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Bipolar mood state reflected in cortico-amygdala resting state connectivity: A cohort and longitudinal study

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ABSTRACT

Background: Using resting-state functional magnetic resonance imaging (rsfMRI), we previously compared cohorts of bipolar I subjects in a manic state to those in a euthymic state to identify mood state-specific patterns of cortico-amygdala connectivity. Our results suggested that mania is reflected in the disruption of emotion regulation circuits. We sought to replicate this finding in a group of subjects with bipolar disorder imaged longitudinally across states of mania and euthymia

Methods: We divided our subjects into three groups: 26 subjects imaged in a manic state, 21 subjects imaged in a euthymic state, and 10 subjects imaged longitudinally across both mood states. We measured differences in amygdala connectivity between the mania and euthymia cohorts. We then used these regions of altered connectivity to examine connectivity in the longitudinal bipolar group using a within-subjects design.

Results: Our findings in the mania vs euthymia cohort comparison were replicated in the longitudinal analysis. Bipolar mania was differentiated from euthymia by decreased connectivity between the amygdala and pregenual anterior cingulate cortex. Mania was also characterized by increased connectivity between amygdala and the supplemental motor area, a region normally anti-correlated to the amygdala in emotion regulation tasks.

Limitations: Stringent controls for movement effects limited the number of subjects in the longitudinal sample.

Conclusions: In this first report of rsfMRI conducted longitudinally across mood states, we find that previously observed between-group differences in amygdala connectivity are also found longitudinally within subjects. These results suggest resting state cortico-amygdala connectivity is a biomarker of mood state in bipolar disorder.

1. Introduction

Bipolar disorders are defined by the appearance of pathological states of depression or mania. A growing body of neuroimaging studies has expanded our understanding of bipolar disorders as disease entities (reviewed in (Strakowski, 2012)). Despite the striking differences in cognition, emotion and behavior between the manic and euthymic states, our understanding of how neurophysiology differs between these mood states is more limited (reviewed in (Salvadore et al., 2010)). To better elucidate the physiology underlying differences in bipolar mood state, we recently utilized resting-state functional magnetic resonance imaging (rsfMRI) to compare differences in functional connectivity between bipolar mania and bipolar euthymia (Brady et al., 2016). In that study we compared two cohorts of subjects, one manic and the other euthymic, and examined whole-brain functional connectivity to several brain regions. We discovered significant differences in functional connectivity between the amygdala and cortical regions between the two populations. Specifically, the manic state was defined by a loss of functional connectivity between the amygdala and the pregenual anterior cingulate cortex (pgACC). This finding extends existing models of bipolar disorder that implicate pathophysiology in the ACC (Phillips et al., 2008; Strakowski et al., 2012). We also observed increased connectivity between the amygdala and the supplemental motor area (SMA) in mania. This latter finding suggested an inversion of the activity observed in these structures during emotion regulation in healthy control subjects (Etkin et al., 2015; Kanske et al., 2011). Taken together, our results suggest that clinical states of dysregulated emotion may be reflected in state-related dysfunction in circuits of emotion regulation.

Additionally, we observed evidence of lateralization with the right

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amygdala showing more significant differences than the left.

These findings extend our understanding of the functional neuroanatomy of bipolar disorder by implicating specific structures in state related differences. One caveat of our analysis was that the experiment was a cross-sectional comparison of two cohorts of subjects rather than a longitudinal, within-subjects design. Few studies in bipolar disorder have employed a longitudinal imaging design across mood states (reviewed in (Brady et al., 2014)). Differences observed cross-sectionally between cohorts selected for mood state could be influenced by other differences between cohorts. To address this, we sought to examine state related amygdala circuit function utilizing a within-subjects design conducted longitudinally across mood states of mania and euthymia.

In the interim since the publication of our initial report we have continued to recruit subjects with bipolar disorder type I in a manic state, bipolar I subjects in a euthymic state, and bipolar I subjects imaged longitudinally in both mood states. Some subjects imaged in a manic state in our initial report subsequently returned for euthymic scans. To avoid the hazard of circular analysis i.e. deriving ROIs from a study sample then re-analyzing a partially overlapping data set with those ROIs (Kriegeskorte et al., 2009), we divided our bipolar subjects into three groups: A cohort of subjects imaged while manic, a cohort of subjects imaged while euthymic, and a third group imaged longitudinally across both mood states. We then conducted two analyses: First we analyzed whole-brain amygdala connectivity in mania and euthymia in a cross-sectional design by comparing the manic cohort to the euthymic cohort. We then used the regions of altered connectivity discovered in this comparison to examine functional connectivity in the group of bipolar subjects imaged longitudinally across mood states of mania and euthymia in a within-subjects design. As an additional control, we examined functional connectivity in these same regions in a group of healthy comparison (HC) subjects imaged longitudinally at a similar interval to the longitudinal bipolar subjects.

