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Age-related volumetric change of limbic structures and subclinical anxious/depressed symptomatology in typically developing children and adolescents

Matthew D. Albaugh[a,*], Tuong-Vi Nguyen[b,c,d], Simon Ducharme[b,d], D. Louis Collins[d], Kelly N. Botteron[e], Nicholas D'Alberto[a], Alan C. Evans[d], Sherif Karama[d,f,1], James J. Hudziak[a,1], The Brain Development Cooperative Group

[a] Vermont Center for Children, Youth, and Families, Department of Psychiatry, University of Vermont College of Medicine, Burlington, VT, USA
[b] McGill University Health Centre, Department of Psychiatry, McGill University, Montreal, QC, Canada
[c] McGill University Health Centre, Department of Obstetrics-Gynecology, McGill University, Montreal, QC, Canada
[d] McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, QC, Canada
[e] Mallinckrodt Institute of Radiology, Washington University in St. Louis, School of Medicine, St. Louis, MO, USA
[f] Douglas Mental Health University Institute, McGill University, Montreal, QC, Canada

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ABSTRACT

Objective: To investigate the extent to which subclinical variation in anxious/depressed psychopathology is associated with volume and age-related volumetric change of limbic structures in a longitudinal sample of healthy youths.
Methods: Linear mixed-effects models were used to analyze longitudinal behavioral and neuroimaging data (up to 3 data points per subject, collected at 2 year-intervals) in 371 typically developing youths, from 4 to 18 years of age (196 females; 723 MRIs). Volumetric measures were obtained using a validated segmentation method. The best-fit model (cubic, quadratic, or first-order linear) was determined for the effect of age on amygdalar and hippocampal volume (adjusted for total brain volume). Next, amygdalar and hippocampal volumes were regressed against Child Behavior Checklist Anxious/Depressed (A/D) scores. Age-by-A/D and sex-by-A/D interactions were tested.
Results: Analyses revealed age-related linear and quadratic volumetric change in the amygdalae and hippocampi, respectively. A/D was positively associated with total amygdalar volume ($p = 0.045$), independent of age and sex. Age-by-A/D and sex-by-A/D interactions were not associated with amygdalar or hippocampal volume.
Conclusions: Results suggest that amygdalar structure is tied to A/D among typically developing youths, independent of age and sex. Developmental trajectories of amygdalar and hippocampal volume were not associated with subclinical anxiety. Taken together, increased amygdalar volume may serve as a significant marker of anxiety, regardless of developmental phase.

1. Introduction

Limbic regions, including the amygdalae and hippocampi, have long been implicated in the mediation of emotional processes, including aspects of fear and anxiety (MacLean, 1949; Papez, 1995). The amygdalae, in particular, are central to neural circuits that have evolved to detect potential threats as well as respond to salient stimuli in the environment (LeDoux, 1996). In animal studies, early life stress has been shown to produce structural and functional alterations in these brain regions, as well as concomitant changes in anxiety-like behavior (Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002; Mitra, Jadhav, McEwen, Vyas, & Chattarji, 2005; Vyas, Jadhav, & Chattarji, 2006; Mitra and Sapolsky, 2008). Non-human primate imaging studies have revealed that metabolic activity in the amygdala and hippocampus is heightened in young animals with anxious temperament (Fox, Shelton, Oakes, Davidson, & Kalin, 2008). Human neuroimaging studies have reported links

* Corresponding author at: The Vermont Center for Children, Youth and Families, University of Vermont College of Medicine, University Health Center campus, 1 South Prospect Street, Burlington VT 05401, USA.
E-mail address: malbaugh@uvm.edu (M.D. Albaugh).
[1] These authors shared senior authorship.

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between amygdalar volume and anxiety in healthy adults (Holmes, Lee, & Hollinshead, 2012; Baur, Hanggi, & Jancke, 2012; Redlich, Grotegerd, & Opel, 2015; Clauss, Seay, & VanDerKlok, 2014), as well as in adults with clinically significant anxiety (Machado-de-Sousa, Osorio Fde, & Jackowski, 2014; Weber, Killgore, & Rosso, 2013; Schienle, Ebner, & Schafer, 2011; Etkin, Prater, Schatzberg, Menon, & Greicius, 2009). A number of neuroimaging studies have tested the association between limbic structure and anxiety symptomatology in pediatric samples; however, discrepant findings are commonplace in this literature. Although there is evidence that increased amygdalar volume is associated with aspects of emotion dysregulation and anxiety in children and adolescents (Barros-Loscertales, Meseguer, & Sanjuan, 2006; De Bellis, Casey, & Dahl, 2000; MacMillan, Szeszko, & Moore, 2003; Tottenham, Hare, & Quinn, 2010; van der Plas, Boes, Wemmie, Tranel, & Nopoulos, 2010; Lupien, Parent, & Evans, 2011; Davidson and McEwen, 2012; Qin et al., 2014), decreased amygdalar volume has also been associated with anxiety in clinical pediatric samples (Milham, Nugent, & Drevets, 2005;Mueller et al., 2013). In addition, some studies have failed to find associations between internalizing symptoms and amygdalar structure (Koolschijn, van, Bakermans-Kranenburg, & Crone, 2013). Critically, there are several factors that may contribute to the lack of consensus in this literature and serve to obfuscate relations between limbic structure and anxious behavior in children.

