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Amygdala enlargement in unaffected offspring of bipolar parents

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ABSTRACT

Background: Bipolar disorder (BD) is a devastating disorder with a strong genetic component. While the frontolimbic profile of individuals suffering from BD is relatively well-established, there is still disagreement over the neuroanatomical features of unaffected BD offspring.
Material and methods: Brain volumetric measures were obtained for 82 children and adolescents including 18 unaffected BD offspring (10.50 ± 3.37 years), 19 BD offspring suffering from psychiatric disorders (12.87 ± 3.28 years) and 45 healthy controls (HC-10.50 ± 3.37 years). Clinical diagnoses were established according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite. Profile analyses compared frontolimbic volumes across groups. Age, gender, testing site, ethnicity and intracranial volume were entered as covariates.
Results: The right amygdala was significantly larger in unaffected BD offspring compared to BD offspring with psychiatric disorders and HC. Volumes of striatal, hippocampal, cingulate, and temporal regions were comparable across groups.
Discussion: The size of the amygdala may be a marker of disease susceptibility in offspring of BD parents. Longitudinal studies are needed to examine rates of conversion to BD as related to specific pre-morbid brain abnormalities.

1. Introduction

Bipolar disorder (BD) is a devastating illness with deleterious functional and social consequences for both the affected individuals and their families (Mathers et al., 2008; Geddes and Miklowitz, 2013). This serious illness has a substantial genetic component (Craddock and Sklar, 2013) with heritability estimates ranging from 70% to 80% (Kieseppa et al., 2005; McGuffin et al., 2003). Alongside the genetic vulnerability to bipolar disorder in BD offspring the prevalence of mood disorders is in the range of 5%–67% compared to 0%–38% in offspring of healthy individuals (Rasic et al., 2013; Chang et al., 2003; DelBello and Geller, 2001; Duffy et al., 2013). In spite of the abundant research in BD, there is still no neural marker of genetic susceptibility for this serious disease.

Volumetric differences in brain areas involved in affect regulation and emotion processing, such as the prefrontal cortex, the amygdala, the striatum, the anterior cingulate, and the hippocampus, have been consistently regarded as potential markers for BD (Lim et al., 2013; Houenou et al., 2011; Sassi et al., 2004; Soares and Mann, 1997; Hajek et al., 2005; Brambilla et al., 2002; Strakowski et al., 2012; Sharma et al., 2003). Adolescents with BD have been found to exhibit smaller orbitofrontal regions, anterior cingulate and medial temporal regions compared to their healthy counterpart (Wilke et al., 2004). By contrast, knowledge of the neuroanatomy of BD offspring is limited. Two studies showed that unaffected BD offspring exhibit smaller hippocampus and parahippocampus volumes, as well as enlarged right inferior frontal gyrus compared to age-matched healthy children (Ladouceur et al., 2008; Hajek et al., 2012). By contrast, other studies found comparable prefrontal, striatal, amygdala, hippocampus and subgenual cortex volumes between affected and unaffected BD offspring and healthy controls (Hajek et al., 2009a, 2010, 2008a, 2008b, Singh et al., 2008). The inconsistencies in the current literature may also be associated to the variety of techniques (manual tracing, semi and fully automated brain segmentation with voxel-based morphometry) used to demarcate brain structures. As a result, the location of some of the brain regions may differ across studies.

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Other potential explanations for these mixed findings could be related to the heterogeneity of the mood disorders suffered by affected BD offspring, the severity of the mood symptoms and the illness duration.

The meaning of these brain abnormalities in relation to the genetic susceptibility for BD has yet to be characterized. While the volumetric reductions could be linked to neurotoxic mechanisms induced by BD (Chang et al., 2005) the enlargement in brain volume has been related to neuroprotective mechanisms (Singh and Chang, 2013). For instance, lithium-treated BD patients have been shown to have larger amygdala, hippocampus and posterior subgenual geniculate cortex volumes than unmedicated BD patients (Foland et al., 2008; Hajek et al., 2013; Mitsunaga et al., 2011). These findings suggest that lithium counteracts the loss of brain tissue associated with BD, possibly via mechanisms of neuroplasticity (Savitz et al., 2010). It becomes apparent that more research is needed to validate current findings and lead to relevant clinical recommendations.

The aim of this study was to compare the volumes of frontolimbic brain structures between affected and unaffected offspring of BD parents using the surface-based method Freesurfer. To the best of our knowledge, no published study has exploited this methodological approach to characterize the neuroanatomy of BD offspring. Based on previous findings we hypothesized that brain volumes would be smaller in BD offspring with psychiatric disorders compared to unaffected BD offspring and healthy individuals.

