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Neurodevelopmental changes in the relationship between stress perception and prefrontal-amygdala functional circuitry

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ABSTRACT

Our brain during distinct developmental phases may show differential responses to perceived psychological stress, yet existing research specifically examining neurodevelopmental changes in stress processing is scarce. To fill in this research gap, this functional magnetic resonance imaging (fMRI) study examined the relationship between perceived stress and resting-state neural connectivity patterns among 67 healthy volunteers belonging to three age groups (adolescents, young adults and adults), who were supposed to be at separate neurodevelopmental phases and exhibit different affect regulatory processes in the brain. While the groups showed no significant difference in self-reported general perceived stress levels, the functional connectivity between amygdala and ventromedial prefrontal cortex (vmPFC) was positively and negatively correlated with perceived stress in adolescents and young adults respectively, while no significant correlations were observed in adults. Furthermore, among adolescents, the causal functional interaction between amygdala and vmPFC exhibited bottom-up connectivity, and that between amygdala and subgenual anterior cingulate cortex exhibited top-down connectivity, both of which changed to bilateral directions, i.e. both bottom-up and top-down connections, in both young adults and adults, supporting the notion that the amygdala and prefrontal cortical circuitries undergo functional reorganizations during brain development. These novel findings have important clinical implications in treating stress-related affective disorders in young individuals.

1. Introduction

Perceived psychological stress is a global, subjective evaluation of the impact of adversities in life that an individual experiences at a given point in time or over a course of time. Such evaluation depends on an individual's appraisal and the resources available for coping with the life adversity experienced (Lazarus and Folkman, 1984). A large body of evidence indicates that high perceived stress predisposes onset of mental illnesses such as depression (Hammen, 2015), anxiety disorders (Glynn et al., 2008), substance use (Rice and Van Arsdale, 2010), and posttraumatic stress disorder (PTSD) (Lagana and Reger, 2009). Notably, high levels of perceived stress and high vulnerabilities to developing affect-related disorders co-occur during adolescence, a period in which individuals undergo rapid and critical psychological and neurobiological developments (Gogtay et al., 2004; Schraml et al., 2011). Yet, existing research specifically investigating the neural correlates of subjective stress during different brain developmental phases is lacking. Such research can advance our understanding of the developmental-dependent neurobiological mechanisms that predispose and precipitate stress-related affective disorders.

Stress-related neural processes generally implicate the functioning of reciprocal brain networks involving the limbic and prefrontal cortical

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(PFC) systems (Lupien et al., 2009; Morey et al., 2012). The amygdala, which is involved in fear processing and emotional memory formation and expression (Becker et al., 2012), is thought to activate the hypothalamus-pituitary-adrenal (HPA) axis in response to threat and challenge. After activation of the HPA axis, the hippocampus and frontal cortex are triggered in order to reduce the HPA axis activation to a homeostatic state (Lupien et al., 2009). Extensive evidence indicates a pivotal role of the amygdala and PFC, especially the ventral medial PFC (vmPFC), for stress-related processing (Gee et al., 2013a, 2013b; McEwen et al., 2016; Tottenham and Galván, 2016). These networks regulate stress-related cognitive, emotional and behavioral processes (Raio et al., 2013; Arnsten et al., 2015). Furthermore, imaging genetic studies suggest that the genotype-related variations in the function of amygdala-vmPFC circuitry implicate a system-level mechanism underlying normal emotional reactivity and genetic susceptibility for affective disorders such as depression, which is closely related to stress (Ressler and Mayberg, 2007; Tost and Meyer-Lindenberg, 2012). The subgenual anterior cingulate cortex that has extensive connections with limbic and paralimbic structures is also considered to play a key role in stress response and emotional regulation (Phillips et al., 2008; Pechtel and Pizzagalli, 2013).

