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Amygdalar volumetric correlates of social anxiety in offspring of parents with bipolar disorder

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ABSTRACT

The prevalence of social anxiety disorder is high in offspring of parents with bipolar disorder (BD) and anxiety may be a significant risk factor in these youth for developing BD. We compared social anxiety symptoms between BD offspring with mood symptoms (high-risk group for developing BD I or II: HR) and healthy controls (HC). We also explored the correlations between the amygdalar volumes and social anxiety symptoms in the HR group with high social anxiety scores (HRHSA) due to the potential involvement of the amygdala in the pathophysiology of both BD and social anxiety. Youth participating in the study included 29 h and 17 HC of comparable age and gender. To assess social anxiety symptoms, we used the Multidimensional Anxiety Scale for Children (MASC) social anxiety subscale. The HR group's MASC social anxiety score was significantly higher than that of the HC group. Among the 29 h, 17 subjects (58.6%) showed high social anxiety and they were classified as the HRHSA group. No significant difference was observed in amygdalar volume between the HRHSA and HC groups. However, there were significant negative correlations between amygdalar volumes and MASC social anxiety score in the HRHSA group. These findings have implications for the link between amygdalar structure and both anxiety and mood control. This link may serve to implicate high social anxiety as a risk marker for future BD development.

1. Introduction

Offspring of parents with bipolar disorder (BD) are at high risk for mood disorder, including BD, and also anxiety disorders (Birmaher et al., 2009). Among different anxiety disorders, the prevalence of social anxiety disorder is remarkably high, along with generalized anxiety disorder, in BD offspring (Birmaher et al., 2009; Duffy et al., 2013). Regardless of the high prevalence rate, social anxiety disorder itself is clinically important in that it may be a significant risk factor for developing mood disorders in BD offspring and for suicide in patients with BD (Duffy et al., 2013).

Several functional magnetic resonance imaging (fMRI) studies of social anxiety disorder have suggested that abnormal brain activity in the amygdala might be involved in the pathophysiology of social anxiety disorder (Birbaumer et al., 1998; Blair et al., 2008; Campbell et al., 2007; Cooney et al., 2006; Gentili et al., 2008; Guyer et al., 2008; Marcinkiewcz et al., 2009; Phan et al., 2006; Schneider et al., 1999; Shah et al., 2009; Stein et al., 2002; Straube et al., 2004; Straube et al., 2005; Yoon et al., 2007). Although, social anxiety pathophysiology has a particularly close relationship with the amygdala (Rauch et al., 2003), to our knowledge only three studies, all in adults, have examined the correlation between amygdalar volume and the degree of social anxiety symptoms, and the results of those studies were inconsistent (Irle et al., 2010; Machado-de-Sousa et al., 2014; Syal et al., 2012). As BD youth have been shown to have decreased amygdalar volumes (Blumberg et al., 2003; Chang et al., 2005; DelBello et al., 2004; Dickstein et al., 2005; Pfeifer et al., 2008), and as social anxiety symptoms are a risk factor for BD offspring for developing BD (Duffy et al., 2013), we hypothesized that social anxiety could be correlated with the amygdalar volumetric alterations in BD offspring.

Therefore, in this study we aimed to 1) compare social anxiety symptoms between BD offspring with subthreshold mood

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symptoms and who are thus at high risk for developing BD I or II (high-risk group: HR) and healthy controls (HCs), 2) compare amygdalar volume between the HR subjects with high social anxiety (HRHSA) and the HC group, and 3) explore the correlation between amygdalar volume and social anxiety symptoms in the HRHSA group.

2. Method

2.1. Subjects and assessment

The protocol was approved by the Stanford University Panel of Medical Research in Human Subjects. Families were recruited from the Stanford Adult Bipolar Disorders Clinic, the Stanford Pediatric Bipolar Disorders Program, physician referrals, local adult bipolar support groups, and the surrounding community and this study was conducted at the Stanford University Department of Psychiatry. Thirty-five BD offspring and 20 HCs were recruited for the initial assessment. Written and oral informed consent was obtained from at least one parent, and written and oral assent was obtained from the youth. Parental diagnosis of BD I or II was confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1995). When available, the other parent was also evaluated for psychopathology in this manner. Family history in all other relatives was obtained using the Family History–Research Diagnostic Criteria (FH-RDC) (Andreasen et al., 1977). Youth were assessed by the affective module of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (Geller et al., 2001) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime (K-SADS-PL). All subjects were evaluated either by a child psychiatrist (MS or KC) or trained masters-level research assistant (MH), who were aware of parental diagnosis. Inter-rater reliability was established by rating videotaped interviews, observing a trained rater, observing trained rater interviews, and performing interviews with observation by a trained rater (kappa $>$ 0.9). Current and lifetime DSM-IV diagnoses were ultimately determined by a board certified child psychiatrist (KC) based on personal interview, discussion with the research assistant, and written notes of responses to individual questions. We assessed current manic symptom severity using the Young Mania Rating Scale (YMRS) (Young et al., 1978) and depression symptom severity using the Children's Depression Rating Scale–Revised (CDRS-R) (Poznanski et al., 1985).

