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Neurostructural abnormalities in pediatric anxiety disorders

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ABSTRACT

Functional neuroimaging studies have consistently demonstrated abnormalities in fear and threat processing systems in youth with anxiety disorders; however, the structural neuroanatomy of these systems in children and adolescents remains largely unknown. Using voxel-based morphometry (VBM), gray matter volumes were compared between 38 medication-free patients with anxiety disorders (generalized anxiety disorder; social phobia; separation anxiety disorder, mean age: 14.4 ± 3 years) and 27 comparison subjects (mean age: 14.8 ± 4 years). Compared to healthy subjects, youth with anxiety disorders had larger gray matter volumes in the dorsal anterior cingulate and had decreased gray matter volumes in the inferior frontal gyrus (ventrolateral prefrontal cortex), postcentral gyrus, and cuneus/precuneus. These data suggest the presence of structural differences in regions previously implicated in the processing and regulation of fear in pediatric patients with anxiety disorders.

1. Introduction

Childhood and adolescence represent vulnerable periods during which many psychiatric disorders first emerge and during which time structural and functional brain changes are rapidly occurring (Alexander-Bloch, Raznahan, Bullmore, & Giedd, 2013; Giedd et al., 1996; Uddin, Supekar, Ryali, & Menon, 2011). It is during this developmental period that anxiety disorders, which are among the most common psychiatric disorders in youth (Beesdo et al., 2007; Costello et al., 1996; Merikangas et al., 2010) and affect 10% of children and adolescents, first manifest clinically (Costello et al., 1996). Importantly, pediatric anxiety disorders are associated with significant functional impairment (Kendall et al., 2010), increased risk of suicidal ideation and suicide attempt (Boden, Fergusson, & Horwood, 2007; Husky et al., 2012) and a greater likelihood of developing secondary mood, substance use and other anxiety disorders (Beesdo-Baum, Pine, Lieb, & Wittchen, 2012).

Among the anxiety disorders affecting children and adolescents, the most common are generalized anxiety disorder (GAD), separation anxiety disorder (SAD) and social anxiety disorder/social phobia (SoP) (Beesdo, Pine, Lieb, & Wittchen, 2010; Kessler et al., 2012). These disorders, which are often referred to as the "pediatric anxiety triad," commonly co-occur (Walkup et al., 2008), exhibit parallel clinical courses (Beesdo et al., 2010; Beesdo, Knappe, & Pine, 2009; Beesdo-Baum & Knappe, 2012) and share risk factors (Beesdo et al., 2010). Additionally, GAD, SAD and SoP respond to similar psychopharmacologic (*e.g.* selective serotonin reuptake inhibitors [SSRIs] and selective serotonin–norepinephrine reuptake inhibitors [SSNRIs]) (for review see Strawn, Sakolsky, & Rynn, 2012) and similar psychotherapeutic treatments (*e.g.* cognitive–behavioral therapy [CBT]) (Compton et al., 2010; Kendall et al., 2010; Verduin and Kendall, 2003). Because of the shared features of these disorders, most (Birmaher et al., 2003; RUPP, 2002; Walkup et al., 2008) but not all (Rynn, Siqueland, & Rickels, 2001; Rynn, Riddle, Yeung, & Kunz, 2007) treatment studies have involved patients with the "pediatric anxiety triad" rather than individual disorders proper.

In addition to the common clinical features and risk factors, the triad disorders, share neuropathophysiologic features (Blackford & Pine, 2012; Strawn, Wehry, et al., 2012). In this regard, the extant

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functional magnetic resonance imaging (fMRI) data from children and adolescents with GAD, SAD and SoP implicate dysfunction within central fear circuitry (Blackford & Pine, 2012). Specifically, most fMRI studies reveal abnormal activation of the amygdala in pediatric GAD (Beesdo, Lau, et al., 2009; Monk et al., 2008) and SoP (Guyer et al., 2008). Additionally, many studies suggest increased activation of the ventrolateral prefrontal cortex (VLPFC) in pediatric patients with GAD (Beesdo, Knappe, et al., 2009; Beesdo, Lau, et al., 2009; Guyer et al., 2008; McClure et al., 2007; Monk et al., 2006; Strawn, Bitter, et al., 2012) and SoP (Guyer et al., 2008) while some studies of pediatric patients with GAD have also noted increased activation of the anterior cingulate cortex (ACC) (McClure et al., 2007). Interestingly, in adolescents with GAD (and some co-morbid SoP or SAD), glutamatergic tone within the ACC is also linked to severity of anxiety symptoms (Strawn, Chu, et al., 2013) suggesting neurochemical and neurofunctional dysregulation within this key structure, which integrates both attentional and emotional processing (Yamasaki, LaBar, & McCarthy, 2002). More recently, several studies have demonstrated altered functional connectivity among these structures in adolescents with GAD and mixed anxiety disorders (McClure et al., 2007; Monk et al., 2008; Strawn, Bitter, et al., 2012). In short, these studies reveal altered functional connectivity between the amygdala and VLPFC in anxious youth (McClure et al., 2007; Monk et al., 2008; Strawn, Bitter, et al., 2012).

