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Subgenual anterior cingulate-insula resting-state connectivity as a neural correlate to trait and state stress resilience



Robin Shao^{a,b,c}, Way K.W. Lau^b, Mei-Kei Leung^a, Tatia M.C. Lee^{a,b,c,d,*}

^a Laboratory of Neuropsychology, The University of Hong Kong, Hong Kong

^b Laboratory of Cognitive Affective Neuroscience, The University of Hong Kong, Hong Kong

^c The State Key Laboratory of Brain and Cognitive Sciences. The University of Hong Kong. Hong Kong

^d Institute of Clinical Neuropsychology, The University of Hong Kong, Hong Kong

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ABSTRACT

Accumulating evidence indicates important roles of the subgenual anterior cingulate cortex and rostral limbic regions such as the anterior insula, in regulating stress-related affective responses and negative affect states in general. However, research is lacking in simultaneously assessing the inter-relations between trait and state affective responses to stress, and the functional connectivity between the subgenual anterior cingulate and anterior insula. This preliminary research involved matched healthy participants with high (N = 10) and low (N = 10) self-reported trait stress resilience, and assessed their affective and subgenual anterior cingulate-anterior insula resting-state functional connectivity patterns before and after a psychosocial stress task. We found that while the low-resilience group displayed higher trait negative affect, along with greater decrease of left subgenual anterior cingulate-right anterior insula connectivity, following stress induction. Moreover, the functional connectivity change mediated group difference in affect change following stress task. We speculate that the contingent increase of negative affect, and the associated temporary decoupling of subgenual anterior cingulate-insula circuitry, may represent a normative and adaptive stress response underpinned by adaptive and dynamic interplay between the default mode and salience networks. Such findings, if consolidated, have important implications for promoting stress resilience and reducing risk for stress-related affective disorders.

1. Introduction

Stress is a common experience that has profound impact on our physical and psychological well-being (Van der Werff, van den Berg, Pannekoek, Elzinga, & Van Der Wee, 2013). Resilience or adaptive response to stress was defined as 'timely neurobiological responses to onset of stressor accompanied by fast subsequent decline of such response' (Rutten et al., 2013). Individuals with trait stress resilience are less adversely affected by stress exposure (Daniels et al., 2012), and less likely to develop stress-related depression, anxiety and posttraumatic stress disorder (PTSD) (Pizzagalli, 2014; Van der Werff et al., 2013). Pinpointing the neural correlates of stress resilience would thus open grounds for therapies aimed at boosting long-lasting adaptive stress responses.

Recent work is beginning to unravel the influence of dynamic interplays between the default mode network (DMN) and the salience network (SN) on stress response characteristics in both healthy and PTSD individuals (Daniels et al., 2010; Brunetti et al., 2017; Tobia, Hayashi, Ballard, Gotlib, & Waugh, 2017; see Van der Werff et al., 2013 for a review). In particular, both chronic and acute stress modulate functioning of the ventral and medial prefrontal cortex (mPFC), as well as the rostral limbic and striatal networks such as the insula and amygdala (Lambert, 2006; Russo, Murrough, Han, Charney, & Nestler, 2012), which may underlie the short- and long-term adverse effects of stress exposure on affect state and regulation (Pizzagalli, 2014). Notably, the ventral mPFC is considered to play important roles in negatively regulating the stress response pathways and in dissipating the effect of stress on potentiating negative affect and emotional reactions, as well as in the acquisition of stress resilience (Franklin, Saab, & Mansuy, 2012; Maier, 2015). Moreover, the ventral mPFC is part of the DMN which is involved in self-referential, self-reflective and selfawareness processes (Buckner, Andrews-Hanna, & Schacter, 2008; Northoff et al., 2006), making this region a critical neural substrate for processing and regulating self-related affective responses that are heightened in stress-related disorders such as PTSD (Daniels et al., 2010). Consistent with this, the ventral mPFC (and the anterior insula)

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^{*} Corresponding author at: Neuropsychology, Rm 656, Jockey Club Tower, The University of Hong Kong, Pokfulam Road, Hong Kong. *E-mail address*: tmclee@hku.hk (T.M.C. Lee).

showed the greatest activations when individuals with snake phobia could exert control over whether a snake stimulus would appear, suggesting a role of these regions in actively regulating stress-elicited affect responses (Kerr, McLaren, Mathy, & Nitschke, 2012). Further, increase of ventral mPFC resting-state functional connectivity (rsFC) with other DMN regions was associated with current PTSD symptom (Lanius et al., 2010), whereas decrease of insular rsFC with other limbic areas was linked with resilience to PTSD following trauma (Rabinak et al., 2011). The anterior insula is critically involved in affective, interoceptive processes and emotional awareness (Craig, 2009; Critchley, 2005). Along with the dorsal anterior cingulate and other limbic-striatal networks, the anterior insula forms part of the SN that is critical for switching between the DMN and the task-positive executive network (Peters, Dunlop, & Downar, 2016; Seeley et al., 2007). The SN is involved in higher-order cognitive control and facilitating the disengagement of task-irrelevant systems, including the DMN (Sridharan, Levitin, & Menon, 2008). As part of the SN, the anterior insula is critical for adaptive assignment of salience to relevant stimuli, dysfunction of which is identified in anxiety disorders (Menon, 2011). Past research examining the cross-network interplay in stress response revealed increased coupling between the DMN and SN (anterior insula) in PTSD (Sripada et al., 2012), and negative correlation between trait resilience and mPFC-insula rsFC (Brunetti et al., 2017), providing initial evidence that stress resilience is related to dynamic interactions of the task-positive and task-negative network functions. However, evidence is still lacking on the association between trait resilience and rsFC following and during recovering from stress.

