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Factor analysis of regional brain activation in bipolar and healthy individuals reveals a consistent modular structure

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ABSTRACT

Background: The neurophysiological substrates of cognition and emotion, as seen with fMRI, are generally explained using modular structures. The present study was designed to probe the modular structure of cognitive-emotional processing in bipolar and healthy individuals using factor analysis and compare the results with current conceptions of the neurophysiology of bipolar disorder.

Methods: Exploratory factor analysis was used to assess patterns of covariation among brain regions-of-interest activated during the Continuous Performance Task with Emotional and Neutral Distractors in healthy and bipolar individuals without *a priori* constraints on the number or composition of latent factors.

Results: Results indicated a common cognitive-emotional network consisting of prefrontal, medial temporal, limbic, parietal, anterior cingulate and posterior cingulate modules. However, reduced brain activation to emotional stimuli in the frontal, medial temporal and limbic modules was apparent in the bipolar relative to the healthy group, potentially accounting for emotional dysregulation in bipolar disorder.

Limitations: This study is limited by a relatively small sample size recruited at a single site. The results have yet to be validated on a larger independent sample.

Conclusions: Although the modular structure of cognitive-emotional processing is similar in bipolar and healthy individuals, activation in response to emotional/neutral cues varies. These findings are not only consistent with recent conceptions of mood regulation in bipolar disorder, but also suggest that regional activation can be considered within tighter modular structures without compromising data interpretation. This demonstration may serve as a template for data reduction in future region-of-interest analyses to increase statistical power.

1. Introduction

The neurophysiological substrates of normal and dysfunctional cognition and behavior are generally explained using modular network structures involving functionally unique and homogenous “nodes” and their interconnections (Park and Friston, 2013). Descriptions of neurophysiological dysfunction in bipolar disorder are no exception and, although the neurophysiology of bipolar disorder is not completely understood, appear to involve tightly linked prefrontal-striatopallidothalamic modules that manage external cognitive-emotional stimuli and internal emotional cues (Strakowski, 2012).

Evidence that bipolar disorder results from dysfunction of brain systems that maintain emotional arousal and homeostasis comes from functional MRI (fMRI) studies which suggest that a ventrolateral prefrontal network modulates processing of external emotional cues, whereas a ventromedial network processes internally referenced emotional states (Strakowski et al., 2005). Yamasaki et al. (2002) developed a visual oddball task with emotional distracters to discriminate between ventral (emotional) and dorsal (cognitive) neural processing streams during human fMRI studies. In particular, unpleasant emotional distracters in this task activated the ventrolateral prefrontal network, consistent with the hypothesis that this pathway responds to external emotional stimuli. One aspect of frontosubcortical cognitive-emotional networks of primary importance is modulation of amygdala function by prefrontal cortex (Chen et al., 1995; Lane et al., 1998; Phan et al., 2002; Yamasaki et al., 2002).

With the above considerations in mind, the present study was designed to probe the modular structure of prefrontal-amygdala

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cognitive-emotional networks in bipolar and healthy participants using exploratory factor analysis (EFA) of functional MRI (fMRI) activation to guide future neuroimaging research employing region-of-interest (ROI) analysis. To do so, time-averaged activation values in 29 predefined ROIs and three stimulus conditions (targets, neutral distractors, emotional distractors) comprising the Continuous Performance Task with Emotional and Neutral Distractors (CPT-END; Strakowski et al., 2011) were stacked in an EFA. This approach was employed to identify functional modules, i.e., groups of regions with similar fMRI activation profiles, and these modules were then examined to identify meaningful groupings (e.g., frontal or limbic modules), especially with respect to cross-correlations between prefrontal cortex (PFC) (e.g., ventrolateral PFC) and the amygdala-hippocampal complex. As we employed EFA to provide data-driven results, we made no *a priori* predictions and did not constrain the model beyond our choice of ROIs.

2. Methods

The study groups, behavioral task, and fMRI acquisition and processing steps have been reported previously (Strakowski et al., 2011). The current methods are consistent with those reported in Strakowski et al. (2011) except a more comprehensive ROI mask is included in this report. While an ROI mask consisting of only eight regions was created to examine hypotheses regarding the ventrolateral emotional arousal pathway specifically in Strakowski et al. (2011) for the present study a more extensive and less model-driven 29-region mask was created as appropriate considering the exploratory and data-driven nature of EFA.