Importantly, the functional characteristics of neural circuitries in relate to stress perception and regulation likely vary across different developmental stages. Adolescence is a developmental period that is particularly sensitive to psychosocial adversity, and the affect regulatory networks undergo considerable reorganizations during adolescence and early adulthood (Lupien et al., 2009; Birn et al., 2014; Casey et al., 2008). Generally, limbic structures such as the amygdala and striatum, which are involved in affective reactivity processes, mature earlier than prefrontal areas including the vmPFC and dorsolateral PFC that monitor and regulate the subcortical limbic functions (Steinberg, 2008). Anatomically, the volume of the amygdala starts to stabilize around late adolescence (Wierenga et al., 2014), whereas the ventromedial prefrontal cortical thickness exhibits continuous change throughout adolescence to young adulthood (Shaw et al., 2008). Such asynchronous development of the amygdala and the vmPFC, with the former developing earlier than the latter, renders the amygdala–vmPFC functional coupling less stable in adolescents than in adults, and may cause significant momentary changes in affective processing in the former age group (John and Gross, 2004; Johnson et al., 2016). Also, white-matter fibers connecting amygdala and cortical regions, especially the medial PFC, continue to mature during adolescence until adulthood (Cunningham et al., 2002), which provides the anatomical basis for the functional connectivity between amygdala and vmPFC to continue developing during brain maturation (Gee et al., 2013a, 2013b). Furthermore, while animal studies show bidirectional connectivity between amygdala and orbitofrontal and medial PFC (Barbas et al., 2003), the amygdala to vmPFC projections were found to emerge earlier than the vmPFC to amygdala projections (Bouwmeester et al., 2002), suggesting that the top-down control from medial PFC to subcortical limbic regions may not fully mature until later in development.

This cross-sectional neuroimaging study examined the relationship between perceived stress and resting-state functional and effective connectivity in three developmental stages, namely adolescence (high school students), young adults (undergraduate students), and adults. While we acknowledge that considerable individual differences exist within each age group, all individuals in a given age group shared common psychosocial environments (school vs. university vs. society), which aligned with and contributed to the neurodevelopmental profiles of those individuals (Lamm et al., 2014; Simmonds et al., 2014). As such, we considered each of the 3 groups as representing, at least to some extents, distinct and relatively homogeneous psychosocial stages of brain development, and findings on these samples would provide a comprehensive cross-sectional view of the relationships between the maturing brain and stress processing. Following the assumption that prefrontal-limbic networks that are not yet fully matured would be more sensitive and responsive to stress experience (Lupien et al., 2009; Birn et al., 2014), we hypothesized: (1) The association between perceived stress and resting-state functional connectivity between the amygdala and the PFC would differ among the three age groups. Specifically, the adolescent group would exhibit more positive coupling between the PFC-amygdala connectivity strength and levels of perceived stress compared to the other age groups; (2) Based on the assumption that the regulatory function of PFC on amygdala does not fully mature until adulthood, we hypothesized that the causal interactions (i.e. effective connectivity) between the amygdala and the PFC would be different across the developmental stages. Specifically, the PFC-amygdala functional connectivity would be primarily directed from the latter to the former in adolescents, and become bi-directional as people mature in adulthood.

2. Materials and methods

2.1. Participants

The study was approved by the Fujian Traditional Chinese Medicine University Institutional Review Board. Prior to the study, written informed consent was obtained from the participant after a detailed description of the study was given. All participants were recruited from the community via advertisement and were screened based on the inclusion criteria. Sixty-seven healthy subjects were included who were assessed as being right-handed by using the Edinburgh Handedness Inventory (Oldfield, 1971), had normal or corrected-to-normal vision and hearing, reported no neurological, neurodegenerative or psychiatric diseases, no history of substance abuse, and were suitable to enter a magnetic resonance image (MRI) scanner. They then completed the Test trait Nonverbal Intelligence, third edition (TONI-III), and the Chinese version of the Perceived Stress Scale (PSS; (Yang and Huang, 2003)). Subjects were divided into three age groups including adolescence (n = 24; 11 females; mean age = 17.02 ± 0.94 years, range = 14.90 to 17.93 years), young adults (n = 22; 9 females; mean age = 19.55 ± 0.43 years, range = 19.00 to 20.61 years), and adults (n = 21; 9 females; mean age = 35.21 ± 4.19 years, range = 30.02 to 45.24 yeas). The three age groups were matched for gender (p = .94)

Table 1
Demographic and psychometric characteristics of the participants.

Variables	Adolescent	Young Adult	Adult	*P* value
N	24	22	21	
Age	17.02 ± 0.94	19.55 ± 0.43	35.21 ± 4.19	< 0.0001**
Range	(14.90–17.93)	(19.00–20.61)	(30.02–45.24)	
Gender (m/f)	13/11	13/9	12/9	0.94
IQ(TONI-III)	105.71 ± 14.20	106.91 ± 12.93	111.90 ± 10.92	0.25
Range	(84–135)	(88–135)	(96–135)	
PSS	25.21 ± 5.87	23.14 ± 6.18	21.24 ± 7.84	0.14
Range	(16–37)	(13–38)	(9–33)	

Note: IQ, TONI-III; PSS, perceived stress scale.

and IQ measured by TONI III (p = .25) (Table 1). While the age difference between the adolescent and young adult groups may be considered small, it is worth noting that i) as stated above, these two groups represent distinct psychosocial and neurodevelopmental phases, and past studies have revealed differences between similarly-aged groups in both regional activations and white-matter structure of affective circuitries (Lamm et al., 2014; Simmonds et al., 2014); ii) existing whole-brain developmental mapping studies show that prefrontal cortical regions undergo considerable changes between late adolescence and early adulthood (Gogtay et al., 2004); and iii) The PSS measure generally lacks validation in children and young adolescent populations.