First, it is possible that anxiety symptomatology is more closely associated with age-related changes in brain structure rather than structure at a single time point. Indeed, particular forms of developmental psychopathology have been closely tied to aspects of structural brain development. For example, longitudinal neuroimaging studies of cortical morphology have revealed that clinical and subclinical attention-deficit/hyperactivity disorder (ADHD) symptoms are associated with lagging cortical development, particularly within fronto-parietal areas (Ducharme, Hudziak, & Botteron, 2012; Shaw, Gilliam, & Liverpool, 2011; Shaw, Eckstrand, & Sharp, 2007). Such findings have led some to postulate that trajectories of anatomic brain development are meaningful phenotypes in the study of developmental psychopathology (Giedd, Lenroot, & Shaw, 2008). Interestingly, two recent studies utilizing large samples of typically developing youths have provided support for anxiety symptomatology being related to indices of cerebral cortical maturation (Ducharme, Albaugh, & Hudziak, 2014; Newman, Thompson, & Bartsch, 2016). Ducharme et al. (2014) demonstrated that anxiety symptoms in typically developing youths were tied to cortical thickness maturation, specifically in the right ventromedial prefrontal cortex—an area of the brain sharing robust anatomical connections with the amygdala (Ducharme et al., 2014; Ghashghaei, Hilgetag, & Barbas, 2007). Despite evidence of anxiety symptomatology in children being associated with cortical development, it remains unclear the extent to which anxiety psychopathology qualifies structural development of limbic regions.

Second, many previous studies investigating the relationship between limbic structure and anxiety symptoms have used categorical diagnoses as opposed to quantitative measures. As a result, previous studies have often focused on clinically significant mood and anxiety symptoms. Using dimensional measures of psychopathology has been recently emphasized by the National Institute of Mental Health's Research Domain Criteria program, encouraging the study of symptom dimensions as opposed to categorical diagnoses (Morris and Cuthbert, 2012). Characterizing brain-behavior relations in typically developing youths may offer insight into the biological processes undergirding normative levels of anxious/depressed symptoms.

Lastly, the amygdalae and hippocampi are among the brain areas with the highest density of sex hormone receptors. As such, sex may represent a significant regulator of limbic structural development, as well as a moderator of the relationship between limbic structure and anxious/depressed behavior. (Simerly, Chang, Muramatsu, & Swanson, 1990) Indeed, previous imaging studies looking at the structural development of limbic regions in youths have reported sex-dependent developmental trajectories (Uematsu, Matsui, & Tanaka, 2012).

The aim of the present study was to: 1) characterize developmental trajectories of amygdalar and hippocampal volume; 2) test for main associations between amygdalar and hippocampal volume and anxious/depressed symptomatology, investigating the degree to which sex serves as a moderator; and 3) determine the extent to which anxious/depressed symptoms are associated with age-related changes in both amygdalar and hippocampal volume using a longitudinal sample of psychiatrically healthy youths screened for clinically significant psychopathology.

2. Methods

2.1. Participants

The NIH MRI Study of Normal Brain Development is a large, multi-site project that establishes a normative database to study relations between healthy brain maturation and behavior (Evans, 2006). Subjects were recruited throughout the United States utilizing a population-based sampling method aimed at minimizing selection bias (Waber, De Moor, & Forbes, 2007). Using available U.S. Census 2000 data, a representative, typically developing sample was recruited at 6 pediatric study centers. The 6 pediatric centers consisted of: Children's Hospital (Boston), Children's Hospital Medical Center (Cincinnati), University of Texas Houston Medical School (Houston), UCLA Neuropsychiatric Institute and Hospital (Los Angeles), Children's Hospital of Philadelphia (Philadelphia) and Washington University (St. Louis). Recruitment was monitored throughout the study, ensuring that enrollment across all pediatric centers was demographically representative with regards to age, sex, ethnicity and socioeconomic status (full demographic features of subjects are provided in Evans, 2006). The study was approved by institutional review board at all sites, and informed consent was obtained from parents, as well as child assent. The Objective 1 database (release 4.0) used in this study included 431 healthy youths, and upon enrollment (i.e., first study visit), ages ranged from 4 years and 6 months to 18 years and 3 months. The study followed a longitudinal design such that participants underwent MRI brain scanning and behavioral testing on three separate visits, occurring at roughly 2-year intervals. With regard to subjects utilized in the present study, the age range at Visit 1 was 4.9–18.4 years; 6.4–18.4 years at Visit 2; and 8.4–18.0 years at Visit 3. Given that the aim of the NIH MRI Study of Normal Brain Development was to study healthy, typically developing children, stringent exclusion criteria were utilized including: meeting criteria for a current or past Axis I disorder on structured parent or child interview (Diagnostic Interview for Children and Adolescents) (exceptions, however, included simple phobia, social phobia, adjustment disorder, oppositional defiant disorder, enuresis, encopresis, nicotine dependency), family history of major Axis I disorder, family history of inherited neurological disorder or mental retardation due to non-traumatic events, abnormality on neurological examination, gestational age at birth less than 37 weeks or greater than 42 weeks, and intra-uterine exposure to substances known or highly suspected to alter brain structure or function (for further information, see Evans, 2006). Structural MRI and behavioral data were stored and analyzed within a database at the Data Coordinating Center of the Montreal Neurological Institute (MNI), McGill University. Behavioral and imaging data were collected at up to three time