NeuroImage 115 (2015) 235–244

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Developmental sex differences in resting state functional connectivity of amygdala sub-regions

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ARTICLE INFO

Article history:
Received 11 December 2014
Accepted 7 April 2015
Available online 14 April 2015

Keywords:
Resting state functional connectivity
Amygdala
Adolescence
Sex differences

ABSTRACT

During adolescence, considerable social and biological changes occur that interact with functional brain maturation, some of which are sex-specific. The amygdala is one brain area that has displayed sexual dimorphism, specifically in socio-affective (superficial amygdala [SFA]), stress (centromedial amygdala [CMA]), and learning and memory (basolateral amygdala [BLA]) processing. The amygdala has also been implicated in mood and anxiety disorders which display sex-specific features, most prominently observed during adolescence. Using functional magnetic resonance imaging (fMRI), the present study examined the interaction of age and sex on resting state functional connectivity (RSFC) of amygdala sub-regions, BLA and SFA, in a sample of healthy adolescents between the ages 10 and 16 years ($n = 122$, 71 boys). Whole-brain, voxel-wise partial correlation analyses were conducted to determine RSFC of bilateral BLA and SFA seed regions, created using the Eickhoff–Zilles maximum probability maps based on cytoarchitectonic mapping and FMRIB's Integrated Registration and Segmentation Tool (FIRST). Monte Carlo simulation was implemented to correct for multiple comparisons (threshold of 53 contiguous voxels with a z-value ≥ 2.25). Results indicated that with increasing age, there was a corresponding decrease in RSFC between both amygdala sub-regions and parieto-occipital cortices, with a concurrent increase in RSFC with medial prefrontal cortex (mPFC). Specifically, boys and girls demonstrated increased coupling of mPFC and left and right SFA with age, respectively; however, neither sex showed increased connectivity between mPFC and BLA, which could indicate relative immaturity of fronto-limbic networks that is similar across sex. A dissociation in connectivity between BLA- and SFA-parieto-occipital RSFC emerged, in which girls had weaker negative RSFC between SFA and parieto-occipital regions and boys had weaker negative RSFC of BLA and parieto-occipital regions with increased age, both standing in contrast to adult patterns of amygdala sub-regional RSFC. The present findings suggest relative immaturity of amygdala sub-regional RSFC with parieto-occipital cortices during adolescence, with unique patterns in both sexes that may support memory and socio-affective processing in boys and girls, respectively. Understanding the underlying normative functional architecture of brain networks associated with the amygdala during adolescence may better inform future research of the neural features associated with increased risk for internalizing psychopathology.

Introduction

Structural and functional connectivity between the amygdala and cortical brain regions undergoes dramatic maturation across adolescence (Qin et al., 2012; Gabard-Durnam et al., 2014). Resting state functional connectivity (RSFC) refers to the coupling of spontaneous blood oxygen level-dependent (BOLD) signal, as measured with functional magnetic resonance imaging (fMRI), in discrete brain regions or networks. Positive functional connectivity between regions is thought to reflect patterns of synchronous activity or increased communication. Limbic structures, including the amygdala, demonstrate emerging functional and structural maturity by early adolescence (Giedd et al., 1996; Ostby et al., 2009; Wierenga et al., 2014); however, prefrontal cortical brain regions display a protracted rate of development that extends into the third decade of life (Giedd et al., 1996; Gogtay et al., 2004). As such, it is believed that amygdalar functioning is not down-regulated effectively by medial prefrontal cortex (mPFC) and rostral anterior cingulate cortex (rACC) during adolescence (i.e. Dual Systems Model), which can manifest as heightened emotional reactivity typical of this developmental period (Hare et al., 2008; Perlman and Pelphrey, 2011; McRae et al., 2012; Gee et al., 2013). An imbalance in maturity of frontal and limbic brain regions is likely insufficient, however, to explain the range of behavior in adolescents. Additionally, there are sex differences

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http://dx.doi.org/10.1016/j.neuroimage.2015.04.013
1053-8119/

in the structural development of the amygdala during adolescence (Giedd et al., 1996) in which males demonstrate significant increases in volume that females do not (Giedd et al., 1996), as well as in prefrontal cortices, with girls peaking in gray matter volume approximately two years earlier than boys (Lenroot et al., 2007). These sex-specific structural developmental trajectories may impact concomitant functional connectivity of these brain regions. Previous studies in adults have reported sex differences in amygdala sub-region shape and volume (Kim et al., 2011, 2012) and in RSFC of non-limbic brain regions using a variety of analytic methods (Kilpatrick et al., 2006; Biswal et al., 2010; Tian et al., 2011; Casanova et al., 2012; Satterthwaite et al., in press). Furthermore, atypical functional connectivity of amygdala-mPFC neurocircuitry has been shown to underlie disrupted emotional and cognitive ability during psychopathologic states, such as schizophrenia, bipolar disorder, and mood disorders (Anand et al., 2005; Das et al., 2007; Henry et al., 2008; Wang et al., 2009; Berking and Wupperman, 2012; Cisler and Olatunji, 2012), many of which emerge in late adolescence and display sex-specific onset and progression of illness.