As part of the ventral mPFC, the subgenual ACC (sgACC) is particularly relevant in the context of stress. The sgACC occupies the ventral portion of the mPFC that is situated below the genu and consisted of the Brodmann area 24 (anteriorly) and 25 (posteriorly). Recent research shows close positive association between cortisol response to social stress and rsFC between the sgACC and the SN (Thomason, Hamilton, & Gotlib, 2011), and negative association between severity of early-life stress and rsFC between the sgACC and limbic regions (Fan et al., 2014). The sgACC, along with the extended rostral limbic and striatal networks, is critically involved in emotional experience and regulation, and is closely implicated in affective/mood disorders such as major depression and bipolar disorder (Drevets, Savitz, & Trimble, 2008; Pizzagalli, 2014). Specifically, increased sgACC-anterior temporal lobe functional connectivity during self-blame predicted major depression relapse (Lythe et al., 2015). Further, remitted depressive patients exhibited reduced left sgACC-anterior temporal lobe functional connectivity during self-blame relative to controls (Green, Ralph, Moll, Deakin, & Zahn, 2012), raising the possibility that such reduction in sgACC connectivity could be a signature for resilience to negative affects during emotional challenge, given abnormally high functional connectivity strength between the sgACC and limbic regions may signal excessive internally-oriented emotional ruminative processing. However, Philippi, Motzkin, Pujara, and Koenigs (2015) found higher subclinical depression levels were associated with lower rsFC between the anterior sgACC and right anterior insula. The discrepant findings may be due to lack of emotional stressor in the latter study, raising the possibility that the sgACC-anterior insula functional connectivity may be modulated by stress exposure.

In this preliminary study, we aimed to explicitly investigate the relationship between DMN-SN interplay and stress resilience, by examining the inter-relations between sgACC rsFC with the rostral limbic/striatal network, self-reported trait stress resilience, and state affective responses to a psychosocial stress task. Acute stress was induced by performing a modified Montreal Imaging Stress Task (MIST), which had been repeatedly shown to elicit modest but reliable affective, behavioural and neural stress responses among nonclinical population (Dedovic et al., 2005, 2014). Following previous research that showed distinct rsFC patterns for left and right sgACC in depressed versus healthy individuals (Connolly et al., 2013; Gaffrey et al., 2010), we

separately examined the sgACC rsFC in the two hemispheres. Based on existing literature, we formed the following *a priori* main hypotheses: (1) Participants with higher self-reported trait resilience would show reduced rsFC between the sgACC and the rostral limbic/striatal network after the psychosocial stress exposure (relative to baseline) compared to those with lower trait resilience; (2) The same sgACC rsFC would mediate the relationship between trait resilience and affective responses to the stress exposure and (3) Difference in sgACC rsFC between high- and low-trait resilience individuals would be dependent on their affective responses to the stress exposure.

2. Material and methods

2.1. Participants

Ethical approval was granted by the University of Hong Kong. Informed consent form was obtained from each participant. In total a hundred and fifty-nine right-handed healthy subjects aged 18-30 years old were recruited through flyers, posters and emails, from which 10 high-resilience and 10 low-resilience participants were recruited (see below). All participants had normal or corrected-to-normal hearing and vision, and reported none of the following: (1) any current or previous episodes of neurological or psychiatric conditions; (2) any previous unexplained loss of consciousness; (3) frequent headaches; (4) magnetic resonance imaging (MRI) incompatibility such as mental implants in the head or body; (5) current medication that may affect the central nervous system functioning; (6) current pregnancy and (7) substance or alcohol abuse. Handedness was assessed using the lateral dominance test (LDT) (Dodrill and Thoreson, 1993). All participants additionally completed the Chinese version of the Connor-Davidson Resilience Scale (CD-RISC) (Yu and Zhang, 2007) and the trait anxiety subsection of the Chinese version of the State-Trait Anxiety Inventory (STAI) (Shek, 1988). Based on these measures, participants with high subjective resilience levels (the fourth quartile) together with low trait anxiety levels (the first quartile) were categorized into the 'high-resilience' group, whereas those with low subjective resilience levels (the first quartile) coupled with high trait anxiety levels (the fourth quartile) were categorized into the 'low-resilience' group. In total each of the high- and low-resilience groups contained 10 male and female participants, who were matched on age, gender and years of education (Table 1).

2.2. The modified Montreal Imaging Stress Task (MIST)

The MIST (Dedovic et al., 2005, 2014) is a neuroimaging-adapted psychosocial stress task that uses mental arithmetic to combine the key situational components for eliciting stress response, including presence of social evaluative threat, atmosphere of high achievement, and low controllability. Our adapted MIST consisted of two repeated runs in a block design, with each run lasting for about 10 min with pseudorandom presentations of a rest, a control, a low-stress and a high-stress condition, each repeated in 3 blocks. During the rest condition, participants were presented with the task interface but did not need to perform. During the control condition, participants were given a series of mental arithmetic tasks (e.g. 23 + 34 - 50 = ?) to perform with plenty of time allowance and no explicit stressor. On each trial, they were notified about the correctness of answer, but the message 'NOT RECORDED' was displayed. The low-stress condition was identical to the rest condition except that participants were under implicit time limit while performing on each trial (i.e. a possible time-out outcome). During the high-stress condition, a performance color bar was displayed on the top of screen indicating the participant's (inevitable poorer) performance relative to a 'mock' average individual, and upon response submission or time-out, the participant's performance on that trial was printed and 'RECORDED'. Further, a time advance bar was displayed that overtly signaled the time limit on a trial (Fig. 1). In both low- and high-stress conditions, the difficulty level and time limits on each trial

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