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Research paper

Endogenous cortisol-related alterations of right anterior insula functional connectivity under acute stress

Yuyang Zhu[a,b], Yituo Wang[c], Zheng Yang[b], Lubin Wang[b,*], Xiangjun Hu[a,**]

[a] Institute of Radiation Medicine, Academy of Military Medical Sciences, Beijing, 100850, China
[b] Institute of Military Cognition and Brain Sciences, Academy of Military Medical Sciences, Beijing, 100850, China
[c] Department of Radiology, Seventh Medical Center of the Chinese PLA General Hospital, Beijing, 100700, China

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ABSTRACT

Background: Previous studies have suggested that the right anterior insula (rAI) plays a vital role in salience processing and stress-related disorders. In this study, we aimed to investigate the relationship between rAI functional connectivity changes and individual differences in cortisol responses after acute stress, in order to provide insights into psychiatric illness vulnerabilities.

Methods: Thirty-five young men were enrolled in a randomized, counterbalanced two-session study, with aversive movie clip combined with electrical shocks as stress stimulation and the neutral movie clip as control stimulation. Resting-state fMRI data was acquired after movie exposure. The rAI was chosen as seed for functional connectivity analysis. We then examined the effect of acute stress on rAI functional connectivity and its association with individuals' cortisol response.

Results: We found decreased rAI functional connectivity in the fronto-parietal regions, but increased functional connectivity in the visual and somatosensory areas following acute stress. Moreover, stress-induced cortisol response was significantly positively correlated with the rAI functional connectivity in the medial prefrontal cortex, and negatively correlated with the orbital-frontal cortex, lingual gyrus, and middle temporal gyrus.

Limitations: Only young Chinese males without any trauma experience were recruited in this study.

Conclusions: The results suggested tight link between specific rAI functional connectivity alterations and individual stress reactivity, which may help elucidate the potential neurobiological mechanism underlying vulnerability to stress-related disorders.

1. Introduction

As part of our daily life, coping with acute stress is essential to a well-adapted life, and even of evolutionary importance (Darwin, 2004). Stress leads to responses at various levels, including the behavioral, physiological and psychological levels. These pluralistic responses harmonize together to effectively cope with h omeostatic challenges. According to the stress-vulnerability model, the interactions between certain stressors with specific vulnerability of an individual are a pathogenetic factor of psychopathology diseases (Faravelli et al., 2012). Inadequate, excessive or prolonged stress responses can lead to such psychopathology disorders as depression, anxiety and post trauma disorders (Faravelli et al., 2012; McEwen and Gianaros, 2011). Therefore, investigation of neural correlates of individual difference in the magnitude of stress-responses may inform our understanding of how stress contributes to psychopathology in vulnerable individuals (Qin et al., 2009; Van Oort et al., 2017).

Exposure to acute stress promotes reorganization of brain systems for salience information processing (Hermans et al., 2014; Liu et al., 2018; Maron-Katz et al., 2016; Van Oort et al., 2017). As a critical hub of the salience network (SN), the anterior insula (AI) is considered a principal brain region in the integration of physiological states, emotions, cognition, and interaction with other essential networks such as the default mode network (DMN) and the central executive network (CEN) (Craig, 2009; Menon, 2011; Menon and Uddin, 2010; White et al., 2010). In particular, the right but not left anterior insula is proved to serve as a "causal node" in initiating the switching between internally (e.g., DMN) and externally focused networks (e.g., CEN)

* Corresponding author at: Department of Cognitive psychology, Institute of Military Cognition and Brain Sciences, Academy of Military Medical Sciences, 27 Taiping Road, Beijing, 100850, China
** Corresponding author at: Department of Experimental Pathology, Institute of Radiation Medicine, Academy of Military Medical Sciences, 27 Taiping Road, Beijing, 100850, China
E-mail addresses: wanglb@bmi.ac.cn (L. Wang), xjhu2003@vip.sina.com (X. Hu).

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(Menon, 2011; Menon and Uddin, 2010; Sridharan et al., 2008; Uddin, 2015). Previous studies have also revealed functional lateralization of the AI, with the preferential involvement of the right AI (rAI) in the internal focus on physical and emotional states (Evrard et al., 2012; Uddin, 2015). .The rAI was activated to a greater extent during the internal focus on physical, emotion and emotional states (Critchley et al., 2004; Napadow et al., 2013; Zaki et al., 2012).

Moreover, rAI dysfunction was found to be related to many stress-related disorders. For instance, rAI functional connectivity with the medial orbital frontal cortex was found to decrease in case of obsessive-compulsive disorders (Fan et al., 2017). Glucose metabolism was found to decline in the rAI in post traumatic stress disorder (PTSD) patients, and the degree of reduction was related to the severity of symptoms (Jeong et al., 2019). Other studies also reported that patients with right anterior insula (rAI) lesions had a greater frequency of depression symptoms than those with left or non-insular lesions (Manes et al., 1999). Taken together, these findings suggest that an appropriate level of rAI activity is needed to provide an appropriate alert signal that initiates brain responses to salient stimuli (Uddin and Menon, 2009), and improper function of the rAI under stress may be a vulnerable factor for mental disorders.

