional 21 healthy comparison participants were recruited from the community. Research diagnoses and determinations of lithium response status were made as part of the PGBD study protocol (Oedegaard et al., 2016; Methods Supplement). Briefly, participants with a research diagnosis of bipolar I disorder were followed through a 16-week stabilization phase to stabilize mood and titrate off psychotropic medications other than lithium, a 4-week observation phase, and a maintenance phase for up to 24 months. Non-response was defined as either a failure to remit over the stabilization and observation phases, or relapse during the maintenance phase. Response was defined as not experiencing relapse during the maintenance phase.

For the current protocol, participants underwent an MRI scan after clinical determination of their response status was made (see Methods Supplement), and in the case of non-responders also after their symptoms had been managed. Participants were required to be euthymic at the time of the scan to minimize the likelihood that observed differences reflected current mood symptoms. Even so, non-responders endorsed more mild depressive symptoms than responders on the day of the scan (mean Beck Depression Inventory score = 14.0 ± 3.37 versus 5.29 ± 4.75, $p = 0.009$; respectively; Beck et al., 1961). Two participants had other mood stabilizer medications on board at the time of the scan. As some patients had initiated treatment with lithium prior to entering the PGBD study, duration of lithium treatment ranged from 5 months to 12 years.

* Corresponding author.
E-mail address: krootesmurdy1@student.gsu.edu (K. Rootes-Murdy).

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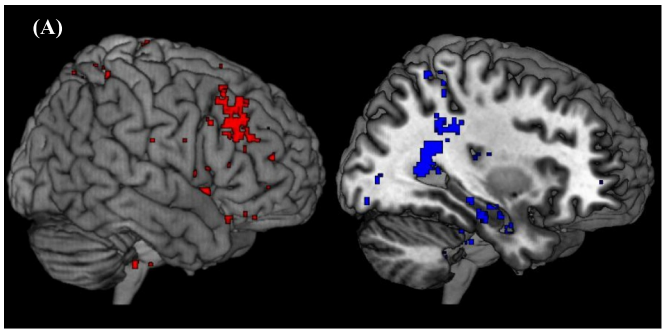

Fig. 1. Task based results for fearful-neutral contrast comparing lithium responders and lithium non-responders. (A) Results showing hyperactivation in lithium responders on the left and hypoactivation in lithium responders on the right. (B) Results from all clusters that were differentially activated at $p < 0.005$ with a voxel extent of 20.

(B)

No. of voxels	*t*-Statistic	MNI coordinates	Regions included
Responders > Non-responders			
86	7.47	58, 14, 6	Inferior Frontal Gyrus/ Precentral Gyrus
24	7.58	46, 36, 26	Middle Frontal Gyrus/Superior Frontal Gyrus
28	5.36	24, -28, 26	Cingulate Gyrus/Caudate
Non-responders > Responders			
209	12.68	30, -54, 6	Superior Temporal Gyrus/Parahippocampal Gyrus/Insula
29	10.39	-16, -20, 24	Caudate/Thalamus
39	9.28	14, -32, -12	Parahippocampal Gyrus
65	8.92	-36, 0, 14	Insula
26	6.00	32, -34, 36	Inferior Parietal Lobule
23	5.24	52, 18, 4	Inferior Frontal Gyrus/Precentral Gyrus
36	4.75	2, -4, -2	Thalamus/Anterior Cingulate

2.2. Measures and analysis

Participants completed an emotional faces task adapted from Malhi et al. (2004) in the scanner. In this task, participants viewed photographs of faces displaying fearful, neutral, and happy emotions in a block design, where each block contained photographs of different faces with the same emotion. Participants viewed eight emotion blocks (2 neutral, 3 happy, 3 fearful), with 10 s focus blocks in between (total time = 4 min, 54 s). In each emotion block, 56 total slides included 7 repetitions of 8 faces, each shown for 200 ms with a 300 ms interval in-between. Each participant completed the same block order, with slides randomly repeated within blocks.

