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Morphology of the subgenual prefrontal cortex in pediatric bipolar disorder

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ABSTRACT

Objectives: The subgenual prefrontal cortex (SGPFC) is an important brain region involved in emotional regulation and reward mechanisms. Volumetric abnormalities in this region have been identified in adults with bipolar disorder but thus far not in pediatric cases. We examined the volume of this brain region in subjects with pediatric bipolar disorder (PBD) and compared them to healthy controls.
Methods: Fifty one children and adolescents (mean age ± SD; 13.2 ± 2.9 y) with DSM-IV PBD and 41 (mean age ± SD; 13.7 ± 2.7 y) healthy comparison subjects (HC) underwent 1.5 T structural magnetic resonance imaging (MRI) brain scans. We traced the SGPFC manually and compared SGPFC gray matter volumes using analysis of covariance with age, gender, and intracranial volume as covariates. We also examined the relationship of family history of affective disorders and medication status to SGPFC volumes.
Results: SGPFC volumes were not significantly different in PBD and HC subjects. However, exploratory analysis showed PBD subjects who had one or more first degree relatives with mood disorders ($n = 33$) had significantly smaller left hemisphere SGPFC compared to HC ($p = 0.03$ Sidak corrected). Current usage of a mood stabilizer was significantly associated with larger right SGPFC volume in PBD ($F = 4.82$, df = 1/41, $p = 0.03$).
Conclusion: Subjects with PBD and a close family history of mood disorders may have smaller left SGPFC volumes than HC. Mood stabilizing medication may also impact SGPFC size and could have masked more subtle abnormalities overall.

1. Introduction

The subgenual prefrontal cortex (SGPFC) is an area of the prefrontal cortex ventral to the genu of the corpus callosum (Drevets et al., 1997). Animal models show it has rich and bidirectional connections to important emotional regulatory regions including the amygdala, hippocampus, and parahippocampus (Musil and Olson, 1988). It also projects to subcortical regions including visceromotoral control neurons such as the nucleus of the solitary tract and spinal autonomic neurons (Musil and Olson,1988). These unique anatomical features suggest an important role in emotional regulation and mood disorders. In adults metabolic and volumetric deficits in the SGPFC are associated with depression and abnormal reward mechanisms (Drevets et al., 1997; Phelps et al., 2004). For example, in unipolar depression SGPFC exhibits abnormally decreased metabolism, small size, and volumetric changes with treatment predictive of response to anti depressive medication (Drevets et al., 1998b; Drevets et al., 1997; Mayberg et al., 2000). In bipolar disorder (BD), SGPFC glucose metabolism is suppressed in depressed states and activated in manic states suggesting an important role in the pathophysiology of this condition (Drevets et al., 1997).

Smaller SGPFC volumes are reported in adults with BD but have not been consistently replicated (Brambilla et al., 2002; Bremner et al., 2002; Drevets et al., 1998a). One recent examination of familial and sporadic cases of bipolar disorder did not demonstrate any differences in the SGPFC from controls (Hajek et al., 2009). This study examined both adults and adolescents in a single sample which could mask subtle differences given the variable stages of neurological development. For example the amygdala is shown to be smaller in

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bipolar adolescents compared to healthy controls but larger than normal in bipolar adults (Brambilla et al., 2008; DelBello et., 2004). In the only pure pediatric bipolar disorder (PBD) sample studied there were no significant volumetric deficits in this region seen (Sanches et al., 2005). This may be because such changes potentially only manifest in adulthood. Other possibilities include insufficient sample size in previous studies and potential heterogeneity in the PBD phenotype. Most structural neuroimaging studies to date have been underpowered (Kempton et al., 2008). One possible method to raise power is to increase the specificity of the phenotype. Phenotypic heterogeneity is especially problematic in PBD due to ongoing debate and uncertainty as to the specific characteristics that constitute PBD (Craney and Geller, 2003; Faedda et al., 2004; Kowatch et al., 2005; Leibenluft et al., 2003; Wozniak et al., 1995).

We attempted in this study to replicate and expand on earlier efforts to examine morphometric changes in the SGPFC in PBD subjects. We posited that given an enhanced sample we would be able to demonstrate similar volumetric brain changes in the SGPFC to those found in adults.

2. Methods

Child and adolescent subjects aged 7–17 years were recruited through the neuroimaging research programs at The University of Texas Health Science Center at San Antonio (UTHSCSA). The Institutional Review Board at UTHSCSA approved this study. Consent was obtained from the parents and written assent from the subjects for this study. All subjects were excluded on the basis of serious medical illness, mental retardation (IQ $<$ 70), developmental disorders, or substance abuse within the past 6 months. Inclusion criteria for PBD subjects included a current DSM-IV diagnosis of bipolar I, II, or NOS. Healthy comparison subjects were excluded on the presence of any current or past psychiatric disorder in themselves or in any first degree relative. There was no overlap in the sample population for this study and an earlier study reported by our group (Sanches et al., 2005).