Cortisol, as an end product of the hypothalamus–pituitary–adrenal (HPA) axis function following stress exposure, is a major marker for stress sensitivity (Ali and Pruessner, 2012; Armario et al., 1996; Bozovic et al., 2013; Russell et al., 2012). Individual cortisol changes are correlated positively with activation in many of the brain structures, including the medial temporal gyrus, amygdala and anterior cingulate cortex (ACC) in acute psychological stress situations (Henckens et al., 2015; Thomason et al., 2011). Besides task-conditions, such associations have also been observed in the absence of ongoing task-demands. For example, functional connectivity within and between large-scale brain systems after acute stress exposure is correlated with multiple physiological and psychological measurements including cortisol (Hermans et al., 2011; Zhang et al., 2019). Given the critical role of the rAI in salience processing, more evidence on cortisol-related rAI alterations is needed to gain insights into psychiatric illness vulnerabilities.

In this study, we evaluated the effect of acute stress on the rAI functional connectivity measured during resting-state functional magnetic resonance imaging (fMRI), and further assessed the association between changes in the rAI functional connectivity and salivary cortisol. We used aversive (vs. neutral) movie clips accompanied by a mild electric shock to induce acute psychological and physiological stress in a group of healthy males. Based on previous findings, we hypothesized that alterations in rAI functional connectivity with regions involved in DMN and CEN might be associated with individual differences in cortisol stress-responsiveness.

2. Materials and methods

2.1. Participants

Thirty-five young healthy males were enrolled in this study by advertisements, and were given compensation for their participation. The age of these subjects ranged from 22 to 31 with a mean ± SD of 26.05 ± 3.31 years. All of them had normal or corrected-to-normal vision, free of color-blindness, and reported no history of neurological, psychiatric, or endocrine diseases. There was no current use of any psychoactive drugs or corticosteroids, and no habit of watching horror movies or playing horror video games. None of them had experienced severe physical or emotional trauma. Written informed consent was obtained before the experiment. Research procedures were approved by the local Research Ethics Committee of Academy of Military Medical Sciences.

2.2. Experimental procedure

This study was part of a project that investigated the effect of acute stress on cognitive functions in the brain and was performed at the Affiliated Hospital of the Academy of Military Medical Sciences. A detailed description of the experimental procedures is available in Wang et al. (2018). In short, an emotional movie clip paradigm combined with mild electrical stimulation was used in this experiment to induce aversive stressful emotions, and resting-state fMRI was acquired soon after movie watching. Participants viewed movie clips inside the scanner from a mirror in front of their eyes and listened to the sound with a pair of fMRI compatible earphones. All the participants took part in a two-session study, with a randomized, counterbalanced order of stress-induction (aversive vs. neutral movie clips) as the within subject factor. There was a minimum of one-week interval between the two sessions. All the sessions were carried out between 6 and 10 pm to ensure relatively stable and low levels of endogenous cortisol.

In this study, we used short movie clips selected from an Asian horror movie, *Shutter* (2004, by Banjong Pisanthanakun), as the stress arousal material. The extract we chose was 63min 15s - 65min 20s (about 2 min) from the original movie. The plot in this clip was unpredictable, novel and uncontrollable, which was in line with the determinants of human stress response described by Mason (1968). For the neutral session, we chose to use an equally long non-arousal documentary clips (*Wonderful town*, 2007, by Aditya Assarat). The time point from the original movie was 20min 10s - 22min 20s. These two movie clips were both performed by Asian actors so that we expected stronger emotional involvement on the part of our participants who were reminded to watch the movies attentively and imagine themselves in the scene from an eyewitness perspective. Luminance, volume and language were controlled for the two clips.

During the stress session, randomly aroused electrical shocks were used to lead to more robust cortisol response (Hermans et al., 2011). Each shock went on for 2 seconds, with inter-stimulus intervals that ranged from 30 to 40 seconds. Each participant was subjected to shock four to six times. The shock intensity varied across participants, depending on their oral report that they felt discomfort rather than pain.

2.3. Psycho-physiological measurements of stress

Heart rate and salivary cortisol were measured to monitor the autonomic response and the HPA axis response during the procedure. Data on heart rate was collected through an MR-compatible Biopac MP150 heart rate module (USA) throughout the experiment. Due to the hysteresis of salivary cortisol, after-stimulus salivary samples were collected after the collection of the rest fMRI, namely twenty minutes after the movie exposure (Hermans et al., 2014). Saliva samples were stored in -20°C immediately after collection before the samples were analyzed using an enzyme-linked immunosorbent assay (ELISA) to determine cortisol levels.

