Psychiatry Research: Neuroimaging 251 (2016) 26–33

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Cortical thickness in symptomatic and asymptomatic bipolar offspring

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ARTICLE INFO

Article history:
Received 23 July 2015
Received in revised form
10 April 2016
Accepted 12 April 2016
Available online 13 April 2016

Keywords:
Bipolar disorder
Bipolar offspring
Cortical thickness
MRI
Biomarkers

ABSTRACT

Children of parents diagnosed with bipolar disorder are at greater risk for developing a variety of psychiatric disorders, however, the reasons remain unknown. The present study aimed to investigate gray matter integrity in high-risk bipolar offspring (HRO) and healthy offspring (HCO) using cortical thickness techniques. Here we examined healthy control offspring (HCO; n=20) and HRO with (n=17) or without (n=13) psychiatric symptoms. T1-weighted images were collected from all offspring, and cortical thickness and age-cortical thickness correlations were compared. HRO showed cortical thinning in superior and inferior temporal regions, supramarginal, and caudal and rostral middle frontal regions compared to HCO. When comparing HRO with and without psychiatric symptoms, we found cortical thinning in symptomatic offspring in the superior frontal and somatosensory related cortices. Age-thickness correlations showed a relatively consistent negative relationship in most regions in HCO, while the reverse was true for the HRO. These regions included parahippocampal, lateral orbitofrontal, and inferior temporal regions. Our study provides evidence of cortical thickness reductions among symptomatic and asymptomatic high-risk offspring during youth. Some of these alterations, found in regions of emotion processing and regulation, are evident only when associated with the presence of psychiatric symptoms.

1. Introduction

Bipolar disorder (BD) is a highly debilitating illness affecting 1–3% of the population globally (Guilbert, 2003; Merikangas et al., 2011). Individuals diagnosed with BD are left with more disability-adjusted life years lost than any other major neurological or health condition, including cancer (Goetzel et al., 2003; Guilbert, 2003; Merikangas et al., 2011). BD is highly heritable, with rates of approximately 0.8 in first-degree relatives (Birmaher et al., 2009; Craddock et al., 2005; DelBello and Geller, 2001; Kieseppa et al., 2004; McGuffin et al., 2003; Rasic et al., 2014; Wray and Gottesman, 2012). Offspring with a parent diagnosed with BD are at 10 times greater risk of developing BD (Birmaher et al., 2009; Dean et al., 2010; Hillegers et al., 2005), as well as 3–8 times more likely to develop other psychiatric disorders (Birmaher et al., 2010; Birmaher et al., 2009; Chang et al., 2000; Henin et al., 2005; Hillegers et al., 2005; Nurnberger et al., 2011). Moreover, BD offspring that present with symptoms of depression, anxiety and/or ADHD at a young age appear to be at highest risk for developing BD (Chang et al., 2006). Studying high-risk offspring (HRO) populations can help elucidate alterations in neuronal circuitry and biological markers of vulnerability that may exist before the onset of BD.

Structural abnormalities in adult and pediatric BD have been reported in regions of the prefrontal-striatal-limbic circuit; a circuit implicated in emotional processing and regulation, and is central to our understanding of the neuroanatomical model of BD (Almeida et al., 2009; Chang et al., 2005; Chepenik et al., 2008; Dickstein et al., 2005; Farrow et al., 2005; James et al., 2011; Martinot et al., 2014; Phillips et al., 2008; Selvaraj et al., 2012; Strakowski et al., 2012; Strakowski et al., 2005). Structural abnormalities in first-degree relatives are less consistent and have been previously reviewed (Fusar-Poli et al., 2012; Nery et al., 2013). Specifically, bipolar offspring have been observed to have increased volume in the right inferior frontal gyrus (Hajek et al., 2013), caudate (Hajek et al., 2009b), right amygdala (Bauer et al., 2014), and left parahippocampal/hippocampal regions (Ladouceur et al., 2008). Several studies also reported no significant differences in gray matter volumes (Hajek et al., 2008a, 2009a, 2010; Karchemskiy et al., 2011; Singh et al., 2008; Sugranyes et al., 2015). Inconsistencies in study findings may be attributed to differences in methodology, including difference in age, whether high-risk offspring presented with symptoms, and/or whether parents were diagnosed with BD type I or type II (Duffy et al., 2011).

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http://dx.doi.org/10.1016/j.pscychresns.2016.04.007
0925-4927/

The relationship between structure and age can be complicated. Adolescence is a time of complex developmental and maturational changes. Previous studies in healthy youth have found that not all structures follow the same developmental trajectory: for example the superior temporal gyrus has shown a linear decrease in volume over time, while the volumes of the postcentral and prefrontal regions follow an inverted quadratic relation over time (Gogtay et al., 2004; Huttenlocher, 1990; Lemaitre et al., 2012; Paus et al., 2008; Sowell et al., 2003). Adolescence is a particularly vulnerable developmental stage, where the emergence of many psychiatric disorders occur (Gogtay and Thompson, 2010; Paus et al., 2008). Comparing regional trajectories across healthy and at-risk populations may help to map the emergence of deficits over time.