All participants underwent an MRI scan wherein they were instructed to keep their heads still and to remain awake. Anatomical imaging (5 min) and resting state imaging (6 min) were acquired and used in this study. Due to a failure in the acquisition of one subject's functional data, the number of functional images for later analysis was 66 instead of 67.

2.2. The stress measure

The PSS is a widely used psychological instrument for measuring nonspecific *perceived* stress, and it is sensitive and valid for measuring *subjective* stress levels in both clinical and non-clinical samples (Cohen et al., 1983). In this context, 'stress' is defined and measured as situations that are perceived as overwhelming, exhausting, uncontrollable and/or unmanageable. Given the questionnaire primarily focuses on assessing the respondent's stress-related feelings, experiences and emotions, high scores on the PSS reflect greater subjective rather than objective stress experience, which is particularly pertinent to our investigation on the functioning of the neural affect regulatory circuitries. We used the 14-item PSS rated on a 5-point scale from *never (0)* to *very often (4)*, with higher scores representing elevations in perceived stress. In this study, we focused on detecting the *normal* perceived stress levels of the participants. Sample items included "Normally, how often have you felt nervous and 'stressed'?" and "Normally, how often have you found that you could not cope with all the things that you had to do?" The PSS showed a good internal consistency in the current sample with the Cronbach's alpha = 0.812.

2.3. Imaging data acquisition and processing

Resting-state fMRI data were acquired on a 3-T GE MRI scanner (GE Medical Systems, Erlangen, USA) with an 8-channel GE head coil. High-resolution T1-weighted anatomical images were acquired using the magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR/TE = 2000 ms /1.75 ms; flip angle = 15°; slice thickness = 1.0 mm; FOV = 240 × 240 × 160 mm^3; resolution matrix = 256 × 256; voxel size = 0.94 × 0.94 × 1 mm^3) for coregistration with the functional images. Using a T2*-weighted gradient-echo-planar imaging sequence, 180 functional volumes were acquired (slice number/TR/TE/flip angle = 40/2000 ms/30 ms/90°, matrix = 64 × 64, FOV = 225 × 225 × 140 mm^3, voxel size = 3.52 × 3.52 × 3.5 mm^3). Participants were instructed to stay awake with their eyes open and focus on the cross in the middle of the screen for the entire duration of the resting-state scanning, which lasted for a total of 6 min.

2.4. Functional connectivity estimation

Resting-state functional MRI (rs-fMRI) data were preprocessed using Conn (www.nitrc.org/projects/conn), including the following steps: slice-timing correction, motion correction, scrubbing, normalization, nuisance regression, quadratic detrending, band-pass temporal filtering (0.008 < f < 0.09 Hz), and smoothing with an 8-mm Gaussian kernel. Outliers for scrubbing that could be due to movement or disequilibrium effect were defined using the threshold of time intensity and motion (global signal z value < 3, and motion mm threshold < 0.5 mm). The nuisance regression included the following regressors: 6 motion parameters, the first 5 principle components of the signals in CSF and white matter, and outlier indicators from the scrubbing step. After scrubbing, the average frame displacement in the three age groups were: 0.073, 0.064 and 0.081 mm in adolescents, young adults and adults respectively, and no significant differences were detected using one-way ANOVA (p = .226). The average number of outlier volumes to be scrubbed off in each age group were 8.46, 7.33 and 10.47 mm in adolescents, young adults and adults respectively, and no significant differences were detected using one-way ANOVA (p = .206).