2.4. fMRI data acquisition

The fMRI data was acquired on a 3.0-T Skyra MR scanner (Siemens, Erlangen, Germany) at the Affiliated Hospital of the Academy of Military Medical Sciences, China. During the resting-state scans, subjects were instructed simply to keep their eyes closed, stay awake, and relax. A series of 240 T2-weighted functional images was acquired using a gradient echo-planar imaging (EPI) sequence with the following parameters: 33 contiguous axial slices, slice thickness = 3.5 mm, voxel size = 3.5 × 3.5 × 3.5 mm; repetition time (TR) = 2000ms, echo time (TE) = 30 ms, flip angle = 90°, field of view (FOV) = 224mm. High-resolution structural images were acquired using a T1-weighted 3D magnetization-prepared rapid gradient echo sequence with the following parameters: 176 contiguous sagittal slices, slice thickness = 1.0 mm, voxel size = 1.0 × 1.0 × 1.0 mm; TR = 4000 ms, TE = 2.98 ms,

flip angle = 4°, FOV = 256 mm.

2.5. fMRI data analysis

Image processing and statistical analysis were implemented in MATLAB using custom scripts and the framework provided by SPM8 (Wellcome Department of Imaging Neuroscience, University College London, UK; http://www.fil.ion.ucl.ac.uk/spm) and REST software (http://restfmri.net/forum/index.php). The first 10 time-points were discarded to avoid transient signal changes due to unsteady magnetization, and to allow participants to become accustomed to the scanning noise. Remaining images were corrected for acquisition delay between slices and realigned to the first volume to eliminate inter-scan head motions. The resulting images were normalized to the Montreal Neurological Institute (MNI) space and resliced to 3 × 3 × 3 mm^3 before being spatially smoothed with a Gaussian filter of 6 mm full-width half-maximum kernel.

Several additional steps were conducted for functional connectivity analysis. These steps included: (1) multiple regression of nuisance variables, (2) temporally filtering with a band-pass filter (0.01-0.1Hz), and (3) linear detrending to remove any residual drift. The nuisance variables included signals averaged from white matter, cerebrospinal fluid and the whole brain, six parameters obtained by head motion correction, and outlier volumes flagged by the artifact detection tool (ART; http://www.nitrc.org/projects/artifact_detect). A volume was defined as an outlier and scrubbed if the absolute head motion was > 0.5 mm from the previous scan, or if the scan-to-scan global signal change was > 3 standard deviations of the global brain signal. Outlier volumes in the global mean signal intensity and motion were scrubbed by including them as nuisance regressors (i.e. one regressor per outlier) during the multiple regression procedure. Four subjects were excluded from this study because of serious head motion during the stress or neutral condition scanning (less than 150 volumes after scrubbing), leaving a final sample of 31 subjects. The remaining subjects did not differ in residual head motion between the two conditions (neutral: 0.093 ± 0.024 mm; stress: 0.091 ± 0.023 mm; paired t-test, P = 0.674).

In this study, the seed region was defined as a 6-mm radius sphere centered on previously published activation peak of the rAI in response to oddball stimuli (MNI coordinate: 37, 25, -4) (Sridharan et al., 2008). The time series of the seed region were calculated by averaging the fMRI time series over all voxels within the region. The correlation map was created by calculating Pearson's correlation coefficients between the ROI time series and the time series of all voxels in the brain for every participant. Fisher's r-to-z transformation was used to convert these correlation maps in order to improve the normality of the correlation coefficients.

Group analysis between stressful condition and neutral condition was performed. One-sample t-test was first applied to assess the whole-brain functional connectivity of the rAI. Then, 31 individual correlation maps of neutral and stress conditions were entered for the paired t-test. The correlation between cortisol changes and stress-induced functional connectivity changes was assessed using a multiple regression model. The individual cortisol changes, which were the subtraction between stressful condition and neutral condition, were defined as the covariate of interest. Significance level was set at a false-positive rate of $P < 0.05$, corrected for multiple comparisons using the AlphaSim method in REST software.

3. Results

3.1. Physiological stress measurements

Heart rates during stressful and neutral movie watching stages and subsequent cortisol levels, namely 20 min after stress exposure, are shown in Fig. 1. During movie watching stages, a paired t-test between two conditions revealed a significant increase in heart rate under the stress condition ($T = 6.785$, $P < 0.0001$, see Fig. 1A).

The consequent salivary cortisol levels (20 - 30 min after movie exposure) between two conditions are shown in Fig. 1B. Under the stressful condition, cortisol levels were significantly higher ($T = 2.265$, $P = 0.03$). And as shown by the graph, some participants had higher cortisol levels under stressful conditions, while some kept their levels stable or even had them lowered, suggesting the existence of inter-individual variation in glucocorticoid sensitivity in response to stress (Lin et al., 2020; Thomason et al., 2011).