2.1. Participants

Bipolar participants (n = 40) were recruited from inpatient units and met DSM-IV criteria for bipolar I disorder, manic or mixed, with a Young Mania Rating Scale (YMRS; Young et al., 1978) score ≥ 20. Thirty-one (78%) of the bipolar participants were taking medications at the time of the scan, although they had been typically non-adherent before hospitalization. Of these, 23 (58%) received second generation antipsychotics, 11 (28%) anticonvulsants, and seven (18%) lithium. Demographically matched healthy control participants (n = 36) were recruited from the same communities. All participants were 16–50 years old and physically and neurologically healthy. Participants were excluded by substance dependence in the previous three months, medical or neurological illnesses that might influence brain function, contraindications to MRI or IQ < 80.

2.2. Instruments

Diagnoses were established using the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (First et al., 1995). Affective symptoms were rated using the YMRS and Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979). Additionally, premorbid intellectual function was estimated using the American Modification of the National Adult Reading Test (ANART; Grober and Sliwinski, 1991) or Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999).

2.3. Behavioral task, image acquisition and image processing

Participants were scanned at the University of Cincinnati's Center for Imaging Research using a 4.0 T Varian, Unity INOVA Whole Body MRI/MRS System. Participants completed two fMRI scans in which whole-brain volumes were acquired every 3-sec using a T2*-weighted gradient-echo echo-planar imaging pulse sequence during the CPT-END. As seen in Fig. 1, The CPT-END is a visual oddball paradigm in which 70% of cues are colored squares (imaging baseline condition), 10% are colored circles (targets), 10% are emotionally neutral pictures and 10% are emotionally unpleasant pictures (distractors). Each visual cue required a response; circles required a unique response (button 2), whereas squares and pictures required the same response (button 1). Imaging sessions included two runs of 158 visual cues each presented at 3 s intervals for 2.75 s each. A fixation cross was presented for 250 ms between cues. Each run of the CPT-END lasted approximately 9 min. Voxelwise fMRI data were processed using Analysis of Functional NeuroImages (AFNI) as previously described (Strakowski et al., 2011).

2.4. ROI creation and analysis

An ROI mask was created for 29 prefrontal-subcortical regions among a number of control regions (See Table 1). This mask was applied to each voxelwise fMRI activation map to obtain activation measurements within ROIs for each cue. Average percent signal change from all voxels within each ROI was extracted from each participant's results for each cue (i.e., circles, neutral and emotional pictures). We used the automatic anatomical labeling atlas in AFNI to create the ROIs (Tzourio-Mazover et al., 2002), the boundaries of which were based on previous reports (Jha and McCarthy, 2000; Yamasaki et al., 2002) and investigator experience.

2.5. Statistical analysis

Statistical analyses were performed using SAS v.9.4 (SAS Institute, Cary, NC, USA) and SPSS Statistics 21 (IBM, Armonk, NY, USA). Initially, EFA was used to assess patterns of covariation among regions without *a priori* constraints on the number or composition of latent factors. We elected to use EFA to determine whether a data-driven approach would produce a factor structure that accords with extant models of bipolar disorder functional neuroanatomy (Chen et al., 1995; Lane et al., 1998; Phan et al., 2002; Yamasaki et al., 2002). The number of relevant factors was selected based on the scree plot of eigenvalues from a principal components analysis, noting the number of eigenvalues that exceeded one since no obvious inflection point in the scree plot indicated the maximum number of factors to retain. For each factor solution, we performed varimax and promax rotation to verify whether loading patterns were robust to this choice and noted which regions had the highest loadings on each factor. We then focused on the solutions that appeared most plausible, in that they tended to group bilateral regions together and regions that serve putatively similar functions. Finally, we conducted analyses on observations of each cue type separately to verify whether or not similar factor structures held for each.

Once an acceptable EFA structure was identified with a relatively small number of interpretable factors and a small number of regions that cross-loaded on multiple factors, we estimated factor scores for each observation and performed mixed-effects analyses for each factor. We used analysis of variance (ANOVA) of percent signal change to identify specific effects of Group (bipolar, healthy), Cue (target, neutral, emotional) and their interaction within network ROIs adjusted for differences in task performance (i.e., target accuracy, the primary response variable).

3. Results

3.1. Demographic, clinical, and performance characteristics

As reported in Strakowski et al. (2011) healthy and bipolar groups were matched for age (30 ± 10 v. 30 ± 10 yrs.), sex (56 v. 60% women), ethnicity (17 v. 23% non-white) and IQ (111 ± 9 v. 108 ± 11 full-scale). The bipolar group had less education (15 ± 2 v. 14 ± 3, p = 0.04) but similar IQ scores. By definition, the bipolar group exhibited significantly more severe affective ratings, and they were significantly more likely to have a past-history of substance use disorder. On the CPT-END, the bipolar group responded significantly more slowly to distractors and less accurately to targets.