The resting-state functional connectivity (rsFC) maps of the amygdala were analyzed using SPM12 and MATLAB (The MathWorks, Inc., Natick, MA, version 2015a). In particular, the right amygdala has been indicated to be crucial in processing negative affective stimuli such as those related to fear (Baker and Kim, 2004; Pegna et al., 2005), and is closely associated with stress processing (Mothersill and Donohoe, 2016). Furthermore, genotypes related to anxiety trait and stress responsiveness, such as the 5-HTTLPR, showed more consistent relations with functions of the right amygdala (Munafo et al., 2008). Therefore the right amygdala was chosen as the seed region-of-interest (ROI). The rsFC of the left amygdala was also computed for sake of completeness. The amygdala ROI was defined following the subcortical delineation in the Harvard-Oxford atlas as provided by FSL (Smith et al., 2004) (see Supplementary Fig. 1 for a depiction of amygdala ROI overlain on the group-level rsFC analysis mask and on a representative participant's unsmoothed image). We included both lateral and mesial amygdala based on existing evidence that 1) the lateral and central amygdala nuclei are tightly interconnected and collectively constitute a coherent affect processing system, with affect-related information passing from the lateral to the mesial portion of amygdala (Maier, 2015); 2) the lateral and central amygdala are respectively involved in acquisition and consolidation of stress-related aversive memory (Haglund et al., 2007); 3) the vmPFC exerts influence on both lateral and mesial amygdala in regulating negative affect and stress (Etkin et al., 2011) and 4) both lateral and mesial amygdala show functional activations to negative affective and stress-related processes (Schiller et al., 2008; Kerr et al., 2012). A functional connectivity map was obtained by computing the correlation between each voxel's time course and the mean time course of the amygdala ROI.

2.5. Statistical analyses on the relationships between age groups, PSS and functional connectivity

The effect of age groups on PSS was tested using one-way ANOVA in SPSS v.22 (IBM Corporation, Armonk, NY), controlling for gender and IQ. To test whether different age groups exhibited distinct associations between functional connectivity measures and perceived stress, a second-level full-factorial analysis in SPM12 was performed which tested the following effects: Age as the between-subject factor with three levels (adolescents, young adults and adults); PSS and the interaction of PSS and age as the covariate of interest; and Gender and IQ as nuisance covariates. We controlled for gender and IQ in both behavioral and imaging analyses in light of previous literature indicating potential modulation of stress perception and processing by those factors (e.g. Eisenegger et al., 2011; Wu et al., 2013; Lambert et al., 2014;). F-contrast was constructed to specifically examine the Age by PSS interactive effect. To account for Type 1 errors, we conducted FWE correction with uncorrected p < .001 at voxel level and p < .05 at cluster-level. As we were primarily interested in the connectivity between the amygdala and the PFC, we applied a searching mask defined by the entire PFC by combining 11 cortical areas defined by the Harvard-Oxford atlas as provided by FSL (see Supplementary Fig. 2). For completeness, we also examined the main gender, age, PSS and IQ effects on right amygdala rsFC using F test.

Moreover, we also tested possible gender effect on perceived stress

(Xu et al., 2015; Burghy et al., 2016) and whether the effect was moderated by different age groups. This was tested in a moderation linear regression model setting age as the moderator on the relationship between gender and PSS, controlling for IQ, using the PROCESS macro (Hayes, 2013) in SPSS v.22 (IBM Corporation, Armonk, NY). The effects were evaluated using bootstrapping (5000 times) as suitable for relatively small samples (Preacher et al., 2007).

2.6. Effective connectivity analyses

Causal interactions between volumes of interest (VOIs) at rest were estimated for each individual by spectral dynamic causal modeling (sDCM) using SPM12. The sDCM analysis is widely applied for rsFC studies (Friston et al., 2013). It was conducted in the following steps: selection of the amygdala seed region and the region(s) exhibiting significant interactive effect of PSS by age on connectivity as VOIs; extraction of the first eigenvariate of the time courses in the seed VOI defined by the same mask used in the rsFC analysis, and other VOI(s) defined by a 6 mm sphere centered at the peak coordinates of the significant cluster(s); specification and estimation of the whole model space; and performing a family-level Bayesian model selection (BMS) analysis by grouping subsets of models based on some common feature shared by the models (Penny et al., 2010). We primarily focused on exploring the directionality of the functional couplings between the VOIs, therefore the models were grouped into 1) a family defined by connections from the amygdala seed to the significant clusters, 2) a family defined by connections from the clusters to the amygdala, and 3) a family defined by bidirectional connections between the amygdala seed and the clusters. The family with a posterior probability > 95% was regarded as the winning family (Stephan et al., 2010).

3. Results

3.1. PSS across ages

One-way ANOVA showed that the three age groups did not differ significantly in general PSS ($p = .14$). Post-hoc pair-wise *t*-tests showed no significant PSS differences between any pair of age groups: $p = .653$ between adolescents and young adults; $p = .183$ between adolescents and adults; and $p = .734$ between young adults and adults.