No significant correlations between heart rates during the movie watching stages or the resting stages with cortisol changes were found ($R = -0.14$, $P = 0.43$).

3.2. fMRI results: functional connectivity of rAI

The resting-state rAI functional connectivity patterns under stressful conditions and neutral conditions are shown in Fig. 2. Under neutral condition (Fig. 2A), rAI showed positive connectivity with the dorsal anterior cingulate cortex, dorsolateral prefrontal cortex and supramarginal gyrus, but was negatively correlated with the medial prefrontal cortex, orbital frontal cortex and visual cortex. Under stressful conditions (Fig. 2B), the functional connectivity revealed mostly the same patterns, except that negative rAI functional connectivity with the visual cortex and medial prefrontal cortex was eased.

The brain areas with altered rAI functional connectivity after stress induction are shown in Fig. 3A. The functional connectivity strength of the significant clusters for stressful and neutral conditions are illustrated in Fig. 3B. By contrasting stressful conditions with neutral ones, we found increased functional connectivity between rAI and sensory-related regions including the bilateral middle occipital gyrus (local maxima at [12, -93, 33] and [-21, -90, 36]) and the right postcentral gyrus (local maxima at [24, -39, 72]). rAI functional connectivity with the right dorsal lateral prefrontal gyrus (dlPFC, local maxima at [45,15, 51]) and bilateral interior parietal lobe (IPL, local maxima at [-66, -42, 18] and [48, -63, 36]) were found to be decreased, So did functional connectivity in the right orbital frontal cortex (local maxima at [33, 57, -6]) and the right middle temporal gyrus (local maxima at [57, -36, -15]) (see Table 1 and Fig. 3).

3.3. fMRI results: correlations with cortisol responses

Regressions of cortisol differences and rAI functional connectivity alterations under acute stress are shown in Fig. 4 and Table 2. Stress-induced cortisol increase was correlated with rAI functional connectivity changes in the right superior frontal gyrus (local maxima at [15, 21, 60]) and the right medial prefrontal cortex (mPFC, local maxima at [3, 51, 9]), both of which belong to the anterior parts of the DMN. Cortisol changes were negatively correlated with rAI functional connectivity changes in the left orbital-frontal gyrus (local maxima at [-42, 42, -9]), left lingual gyrus (local maxima at [-33, -66, -12]), and bilateral middle temporal gyrus (local maxima at [-63, -57, -3] and [69, -33, 24]).

4. Discussion

In this study, we investigated rapid, stress-induced connectivity changes of the rAI, and analyzed rAI functional connectivity changes as a function of the individual stress-response magnitude, measured by the stress-hormone cortisol. In sum, decreased connectivity was found between rAI and pivotal nodes in CEN (dlPFC and IPL), the network that is essential for cognitive execution and attentional control. Cortisol stress response levels were positively associated with connectivity between rAI and anterior areas of DMN (aDMN) that were known to be responsible for internal processing and homeostasis. These findings matched the well-known assumption of stress-induced network

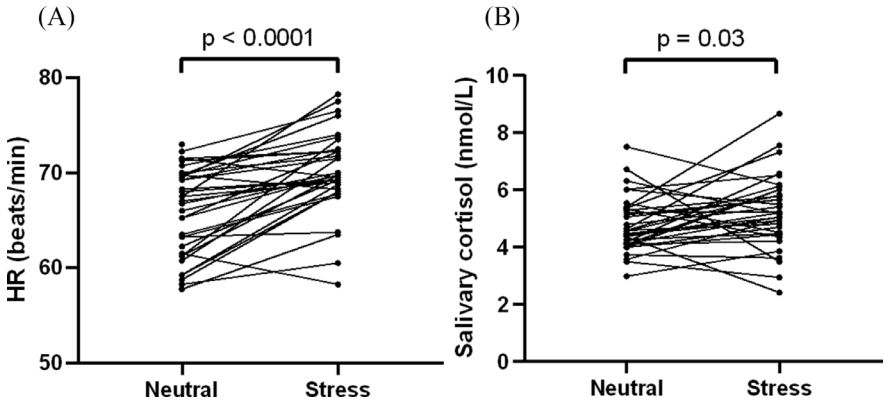

Fig 1. Psycho-physiological Measurements of Stress. (A). Individual heart rates during resting states; and (B). Afterwards individual cortisol levels in neutral condition and stressful condition.

