



Cortical surface anatomy in pediatric patients with generalized anxiety disorder



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ABSTRACT

Background: It is established that pediatric patients with generalized anxiety disorder (GAD) exhibit functional abnormalities and altered gray matter volumes in neural structures that subserve emotional processing, yet there are no data regarding the surface anatomy of the cerebral cortex in youth with GAD. **Methods:** Using an automated surface-based approach (FreeSurfer), cortical thickness was assessed node-by-node over the entire cerebral cortex in adolescents with GAD and no co-occurring major depressive disorder ($n = 13$) and healthy subjects ($n = 19$).

Results: Compared with healthy adolescents, youth with GAD exhibited increased cortical thickness in the right inferolateral and ventromedial prefrontal cortex (*i.e.*, inferior frontal gyrus), the left inferior and middle temporal cortex as well as the right lateral occipital cortex. No relationships were observed between cortical thickness and the severity of anxiety symptoms in the significant regions that were identified in the vertex-wise analysis.

Conclusions: These findings suggest that, in adolescents with GAD, abnormalities in cortical thickness are present in an ensemble of regions responsible for fear learning, fear extinction, reflective functioning (*e.g.*, mentalization), and regulation of the amygdala.

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1. Introduction

Anxiety disorders are among the most common psychiatric conditions affecting children and adolescents (Beesdo, Pine, Lieb, & Wittchen, 2010) and are associated with an increased risk of suicidality (Foley, Goldston, Costello, & Angold, 2006; Jacobson, Muehlenkamp, Miller, & Turner, 2008), and also increase the likelihood of other mood and anxiety disorders later in life (Beesdo-Baum, Pine, Lieb, & Wittchen, 2012). Of the anxiety disorders, generalized anxiety disorder (GAD) is among the most prevalent (Beesdo et al., 2010) in the pediatric population. However, only recently has the neuroanatomy of GAD been systematically evaluated.

Functional neuroimaging studies of pediatric patients with GAD suggest dysfunction within the anterior limbic network, a collection of subcortical and cortical structures involved in the modulation and expression of complex affective states (Beesdo et al., 2009; McClure et al., 2007; Monk et al., 2006, 2008; Strawn, Wehry, et al., 2012; Strawn et al., in press). Specifically, this research suggests hyperactivation of amygdala (Beesdo et al., 2009; Monk et al., 2008) as well as ventrolateral prefrontal cortex (Beesdo et al., 2009; Guyer, Lau, & McClure-Tone, 2008; McClure et al., 2007; Strawn, Bitter, et al., 2012) and ventromedial prefrontal cortex (Strawn, Bitter, et al., 2012) in addition to altered functional connectivity among these structures (McClure et al., 2007; Strawn, Bitter, et al., 2012). In parallel, neurostructural studies of the circuits that subserve emotional processing have identified abnormalities in structures within (De Bellis et al., 2000, 2002; Milham et al., 2005; Mueller et al., 2013) and beyond the anterior limbic network (Strawn, Wehry, et al., 2013). For example, the superior temporal gyrus (STG), a region which is dense with afferent projections from the amygdala, was shown to have increased gray and white matter volumes in adolescents with anxiety disorders (De Bellis

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et al., 2002). Additionally, the amygdala, in some studies exhibits increased gray matter volumes (De Bellis et al., 2000; Milham et al., 2005), while conflicting studies suggest reduced gray matter volumes (Mueller et al., 2013) in adolescents with GAD compared to healthy controls. Other areas in which gray matter volumes have been shown to be increased in youth with anxiety disorders include the right insula (Mueller et al., 2013) as well as the right precuneus, right precentral gyrus and orbitofrontal cortex (Strawn, Wehry, et al., 2013). Additionally, the right anterior hippocampus (Mueller et al., 2013), left orbitofrontal cortex, and posterior cingulate cortex (Strawn, Wehry, et al., 2013) have been shown to exhibit decreased gray matter volumes in anxious youth compared to healthy controls. Importantly, these voxel-based morphometry studies and “tracing” studies may reflect multiple changes in gray matter density, as well as cortical surface area and cortical folding, so interpretation can be problematic (Hutton, Draganski, Ashburner, & Weiskopf, 2009). Additionally, voxel-based morphometry measurements are highly dependent on the degree of smoothing (Jones, Symms, Cercignani, & Howard, 2005) as well as the templates which are used for normalization (Bookstein, 2001).