The inclusion criteria for the HR group were being 9–17 years of age, having a biological parent with bipolar I or II disorder and having subthreshold mood symptoms (YMRS $>$ 12 or CDRS $>$ 27). BD offspring with the following disorders or conditions were excluded from the HR group: BD I or II, pervasive developmental disorders, obsessive-compulsive disorder (OCD), panic disorder, post-traumatic stress disorder (PTSD), Tourette's syndrome, substance use disorders, or neurological conditions (such as a seizure disorder).After applying the inclusion and exclusion criteria, 29 BD offspring were included in the HR group. Within the HR group, those who showed higher social anxiety than the upper limit of normal (MASC social anxiety T score $>$ 55) were classified as the HRHSA group.

Healthy controls (HC) were similarly interviewed, and determined to have no DSM-IV diagnoses, were not taking psychotropic medications, had both parents without any psychiatric diagnosis (determined by the SCID), did not have a first- or second-degree relative with BD as determined by the FH-RDC, and were excluded with current YMRS scores greater than 8 or CDRS-R greater than 26. After applying these exclusion criteria, 17 youths were left for statistical analysis as the HC group.

2.2. Multidimensional anxiety scale for children (MASC) social anxiety subscale

To assess social anxiety symptoms, we used the MASC social anxiety scale (March et al., 1997). This scale is comprised of 9 items. A T-score of 45 to 55 is considered normal range. The MASC social anxiety subscale was found to be significantly predictive of the presence and severity of social anxiety disorder (Wei et al., 2014) and the validity of this scale is comparable to that of well-established measures of social anxiety disorder (Anderson et al., 2009).

2.3. MRI acquisition

Subjects were scanned on a 3T GE Signa scanner using a custom-built head coil. Functional MRI data were collected with thirty axial slices (4 mm thick,.5 mm skip), parallel to the axis of anterior and posterior commissures, covering the entire brain (FOV=20 cm, 64 $\times$ 64 matrix, inplane spatial resolution=3.43 mm). A spiral in-out pulse sequence 35 (Glover and Lai, 1998) used the following parameters: TR=2000 ms, TE=30 ms, flip angle=80° and one interleave. An individually calculated high-order shim was used to reduce B0 heterogeneity prior to acquiring the functional scans. To aid with normalization, a 3D high resolution T1-weighted image was acquired using a fast spoiled gradient recall (FSPGR) pulse sequence: TR/TI /TE=5.9/1.5/300 ms, flip angle=15°, field of view=22 cm, 256 $\times$ 256 matrix, inplane resolution=0.86 mm^2, and slice thickness=1.5 mm (Barnea-Goraly et al., 2014; Hoeft et al., 2014; Weems et al., 2013).

2.4. Image analysis

Subcortical volumetric segmentation of the amygdalas was performed with the Freesurfer image analysis suite, a semi-automated volumetric analysis pipeline which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Dale et al., 1999; Fischl et al., 2002). Before the Freesurfer analysis, we applied an image bias correction using SPM8 (http://www.fil.ion.ucl.ac.uk/spm), with a 30 mm full-width half-maximum Gaussian smoothing kernel and an extremely light regularization coefficient of.0001. Total tissue volume was also calculated using SPM8. All subcortical segmentations were visually inspected and manually edited for quality by one reviewer (SB). Four baseline subcortical segmentations required editing: 3 patients and 7 healthy controls. The analysis results in measures of total amygdala volume (left plus right hemispheres).These edits included removing non-brain voxels from the amygdala region of interest. ROI inspection and editing were performed blind to group. The final outputs of the FreeSurfer analysis are left and right amygdala volume.

2.5. Statistical analyses

The $\chi 2$ test and independent t test were conducted to compare the categorical and continuous variables to compare the demographic and clinical characteristics of both groups. Beta correlation coefficients, controlling for age, gender and total brain volume (TBV), YMRS score and CDRS-R score were calculated to examine the correlation between anxiety symptoms and the morphometric regions of interest (ROIs) by using linear regression. The statistical significance for all tests was set at $p < 0.05$. In cases in which it is assumed that statistical significance was not reached because the number of subjects was insufficient, we calculated effect sizes based on the difference in the means divided by the mean