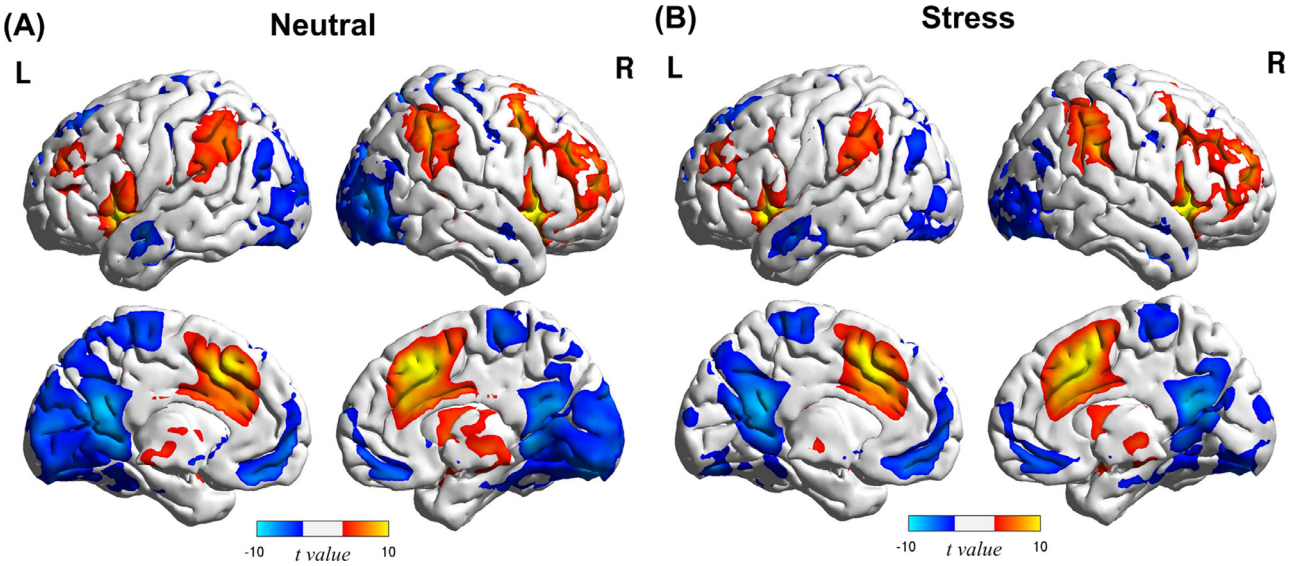

Fig 2. Whole-brain functional connectivity patterns of the rAI in both experimental conditions. (A): Neutral condition; (B): Stress condition.

reorganization, and suggested that individual stress response sensibility might function with self related internal processing.

4.1. Stress induced rAI functional connectivity alterations

In line with a well-accepted assumption that exposure to acute stress would impair cognitive function (Diamond, 2013; Hermans et al., 2014), we observed decreased rAI functional connectivity with the dlPFC and IPL (Fig 3B; Table 1), both of which are main nodes in the CEN. The interactions between SN and CEN have been proved to play a key role in higher-order cognitive processing. As reviewed by Hermans and colleagues, exposure to acute stress would quickly prompt a re-allocation of resources to the SN at the cost of CEN, and inadequate rebalance of these networks may be responsible for stress-related psychiatric disorders like PTSD (Hermans et al., 2014). Our findings suggested that acute stress might block the interaction between salience and cognitive processing areas.

We also found decreased rAI functional connectivity in the right OFC and MTG. (Fig. 3B; Table 1). The OFC is implicated in a variety of functions, particularly in regulating emotional responses (for review, see (Milad and Rauch, 2007)). In patients with PTSD and panic disorder, both the OFC volume and functional activity were decreased (for review, see Jackowski et al., 2012). Studies also found that social anxiety disorder patients have impaired MTG connectivity with insula when exposed to social threats, which may lead to faulty perception of emotional threats from others (Berthier et al., 2016; Choi et al., 2016; Cremers et al., 2015). In combination with former findings, our results suggested that rAI functional connectivity with emotion related regions decreased after acute stress.

On the other hand, we found stress-induced increases of rAI functional connectivity in the bilateral middle occipital gyrus and right postcentral gyrus. Research showed that stress induction may lead to a hypervigilant state with increased and equally high responses of the SN for emotionally valenced faces (Van Marle et al., 2010) and increased activity in the visual system for emotional pictures (Henckens et al., 2009). Physical stressors like cold water (Jarrahi et al., 2018; Lapotka et al., 2017) and electric shocks (Kurth et al., 1998) would also arouse the activity of somatosensory regions. Therefore, this increased rAI connectivity in visual and somatosensory regions might have been due to rich salient information contained in aversive movie clips and feelings of mild electric shocks under stressful conditions.