4. rsFC and stress across ages

Using the right amygdala as seed, an interaction effect of PSS by age in rsFC was observed in two clusters in the subgenual anterior cingulate cortex (sgACC) with p (FWE corrected) = 0.007 and in the vmPFC with p (FWE corrected) = 0.037 (Fig. 1 and Table 2). To further examine the correlation patterns within the sgACC and vmPFC clusters in each age group, we extracted the average rsFC values in the clusters showing significant interactive effect of PSS by age from each individual subject. The partial correlation analyses were conducted between the extracted rsFC values of each significant cluster and the PSS in each age group, controlling for gender and IQ, using SPSS. Bonferroni correction was used to account for the six comparisons (three age groups and two clusters) (i.e. $p_{corrected} = p^*6$). In the adolescent group, there was a significant positive correlation between PSS and the extracted rsFC of the amygdala–vmPFC connectivity with $r = 0.570$, $p_{corrected} = 0.048$, and between PSS and the rsFC of the amygdala-sgACC connectivity with $r = 0.715$, $p_{corrected} < 0.001$ (Fig. 2). In young adults, a significant negative correlation was found between PSS and the rsFC of the amygdala–vmPFC circuit, with $r = -0.648$, $p_{corrected} = 0.018$, while the negative correlation between PSS and the rsFC of the amygdala-sgACC circuit did not survive multiple correction ($r = -0.546$, $p_{corrected} = 0.096$). In adults, no significant correlation was observed between PSS and amygdala-vmPFC rsFC($r = 0.310$, $p = .196$), or between PSS and amygdala-sgACC rsFC ($r = -0.386$, $p = .103$). No significant cluster was observed for the PSS-by-age interactive effect on the rsFC of the left amygdala ($p > .1$).

We also tested the main effect of age, PSS and IQ on amygdala rsFC, respectively. There was no significant main age or IQ effect on either left or right amygdala rsFC. There was one cluster showing significant main PSS effect on right amygdala rsFC (see Supplementary Fig. 3), but no PSS main effect was observed on left amygdala rsFC (p (FWE) > 0.1).

4.1. Gender effect

There was no significant effect of gender on PSS (b = −0.0489, SE = 1.7059, $p = .9772$), and the age moderation on the association between gender and PSS was not significant (b = 2.8121, SE = 2.1518, $p = .1961$). The main effect of gender on the rsFC of right amygdala was significant in a cluster localized in the anterior cingulate (X/Y/Z = 2, 28, 32, cluster size = 155 voxels, Fmax = 22.90, p (FWE corrected) = 0.007), with males showing more positive rsFC than females, consistent with existing literature (Gong et al., 2011) (Supplementary Fig. 4). However, the interactive effect of gender and PSS was not significant (p (FWE corrected > 0.1). No significant gender or gender-by-PSS effect was observed for the left amygdala rsFC.

4.2. Effective connectivity

As there was significant PSS by age interactive effect on the rsFC in the clusters of vmPFC and sgACC, we focused on detecting the directionality of the effective connectivities between the amygdala seed and those two clusters in each of the three age groups. The amygdala seed was defined as one VOI, and two 6-mm spheres were defined as the other two VOIs, centered at the peak coordinate (−4, 14, −24) for the sgACC cluster, and at the peak coordinate (−2, 48, −26) for the vmPFC cluster. The time courses of the three VOIs were extracted. A total of 2^6–1 = 63 models were estimated for each individual, which were classified into families based on connection directionality.

In adolescents, the winning families were defined by effective connectivity from the amygdala to vmPFC with probability = .985, and from the sgACC to amygdala with probability = .956 (Fig. 3a), showing strong evidence for unidirectional connectivity pattern in both cases. In the young adult group, the clearly winning families were bidirectional connectivity between the amygdala and vmPFC (probability = 1), and bidirectional connectivity between the amygdala and sgACC (probability = 1) (Fig. 3b). In the adult group, again, the clearly winning families showed bidirectional connectivity between the amygdala and vmPFC (probability = 1), and bidirectional connectivity between the amygdala and sgACC (probability = 1) (Fig. 3b).

5. Discussion

By examining the correlations between perceived stress and brain functional networks in adolescents, young adults and adults, we revealed distinct neural functional correlates with perceived stress during different developmental periods. In adolescents, the functional connectivity between right amygdala and both the vmPFC and sgACC correlated positively with perceived stress, with the directionality being from the right amygdala to vmPFC and from the sgACC to right amygdala. In young adults, the right amygdala-vmPFC functional connectivity negatively correlated with perceived stress and showed bidirectional patterns, while no significant correlations between the amygdala connectivity and perceived stress was observed in adults. Based on these results, we propose that the amygdala-vmPFC network continues to mature and engages in different patterns of stress regulatory processes across different developmental periods.