Gray matter integrity can also be examined by investigating cortical thickness. Cortical thickness methods are thought to directly measure the number of cells within a microcolumn of the cortex (Panizzon et al., 2009; Rakic, 1988, 2007), and may be more sensitive to detecting subtle changes within the cortex that are associated with being at-risk. To our knowledge, only one study has reported cortical thickness differences in first-degree relatives, 16–25 years of age, of individuals diagnosed with BD (Papmeyer et al., 2015). This study reported reduced parahippocampal and fusiform regions in both first-degree relatives who went on to develop depression and first-degree relatives who remained unaffected (Papmeyer et al., 2015). Papmeyer et al. further observed differential reductions in the inferior frontal and precentral cortices as a function of group and time (Papmeyer et al., 2015).

1.1. Aims of the study

It was the aim of this study: (1) to evaluate cortical thickness in HRO compared to healthy control offspring (HCO), and (2) to compare age -cortical thickness correlations between offspring groups to give insight to potential regional developmental trajectories associated with risk. We further aimed to investigate cortical thickness patterns in relation to (i) the presence of psychiatric symptoms in these offspring or (ii) differences in parental psychopathology. While previous work supports minimal volume differences in HRO compared to HCO, some studies did demonstrate cortical thickening of the inferior frontal gyrus, and thinning of the subgenual cingulate, parahippocampal and fusiform gyri (Hajek et al., 2013, 2008b; Ladouceur et al., 2008; Papmeyer et al., 2015) in HRO. We expect cortical thickness measures to be more apt at detecting subtle changes in gray matter structure. Moreover, by investigating subsets of HRO, we predict these investigations might help to augment our ability to detect cortical thickness differences within HRO.

2. Methods

This study was conducted in accordance with the Hamilton Integrated Research Ethics Board. As recruitment of this population is difficult, we employed multiple avenues of advertisement. Parents of HRO were recruited through adult inpatient and outpatient mental health services at St. Joseph's Healthcare Hamilton, and Hamilton Health Services. Similarly, advertisements were placed in the waiting rooms of inpatient and outpatient children's services at McMaster Children's Hospital (McMaster University Medical Centre and Chedoke Hospital sites) in Hamilton, ON. HCO populations were recruited through the Psychology Department at McMaster University and local advertisements throughout the greater Hamilton area, Ontario, Canada. Written parental consent and child assent were obtained. All participants were compensated for their time and expenses.

2.1. Participants

Thirty high-risk bipolar offspring (HRO) and twenty age- and sex- matched healthy offspring (HCO) were recruited for this study. All participants were between 8 and 16 years of age. The HRO group was required to have at least one biological parent diagnosed with BD (type I or II), which was confirmed during the study. It was not an exclusion factor for HR offspring to have a diagnosis or symptoms of depression, anxiety and/or ADHD. Healthy offspring and their first-degree relatives were required to be free of any psychiatric disorders. Other exclusion criteria for all participants included the presence of a pervasive developmental disorder, a substance use disorder, a neurological condition, intelligence quotient (IQ) less than 70, or the presence of any contraindications for an MRI scan.

2.2. Psychological assessments

All participants underwent a structured diagnostic interview using the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime (K-SADS-PL) (Kaufman et al., 1997), during which raters were blind of parental diagnosis. This assessment was used to further classify HRO as partially affected (PAHRO: the presence of psychiatric diagnoses or symptoms at present of lifetime) or unaffected (UAHRO: the absence of any psychiatric disorders or symptoms, past or present). One biological parent for each participant was clinically assessed using the Structured Clinical Interview for the DSM-IV (SCID) (First et al., 2012) to confirm a diagnosis of BD (for the HRO group), or the absence of any psychiatric disorders (for the HCO group). Trained clinical nurses conducted all interviews and a board certified child psychiatrist (RBS) reviewed all diagnoses. IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999).

2.3. Data acquisition

Before undergoing an magnetic resonance imaging (MRI) scan, participants were introduced to a mock scanner to acquaint them to the sounds and procedures of the MR; shown to improve image quality by reducing movement during the scan (de Bie et al., 2010; Nora et al., 2009). Magnetic Resonance Images were collected at St. Joseph's Healthcare Hamilton using a General Electric 3 T whole-body short-bore scanner (Milwaukee, WI). High-resolution T1-weighted images were collected using a 3D spoiled gradient recall pulse sequence: repetition time = 10.8 ms, echo time = 2 ms, flip angle = 20, field of view = 240 mm, 256 × 256 mm matrix size, slice thickness = 1 mm, no skip.

2.4. Image processing

Cortical thickness analysis was conducted using FreeSurfer 5.1.0 software (http://surfer.nmr.harvard.edu). This program uses a surface-based analytical approach described previously (Dale et al., 1999; Fischl et al., 1999; Greve, 2011). Briefly, this semi-automated process involves the normalization and correction of signal intensity, removal of extra-cerebral voxels; also known as skull stripping, and the creation of triangular tessellated boundaries bordering the gray/white and pial surfaces. This meshwork was created through classification of voxels as white or gray matter. Those voxels containing both were classified as “boundary voxels” and were used for the calculation and smoothing of surface tessellations. At this point, boundaries were visually inspected and manual edits were performed in the case of misclassified gray or white matter. Once data passed careful visual inspection, it was normalized to a spherical template, and projected back onto a