4.2. Relationship between changes in cortisol level and rAI connectivity

The functional connectivity between rAI and anterior areas of DMN (SFG and mPFC) was positively correlated with salivary cortisol changes (Fig. 4A, B; Table 2). This finding was consistent with that of Vaisvaser et al. (2013), who discovered increased connectivity of the mPFC seed with the AI during stress induction. The anterior areas of DMN (aDMN) were consistently activated in tasks of emotion,

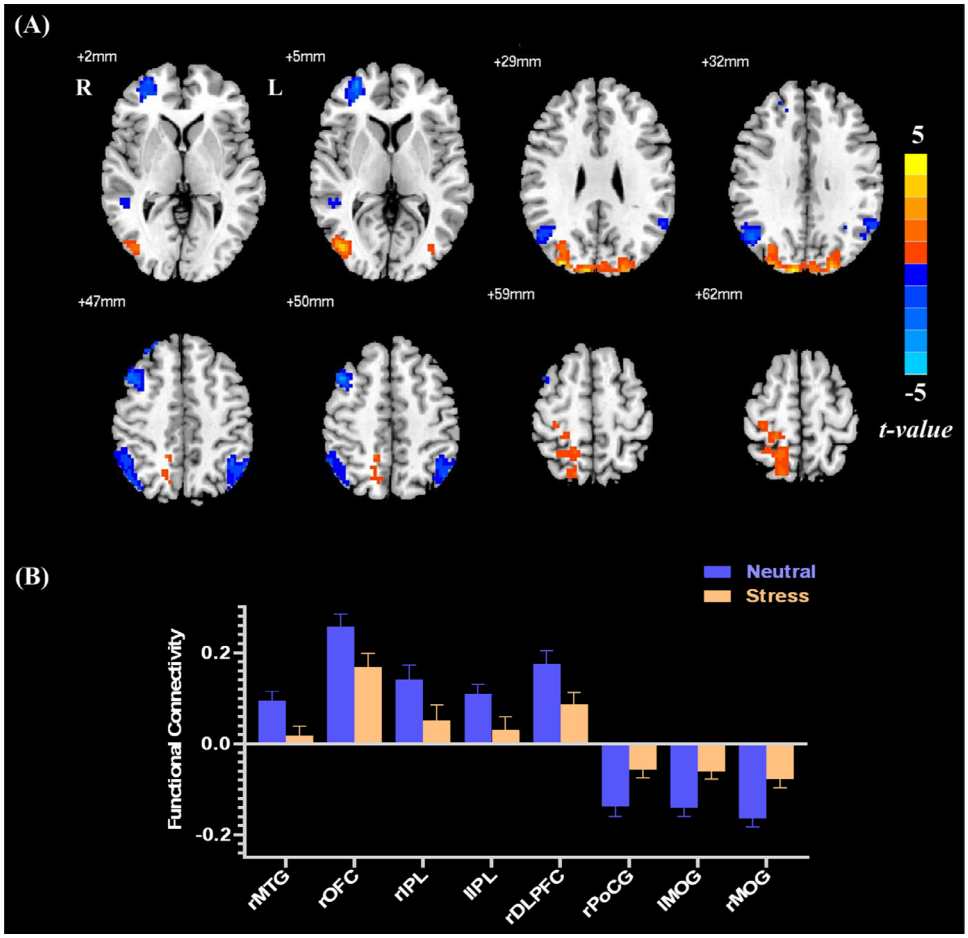

Fig. 3. Brain areas with altered rAI functional connectivity after stress induction. Error bars indicates SEM. L and R indicate the left and right side of the brain. MTG: middle temporal gyrus; OFC: orbital-frontal cortex; IPL: interior parietal lobe; DLPFC: dorsal-lateral prefrontal cortex; PoCG: postcentral gyrus; MOG: middle occipital gyrus.

interoception (Laird et al., 2009), and self-referential processing (Lord et al., 2012; Pruessner et al., 2008; Van Oort et al., 2017). Altered rAI and DMN connectivity changes were also related to psychopathology. For example, among patients with major depression, who are characterized by an excessive focus on negative internal processing, there is an increased connectivity between the insula and DMN (Andrews-Hanna et al., 2014). PTSD patients also revealed elevated connectivity between AI and DMN (Sripada et al., 2012). Therefore, the positive relationship between rAI-aDMN connectivity changes and cortisol stress responses indicates that more stress-sensitive individuals would have increased functional links between the salience processing hub and self-referential processing areas, which may be a dispositional factor for psychopathology (Wang et al., 2015). .

On the other hand, we found negative correlations between cortisol changes and rAI functional connectivity with the OFC, MTG and lingual gyrus (Fig. 4C–F; Table 2). OFC is characterized by large numbers of glucocorticoid receptors, thus increasing the sensitivity to HPA responses (Amat and José, 2005; Herman et al., 2005). In this study, we found significantly decreased rAI functional connectivity in OFC and MTG after acute stress, as well as significant negative correlations between cortisol stress responses and changes of rAI functional connectivity in OFC and MTG (see Figs. 3 and 4). This indicates that the stronger the cortisol responses, the greater decreases of functional connectivity between these regions and rAI. LG has also been found to be part of the fear network, which acts in concert with medial structures (such as the thalamus and the amygdala), frontal regions and other sensory regions to process the identification and adaptation of fear (Leitman et al., 2008). Therefore, our results might reveal that after acute stress, all participants went through a functional deficit in emotion processing, and that more sensitive participants (those with higher

Table 1
Clusters and coordinates of stress induced changes in rAI functional connectivity.