The amygdala is the first relay station in the processing of psychosocial stress stimuli, and it continues to develop during adolescence (Ostby et al., 2009). With abundant HPA axis hormone receptors, the

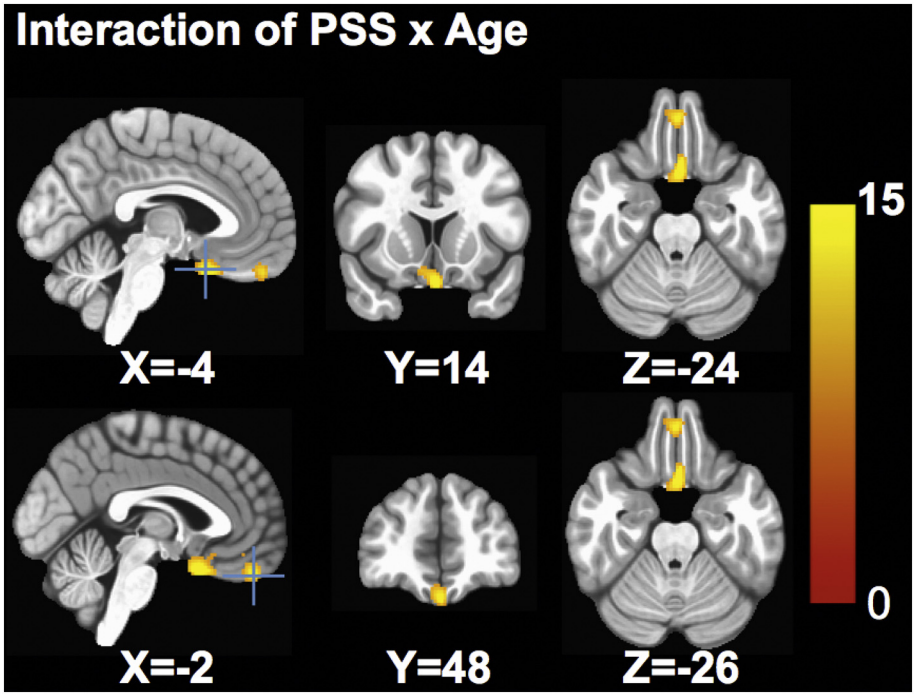

Fig. 1. Interaction effect of PSS by age in rsFC with the right amygdala as seed. Both the subgenual cluster (top panel) and the vmPFC cluster (bottom panel) show significant interactive effect. Color bar denotes F statistics. NOTE: rsFC – resting-state functional connectivity; vmPFC – ventral medial prefrontal cortex.

Table 2
Clusters showing significant perceived stress by age interactive effect on the resting-state functional connectivity with right amygdala as the seed.

Anatomical regions	Cluster Size (# voxels)	MNI Coordinates (mm)			F-Score	Corrected p
		X	y	z		
Subgenual ACC, rectal gyrus, BA25	297	−4	14	−24	20.04	0.007
vmPFC, Rectal Gyrus, BA11	152	−2	48	−26	14.90	0.037

amygdala is particularly responsive to stress and may be more sensitive to stress exposures during development than other stress-related regions. Animal studies have shown that the basolateral amygdala exhibits dendrite expansion in response to chronic stress (Boyle, 2013). Neuroimaging studies in humans have also found increased amygdala activity in associate with higher stress levels or greater stress disorder severity (Weber et al., 2013; Savic, 2015). After the amygdala activates the HPA axis in response to adverse stimuli, the medial PFC is then triggered to reduce the HPA axis activation to a homeostatic state (Lupien et al., 2009). Existing neuroimaging evidence indicates both structural (Kim and Richardson, 2009) and functional (Hare et al., 2008) connections between the amygdala and the medial PFC in humans. This circuit not only contributes to various fundamental aspects of emotional behavior including learning and regulation, but is also involved in stress processing and many stress-related disorders at different life stages. For example, weaker connectivity between the amygdala and the vmPFC has been shown to be associated with increased trait anxiety (Kim et al., 2011) and chronic stress (Jovanovic et al., 2011) in the adult population. Furthermore, adolescents with a history of childhood maltreatment (Herringa et al., 2013) or trauma (Pagliaccio et al., 2015) exhibit weaker connectivity between the amygdala and the vmPFC (Nooner et al., 2013). Weaker amygdala and vmPFC connectivity in adolescence has also been shown to mediate the associations between stress and anxiety symptoms (Pagliaccio et al., 2015) and PTSD symptoms (Cisler et al., 2013). Together with our findings of significant correlations between PSS and the amygdala–vmPFC rsFC, the right amygdala–vmPFC connectivity appears to have great implications for stress-related mental health.

