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ORIGINAL RESEARCH

Acute social stress modulates coherence regional homogeneity

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Abstract

It is a generally accepted observation that individuals act differently under stress. Recent task-based neuroimaging studies have shown that individuals under stress favor the intuitive and fast system over the deliberative and reflective system. In the present study, using a within-subjects design in thirty young adults, we examined whether and how acute social stress impacts regional neural activity in resting state. The results showed that stress induced lower coherence regional homogeneity (Cohe-ReHo) values in left hippocampus and right superior frontal gyrus, both of which are regions associated with deliberative decision making. Stress-induced cortisol change was significantly and positively correlated with the change in Cohe-ReHo value in the right midbrain, a region involved in habitual decision making. These results extend previous findings by demonstrating that stress modulates local synchrony in brain regions implicated in deliberative and intuitive decision making. Our findings might be useful in understanding the neural mechanisms underlying stress-related mental disorders.

Keywords Cohe-ReHo · Stress · Hippocampus · Prefrontal cortex · Midbrain

Introduction

Stress is ubiquitous in everyday life. Stress could be caused by various factors, ranging from trivial events, for example, the time pressure to get up for school, to a fierce change in external environment, such as a natural disaster. Stress and the hormones induced by stress, adrenaline and glucocorticoids (cortisol in humans), affect a number of cognitive processes, from basic cognitive function, such as attention, to complex tasks, like memory and decision making (Sandi 2013; Lars Schwabe and Wolf 2013; Olver et al. 2015; Yu 2016). Long-term exposure to stress increases the risk of developing stress-related mental disorders, such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) (Vinkers et al. 2014; Sterlemann et al. 2008).

The dual process theory is a widely accepted model in cognitive psychology (Evans and Frankish 2009). The model argues that there are two fundamentally different systems to process information. One system is independent of cognitive ability, and works in a rapid, automatic, and intuitive way. The other system supports reflective thinking, which is associated with control processes, and is hence seemingly more analytical and rational (Evans and Stanovich 2013). Previous studies found that stress modulates the engagement of these systems in various cognitive processes (Youssef et al. 2012; Haeffel et al. 2007; Simonovic et al. 2017; L. Schwabe and Wolf 2012). Recent functional imaging studies have also supported the manipulation effect of stress on the dual systems. Stress has been documented to promote a shift from the cognition-demanding deliberative system to the fast habitual system in a wide variety of tasks (Yu 2016; Vogel et al. 2016).

The prefrontal cortex and hippocampus, the critical brain regions involved in deliberative and reflective processes, are the core brain regions responsive to stress (Bruce S. McEwen et al. 2015; B. S. McEwen et al. 2016; Lars Schwabe and Bolam 2017; Arnsten 2009). Chronic glucocorticoid administration dramatically reorganized the dendritic morphology of medial prefrontal cortex, possibly due to stress-induced cognitive changes (Wellman 2001; Gray et al. 2014). The hippocampus plays an important role in declarative memory and learning under stress (Lars Schwabe et al. 2008; Sandi 2013). Previous studies have detected that stress induces morphological changes and synaptic strength reduction in whole hippocampal structure or specific subregions (Lee et al. 2009; Brunson 2005; Pittenger and Duman 2008). For example, the

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dendrites of hippocampal CA3 and CA1 shrank on exposure to chronic stress (Brunson 2005; Bruce S McEwen 1999). Further, Travis et al. found that the mean cortisol level at multiple time points after waking up in healthy controls was negatively related with right CA1–3, right hippocampal head and right total hippocampus volume, and the salivary cortisol levels measured 8 h after awakening were negatively associated with the performance in memory task which demanded cognitive resource (Travis et al. 2016). In addition, accumulating evidence suggests that stress also affects brain regions related to intuitive and fast system, for example, the dorsal striatum (including putamen and caudate) and the midbrain (especially periaqueductal gray) (Lars Schwabe and Wolf 2013; L. Schwabe and Wolf 2012; D. Mobbs et al. 2007). In studies using artificial predators as a threat, the midbrain region was activated with more automatic and quick reactions observed as threat became closer (D. Mobbs et al. 2009; D. Mobbs et al. 2007). Moreover, recent neuroimaging studies found that stress favored the striatum-based procedural memory system over the hippocampus-based cognitive memory system, displaying a decrease in hippocampal activity but unchanged striatal cortical activity under stress (L. Schwabe and Wolf 2012; Lars Schwabe and Wolf 2013; Lars Schwabe et al. 2012).

To date, majority of studies focus on stress-induced changes in brain regions related to deliberative and habitual decision making during various tasks (L. Schwabe and Wolf 2012; D. Mobbs et al. 2009; Atsak et al. 2016). However, the observed intensity of brain activity in response to an external task is based on the resting state of the brain (Ances et al. 2008; Fleisher et al. 2009b). For example, Fleisher et al. found that a group with high risk for Alzheimer's disease had increased activity in the medial temporal lobe compared with a low risk group during a face/name encoding task (Fleisher et al. 2009a). However, this difference between the two groups disappeared when the resting state was considered (Fleisher et al. 2009a). Thus, there is a need to explore whether and how stress affects deliberative and habitual systems in resting state. In the present study, using a within-subjects design, we examined how acute psychological social stress orchestrated regional brain activity in target brain regions associated with the two systems at rest. Compared with previous studies adopting between-subject design (Kruse et al. 2017; Maier et al. 2015), we adopted the within-subject design to avoid any influence of individual variations on the dependent variable (i.e. regional brain activity). Being complementary to the traditional functional connectivity analysis that measures the connectivity between two remote brain regions, the regional homogeneity value (ReHo) measures the similarity of the time series of a given voxel to its nearest 26 voxels within a single region using Kendall's coefficient concordance (KCC) and provides information about local temporal synchrony in the brain (Zang et al. 2004). KCC is based on temporal information and it decreases if there are lags in time courses (F. Liu et al. 2012). To overcome these limitations, coherence regional homogeneity (Cohe-ReHo) is proposed to measure regional synchronization in frequency domains. Cohe-ReHo is considered to be more suitable when there are large random noises due to phase delay among time series (F. Liu et al. 2012; Y. Liu et al. 2017; D. Liu et al. 2010). A previous study comparing Cohe-Reho to KCC-Reho found that the former is more sensitive to the differences in spontaneous activity between different conditions (eye-open vs. eye-close) and groups (attention deficit hyperactivity disorder vs. normal controls) (D. Liu et al. 2010). In this study, based on previous studies, we focus on the impact of stress on the Cohe-Reho value in the regions that have been shown to be vulnerable to stress and involved in dual processing, including hippocampus, prefrontal cortex, dorsal striatum (putamen and caudate) and midbrain (D. Mobbs et al. 2007; Arnsten 2009; Gray et al. 2014; B. S. McEwen et al. 2016). Previous research used striatum and periaqueductal gray as seeds to conduct functional connectivity analysis, and found hyper-connectivity of these seeds with other brain regions in resting state in social anxiety disorder patients (SAD) relative to controls, and therefore revealed the active state in the striatum and periaqueductal gray in the resting state in SAD (Arnold Anteraper et al. 2014). After injection of hydrocortisone, the activity of hippocampus decreased in resting subjects compared to the placebo group with the effect reaching its peak at 25–30 min post injection (Lovallo et al. 2010). In addition, a subdued regional activity in prefrontal cortex was found in post-traumatic stress disorder patients by using ReHo analysis, and this finding was believed to be associated with the unregulated emotion rumination (Zhong et al. 2015). According to previous studies, we speculate that acute social stress should depress the Cohe-Reho value in hippocampus and prefrontal cortex, while improving the Cohe-Reho value in striatum cortex and midbrain.