Region	Broadmann area	Hemisphere	Cluster size	Peak MNI Coordinates			*t-value*
				x	y	z	
Stress > neutral							
Middle occipital gyrus	19	Right	350	12	-93	33	4.36
Middle occipital gyrus	19	Left	276	-21	-90	36	4.36
Postcentral gyrus	7	Right	256	24	-39	72	3.22
Stress < neutral							
Middle temporal gyrus	21	Right	246	57	-36	-15	-3.56
Orbital frontal cortex	10	Right	266	33	57	-6	-4.55
Inferior parietal lobe	40	Left	277	-66	-42	18	-3.42
Inferior parietal lobe	40	Right	331	48	-63	36	-3.39
dlPFC	9	Right	241	45	15	51	-3.77
dlPFC: dorsal lateral prefrontal gyrus							

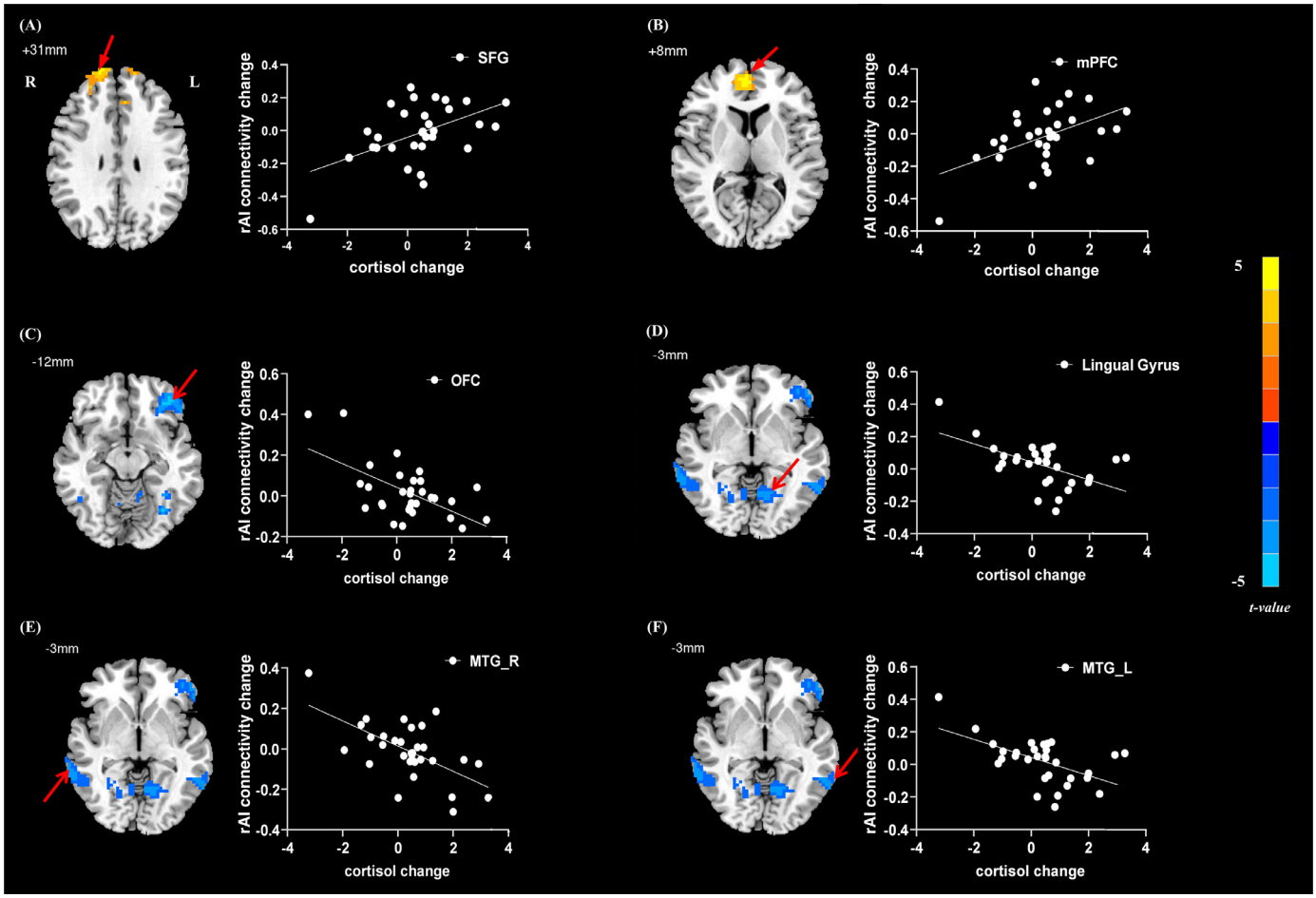

Fig 4. Correlations between cortisol changes and changes in rAI resting-state functional connectivity by contrasting stressful with neutral condition. L and R indicate the left and right side of the brain. SFG: superior frontal gyrus; mPFC: middle prefrontal cortex; OFC: orbital-frontal cortex; MTG: middle temporal gyrus.

cortisol response levels) were likely to undergo severer deficits while regulating stress-induced negative emotional stimulations.