As a solution to the inherent limitations of these voxel-based morphometry and “tracing” techniques that measure *volume* rather than *thickness*, surface-based cortical morphology analyses have been recently employed to evaluate cortical structure and may provide improved signal-to-noise ratios compared with voxel-based morphometry (Kuhn, Schubert, & Galliant, 2010). However, it should be emphasized that these cortical thickness measures only permit evaluation of the cortical surface and thus do not allow analysis of “non-cortical” (e.g., subcortical) structures such as the amygdala, hippocampus, etc. Nonetheless, given that patterns of cortical thickness are regionally specific and determined early in development (Fischl & Dale, 2000; Rosas et al., 2002), an understanding of cortical thickness in pediatric patients with GAD could be helpful in understanding the neurostructural basis for the neurofunctional abnormalities observed in pediatric patients with GAD (for review see Strawn, Wehry, et al., 2012). In this study, we sought to examine differences in cortical thickness in youth with GAD and age- and sex-matched healthy control subjects and hypothesized that differences in cortical thickness would be observed in the ventromedial and ventrolateral prefrontal cortex consistent with functional abnormalities.

2. Methods

2.1. Subjects

Patients and their parents/legal guardians provided written assent and consent, respectively, after study procedures were fully explained; this study was approved by the University of

Cincinnati Institutional Review Board. Diagnoses were established or excluded using the Kiddie Schedule for Affective Disorders Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997) and were supplemented by unstructured clinical interviews with a child & adolescent psychiatrist. Additionally, GAD patients were excluded for an IQ <70, a current mood disorder (e.g., major depressive disorder), a lifetime diagnosis of substance dependence, posttraumatic stress disorder, bipolar disorder, psychosis, obsessive compulsive disorder or a pervasive developmental disorder. Healthy subjects were free of any DSM-IV Axis I psychiatric conditions, and were not receiving psychotropic medication at the time of the study. All participants were excluded by a history of any unstable medical or neurologic illness, or any contraindication to participating in a MRI scan.

Thirteen patients with primary diagnoses of GAD (7 male, mean age 14 ± 2 years) were recruited from ongoing outcome studies or a cross-sectional study of the neurophysiology of GAD (Strawn, Bitter, et al., 2012) and 19 healthy subjects (6 male, mean age 14 ± 2 years) were recruited from the local community by word of mouth. Of note, 10 of the GAD patients examined in the current study were evaluated in an fMRI study of adolescents with GAD (Strawn, Bitter, et al., 2012) and in a voxel-based morphometry study of GAD (Strawn, Wehry, et al., 2013). GAD patients and healthy subjects did not statistically differ in age, sex, pubertal status, race and IQ (Table 1); however patients with GAD had higher CDRS-R scores than healthy adolescents ($p = 0.003$), likely related to symptomatic overlap between items on this inventory (e.g., irritability, physical symptoms, sleep disturbance, excessive fatigue, physical complaints) and core symptoms of GAD. Additionally, no patient or healthy control subject had a co-morbid mood disorder, although 4 of the GAD patients had co-morbid anxiety disorders (Table 1). Finally, no patients (or healthy control subjects) were receiving psychotherapy or psychopharmacologic treatment at the time of scanning and no psychoactive medications had been taken for ≥ 5 half-lives.

2.2. Assessments and analyses

All subjects were evaluated as previously described (Strawn, Bitter, et al., 2012; Strawn, Wehry, et al., 2013; Strawn, Chu, et al., 2013): handedness was assessed using the Crovitz Handedness Questionnaire (Crovitz & Zener, 1962), pubertal development was assessed with the Duke Tanner stage self-assessment (Duke, Litt, & Gross, 1980) and IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI). In addition, healthy subjects were assessed using the Family History Research Diagnostic Criteria (Andreasen, Endicott, Spitzer, & Winokur, 1977); no healthy subject was included if there was a family history of mood,

Table 1
Comparison of demographic and clinical variables among adolescents with generalized anxiety disorder (GAD) ($n = 13$) and healthy subjects ($n = 19$).

Variable	Healthy controls ($n = 19$)	GAD patients ($n = 13$)	Significance
Age, mean \pm SD (years)	14 ± 2	14 ± 2	$p = 0.3$
Sex, males, n (%)	6 (32)	7 (54)	$p = 0.21$
Race, white, n (%)	18 (89)	12 (92)	$p = 0.79$
Tanner growth, mean ^b	3.8	3.3	$p = 0.2$
Tanner pubic, mean ^b	3.8	3.3	$p = 0.32$
Full Scale Intelligence Quotient ^b	110 ± 8	108 ± 9	$p = 0.55$
Children's Depression Rating Scale-Revised Score (CDRS) ^b	17.5 ± 0.7	35.5 ± 13.6	$p = 0.001$
Pediatric Anxiety Rating Scale Score ^a		21.5 ± 3.3	
Anxiety disorders	0	4	
Social phobia	0	3	
Separation anxiety disorder	0	0	
Specific phobia	0	1	

^a Non-clinical trials scoring method.

^b IQ and Tanner scores were not obtained for 2 healthy control subjects. PARS scores and CDRS scores were not obtained for 2 GAD subjects.

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