Experimental procedures

Participants

Thirty volunteers (age: 20.6 ± 2.0 years (18–25 years); 15 females) were recruited from the local community. None of the participants reported any history of major medical, psychiatric, or neurological diseases. Participants were instructed to refrain from heavy exercise and caffeine for at least 12 h before the experiment. All participants provided written informed consent according to the study protocol approved by the South China Normal University Institutional Review Board.

Experimental design and procedure

Participants were exposed to acute stress and control conditions across two sessions spaced at least 30 days apart, with the order of exposures counter-balanced across subjects. All experiments were conducted between 1300 h and 1800 h to control for diurnal variations of cortisol secretion. As showed in Fig. 1, after an acclimation period of 20 min following arrival (T1), baseline saliva samples and affect ratings were collected. Participants were given 5 min to prepare for the following stress or control task (see *stress induction*). After preparation (T2), affect ratings were recorded again. Following this, the participants went through the formal stress or control task, with saliva samples and affect ratings collected upon task completion (T3). After about 10 min, participants were required to lie still in the magnetic resonance imaging (MRI) or functional MRI (fMRI) scanner with their eyes closed and 8 min of resting-state functional MRI data were collected. On completion of the resting state fMRI scan, 3 sessions of the stop signal task (SST) were administered (Hu et al. 2016). After each session of SST (T4, T5, and T6), saliva samples and affect ratings were collected. The current study focuses on findings from the resting state fMRI scan.

Stress induction

Participants were required to complete the Trier Social Stress Test (TSST), a well-validated stressor consisting of an impromptu speech and a mental arithmetic task (Kirschbaum et al. 1993). The TSST included a preparation period (of 5 mins), and a formal task period (including a 5-min public speaking task and 5-min mental arithmetic task). In the stress condition, participants were instructed to prepare for a job application of their choice and to introduce themselves with a free speech of 5 min in front of a committee and a video camera. They were to convince the committee that they were the most suitable candidate for this position. Unbeknown to participants before, on completion of the speech, they were required to subtract the number 13 serially from 1022 and respond verbally in English as fast and accurately as possible for 5 mins. On committing any error the participant was asked to restart from 1022. Reporting in a foreign language (i.e. English) should increase the difficulty of the mental arithmetic task in Chinese college students and possibly further enhance their stress levels. During the task, the committee, including one woman and one man, were trained to remain emotionally neutral. In the control condition, to ensure a comparable cognitive load, participants went through the same tasks without the committee and video camera. In other words, there was no social evaluative stress in the control condition.

Physiological and psychological measures

Salivary cortisol was assessed at multiple time points throughout the experiment (Fig. 1a). Saliva samples were collected with Salivettes (Sarstedt, Germany) and were stored at -15 °C