2.1. Assessment

Trained clinicians administered the Kiddie Schedule for Affective Disorders and Schizophrenia for School-age Children – Present and Lifetime version (K-SADS-PL) to assess for diagnosis (Kaufman et al., 1997). These clinicians were all M.D. and Ph.D. level in training and prior to administering the KSADS-PL in this study they achieved 100% inter-rater agreement on diagnosis of bipolar disorder using this instrument with a board certified child and adolescent psychiatrist. Final diagnoses were made in a consensus conference with senior psychiatrists. Family history of psychiatric illness was obtained as part of the initial examination with a clinician administered form which screened for psychiatric illness in 1st and 2nd degree relatives. Any major affective disorder (major depressive disorder or BD) in a first degree relative was considered a positive screen for a family history of mood disorders. Sociodemographic status was assigned using the Hollingshead Socioeconomic Scale (Hollingshead Four Factor Index Total Score) (Hollingshead, 1975). IQ was assessed using the four subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI)(Wechsler, 2001). Pubertal status was assessed using the Peterson Puberty Scale (Peterson et al., 1988). Handedness was determined using the Oldfield Handedness Inventory (Oldfield, 1971).

2.2. MRI Acquisition

All subjects were scanned on a 1.5 T Phillips MRI scanner (Phillips Medical System, Andover, MA). Images were acquired using an axial three-dimensional T1-weighted fast field echo sequence (field of view 256 mm, view matrix 256 $\times$ 256, repetition time 24 ms, echo time 5 ms, flip angle 40°, slice thickness 1 mm).

2.3. Tracing

The brain was first segmented into gray matter, white matter and CSF using the semiautomated software Brains2 (University of Iowa)(Magnotta et al., 2002). All ROIs were then traced on the T1-weighted image and over-laid onto the segmented image to obtain gray matter volume (Figs 1 and 2).

Total brain volume (TBV) was also traced in coronal plane. Tracing began on the most anterior slice in which brain matter was visible and continued posteriorly including only brain matter and excluding CSF, dura matter, sinuses and brainstem, until brain matter was no longer visible. The base of the cerebellum served as the inferior border.

The SGPFC was manually traced in the coronal plane. The borders of the SGPFC were defined rostrally as gray matter of the first full gyrus below the corpus callosum and caudally to the slice anterior to where the internal capsule no longer divided the striatum. All of the tracings were performed by the same M.D. level technician who was blind to the diagnosis. This technician was trained in the method previously utilized by our group and described in detail in an earlier manuscript (Brambilla et al., 2002).

2.4. Data analysis

Statistical analyses were conducted using SPSS for Windows version 15.0 (SPSS Inc., Chicago, Ill.). Samples were compared on demographic variables using independent sample *t*-tests and chi square tests. SGPFC volumes of HC and PBD subjects were compared using analysis of covariance (ANCOVA) with age, gender, and total brain volume as covariates. We tested the effects of a narrowly defined BD diagnoses (excluding BD NOS), comorbid ADHD, medication and family history using ANCOVA and pairwise comparisons with Sidak correction for multiple comparisons where appropriate. All tests were two-sided with significance defined at the $p < 0.05$ level.

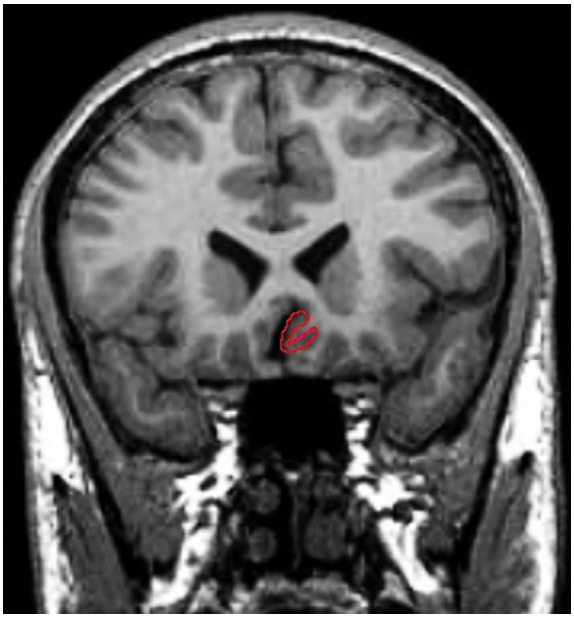

Fig. 1. Tracing of the SGPFC in the coronal plane.