EPI data were acquired on a 7 Tesla Philips Intera-NT system using a 32 channel head coil (TR = 2000 ms, flip angle = 70°, FOV 192 × 192 mm, 96 × 96 matrix, 39 interleaved sagittal slices, 2 × 2 × 3 mm voxel size, 1 mm gap). Data were processed and analyzed using SPM12 (Wellcome Department of Cognitive Neurology, London, UK). Functional images underwent standard processing including slice-timing correction, motion correction, realignment using windowed sinc-interpolation, and normalization to the Montreal Neurological Institute (MNI-EPI) template. Group fMRI data were analyzed comparing fearful to neutral cues, based on literature showing this contrast to have the most activation differences in BD (Sheline et al., 2001). Our primary analysis aimed to identify features that differ in lithium responders and non-responders. We used analysis of variance to examine differences in levels of activation across the entire brain, adjusting for age, sex, and education. A voxel threshold of $p < 0.005$ and spatial extent threshold of $k = 20$ voxels was used to select areas of task-related activation (Lieberman and Cunningham, 2009). For each cluster identified as differentially activated in the primary analysis, we performed *post hoc* tests for correlation with duration of treatment and for comparison with a healthy control group.

3. Results

Of the 12 BD participants, eight were classified as lithium responders and four as non-responders (2 fail to remit, 2 relapse). Demographic and clinical characteristics are shown in the Methods Supplement. There were no male participants in the non-responder group. As expected, non-responders had less time on lithium than responders (mean time on lithium = 11.75 ± 7.27 months versus 70.87 ± 55.36 months, $p = 0.02$; respectively).

For the comparison of lithium responders versus non-responders, we identified several brain regions that were differentially activated when comparing the fearful and neutral faces conditions (see Fig. 1). The largest cluster of differential activation was observed in the superior temporal gyrus and surrounding regions ($t_{max} = 12.68$, $p < 0.001$, voxel cluster size = 209), where lithium non-responders showed greater activation than did lithium responders. Lithium non-responders also displayed greater activation in the caudate, insula, and inferior frontal gyrus than lithium responders (all $t_{max} > 5.24$, $p < 0.001$). Conversely, lithium responders displayed more activation in the inferior frontal gyrus, middle frontal gyrus, and cingulate gyrus than lithium non-responders (all $t_{max} > 5.36$, $p < 0.001$).

In *post hoc* analyses for the clusters identified, no significant correlation was found between duration of lithium response and any of the significant beta estimates from the comparison of responders and non-responders (all $p > 0.55$). Healthy comparison participants displayed greater activation to the fearful-neutral contrast than lithium responders in the superior temporal gyrus (voxel cluster size = 141, $t_{max} = 3.35$, $p = 0.001$, $x = 38$, $y = -46$, $z = 22$). No other activation differences were detected between healthy comparison subjects and lithium responders or non-responders (results not shown).

4. Discussion

Despite the important role of lithium in the treatment of BD, there are relatively few neuroimaging studies that have examined response to lithium treatment. We tested for correlates of long-term response to lithium treatment in BD utilizing an emotional faces task, and identified greater cortical activity and less subcortical-limbic activity in lithium responders as compared to non-responders. Our results are consistent with and extend the findings of one previous fMRI study of first mania patients treated with either lithium or quetiapine that identified differential activation in subcortical regions in response to a continuous performance task with emotional distractors associated with whether or not patients were able to achieve remission after eight weeks (Strakowski et al., 2016). After treatment, brain activation in BD participants approached values seen in healthy controls. Similarly, Passarotti et al. (2011) found that treatment with second generation antipsychotics and lamotrigine normalized cortical activation in response to an affective faces task in a pediatric BD sample, though amygdala activation remained disrupted. Our observed lack of differences in brain activation between BD patients treated with lithium and healthy controls in most regions is consistent with previous studies that treatment normalizes brain activation in BD (Hafeman et al., 2012). Our finding of greater activation in superior temporal gyrus in healthy controls than in lithium responders may reflect continued disruption in emotional processing, as euthymic BD patients show diminished neural activity during emotion induction tasks compared to healthy controls (Malhi et al., 2007).

Limitations in our study include lack of MRI scans prior to initiation of lithium monotherapy and lack of data on lithium levels and lifetime substance dependence in all participants. Our sample is predominantly female, potentially limiting the generalizability of the findings. Differences in mild depressive symptoms and medication on the day of the scan could also impact on the interpretation of the findings.

In conclusion, this pilot study found differences in brain activation after lithium treatment related to long-term response in regions previously implicated in BD pathophysiology. These findings identify candidate brain features with potential to predict long-term response to lithium treatment in future studies utilizing larger samples and longitudinal neuroimaging.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.02.003.

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