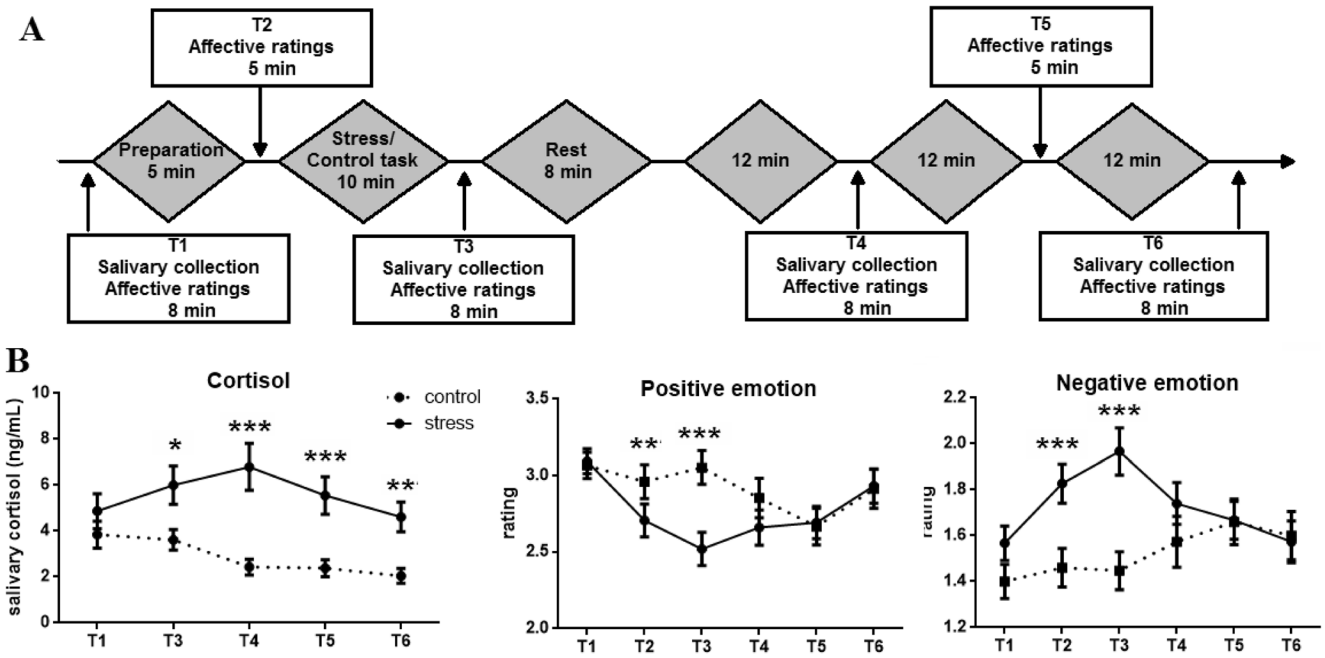

Fig. 1 Experimental procedure and manipulation check. **a** The timeline of the experiment. After acclimation period of 20 min following arrival, participants were required to go through the Trier Social Stress Test (TSST) with (stress condition) or without (control condition) social evaluative processes. After the formal tasks, resting state data were collected. Saliva samples were collected at T1, T3, T4, T5, and T6. Affective ratings were collected at T1, T2, T3, T4, T5, and T6. **b** Cortisol and positive/negative emotional responses under control and stress condition

until assayed. Cortisol concentrations in saliva (in ng/mL) were measured using ELISA (DRG, Germany). Five positive (calm, relaxed, peaceful, confident, and energetic) and five negative (nervous, anxious, scared, tired, and upset) emotions were rated on a four-point scale from 1 "not at all" to 4 "extremely" at multiple time points throughout the procedure (Fig. 1a).

Image data acquisition

Images were obtained with a 3-Tesla MRI scanner (Siemens) in the Brain Imaging Center at South China Normal University. T1-weighted images were acquired with the following parameters: repetition time = 1900 ms, echo time = 2.52 ms, field of view = 256 × 256 mm^2, flip angle = 9°, and matrix size = 256 × 256. T2*-weighted echo-planar images (EPI) were obtained with blood oxygenation level-dependent (BOLD) contrast. Thirty-two axial slices covering the whole brain were acquired with TR = 2000 ms, TE = 25 ms, flip angle = 85°, field of view = 220 × 220 mm, matrix = 64 × 64, 32 slices with slice thickness = 4 mm and no gap. Slices were scanned in an ascending and interleaved order. Two hundred and forty images were acquired for the resting state scan.

Imaging processing

The fMRI data were preprocessed and analyzed using Statistical Parametric Mapping version 8 (SPM8, Wellcome Department of Imaging Neuroscience, University College London, U.K.), and Data Processing & Analysis for (Resting-State) Brain Imaging (DPABI; http://rfmri.org/DPABI) (Yan et al. 2016). After discarding the first 10 volumes, the remaining 230 fMRI volumes were first slice-time corrected and later motion corrected using a least squares approach and a 24-parameter autoregressive model (Friston 24-parameter model) (Friston et al. 1996). No participant's head motion exceeded 2.0 mm in translation or 2° in rotation. We further calculated frame-wise displacement (FD), which indexes volume-to-volume changes in head position (Power et al. 2014). The mean FD in stress and control groups were 0.11 ± 0.03 and 0.12 ± 0.03, respectively. One-sample t-test showed that they were significantly less than 0.2 mm (both $p < 0.001$). Furthermore, paired t-test showed no significant differences in FD between the two conditions ($p = 0.43$).

Motion-corrected functional data were next co-registered to the subject's own structural T1-weighted images, and segmented into grey matter, white matter, and cerebrospinal fluid. We created an average structural brain template from all participants' T1 images (Ashburner 2007) using the DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) technique. The segmented BOLD volumes were normalized into standardized MNI space using the DARTEL template, re-sampled to 3 mm × 3 mm × 4 mm voxel, spatially smoothed with a 6 mm full width at half maximum (FWHM) Gaussian filter, and temporally band-pass filtered into 0.01–0.1 Hz to reduce the effect of very low frequency drift and high frequency physiological noise. Nuisance signal corrections were performed on the 24 head-motion parameters, cerebrospinal fluid (CSF), and white matter.

Preprocessed resting state fMRI data were analyzed using the REST toolkit (Song et al. 2011). The algorithm for calculating Cohe-ReHo involved the following three steps. The first step involved power spectrum and cross spectrum estimation. For any two time series in a given cluster, we used Welch's modified periodogram averaging methods to estimate their power- and cross-spectrums. The second step was the estimation of coherence across low-frequency bands (0.01–0.1 Hz). For any two series in the first step, we estimated coherence with their band-averaged estimates of the cross spectrum and power spectra. The last step was the calculation of Cohe-ReHo within a given cluster. In the present study, we used a cluster size of 27 voxels to include all the neighboring voxels adjacent to a given voxel. We assigned the averaged band-averaged coherence estimated in Step 2 across all pairs of voxels in the cluster to its center voxel to represent the Cohe-ReHo value of the cluster. An individual Cohe-ReHo map was obtained in a voxel-wise manner. The resulting fMRI data were then spatially smoothed with a Gaussian kernel of 6 × 6 × 6 mm^3 full-width at half-maximum (D. Liu et al. 2010; Y. Liu et al. 2017).

