Archival Report

Biological Psychiatry: CNNI

Altered Development of Amygdala-Anterior Cingulate Cortex Connectivity in Anxious Youth and Young Adults

Autumn Kujawa, Minjie Wu, Heide Klumpp, Daniel S. Pine, James E. Swain, Kate D. Fitzgerald, Christopher S. Monk, and K. Luan Phan

ABSTRACT

BACKGROUND: Development of corticoamygdala circuitry underlies the maturation of emotion processing and regulation, and age-related changes in amygdala connectivity with anterior cingulate cortex (ACC) have been shown to mediate normative developmental decreases in anxiety. It remains unclear whether developmental changes in this circuitry relate to pathological anxiety in youth. The current functional magnetic resonance imaging study addresses this question by examining amygdala functional connectivity in anxious and healthy individuals spanning the developmental period from childhood through adulthood.

METHODS: Youth and young adults (ages 7–25) with current anxiety disorders (n = 57) and healthy comparison subjects (n = 61) completed a functional magnetic resonance imaging emotional face processing task known to elicit amygdala activation in youth and adults. We examined interaction effects of anxiety group and age on amygdala connectivity with frontolimbic regions during processing of happy, angry, and fearful faces.

RESULTS: Anxiety interacted with age to predict amygdala-ACC connectivity across emotional faces. Among healthy youth and young adults, age was negatively related to connectivity. In contrast, age was positively associated with amygdala-ACC connectivity in the anxious group. Group effects were also observed on amygdala connectivity with midcingulate and middle frontal gyri. Effects of anxiety and age on amygdala activation were not significant.

CONCLUSIONS: Results indicate that anxiety is characterized by altered patterns of age-related changes in amygdala connectivity during emotional face processing. Positive associations between age and amygdala-ACC connectivity among anxious youth and young adults may indicate failure to establish early bottom-up connections in childhood and/or less top-down regulation of the amygdala into adulthood.

Keywords: Amygdala, Anterior cingulate cortex, Anxiety, Development, Emotional faces, Functional connectivity

http://dx.doi.org/10.1016/j.bpsc.2016.01.006

Anxiety disorders are among the most prevalent disorders in youth and are characterized by abnormalities in emotion processing (1,2), raising the importance of identifying the neural pathology underlying these deficits (3). Emotion processing involves the amygdala, which signals the presence of threat and salient information, as well as the prefrontal cortex (PFC) and anterior cingulate cortex (ACC), which appraise stimuli and monitor and regulate emotion (4–6). There is evidence of a mismatch in the development of corticoamygdala circuitry, with the amygdala maturing earlier in childhood or adolescence and the PFC continuing to develop into adulthood (7,8). That is, systems involved in identifying emotional information develop relatively early, with regions involved in top-down regulation of emotions maturing later.

Corticoamygdala circuitry appears to be disrupted in anxiety disorders (6,9–11), particularly when processing threatening information. For example, anxiety disorders in youth (including generalized anxiety disorder, social anxiety disorder, and panic disorder) have been associated with greater amygdala reactivity to threatening faces (12–16). In addition, anxious youth exhibit abnormalities in frontal regions during processing of emotional information, including enhanced activation in ventrolateral PFC and ACC in response to threatening faces, possibly indicating the need for greater activation in these regions to regulate emotional responses (13,14,16).

Along with activation, amygdala interactions with the PFC and ACC are particularly important for emotional reactivity and regulation (9). Recent work has identified age-related differences in amygdala-ACC connectivity that may underlie the development of emotion regulation abilities. In a sample of 4- to 22-year-old healthy participants, connectivity between the amygdala and ACC during viewing of fearful faces decreased with age, such that young children showed positive connectivity while adolescents and adults showed

ISSN: 2451-9022

negative connectivity, possibly indicating greater bottom-up signaling of the ACC by the amygdala in childhood and greater top-down regulation of the amygdala into adulthood (17). In addition, development of amygdala-ACC connectivity mediated associations between age and normative developmental declines in separation anxiety (17). Though there is evidence of abnormal amygdala connectivity in youth with clinical anxiety (14,18), age-related differences in amygdala-ACC connectivity have yet to be examined in anxious youth, an important direction for understanding the emergence of atypical brain development.

