NeuroImage: Clinical 20 (2018) 267–274

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

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

Jingsong Wu[a,1], Xiujuan Geng[b,1], Robin Shao[c,d,1], Nichol M.L. Wong[c], Jing Tao[a], Lidian Chen[e,***], Chetwyn C.H. Chan[f,**], Tatia M.C. Lee[b,c,d,*]

[a] *Rehabilitation Medicine College, Fujian University of Traditional Chinese Medicine, Fuzhou, China*
[b] *State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong*
[c] *Laboratory of Neuropsychology, The University of Hong Kong, Hong Kong*
[d] *Laboratory of Social Cognitive Affective Neuroscience, The University of Hong Kong, Hong Kong*
[e] *Fujian University of Traditional Chinese Medicine, Fuzhou, China*
[f] *Applied Cognitive Neuroscience Laboratory, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong*

ARTICLE INFO

Keywords:
Amygdala, brain development
Dynamic causal modeling
Resting-state functional connectivity
Stress
Ventromedial prefrontal cortex

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

---

* Correspondence to: T.M.C. Lee, Laboratory of Neuropsychology, The University of Hong Kong, Pokfulam Road, Hong Kong.

** Correspondence to: C. C.H. Chan, Applied Cognitive Neuroscience Laboratory, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hung Hom, Hong Kong.

*** Correspondence to: L. Chen, Fujian University of Traditional Chinese Medicine, No. 1 Huatuo Road Shangjie Minhou, Fuzhou 350122, China.

E-mail addresses: cld@fjtcm.edu.cn (L. Chen), chetwyn.chan@polyu.edu.hk (C.C.H. Chan), tmclee@hku.hk (T.M.C. Lee).

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.nicl.2018.07.022
Received 15 January 2018; Received in revised form 27 March 2018; Accepted 21 July 2018
Available online 23 July 2018

(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.