To explore the Cohe-ReHo differences between the conditions, a paired-samples t-test was performed on the individual normalized Cohe-ReHo maps in a voxel-by-voxel manner. In order to examine further whether the Cohe-ReHo value changes between the two conditions varied with individual difference in stress response (i.e., the amount of salivary cortisol), we conducted a whole brain multiple regression using the stress-induced Cohe-ReHo value changes (stress condition minus control condition) as the dependent variable, and stress-induced changes in salivary cortisol ($stress_{(t3\text{-}t1)}$- $control_{(t3\text{-}t1)}$) as the independent variable. To exclude the influence of order of conditions (whether the participant was administered the stress condition or the control condition first), we conducted the second level analyses again, including group-level analysis and multiple regression analysis, adding order as a covariate. Small volume correction (svc) was performed on a priori regions of interest. The putamen, caudate and midbrain, which are involved in the habit system, are defined using the corresponding AAL mask (Tzourio-Mazoyer et al. 2007). The subregions of the prefrontal cortex, including right and left superior frontal gyrus, middle frontal gyrus, and inferior frontal gyrus, were also defined using the corresponding AAL mask. Further, we used the maximum probabilistic map of five hippocampus subregions derived by Amount et al., using SPM Anatomy Toolbox v2.2 (Amunts et al. 2005). These five

subregions of the hippocampus were the cornu ammonis (CA1-CA3), dentate gyrus (DG), and subicular complex (Subc). Each ROI was separately used in svc. Activations in other areas are reported if they meet the $P < 0.001$ criteria in the paired t-test uncorrected, cluster size k > 10. For display purposes, all images are depicted at $P < 0.005$.

Results

Physiological responses to acute stress

For salivary cortisol, we carried out a repeated-measures ANOVA on cortisol volumes with treatment (stress vs. control) and time points (T1, T3, T4, T5, and T6) as independent variables (Fig. 1b). For all reported analysis, Greenhouse-Geisser correction was applied when the assumption of sphericity was violated. 3 participants were excluded from the analysis due to insufficient or no saliva at few time points, leaving data from 27 participants. Results of the ANOVA showed that the main effect of treatment, ($F(1, 26) = 16.258$, $p < 0.001$, $\eta^2 = 0.385$), and time point ($F(4, 104) = 4.159$, $p = 0.010$, $\eta^2 = 0.138$) as well as the interaction between treatment and time point were significant ($F(4, 104) = 4.453$, $p = 0.006$, $\eta^2 = 0.146$). Post-hoc *t*-tests showed that stress condition induced higher cortisol than control condition at T3 ($t(26) = 2.677$, $p = 0.013$), T4 ($t(26) = 4.503$, $p < 0.001$), T5 ($t(26) = 4.112$, $p < 0.001$) and T6 ($t(26) = 3.947$, $p = 0.001$).

For positive and negative emotion ratings, treatment (control vs. stress) by Time point (T1, T2, T3, T4, T5, and T6) repeated-measures ANOVAs was conducted (Fig. 1b). For positive emotions ratings, the main effect of treatment ($F(1, 29) = 4.355$, $p = 0.046$, $\eta^2 = 0.131$) and time point ($F(5, 145) = 6.556$, $p < 0.001$, $\eta^2 = 0.184$) and the interaction between the two were significant ($F(5, 145) = 7.505$, $p < 0.001$, $\eta^2 = 0.206$). Post-hoc *t*-tests showed that positive affect was lower in the stress condition than the control condition at T2 ($t(29) = -2.801$, $p = 0.009$), and T3 ($t(29) = -4.817$, $p < 0.001$). For negative emotion ratings, results revealed a significant main effect of treatment (F (1, 29) = 8.553, $p = 0.007$, $\eta^2 = 0.228$), and a significant main effect of time (F (5, 145) = 3.354, $p = 0.015$, $\eta^2 = 0.104$). The interaction between treatment and time was also significant (F (5, 145) = 7.495, $p < 0.001$, $\eta^2 = 0.205$). Post-hoc *t*-tests revealed significantly higher negative emotion ratings in the stress condition than in the control condition at T2 ($t(29) = 4.413$, $p < 0.001$) and T3 ($t(29) = 4.763$, $p < 0.001$). All these findings suggest that our manipulation to induce acute stress was successful.

Resting state fMRI results

As hypothesized, a small volume correction analysis showed significantly higher Cohe-ReHo values in the left CA1 ([−30–9 −20], voxel = 4, $p = 0.014$, svc), CA2 ([−30–12 −20], voxel = 1, $p = 0.018$, svc) and right SFG ([24–3 48], voxel = 20, $p = 0.008$, svc) in the control condition compared to the stress condition (see Fig. 2a). Since the voxels that showed a significant difference in CA1 and CA2 ROIs were neighboring voxels, we combined the left CA1 and CA2 ROIs to CA1/CA2 ROI and carried out small volume correction again. The results showed that Cohe-ReHo values in the left CA1/CA2 ([−30–9 −20], voxel = 5) were significantly different across both conditions ($p = 0.017$, svc). No significant differences were found for the stress condition minus control condition comparison in a priori regions of interest. Furthermore, a whole brain multiple regression analysis, using stress-induced changes in salivary cortisol ($stress_{(t3\text{-}t1)}$- $control_{(t3\text{-}t1)}$) as the independent variable, showed a positive association in the right midbrain ([6–33 −4], voxel = 12, $p = 0.016$, svc) (Fig. 2b), i.e., the higher the salivary cortisol change induced by stress was for an individual, the higher the change in Cohe-ReHo value in the right midbrain for stress minus control condition. There was no significant activation in the striatum for both group comparison and whole brain multiple regression analyses. Adding order of conditions as a covariate yielded similar results.

Discussion

In the present study, we used resting-state fMRI and coherence regional homogeneity (Cohe-ReHo) to detect whether and how acute stress affects local synchronization in brain regions related to deliberative and habitual systems. Our results indicate that stress suppressed Cohe-ReHo values in left hippocampus CA1/CA2 and right SFG, the core brain regions associated with the deliberative and analytic system, whereas stress-induced cortisol change was significantly and positively correlated with Cohe-ReHo value changes in the right midbrain, a brain region involved in fast and habitual responses.