The connectivity of the amygdala–vmPFC circuit is immature in childhood and continues to develop during adolescence until adulthood (Cunningham et al., 2002; Pattwell et al., 2016). Neuroimaging studies have shown that the amygdala and medial PFC connectivity changes during brain maturation (Gee et al., 2013a, 2013b). The inconsistent functional couplings between the amygdala and the medial PFC during development may be associated with changes in emotional processing (John and Gross, 2004). The functional couplings between amygdala and medial PFC to emotional stimuli has been shown to shift from positive connectivity strength in childhood with average age of 10 years to negative connectivity in adolescence aged around 18 years (Gee et al., 2013a, 2013b). Our results also revealed a shift in the relationships between the perceived stress and the amygdala-vmPFC connectivity during brain maturation, i.e., positive correlation in adolescents and negative correlation in young adults.

Furthermore, our effective connectivity analysis showed that the right amygdala-vmPFC connectivity was directed from the former to the latter structure in adolescents, but was bidirectional in young adults and adults. Previous studies revealed that the amygdala has strong bidirectional projections with the PFC (Barbas et al., 2003), and the vmPFC is thought to regulate the activity of the amygdala (Motzkin et al., 2015). In adults, the amygdala and the vmPFC are functionally coupled and work together in stress perception and regulation. Under non-stressed situations, the top-down regulation of the PFC on amygdala provides control over thoughts, emotions and behaviors (Cunningham et al., 2002). Our findings of a negative correlation between PSS and amygdala–vmPFC connectivity in young adults, with a bidirectional connectivity between the amygdala and the vmPFC, further support the top-down regulation model. The lack of correlation between PSS and the amygdala–vmPFC connectivity in well-matured adult brains may suggest that the fully developed circuit in adulthood is more stable, and may thus be less sensitive to stress. On the other hand, the amygdala and the vmPFC have asynchronous developmental

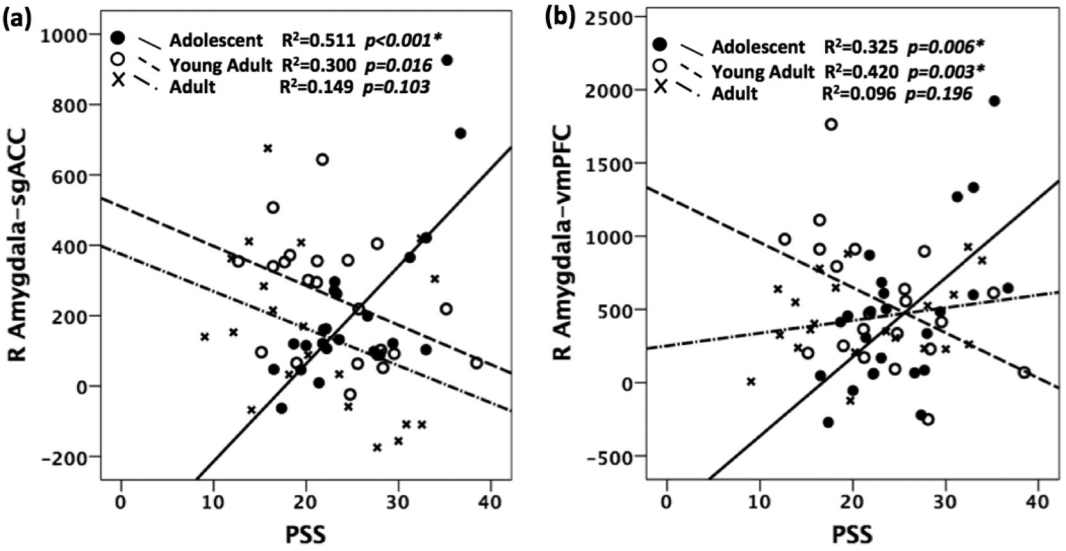

Fig. 2. Scatter plots between the PSS and the rsFC (averaged rsFC over the cluster showing significant interactive effect) in three age groups of adolescents, young adults, and adults. Note: rsFC – resting-state functional connectivity; vmPFC – ventral medial prefrontal cortex; sgACC – subgenual ACC.

trajectories. The amygdala matures relatively early both structurally and functionally (Ulfig et al., 2003; Hare et al., 2008). In contrast, the vmPFC shows protracted structural and functional developments (Gogtay et al., 2004). Tracing studies have also revealed that amygdala-to-vmPFC projections emerge earlier than vmPFC-to-amygdala projections (Bouwmeester et al., 2002), and these connections continue to develop through adolescence in rodents (Cunningham et al., 2002). Neuroimaging studies also reported that effective amygdala–vmPFC connectivity in emotional regulation tasks increases with age in childhood (Perlman and Pelphrey, 2011). Thus, the positive correlation between the PSS and the amygdala–to-vmPFC connectivity observed in adolescents may suggest robustly activated amygdala to stress that provides strong bottom-up affective inputs to the vmPFC, but insufficient top-down control of the yet immature vmPFC on the amygdala.