Examination of the functional interactions of amygdala-cortical neurocircuitry is complicated by the fact that the amygdala is not one homogenous structure (LeDoux, 2003; Price, 2003; Amunts et al., 2005). The amygdala can be sub-divided into basolateral (BLA), centromedial (CMA) and superficial (SFA) nuclei, each with distinct functional connections to the cortex supporting different brain functions. The BLA facilitates associative learning processes, like fear conditioning, through afferent projections from the frontal cortex and other subcortical regions (LeDoux, 2003; Phelps and LeDoux, 2005). The CMA is critical in the generation of behavioral responses through projections to the brainstem, striatum, and regions of the cortex (LeDoux, 2003). Finally, the SFA is relevant for olfactory (Price, 2003; Heimer and Van Hoesen, 2006) and affective processes (Bzdok et al., 2013a). Previous work has found distinct functional connectivity patterns, as measured with RSFC, across amygdalar nuclei (Roy et al., 2009; Li et al., 2012; Qin et al., 2012; Gabard-Durnam et al., 2014), specifically different patterns of age-dependent positive connectivity between amygdalar nuclei and ventromedial PFC (vmPFC), temporal, and subcortical regions, as well as negative connectivity with parietal and occipital cortices (Qin et al., 2012; Gabard-Durnam et al., 2014). However, only one study performed a secondary analysis to examine sex differences in adolescents, which did not yield a significant effect of sex (Gabard-Durnam et al., 2014).

The current study examined sex differences in age-dependent RSFC of amygdalar nuclei in a relatively large adolescent sample. Previous studies attempting to characterize developmental differences in amygdalar RSFC have appropriately used samples with broad age ranges spanning childhood and adulthood (Qin et al., 2012; Gabard-Durnam et al., 2014); however, sex differences may be obscured when collapsing data across a variety of developmental stages. Given the dynamic nature of adolescent brain development and sex differences in amygdalar and frontal lobe gray matter maturation (Giedd et al., 1996; Lenroot et al., 2007), additional examination of amygdalar RSFC during adolescence may better address whether sex differences in amygdala sub-nuclei RSFC exist over the span of this period. Previous research has shown coupling of mPFC and all amygdala sub-regions with increasing age (Roy et al., 2009; Qin et al., 2012; Gabard-Durnam et al., 2014), while different studies have also shown protracted prefrontal cortical development through adolescence, with girls showing relative maturity as compared to boys (Giedd et al., 1996; Lenroot et al., 2007). In light of this research, we hypothesized a positive relationship between age and RSFC of amygdalar sub-regions and mPFC across the sampled age range that would be stronger in girls, compared to boys. Sex differences in the developmental trajectory of RSFC of amygdala sub-regions may provide insight on the mechanisms that support sex differences in the onset and progression of mental illness.

Materials and methods

Participants

Data from an ongoing adolescent neurodevelopment protocol were used for this study. Participants with anatomical magnetic resonance imaging (MRI) and resting state functional (RSFC) MRI data, acceptable amygdala sub-nuclei region of interest (ROI) masks (see Definition of amygdala sub-region ROIs) and limited head movement (see Motion correction) were included in functional connectivity analyses. The total sample included 122 adolescents (boys = 71) between the ages of 10 and 16 years. A restricted age range was employed to capture developmental effects and sex differences in amygdalar functional connectivity specific to adolescence.

Written assent and consent from children and their parents, respectively, were obtained in accordance with the Oregon Health & Science University (OHSU) Institutional Review Board. Exclusionary criteria included current (past 12 month) diagnosis of DSM-IV psychiatric disorders, significant substance use (>10 lifetime alcoholic drinks or >2 drinks/occasion, >5 uses of marijuana, any other drug use, or >4 cigarettes per day), neurological illness, significant head trauma, chronic medical problems affecting the central nervous system, prenatal exposure to drugs or alcohol, reported history of psychotic disorders in biological parents, current pharmacological treatment that may affect neural function (e.g. psychoactive medication), the inability of a parent to provide family history information, left-handedness (Edinburgh Handedness Inventory, (Oldfield, 1971)), pregnancy, and MRI contraindications (e.g. braces, irremovable ferrous material).

Once eligibility was established, youth were administered the Wechsler Abbreviated Scale of Intelligence (Weschler, 1999)—short form and the self-rated Pubertal Development Scale (PDS) (Petersen et al., 1988). Self-report on the PDS has been shown to correlate moderately with other measurements of pubertal status, like Tanner's Sexual Maturation Scale (Bond et al., 2006). Parents of youth were administered the Hollingshead Index of Social Position (Hollingshead, 1975) to determine socioeconomic status (SES), which is based on occupation and educational attainment of each parent.

Image acquisition

Participants were scanned on a Siemens Tim Trio 3.0 Tesla MRI scanner at the Advanced Imaging Research Center at OHSU. One high-resolution T1-weighted MPRAGE sequence of 9 min and 14 s was acquired (TR = 2300 ms, TE = 3.58 ms, flip angle = 10°, orientation = sagittal, 256 × 256 matrix, resolution = 1 × 1 × 1.1 mm). BOLD-weighted functional images were collected (along the anterior–posterior commissure) using T2*-weighted echo planar imaging (TR = 2500 ms, TE = 30 ms, flip angle = 90°, FOV = 240 mm^2, 36 slices covering the entire brain, slice thickness = 3.8 mm, resolution = 3.75 × 3.75 × 3.8 mm). Two runs of 4 min and 17 s of resting state BOLD data were acquired, during which participants were instructed to stay still and fixate on a white cross in the center of a black screen projected from the head of the scanner and viewed with a mirror mounted on 12-channel head coil. The resting state runs were separated by a 10-minute task that was the same for every participant. Following completion of the scan, youth confirmed wakefulness during resting state scans.

Image processing

Data processing followed commonly used procedures to reduce spurious noise and artifacts (Fair et al., 2007, 2009, 2012; Mills et al., 2012; Costa Dias et al., 2013). In order, these steps included slice time correction, debanding, rigid body head motion correction with regression of 3 translational and 3 rotational parameters, and signal normalization to a mode value of 1000. Resting state runs were then concatenated and