2. Methods

2.1. Participants

Study recruitment was performed as in our previous study (Brady et al., 2016). All participants gave written informed consent before participating. To ensure that participants understood the study, we conducted an informed consent survey, including simple questions about risks and benefits and the ability to withdraw consent. If the participants did not answer all questions correctly, the informed consent document was re-reviewed and understanding retested to ensure comprehension. Bipolar subjects in the mania cohort were typically recruited from McLean Hospital inpatient units during hospitalization for a manic episode.

Euthymic bipolar subjects were typically recruited from patients who had previously been hospitalized on these inpatient units. Longitudinal subjects were all recruited, characterized, and imaged while hospitalized for mania and were then contacted post-hospitalization for imaging and clinical characterization while euthymic. There was no overlap in subjects between the manic, euthymic, and longitudinal cohorts.

Diagnosis was determined using the Structured Clinical Interview for the DSM-IV (SCID)(First and New York State Psychiatric Institute Biometrics Research, 2007)). All subjects were assessed using the Young Mania Rating Scale (YMRS), Montgomery–Asberg Depression Rating Scale (MADRS), and Positive And Negative Syndrome Scale (PANSS) at the time of imaging. All subjects met criteria for the diagnosis of bipolar disorder type I. Subjects imaged in a manic state all had a YMRS score of 20 or greater. Subjects in a euthymic state all had a YMRS score of 12 or less. In addition, all longitudinal subjects did not meet DSM criteria for any mood episode for at least one month prior to imaging in the euthymic state. All longitudinal HC comparison subjects had no history of psychiatric illness nor any family history of first degree relatives with psychiatric illness.

Exclusion criteria included age outside the range of 18–65, neurological illness, pregnancy or lactation, electroconvulsive therapy in the last three months, history of head trauma with a loss of consciousness lasting more than a few minutes, and contraindications to magnetic resonance imaging.

2.2. MRI data acquisition

All data were acquired on a 3 T Siemens Trio-TIM scanner using a standard 12-channel head coil. No scanner upgrade occurred during the duration of data collection. Each scan consisted of two 6.2 min rsfMRI runs with imaging parameters as follows: repetition time=3000 ms; echo time=30 ms; flip angle=85°; 47 axial 3 mm sections collected with interleaved acquisition. Structural data included a high-resolution, multiecho, T1-weighted, magnetization-prepared, gradient-echo image. All participants were told ‘remain still, stay awake, and keep your eyes open’. Video recording of the eyes was used to confirm the awake, eye-open state.

2.3. MRI data processing

Imaging data were preprocessed using the DPABI (Yan et al., 2016). rsfMRI runs with head motion exceeding 3 mm in any dimension or 3^0 of maximum rotation about three axes were discarded from further analysis. After realigning, slice timing correction, and co-registration, framewise displacement (FD) was calculated for all volumes (Power et al., 2012). Volumes with a FD greater than .2 mm were regressed out during nuisance covariate regression. Any rsfMRI run with 50% or more of volumes regressed out was discarded from further analysis. Structural images from each subject were then normalized and segmented into gray, white and CSF partitions using the DARTEL technique (Ashburner, 2007). A Friston 24-parameter model was used to regress out head motion effects (Friston et al., 1996). The CSF and white matter signals, global mean signal as well as the linear trend were also regressed as nuisance covariates. The resultant data were band pass filtered to select low frequency (.01–.08 Hz) signals. Functional images were brought into MNI (Montreal Neurological Institute) space and then smoothed by a Gaussian kernel of 8 mm^3 full-width at half maximum. Voxels within a gray matter mask were used for further analyses.

2.4. Functional connectivity analysis

2.4.1. Bipolar mania cohort vs Bipolar euthymia cohort

In our comparison of the mania cohort to the euthymia cohort we measured whole-brain functional connectivity (FC) to the right amygdala using a ROI generated using Wake Forest University Pickatlas software (version 3.0.5)(Maldjian et al., 2003). The time course of voxels in this ROI was extracted and Pearson correlation coefficients between this time course and those of all other voxels were calculated. These values were transformed to Fisher's z scores to generate FC maps. Two –sample T- contrasts were then performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) to examine differences in FC between the mania and euthymia groups. Age, sex, and prescribed antipsychotic dosage in chlorpromazine equivalents (CPZE) covariates were regressed from the T-Tests as nuisance variables. The resulting contrast maps were thresholded for voxels with a P value $< .005$. The threshold for cluster level significance was determined using Monte Carlo simulation using AlphaSim as implemented in REST (Song et al., 2011). This resulted in a threshold of k=46 voxels for $p < .05$ clusterwise significance.

2.4.2. Longitudinal cohort

We then used the regions of altered functional connectivity derived