Similar to the amygdala-vmPFC circuitry, the amgydala-sgACC rsFC was also shown to be positively correlated with PSS in adolescents, negatively (although not surviving multiple-test correction) correlated with PSS in young adults, and not correlated in adults. The amygdala-sgACC circuitry showed weaker functional connectivity during emotional processing among the short allele carriers of the 5′ promoter region (5-HTTLPR) of the human serotonin transporter gene, who were shown to possess higher risk for affective disorders (Lotrich and Pollock, 2004), compared to the long allele carriers (Pezawas et al., 2005). In the groups of young adults and adults, the amygdala-sgACC pathway showed bidirectional couplings, similar to the amygdala-vmPFC connectivity. However, the connectivity was directed from sgACC to amygdala in adolescents. Studies have revealed that sgACC is associated with automatic regulation of stress response, whereas regions in ventral and dorsal PFC are involved in voluntary emotional regulation (Phillips et al., 2008). Our findings of the bottom-up projection of amygdala to vmPFC and top-down projection of sgACC-to-amygdala in adolescents not only indicate divergent roles of various areas in medial PFC in stress processing, but also suggest that the automatic emotional regulation starts with a top-down model and develops to a model with bidirectional connections, whereas the voluntary emotional regulation starts with a bottom-up direction and matures to a bidirectional connectivity pattern after adolescence.

The current findings should be considered in view of the following limitations. The present study used a cross-sectional design and was thus limited in delineating the complete longitudinal brain developmental trajectories. Future longitudinal studies are needed to provide more definitive evidence on the transitional relationship between perceived stress and prefrontal-amygdala connectivity patterns across different developmental stages. Also, while our imaging results suggested less-developed top-down affect regulatory functions between the vmPFC and amygdala, we obtained no significant differences across age groups on self-reported perceived stress. Two reasons may explain such null finding. First, all our participants were psychologically healthy, thus their levels of stress experience may tend to be more uniform and normalized (Yang and Huang, 2003). Second, the PSS focuses solely on subjective stress experience and provides no objective stress measures.

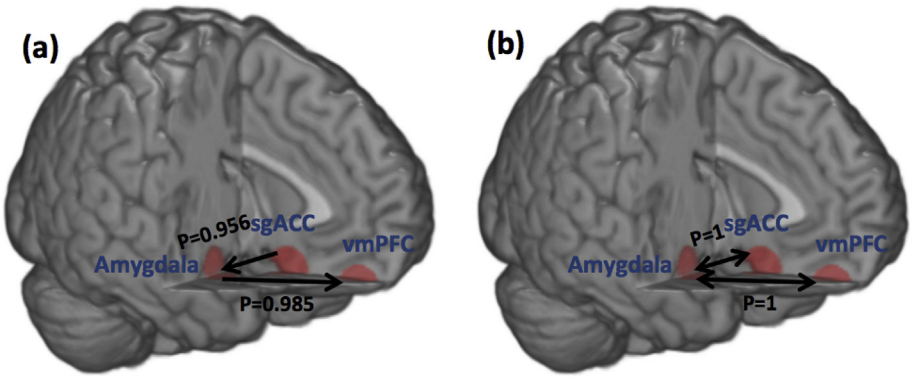

Fig. 3. Effective connectivity estimated using spectral dynamic causal modeling analyses in adolescent group (a), young adult and adult groups (b).

It is thus possible that the adolescent age group generally experienced less objective stress than the older age groups, resulting in comparable levels of perceived stress. Future research could complement the current findings by including clinical samples and employ laboratory stress-manipulation techniques to provide more direct evidence on the implication of vmPFC-amygdala connectivity patterns on affect/stress regulation.

6. Conclusions

Our findings support the notion that the neurodevelopmental trajectories from adolescence to adulthood contribute to changes in the relationship between perceived stress and PFC-limbic network functioning. Specifically, the amygdala-vmPFC circuitry was critically involved in regulation of stress processing, the nature and extents of which differed across adolescents, young adults and adults. Findings from this study help to further our understanding of the complex interplay between brain development, stress perception and PFC-limbic network functioning, with clinical implications in understanding and treatment of stress-related affective disorders in young individuals.

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Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2018.07.022.

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