Hippocampus is highly concentrated with mineralocorticoid receptors (MR) and glucocorticoid receptors (GR), both of which are targeted by glucocorticoid. They play key roles in modulating the effects of glucocorticoid on brain functions (de Kloet et al. 2005; Sandi 2013; Travis et al. 2016). A resting-state fMRI study found a decrease in hippocambal activity 15–18 min after hydrocortisone injection, with the highest suppression at 25–30 min post injection (Lovallo et al. 2010). In addition, previous human and rodent studies found that acute and chronic stress could induce morphological changes, reduce synaptic strength and suppress neuronal propagation in hippocampus (Diamond et al. 2007; Lee et al. 2009). For example, after being exposed to psychosocial stress, the synaptic plasticity in the CA1 area was reduced in mouse (Alfarez et al. 2002). Furthermore, it has been shown that the decrease in hippocambal activity under stress is negatively correlated with behavioral performance in cognitively

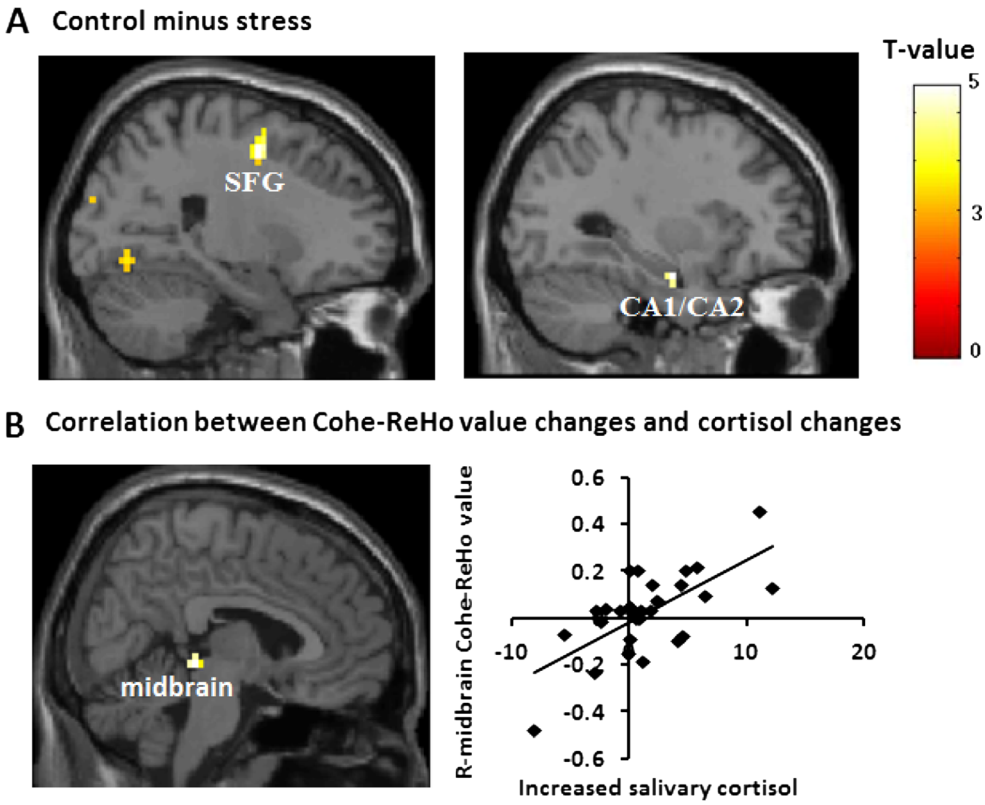

Fig. 2 **a** Cohe-Reho decreases in response to stress in left CA1/CA2 and right superior frontal gyrus; **b** Significant correlations between stress-induced changes in salivary cortisol ($stress_{(t3\text{-}t1)}$-$control_{(t3\text{-}t1)}$) and Cohe-Reho value changes in right midbrain

demanding tasks, e.g. probabilistic classification learning (PCL) (L. Schwabe and Wolf 2012). In addition to the studies on whole hippocambal area, more recent studies in humans and rodents have begun to examine the effects of stress and stress hormones on hippocampal subfields, including cornu ammonis (CA1–3) and dentate gyrus (Travis et al. 2016; Nguyen et al. 2017). For example, after injection of MR/GR modulator, the central stress response (c-Fos) was reduced only in the CA1 subfield of the hippocampus (Nguyen et al. 2017). Additionally, cortisol levels were negatively correlated with the CA1, CA2 and CA3 volumes in both major depressive disorder patients and healthy subjects (Travis et al. 2016). CA3 has been documented to be most susceptible to stress and stress hormones, however, CA1 has been found to be more sensitive to acute stressors (Sapolsky 2000; Alfarez et al. 2002). Our results showing that the local synchronization in hippocampus, the core region of the deliberative system, was disrupted by acute stress are consistent with these previous findings and complement them.

Prefrontal cortex plays an important role in working memory and goal-directed behaviors, and its structure and functional activity are affected dramatically by chronic and acute stress (Oei et al. 2007; Hermans et al. 2014; Rubin et al. 2016; Buckner and Wheeler 2001; Stokes et al. 2013; Arnsten 2009). On exposure to stress for one week or even once, the dendrites in the PFC showed a reduction in length and spine density, with the changes reversing when the stress weakened or disappeared (Radley et al. 2005; Brown et al. 2005; Arnsten 2009). Furthermore, previous fMRI studies found that acute stressors (for e.g. the Trier social stress test) impaired functions associated with the PFC, such as working memory and cognitive control (Alexander et al. 2007; Luethi et al. 2009). A recent study reported that HIV-infected women with high stress performed worse than HIV-infected women with low stress in verbal memory task, with the volumes of prefrontal cortex, including middle frontal gyrus, superior frontal gryus and inferior frontal gyrus, being reduced (Rubin et al. 2016). In accordance with previous findings, our results showed that stress suppressed the Cohe-ReHo values in left superior frontal gyrus in resting state.

We also demonstrated that stress-induced changes in salivary cortisol (stress(t3-t1)- control(t3-t1)) showed a significant and positive correlation with Cohe-ReHo value change in right midbrain, mainly in the periaqueductal gray (PAG, see Fig. 2b). These findings are consistent with previous studies, suggesting a stress-driven promotion in intuitive processes (Lars Schwabe and Wolf 2013; D. Mobbs et al. 2009; Yu 2016; Dean Mobbs et al. 2015). Previous studies showed that midbrain PAG became predominant over high-order cortical areas and triggered defense responses when threat was imminent (D. Mobbs et al. 2007; D. Mobbs et al. 2009). For instance, using a computer game in which subjects were pursued by a predator, Dean et al. found that the midbrain, but not the forebrain areas (e.g. ventromedial prefrontal cortex), were

activated in subjects (prey) when the predator approached (D. Mobbs et al. 2007; D. Mobbs et al. 2009). This shift to the habitual system under stress is also detected in memory domain. For example, after acute or chronic stress, subjects favored stimulus-response strategy over cognitively-demanding spatial strategy to resolve the 'win-card' task (Lars Schwabe et al. 2008; Lars Schwabe et al. 2009). Our finding extends previous findings showing that acute social stress promoted the local temporal synchrony in midbrain cortex by displaying enhanced Cohe-ReHo in the midbrain in the task-free resting state.