2. Methods and materials

2.1. Subjects

Participants were recruited from inpatient and outpatient clinics of the University of Texas Health Science Center at San Antonio (UTHSCSA) and at the University of North Carolina at Chapel Hill (UNC). The recruitment strategies were the same between the two clinical sites. The affected parent of participating offspring was required to complete a Structured Clinical Interview for DSM Disorders (SCID) to confirm the diagnosis of BD. If the diagnosis was confirmed, BD offspring were considered to be eligible to participate in the study. The study protocol was approved by the local Institutional Review board and informed consent was obtained from all the participants.

The sample ($N = 82$ children and adolescents) included 18 unaffected offspring of a BD parent (10.50 ± 3.37 years, 9 males), 19 BD offspring with psychiatric disorders (12.87 ± 3.28 years, 10 males), and 45 healthy controls (HC-12.73 ± 3.37 years, 23 males). The affected BD sample included children and adolescents with BD (Geddes and Miklowitz, 2013), BD not otherwise specified (NOS) (Chang et al., 2003), generalized anxiety disorder (GAD − 3), Adjustment disorder (Mathers et al., 2008), Major depressive disorder (Geddes and Miklowitz, 2013), Major Depressive Disorder Not Otherwise specified (Geddes and Miklowitz, 2013), and Attention Deficit Hyperactivity Disorder (ADHD - 2). 7 of the 19 affected BD offspring were on psychiatric medication (atypical antipsychotics, antidepressants, anticonvulsants, stimulants) at the time of assessment. Participating offspring and healthy controls were aged between 6 and 17 years, had no history of substance abuse in the previous 6 months and no current medical problems. BD offspring with psychiatric disorders included individuals suffering from BD, depression, mood dysregulation, anxiety and attention deficit hyperactivity disorder (ADHD). Healthy controls with a history of any Axis I disorder in first-degree relatives and use of psychoactive medication less than 2 weeks prior to the start of the study were excluded. Female participants of reproductive age underwent a urine pregnancy test. All participants underwent a urine drug screen to exclude illegal drug use.

2.2. Clinical measures

Psychiatric diagnosis was established using the Kiddie-Sads-Present and Lifetime Version (K-SADS-PL) interview (Kaufman et al., 1996) based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria, and confirmed subsequently in a clinical evaluation with a research psychiatrist. All parents who reported previous BD I diagnosis had their diagnosis ascertained by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders Axis I (SCID I) (First et al., 2012). The affective state was assessed with the Hamilton Depression Rating Scale (HAM-D) - 21 items and the Young Mania Rating Scale (YMRS) (Young et al., 1978). At enrollment participants were asked to complete the Pubertal Development Scale (Petersen et al., 1988), a self-report questionnaire comprising 5 statements rated on a 5-point Likert scale.

2.3. MRI data acquisition and preprocessing

All images were acquired on a Siemens 3 T Trio scanner using an axial three-dimensional, T1 weighted MP-RAGE (Magnetization Prepared Rapid Acquisition gradient echo) sequence (repetition time 22 msec; echo time 3 msec; flip angle 13 degrees, slice thickness 0.8 mm), while at UNC, images were obtained on a Siemens 3 T Allegra scanner by means of an axial three-dimensional, T1 weighted MP-RAGE sequence (repetition time 17.5 ms; echo time 4 msec; flip angle 8°, slice thickness 0.8 mm). Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite (Freesurfer v5.00, http://surfer.nmr.mgh.harvard.edu) (Dale et al., 1999; Fischl et al., 2002). Freesurfer estimates cortical and subcortical volumes via a whole brain segmentation procedure (Fischl et al., 2002). This method is based on an atlas containing probabilistic information on the location of structures (Fischl et al., 2002). The post-processing outputs for each subject were examined visually to ensure processing accuracy and image quality and no manual edits were required. Freesurfer volumetric measures have been shown to have satisfactory test-retest reliability across scanner manufacturers and across field strengths (Han et al., 2006). As part of the intersubject registration, Freesurfer uses a surface geometry approach which improves the reliability of the matching of homologous cortical regions. Furthermore, the intersubject registration is based on the white matter surface geometry rather than the gray matter. This approach excludes coregistration errors associated with the morphometric anomalies observed in BD, such as brain atrophy (Duffy et al., 2013).

2.4. Statistical analyses

Statistical analyses were performed using Statistical Analysis System Software, version 9.1 (SAS Institute, Cary, NC) and SPSS statistical software, version 10.0 (ISI ResearchSoft, Berkeley, CA). The Shapiro–Wilks test was conducted to check whether the data distribution approached normality. PROC POWER in SAS was used for power calculations. One-way analysis of variance (ANOVA), and chi-square of independence tests (χ^2) were conducted to compare demographic and clinical characteristics across groups. Profile analyses compared the volumes of 20 regions of interest (frontal and temporal poles, caudate, pallidum, putamen, amygdala, fusiform gyrus, parahippocampus, hippocampus, anterior cingulate gyrus) in the right and left hemisphere. The anterior cingulate gyrus included the caudal and rostral components of the