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Brief report

Contrasting and convergent patterns of amygdala connectivity in mania and depression: A resting-state study

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ABSTRACT

Background: wMania and depression in bipolar disorder (BP) manifest two extremes of aberrant emotional, physiologic and behavioral arousal states despite similarities in treatment response and neurocognitive deficits. We used resting-state functional magnetic resonance imaging (rsfMRI) to explore the common and unique abnormal functional connectivity underlying acute manic or depressed state in BP.

Methods: 18 Patients with bipolar mania (BM), 10 patients with bipolar depression (BD) and 28 healthy controls underwent resting-state functional magnetic resonance imaging scanning. Left and right amygdala seed-to-voxel based functional connectivity were assessed and compared among the three groups. The relationships between aberrant functional connectivity and the severity of clinical symptoms, number of episodes, illness duration were investigated.

Results: Compared to healthy controls, both BM and BD groups showed reduced functional connectivity between bilateral amygdala and inferior frontal gyrus (orbital), striatum, right lingual gyrus and posterior cerebellar lobe. Furthermore right amygdala–hippocampal connectivity was decreased in BD but increased in BM. No significant correlations were found between strength of abnormal functional connectivity and clinical characteristic in BD or BM.

Limitations: No euthymic subjects were recruited, and the patients in current study were all on medication.

Conclusions: The presence of substantial overlap in the pattern of disturbed connectivity between amygdala and frontal, striatal, lingual and cerebellar regions suggests mood state-independent dysconnectivity. The contrasting pattern of functional connectivity between right amygdala and hippocampus in BD and BM provides a novel lead to the probable mechanistic differences in these two extremes of mood states.

1. Introduction

Bipolar mania (BM) and bipolar depression (BD) manifest two seemingly opposite extremes of aberrant emotional, physiologic and behavioral arousal states in patients with bipolar disorder. Several studies have highlighted the vital role of prefrontal cortex and amygdala in the pathogenesis of bipolar disorder. Functional-MRI reveals state-dependent abnormalities in amygdala reactivity (Altshuler et al., 2005; Foland-Ross et al., 2012; Hariri, 2012) and trait-related orbitofrontal hypoactivation across manic, depressed, and euthymic episodes, indicating reduced frontal regulation of limbic reactivity in bipolar disorder (Hariri, 2012; Hariri et al., 2000). Despite the overall consistency, contrary results also exist, as inferior frontal cortex underactivation being seen in mania but not depression, while enhanced amygdala activation being independent of mood states as revealed by a recent meta-analysis (Chen et al., 2011). In part, this is due to a scarcity of studies that directly compare BM with BD and the interaction between mood states and task performance when various activation paradigms are employed.

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Among the several limbic regions, amygdala is increasingly being considered as central to the pathophysiology of bipolar disorder (Strakowski et al., 2012). Here we employ resting state fMRI in patients with acute mania or depression to investigate whether the frontolimbic connectivity, centred on amygdala, varies depending on the bipolar mood state.

2. Materials and methods

2.1. Subjects

30 medicated patients with bipolar disorder (18 with mania/hypomania; 10 with depression) were enrolled from the Mental Health Center in West China Hospital. The diagnosis was based on the Structured Clinical Interview for DSM-IV (SCID-IP). Subjects were rated on the Hamilton Depression Rating Scale (HDRS) and Young Mania Rating Scale (YMRS) at the time of the baseline scan. Patients with other mental diseases, nervous system diseases, severe physical diseases, personality disorders and abuse of alcohol and drugs were excluded. A total of 28 healthy controls, screened using SCID-NP, were also recruited from the same area. All participants were Han Chinese. This study complied with the Declaration of Helsinki and was approved by the Institutional Review Broad of West China Hospital, Sichuan University. All subjects provided written informed consent.

2.2. MRI data acquisition and image processing

Participants were scanned using a Signa 3.0-T scanner (General Electric, Medical Systems, Milwaukee, WI, USA). rsfMRI image processing was carried out using Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI (Yan and Zang, 2010). Data from 2 out of 30 patients were discarded due to excessive head motion (translational movement >1.5 mm and/or rotation $>1.5^{\circ}$). Scanning parameters and processing details are presented in Supplementary material.