In contrast to the literature on amygdala connectivity with the ACC, there is evidence of normative developmental increases in amygdala connectivity with other frontal regions. For example, a study of 10- to 24-year-olds found age-related increases in amygdala and hippocampus connectivity with orbitofrontal cortex and ventrolateral PFC during emotional image viewing (19). In addition, in a study of 8- to 18-year-olds, healthy youth exhibited age-related increases in amygdala connectivity with ventrolateral PFC during threat processing, while youth with posttraumatic stress disorder exhibited age-related decreases in connectivity (20).

Given evidence of developmental changes in amygdala connectivity with frontal regions, we sought to compare age-related differences in youth and young adults (ages 7 to 25 years) with clinical anxiety to healthy comparison subjects. Participants included 61 healthy control subjects and 57 youth and young adults with primary diagnoses of generalized anxiety disorder, social anxiety disorder, or separation anxiety disorder, which tend to have earlier ages of onset than other anxiety disorders and often co-occur (21). Because faces are developmentally appropriate and relevant to adaptive social behavior, we used a functional magnetic resonance imaging emotional face matching task known to elicit amygdala activation in both youth and adults (18,22). We hypothesized that age would be negatively related to amygdala-ACC connectivity in healthy youth and young adults, consistent with prior work (17,23), but this developmental process would be disrupted in anxiety. We evaluated neural responses to angry, fearful, and happy faces to evaluate whether effects are apparent for broad emotion processing or threat processing specifically. Additional analyses examined age and group effects on amygdala connectivity with other frontolimbic regions.

METHODS AND MATERIALS

Participants

The initial sample included 136 participants, but 18 participants were excluded for movement (see Preprocessing), leaving a final sample of 57 anxious participants and 61 healthy comparison participants. The sample was 57.6% Caucasian, 13.6% African American, 12.7% Latino, and 16.1% Asian or Pacific Islander. Procedures were approved by the Institutional Review Boards at University of Illinois at Chicago and University of Michigan, and participants were recruited at both sites (Table 1). Adult participants and parents of children under the age of 18 provided written informed consent, and verbal assent was obtained from minors. We previously reported on typical age-related changes in brain activation and amygdala connectivity during emotional face processing in this sample of healthy volunteers (23) and on neural processing of emotional faces in separate studies of anxious youth (18) and young adults (24,25). In this article, we extend this work by combining pediatric and adult samples to examine age-related changes in amygdala connectivity in anxiety.

Table 1. Demographics and Current Diagnoses for Each Group

	Anxiety Disorder (n = 57)		Healthy Control (n = 61)	
	Mean or %	SD or n	Mean or %	SD or n
Age	17.14	4.81	16.69	5.06
Female	59.6%	34	57.4%	35
Caucasian	56.1%	32	59.0%	36
African American	12.3%	7	14.8%	9
Asian or Pacific Islander	17.5%	10	14.8%	9
Hispanic/Latino	14.0%	8	11.5%	7
Site (scanned at UM)	66.7%	38	57.4%	35
Social Anxiety Disorder	80.7%	46	0%	0
Generalized Anxiety Disorder	50.9%	29	0%	0
Separation Anxiety	12.3%	7	0%	0
Depressive Disorder	5.3%	3	0%	0
Other Comorbid Anxiety Disorder	21.1%	12	0%	0

UM, University of Michigan.

Diagnostic Assessment

Participants were screened for current and lifetime psychopathology using a semistructured interview administered by master's-level or doctoral-level clinicians: the Kiddie Schedule of Affective Disorders and Schizophrenia (26) for children and adolescents and the Structured Clinical Interview for DSM-IV (27) for adults. Anxious participants had current primary diagnoses of generalized anxiety disorder, social anxiety disorder, or separation anxiety disorder. Participants with secondary comorbid anxiety or depressive disorders were eligible, but those with histories of bipolar disorder, schizophrenia, intellectual disability, or pervasive development disorders, as well as those with current substance use disorders, severe current depression, or current suicidal ideation, were excluded. Participants were not taking psychotropic medications or participating in psychotherapy at the time of the study.

Anxiety Symptoms

Social Anxiety Severity. As the majority of the anxious group met criteria for current social anxiety disorder, children and adolescents completed the interviewer-administered Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA) (28), and adults completed the adult version of the LSAS (29). Separate Z scores were computed for each version to compare relative level of anxiety severity across both measures. LSAS data were missing for two healthy comparisons.