Although we found overall decreased rAI functional connectivity with dlPFC and IPL, correlations between rAI functional connectivity changes in CEN regions and cortisol changes were absent. Cortisol-related functional connectivity studies revealed that individual differences in cortisol responses mainly were mapped onto variability in brain regions related to autonomic arousal and subjective feeling states, like ACC and mPFC (Kiem et al., 2013; Thomason et al., 2011). In conjunction with our previous findings, our results suggested that acute stress-induced cortisol responses might be more sensitive with internally focused (e. g. DMN) rather than externally focused (e.g. CEN) brain areas.

It is worth noticing that although heart rate in the process of watching stressful and neutral movies changed significantly, no heart rate changes were observed during resting-state fMRI scanning ($P = 0.43$). This conformed with physiological mechanisms and previous studies (Everaerd et al., 2015; Hermans et al., 2014) in that stressful movies led to a significant but short-lived change in heart rate but chronic increases in cortisol levels. As the salient information processing center, SN activity and connectivity during acute stress are correlated with multiple physiological and psychological measures of stress (Hermans et al., 2011), especially for the increased heart rate (Gogolla, 2017; Wager et al., 2009; Young and Wek, 2016). In the current study, heart rates during the resting-state fMRI scanning period did not vary across conditions, therefore mitigating the concern that rAI functional alterations were the result of vascular rather than neural processes (Chang et al., 2013). We have also found no significant correlation between stress-induced heart rate change and cortisol response. A possible explanation is that heart rate change is more short-lived than

Table 2
Clusters and coordinates of the association between cortisol change and changes in rAI functional connectivity: comparison of stressful and neutral conditions.

Region	Broadmann Area	Hemisphere	Cluster size	Peak MNI Coordinates			*t-value*
				x	y	z	
positive							
midial Prefrontal cortex	10	Right	380	3	51	9	3.21
Superior frontal gyrus	6	Right	293	15	21	60	2.89
negative							
Orbital frontal cortex	10	Left	370	-42	42	-9	3.96
Lingual gyrus	30	Left	360	-33	-66	-12	3.33
Middle temporal gyrus	21	Left	72	-63	-57	-3	3.09
Middle temporal gyrus	21	Right	269	69	-33	24	3.56

cortisol response after acute stress (Zandara et al., 2016). The timely variable responses of neurochemicals and sophisticated interaction between the automatic nervous system and HPA axis need to be explored further.

4.3. Limitations and further directions

We have to acknowledge that this study has some limitations. Firstly, participants in this study were all young Chinese males without trauma experience. Factors such as gender, age range, race/ethnicity, and previous trauma exposure could have potential impacts on the findings (Autry et al., 2009; Van Cauter et al., 1996; Young and Korszun, 2010) Secondly, we used only static functional connectivity to measure the temporal synchronization of rs-fMRI time series. Recently, there is increasing evidence that resting-state functional connectivity is dynamic and exhibits spontaneous fluctuation on a smaller timescale (Hutchison et al., 2013; Wee et al., 2016). Identification of such non-stationary connectivity patterns would provide additional information regarding relationships between the brain's functional organization and individual's stress reactivity. Thirdly, this study investigated cortisol changes and RSFC in rAI and other regions. Stress-related neuromodulators (in particular noradrenaline) can trigger brain-state alterations by reorganizing neural activity within large-scale neuronal systems (Hermans et al., 2014). Considering the sophistication of neuromodulators and their functions, further investigations are needed to reveal how neurochemicals and brain functions interact with each other under acute stress.

5. Conclusions

In conclusion, this study revealed acute stress induced resting-state functional connectivity changes using rAI as the seed and the relationship with stress response cortisol changes. The rAI functional connectivity was found to decrease with pivotal nodes in CEN. Sensory related cortices and visual imaginary related regions were also altered after stress. Cortisol stress response levels were positively associated with connectivity between rAI and anterior areas of DMN. These findings match the idea of a stress-induced network reorganization and suggest that increased aDMN and decreased regions in CEN connectivity with rAI may function as relevant neural indicators for stress responsiveness and interacts with individual stress response sensitivity.

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Declarations of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.05.123.

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