2.3. Amygdala functional connectivity analyses: Seed-to-voxel analysis

Left and right amygdala masks were derived from the Wake Forest University Pick atlas software and applied to all preprocessed images after reslicing. The time courses averaged over all voxels of each amygdala were extracted. Pearson correlation coefficients (r) between time courses of each amygdala and all other voxels included within a gray-matter mask (generated from anatomical DARTEL-based grey matter segmentation of individual subjects, number of voxels=67,632) were calculated and transformed to Fisher's z scores to derive functional connectivity maps (FCM). One sample t-test was applied to test the connectivity of the right/left amygdala within the healthy controls group ($t>10$ and cluster >500 voxels) (FCM of amygdala in controls is shown in Fig. S1 in Supplementary material).

2.4. Group statistical analysis

Demographic and clinical data were analyzed using one-way ANOVA, independent two-sample t-test and χ^2 test with threshold $P<0.05$. Statistical tests on the functional connectivity maps of amygdala across groups were performed using a voxel-based, one-way analysis of covariance (ANCOVA) with sex, age and education years as covariates followed by post hoc, two-sample t-tests using SPM8. Correction for multiple comparisons was performed by Monte Carlo simulations (Ledberg et al., 1998) using the AFNI AlphaSim program (http://afni.nih.gov/afni/docpdf/AlphaSim.pdf). A corrected significance level of 0.05 was obtained with a combined $P<0.05$ and cluster size >3483 mm^3 for the ANCOVA analysis, and a combined $P<0.05$ and cluster size >621 mm^3 for right amygdala FCM and >918 mm^3 for left amygdala FCM for post hoc, two-sample t-tests analysis (which was conducted within a mask showing group FCM differences from the ANCOVA analysis) (Wang et al., 2014).

The correlation between functional connectivity strength and HDRS/YMRS scores were assessed using partial correlation controlling for sex, age and education years. We also evaluated the relationship between functional connectivity and the number of episodes/illness duration using Spearman correlation analysis in the two patient groups with a threshold $P<0.05$, uncorrected.

3. Result

3.1. Clinical characteristics

Table 1 shows demographic and clinical characteristics. No significant differences were found among the groups on age, sex, education years, disease duration, number of episodes and proportion of patients with psychotic features.

Table 1
Demographic and clinical characteristics of participants.

	Bipolar mania ($n=18$)	Bipolar depression ($n=10$)	Control ($n=28$)	$F/\chi^2/T$	df	P
Age in years	31.67 ± 6.98	30.90 ± 8.94	31.05 ± 7.53	0.87	2	0.92
Sex (male/female)	10/8	7/3	16/12	0.65	2	0.72
Years of education	13.22 ± 3.75	13.90 ± 1.79	13.34 ± 3.81	0.13	2	0.88
Number of episodes	3.61 ± 2.85	5.10 ± 3.28		−1.26	26	0.22
Type I/II	16/2	7/3				0.32
Number of patients with history of psychotic features, n (%)	3 (17)	3 (30)				0.63
Illness duration: months	62.89 ± 74.24	79.80 ± 78.59		−0.84	26	0.41
<1 years, n (%)	7(39)	2(20)				
1–4 years, n (%)	4(22)	2(20)				
>4 years, n (%)	7(39)	6(60)				
Medication						
Antipsychotics, n (%)	9(50)	4(40)				0.71
Lithium, n (%)	12(67)	6(60)				1
Valproate, n (%)	6 (33)	3(30)				1
Lamotrigine, n (%)	–	1(10)				0.36
YMRS[a]	24.61 ± 5.80	2.10 ± 2.96		13.58	25.92	0.00
HDRS[a]	3.67 ± 2.47	20.60 ± 3.63		−14.68	26	0.00

[a] Abbreviation: YMRS (Young Mania Rating Scale); HDRS (Hamilton Depression Rating Scale).