To the best of our knowledge, this is the first study using resting-state functional magnetic resonance imaging (fMRI) and the Cohe-ReHo method to examine whether and how stress impacts regional activity in brain regions associated with deliberative and habitual systems. Our results showed that after exposure to acute social stress, the Cohe-ReHo values in left hippocampus CA1, CA2 and right SFG decreased, whereas stress-induced cortisol change was significantly and positively correlated with Cohe-ReHo value changes in the right midbrain. These findings are consistent with previous studies and complement them; stress depressed the local synchronization in brain regions related to the flexible and analytic system, and promoted the local synchronization in brain regions associated with the habitual system in resting state (Lars Schwabe et al. 2013; D. Mobbs et al. 2009). Our results might be helpful to understand the neural mechanisms underlying the symptoms of stress-related disorders (e.G. *major* depressive disorder and post-traumatic stress disorder), for example, negative emotion rumination and automatic reaction, from the perspective of the local synchronization changes in brain structures (Hamilton et al. 2011; Roley et al. 2015; Bomyea and Lang 2016).

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Compliance with ethical standards

Conflict of interest Both authors have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

Alexander, J. K., Hillier, A., Smith, R. M., Tivarus, M. E., & Beversdorf, D. Q. (2007). Beta-adrenergic modulation of cognitive flexibility during stress. *Journal of Cognitive Neuroscience, 19*(3), 468–478.

Alfarez, D., Wiegert, O., Joels, M., & Krugers, H. (2002). Corticosterone and stress reduce synaptic potentiation in mouse hippocampal slices with mild stimulation. *Neuroscience, 115*(4), 1119–1126.

Amunts, K., Kedo, O., Kindler, M., Pieperhoff, P., Mohlberg, H., Shah, N. J., Habel, U., Schneider, F., & Zilles, K. (2005). Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: Intersubject variability and probability maps. *Anatomy and Embryology, 210*(5–6), 343–352.

Ances, B. M., Leontiev, O., Perthen, J. E., Liang, C., Lansing, A. E., & Buxton, R. B. (2008). Regional differences in the coupling of cerebral blood flow and oxygen metabolism changes in response to activation: Implications for BOLD-fMRI. *NeuroImage, 39*(4), 1510–1521.

Arnold Anteraper, S., Triantafyllou, C., Sawyer, A. T., Hofmann, S. G., Gabrieli, J. D., & Whitfield-Gabrieli, S. (2014). Hyper-connectivity of subcortical resting-state networks in social anxiety disorder. *Brain Connectivity, 4*(2), 81–90.

Arnsten, A. F. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience, 10*(6), 410–422.

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage, 38*(1), 95–113.

Atsak, P., Guenzel, F. M., Kantar-Gok, D., Zalachoras, I., Yargicoglu, P., Meijer, O. C., Quirarte, G. L., Wolf, O. T., Schwabe, L., & Roozendaal, B. (2016). Glucocorticoids mediate stress-induced impairment of retrieval of stimulus-response memory. *Psychoneuroendocrinology, 67*, 207–215.

Bomyea, J., & Lang, A. J. (2016). Accounting for intrusive thoughts in PTSD: Contributions of cognitive control and deliberate regulation strategies. *Journal of Affecitive Disorder, 192*, 184–190.

Brown, S. M., Henning, S., & Wellman, C. L. (2005). Mild, short-term stress alters dendritic morphology in rat medial prefrontal cortex. *Cerebral Cortex, 15*(11), 1714–1722.

Brunson, K. L. (2005). Mechanisms of late-onset cognitive decline after early-life stress. *Journal of Neuroscience, 25*(41), 9328–9338.

Buckner, R. L., & Wheeler, M. E. (2001). The cognitive neuroscience of remembering. *Nature Reviews Neuroscience, 2*(9), 624–634.

Diamond, D. M., Campbell, A. M., Park, C. R., Halonen, J., & Zoladz, P. R. (2007). The temporal dynamics model of emotional memory processing: A synthesis on the neurobiological basis of stress-induced amnesia, flashbulb and traumatic memories, and the yerkes-Dodson law. *Neural Plasticity, 2007*, 1–33.

Evans, J. S. B., & Frankish, K. E. (2009). *In two minds: Dual processes and beyond*. Oxford University Press.

Evans, J. S. B., & Stanovich, K. E. (2013). Dual-process theories of higher cognition: Advancing the debate. *Perspectives on Psychological Science, 8*(3), 223–241.

Fleisher, A. S., Podraza, K. M., Bangen, K. J., Taylor, C., Sherzai, A., Sidhar, K., Liu, T. T., Dale, A. M., & Buxton, R. B. (2009a). Cerebral perfusion and oxygenation differences in Alzheimer's disease risk. *Neurobiology of Aging, 30*(11), 1737–1748.

Fleisher, A. S., Sherzai, A., Taylor, C., Langbaum, J. B., Chen, K., & Buxton, R. B. (2009b). Resting-state BOLD networks versus task-associated functional MRI for distinguishing Alzheimer's disease risk groups. *NeuroImage, 47*(4), 1678–1690.

Friston, K. J., Williams, S., Howard, R., Frackowiak, R. S., & Turner, R. (1996). Movement-related effects in fMRI time-series. *Magnetic Resonance in Medicine, 35*(3), 346–355.

Gray, J. D., Rubin, T. G., Hunter, R. G., & McEwen, B. S. (2014). Hippocampal gene expression changes underlying stress sensitization and recovery. *Molecular Psychiatry, 19*(11), 1171–1178.