While many studies in pediatric GAD, SoP and SAD have demonstrated functional abnormalities in central fear circuits, relatively few structural studies have examined these systems. In one study of adolescents with GAD (many of whom had other triad disorders), De Bellis, Keshavan, and Shifflett (2002) observed increased right amygdala volumes in adolescents with GAD ($n = 12$) compared to healthy adolescents; however, in another cohort of anxious adolescents ($n = 17$), left amygdala volumes were decreased compared to healthy comparison subjects (Milham et al., 2005). Additionally, a study of adolescents with GAD, using voxel-based morphometry (VBM), found increased gray matter in the superior temporal gyrus, a structure which shares numerous connections with the amygdala (De Bellis et al., 2002). Finally, two very recent studies have utilized VBM to evaluate gray matter volumes in anxious youth (Mueller et al., 2013) and in adolescents with a primary diagnosis of GAD (Strawn, Wehry, et al., 2013). In the first, Mueller and colleagues (2013), using a region-of-interest (ROI) approach (ROIs: amygdala, hippocampus, insula and ACC), observed decreased gray matter volumes in adolescents with anxiety in the amygdala and right anterior hippocampus and noted increased gray matter volume in the right insula. In this study, a group-by-genotype effect for a $Val^{66}Met$ polymorphism in the brain-derived neurotropic factor gene was observed in the insula and ACC (Mueller et al., 2013). In another recent study of adolescents with GAD, in which we did not restrict our analyses to specific ROIs, we observed that, compared to healthy adolescents, youth with GAD had increased gray matter volumes in the right precuneus and right precentral gyrus and decreased gray matter volumes in the left orbital gyrus and posterior cingulate. However, we did not observe structural differences in the amygdala (Strawn, Chu, et al., 2013).

Given the prevalence and morbidity associated with the triad anxiety disorders in youth and rapidly accumulating data regarding the functional neurocircuitry of these conditions, understanding their structural basis may clarify potential pathogenic mechanisms and may inform the development of more effective or perhaps novel treatments (Strawn, Sakolsky, et al., 2012). With this in mind, in the present study, gray matter volumes were compared between children and adolescents with GAD, SAD and SoP and healthy comparison subjects using VBM (Ashburner & Friston, 2000). Of note, the current cohort represents a completely independent sample from the GAD and healthy control groups previously reported (Strawn, Chu, et al., 2013). We hypothesized that structural abnormalities would be present in the amygdala and in regions that functionally modulate the amygdala (*e.g.* ACC, ventrolateral prefrontal cortex and medial prefrontal cortex).

2. Materials and methods

2.1. Participants

Participants included 38 children and adolescents, aged 7–19 years of age (mean age 14.4 ± 3.0 years; 28 female) with a *DSM-IV* primary diagnosis of GAD, SoP, and/or SAD and 27 matched healthy controls (14.8 ± 3.9 years; 15 female). There is no overlap in the current sample with the sample previously investigated by Strawn and colleagues (Strawn, Chu, et al., 2013). All patients and controls were medication-free at the time of testing, and were recruited via referrals from the University of Michigan Pediatric Anxiety Disorders Clinic and from advertisements posted in the local community. Study participants were administered the Kiddie-Schedule for Affective Disorders-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997) by masters level, clinical social workers and diagnoses were confirmed by a board-certified psychiatrist (KLP). Additionally, anxiety symptom severity was assessed with the Multidimensional Anxiety Scale for Children (MASC, March, Parker, Sullivan, Stallings, & Conners, 1997) and the Pediatric Anxiety Rating Scale (PARS, RUPP, 2002); social anxiety symptoms were assessed with the Liebowitz Social Anxiety Scale-Child and Adolescent Version (LSAS-CA, Masia-Warner et al., 2003) and depressive symptoms were evaluated with the Children's Depression Inventory (CDI, Kovacs, 1985). Exclusionary criteria for patient participants were: an IQ < 70, a lifetime diagnosis of bipolar disorder, schizophrenia, or a pervasive developmental disorder, and current diagnosis of major depressive disorder. Healthy comparison subjects were free of lifetime diagnosis of *DSM-IV* Axis I disorders. Legal guardians and participants provided written, informed consent and assent, respectively and this study was approved by the University of Michigan Institutional Review Board.

2.2. Image acquisition and analysis

A 3.0 T GE Signa Scanner (General Electric; Milwaukee, Wisconsin, USA) with a GE quad head coil was used to acquire high resolution, T1-weighted volumetric anatomical scans (3D spoiled-gradient echo sequence, 9 ms repetition time, 1.8 ms echo time, 500 ms inversion time, 15° flip angle, 256×256 matrix, 256 mm field of view; 124 slices, 1.2 mm slice thickness). Whole-brain structural data were processed using the VBM toolbox (http://dbm.neuro.uni-jena.de/vbm/) in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) running on the MATLAB (Math Works, Natick, MA) platform. A customized tissue probability map was generated with the Template-O-Matic (TOM8) Toolbox (Wilke, Holland, Altaye, & Gaser, 2008) using the matched-pairs approach to accurately reflect the specific brain morphometry for the age and gender of the pediatric population in this study. The anterior commissure was identified in each image and images were uniformly aligned to provide optimal starting estimates for subsequent spatial normalization. T1-weighted images were spatially normalized and segmented into gray matter, white matter, and cerebrospinal fluid (CSF) according to the unified segmentation model. Segmented images were resampled to a $1.5 \times 1.5 \times 1.5\ mm^3$ resolution. Voxel values from the gray matter and white matter images were subsequently multiplied by the Jacobian determinants of the normalization matrix to produce modulated data accounting for global and regional differences in the absolute amount (volume) of gray matter (Ashburner & Friston, 2000). To ensure data quality, orientations of the native images were inspected, guided by boxplots