Haeffel, G. J., Abramson, L. Y., Brazy, P. C., Shah, J. Y., Teachman, B. A., & Nosek, B. A. (2007). Explicit and implicit cognition: A preliminary test of a dual-process theory of cognitive vulnerability to depression. *Behaviour Research and Therapy, 45*(6), 1155–1167.

Hamilton, J. P., Furman, D. J., Chang, C., Thomason, M. E., Dennis, E., & Gotlib, I. H. (2011). Default-mode and task-positive network activity in major depressive disorder: Implications for adaptive and maladaptive rumination. *Biological Psychiatry, 70*(4), 327–333.

Hermans, E. J., Henckens, M. J., Joels, M., & Fernandez, G. (2014). Dynamic adaptation of large-scale brain networks in response to acute stressors. *Trends in Neuroscience, 37*(6), 304–314.

Hu, J., Lee, D., Hu, S., Zhang, S., Chao, H., & Li, C. S. (2016). Individual variation in the neural processes of motor decisions in the stop signal task: The influence of novelty seeking and harm avoidance personality traits. *Brain Structure and Function, 221*(5), 2607–2618.

Kirschbaum, C., Pirke, K.-M., & Hellhammer, D. H. (1993). The 'Trier social stress Test' - a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology, 28*, 76–81.

de Kloet, E. R., Sibug, R. M., Helmerhorst, F. M., & Schmidt, M. V. (2005). Stress, genes and the mechanism of programming the brain for later life. *Neuroscience and Biobehavior Review, 29*(2), 271–281.

Kruse, O., León, I. T., Stalder, T., Stark, R., & Klucken, T. (2017). Altered reward learning and hippocampal connectivity following psychosocial stress. *NeuroImage, 171*, 15–25.

Lee, T., Jarome, T., Li, S.-J., Kim, J. J., & Helmstetter, F. J. (2009). Chronic stress selectively reduces hippocampal volume in rats: A longitudinal magnetic resonance imaging study. *Neuroreport, 20*(17), 1554–1558.

Liu, D., Yan, C., Ren, J., Yao, L., Kiviniemi, V. j., & Zang, Y. (2010). Using coherence to measure regional homogeneity of resting-state fMRI signal. *Frontier in Systems Neuroscience, 4*, 24.

Liu, F., Hu, M., Wang, S., Guo, W., Zhao, J., Li, J., et al. (2012). Abnormal regional spontaneous neural activity in first-episode, treatment-naive patients with late-life depression: A resting-state fMRI study. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 39(2), 326–331.

Liu, Y., Zhao, X., Cheng, Z., Zhang, F., Chang, J., Wang, H., Xie, R., Wang, Z., Cao, L., & Wang, G. (2017). Regional homogeneity associated with overgeneral autobiographical memory of first-episode treatment-naive patients with major depressive disorder in the orbitofrontal cortex: Aresting-state fMRI study. *Journal of Affective Disorder, 209*, 163–168.

Lovallo, W. R., Robinson, J. L., Glahn, D. C., & Fox, P. T. (2010). Acute effects of hydrocortisone on the human brain: An fMRI study. *Psychoneuroendocrinology, 35*(1), 15–20.

Luethi, M., Meier, B., & Sandi, C. (2009). Stress effects on working memory, explicit memory, and implicit memory for neutral and emotional stimuli in healthy men. *Frontiers in Behavioral Neuroscience, 2*, 5.

Maier, S. U., Makwana, A. B., & Hare, T. A. (2015). Acute stress impairs self-control in goal-directed choice by altering multiple functional connections within the brain's decision circuits. *Neuron, 87*(3), 621–631.

McEwen, B. S. (1999). Stress and the aging hippocampus. *Frontiers in Neuroendocrinology, 20*(1), 49–70.

McEwen, B. S., Bowles, N. P., Gray, J. D., Hill, M. N., Hunter, R. G., Karatsoreos, I. N., & Nasca, C. (2015). Mechanisms of stress in the brain. *Nature Neuroscience, 18*(10), 1353–1363.

McEwen, B. S., Nasca, C., & Gray, J. D. (2016). Stress effects on neuronal structure: Hippocampus, amygdala, and prefrontal cortex. *Neuropsychopharmacology, 41*(1), 3–23.

Mobbs, D., Petrovic, P., Marchant, J. L., Hassabis, D., Weiskopf, N., Seymour, B., Dolan, R. J., & Frith, C. D. (2007). When fear is near: Threat imminence elicits prefrontal-periaqueductal gray shifts in humans. *Science, 317*(5841), 1079–1083.

Mobbs, D., Marchant, J. L., Hassabis, D., Seymour, B., Tan, G., Gray, M., Petrovic, P., Dolan, R. J., & Frith, C. D. (2009). From threat to fear: The neural organization of defensive fear systems in humans. *Journal of Neuroscience, 29*(39), 12236–12243.

Mobbs, D., Hagan, C. C., Dalgleish, T., Silston, B., & Prévost, C. (2015). The ecology of human fear: Survival optimization and the nervous system. *Frontiers in Neuroscience, 9*.

Nguyen, E. T., Streicher, J., Berman, S., Caldwell, J. L., Ghisays, V., Estrada, C. M., Wulsin, A. C., & Solomon, M. B. (2017). A mixed glucocorticoid/mineralocorticoid receptor modulator dampens endocrine and hippocampal stress responsivity in male rats. *Physiology & Behavior, 178*, 82–92.

Oei, N. Y. L., Elzinga, B. M., Wolf, O. T., de Ruiter, M. B., Damoiseaux, J. S., Kuijer, J. P. A., Veltman, D. J., Scheltens, P., & Rombouts, S. A. R. B. (2007). Glucocorticoids decrease hippocampal and prefrontal activation during declarative memory retrieval in young men. *Brain Imaging and Behavior, 1*(1–2), 31–41.

Olver, J. S., Pinney, M., Maruff, P., & Norman, T. R. (2015). Impairments of spatial working memory and attention following acute psychosocial stress. *Stress and Health, 31*(2), 115–123.

Pittenger, C., & Duman, R. S. (2008). Stress, depression, and neuroplasticity: A convergence of mechanisms. *Neuropsychopharmacology, 33*(1), 88–109.

Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage, 84*, 320–341.

Radley, J. J., Rocher, A. B., Miller, M., Janssen, W. G., Liston, C., Hof, P. R., McEwen, B., & Morrison, J. H. (2005). Repeated stress induces dendritic spine loss in the rat medial prefrontal cortex. *Cerebral Cortex, 16*(3), 313–320.

Roley, M. E., Claycomb, M. A., Contractor, A. A., Dranger, P., Armour, C., & Elhai, J. D. (2015). The relationship between rumination, PTSD, and depression symptoms. *Journal of Affective Disorder, 180*, 116–121.

Rubin, L. H., Meyer, V. J., J. Conant, R., Sundermann, E. E., Wu, M., Weber, K. M., et al. (2016). Prefrontal cortical volume loss is associated with stress-related deficits in verbal learning and memory in HIV-infected women. Neurobiology of Disease, 92, 166–174.

Sandi, C. (2013). Stress and cognition. *Wiley Interdisciplinary Reviews: Cognitive Science, 4*(3), 245–261.

Sapolsky, R. M. (2000). The possibility of neurotoxicity in the hippocampus in major depression: A primer on neuron death. *Biological Psychiatry, 48*, 755–765.

Schwabe, L., & Bolam, P. (2017). Memory under stress: From single systems to network changes. *European Journal of Neuroscience, 45*(4), 478–489.

Schwabe, L., & Wolf, O. T. (2012). Stress modulates the engagement of multiple memory systems in classification learning. *Journal of Neuroscience, 32*(32), 11042–11049.

Schwabe, L., & Wolf, O. T. (2013). Stress and multiple memory systems: From 'thinking' to 'doing'. *Trends in Cognitive Sciences, 17*(2), 60–68.

Schwabe, L., Dalm, S., Schächinger, H., & Oitzl, M. S. (2008). Chronic stress modulates the use of spatial and stimulus-response learning strategies in mice and man. *Neurobiology of Learning and Memory, 90*(3), 495–503.

Schwabe, L., Oitzl, M. S., Richter, S., & Schächinger, H. (2009). Modulation of spatial and stimulus–response learning strategies by exogenous cortisol in healthy young women. *Psychoneuroendocrinology, 34*(3), 358–366.

Schwabe, L., Joëls, M., Roozendaal, B., Wolf, O. T., & Oitzl, M. S. (2012). Stress effects on memory: An update and integration. *Neuroscience & Biobehavioral Reviews, 36*(7), 1740–1749.

Schwabe, L., Tegenthoff, M., Höffken, O., & Wolf, O. T. (2013). Mineralocorticoid receptor blockade prevents stress-induced modulation of multiple memory systems in the human brain. *Biological Psychiatry, 74*(11), 801–808.

Simonovic, B., Stupple, E. J., Gale, M., & Sheffield, D. (2017). Stress and risky decision making: Cognitive reflection, emotional learning or both. *Journal of Behavioral Decision Making, 30*(2), 658–665.

Song, X. W., Dong, Z. Y., Long, X. Y., Li, S. F., Zuo, X. N., Zhu, C. Z., He, Y., Yan, C. G., & Zang, Y. F. (2011). REST: A toolkit for resting-state functional magnetic resonance imaging data processing. *PLoS One, 6*(9), e25031.

Sterlemann, V., Ganea, K., Liebl, C., Harbich, D., Alam, S., Holsboer, F., Müller, M. B., & Schmidt, M. V. (2008). Long-term behavioral and neuroendocrine alterations following chronic social stress in mice: Implications for stress-related disorders. *Hormones and Behavior, 53*(2), 386–394.

Stokes, M. G., Kusunoki, M., Sigala, N., Nili, H., Gaffan, D., & Duncan, J. (2013). Dynamic coding for cognitive control in prefrontal cortex. *Neuron, 78*(2), 364–375.

Travis, S. G., Coupland, N. J., Hegadoren, K., Silverstone, P. H., Huang, Y., Carter, R., Fujiwara, E., Seres, P., & Malykhin, N. V. (2016). Effects of cortisol on hippocampal subfields volumes and memory performance in healthy control subjects and patients with major depressive disorder. *Journal of Affective Disorder, 201*, 34–41.

Tzourio-Mazoyer, N., Hervé, P. Y., & Mazoyer, B. (2007). Neuroanatomy: Tool for functional localization, key to brain organization. *NeuroImage, 37*(4), 1059–1060.

Vinkers, C. H., Joels, M., Milaneschi, Y., Kahn, R. S., Penninx, B. W., & Boks, M. P. (2014). Stress exposure across the life span cumulatively increases depression risk and is moderated by neuroticism. *Depression and Anxiety, 31*(9), 737–745.

Vogel, S., Fernández, G., Joëls, M., & Schwabe, L. (2016). Cognitive adaptation under stress: A case for the mineralocorticoid receptor. *Trends in Cognitive Sciences, 20*(3), 192–203.

Wellman, C. L. (2001). Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. *Developmental Neurobiology, 49*(3), 245–253.

Yan, C. G., Wang, X. D., Zuo, X. N., & Zang, Y. F. (2016). DPABI: Data processing & analysis for (resting-state) brain imaging. *Neuroinformatics, 14*(3), 339–351.

Youssef, F. F., Dookeeram, K., Basdeo, V., Francis, E., Doman, M., Mamed, D., Maloo, S., Degannes, J., Dobo, L., Ditshotlo, P., & Legall, G. (2012). Stress alters personal moral decision making. *Psychoneuroendocrinology, 37*(4), 491–498.

Yu, R. (2016). Stress potentiates decision biases: A stress induced deliberation-to-intuition (SIDI) model. *Neurobiology of Stress, 3*, 83–95.

Zang, Y., Jiang, T., Lu, Y., He, Y., & Tian, L. (2004). Regional homogeneity approach to fMRI data analysis. *NeuroImage, 22*(1), 394–400.

Zhong, Y., Zhang, R., Li, K., Qi, R., Zhang, Z., Huang, Q., & Lu, G. (2015). Altered cortical and subcortical local coherence in PTSD: Evidence from resting-state fMRI. *Acta Radiologica, 56*(6), 746–753.