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Cortisol awakening response predicts intrinsic functional connectivity of the medial prefrontal cortex in the afternoon of the same day

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ABSTRACT

Cortisol awakening response (CAR) is the cortisol secretory activity in the first 30–60 min immediately after awakening in the morning. Alterations in CAR as a trait have been associated with changes in the brain structure and function. CAR also fluctuates over days. Little, however, is known about the relationship between CAR as a state and brain activity. Using resting-state functional magnetic resonance imaging (fMRI), we investigated whether the CAR predicts intrinsic functional connectivity (FC) of the brain in the afternoon of the same day. Data from forty-nine healthy participants were analyzed. Salivary cortisol levels were assessed immediately after awakening and 15, 30 and 60 min after awakening, and resting-state fMRI data were obtained in the afternoon. Global FC strength (FCS) of each voxel was computed to provide a whole-brain characterization of intrinsic functional architecture. Correlation analysis was used to examine whether CAR predicts the intrinsic FC of core brain networks. We observed that the CAR was positively correlated with the FCS of the medial prefrontal cortex (mPFC). Further analysis revealed that higher CAR predicted stronger positive mPFC connectivity with regions in the default mode network. Our findings suggest that the HPA activity after awakening in the early morning may predict intrinsic functional connectivity of mPFC at rest in the afternoon of the same day.

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Introduction

The activity of the hypothalamic–pituitary–adrenal (HPA) axis is characterized by peak levels of cortisol secretory activity following awakening in the morning (Pruessner et al., 1997). The cortisol secretory activity in the first 30–60 min immediately after awakening, known as the cortisol awakening response (CAR), has been proposed to provide the energetic resources necessary for shifting from a resting to an active state in the face of the anticipated demands of the upcoming day (Pruessner et al., 1997; Clow et al., 2004; Rohleder et al., 2007; Fries et al., 2009). Alterations in the CAR have been associated with hippocampal and frontal volumes (Buchanan et al., 2004; Pruessner et al., 2007; Bruehl et al., 2009; Ursache et al., 2012) and a variety of mental disorders, such as depression and acute stress disorder (Chida and Steptoe, 2009; Inslicht et al., 2011).

Several studies have focused on the relationship between CAR and cognitive and behavioral measures. A longitudinal study found that decreased CAR is involved in the transition from intact cognitive functioning to mild cognitive impairment in older adults (Peavy et al., 2012). Bohnke et al. (2010) found that CAR negatively predicted aggressive behavior in a provoked group and explained 67% of the behavioral variance. In that study, cortisol samples were collected in the mornings before the day of behavioral experiments. Van der Werf-Eldering et al. (2012) collected cortisol samples in the morning after a cognitive testing day and did not find a significant association between CAR and executive functioning, visual or verbal memory, or the speed of information processing.

Although the CAR was originally considered a stable trait measure and previous studies have mostly focused on the relationship between CAR as a trait and cognition (e.g., Bohnke et al., 2010), more recent studies suggest that CAR fluctuates over days and is state dependent (for a recent review, see Law et al., 2013). In their review, Law et al. (2013) further assume that state variation in the CAR is associated with brain function later in the day. A recent study examined the relationship between CAR and spatial working memory performance on the afternoon of the day on which the CAR samples were collected (Moriarty et al., 2014). Results showed an inverted U-shaped relationship between

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CAR and working memory performance. This result supports the idea that CAR serves as an index for predicting the brain function and behavioral performance on the same day.

The relationship between cortisol and medial prefrontal cortex (mPFC) function has received considerable research attention. The prefrontal cortex, especially the mPFC contains high levels of glucocorticoid receptors (GRs) and is considered to be one of the most important target brain areas of glucocorticoids (McEwen et al., 1986; Diorio et al., 1993; Wellman, 2001; Sullivan and Gratton, 2002; Cook and Wellman, 2004; Radley et al., 2004, 2005; Hinwood et al., 2012). Numerous studies have demonstrated that exogenous or endogenous cortisol plays a critical role in modulating mPFC function (Oei et al., 2007; Ossewaarde et al., 2011; Veer et al., 2012). Additionally, the mPFC is considered one of the critical brain regions in the regulation of HPA activity in response to stress (Diorio et al., 1993; Radley et al., 2004; Kern et al., 2008; Buchanan et al., 2010). Some studies have reported an association between pre-test baseline cortisol levels and prefrontal cognitive function. Higher cortisol levels before cognitive testing are correlated with an increased amplitude of error-related negativity (ERN) and more pronounced post-error slowing (Tops et al., 2006; Tops and Boksem, 2011). These cognitive components reflect error monitoring and cognitive control, functions that are mediated by the mPFC (Hester et al., 2009). Veer et al. (2012) suggested that baseline cortisol is predictive of the resting-state functional coupling between the amygdala and mPFC using functional magnetic resonance imaging (fMRI). In these studies, the cortisol levels were assessed immediately before measures of neural activity were collected.

Importantly, previous studies have also demonstrated that corticosteroids modulate brain function by slow, genomic changes that manifest themselves several hours after exogenous administration (Wiegert et al., 2005; Joels et al., 2006). Henckens et al. (2010, 2011, 2012) have suggested that the slow effects of corticosteroids might manifest itself by "shifting the brain back from a stimulus-driven response mode to a more controlled mode", which is evidenced by enhanced PFC function and increased coupling between the amygdala and the mPFC several hours after exogenous administration.

Resting-state functional connectivity (FC) analysis has emerged as a powerful systems-level approach for uncovering key features of large-scale intrinsic functional networks associated with cognitive and affective functions (Greicius et al., 2003; Fox and Raichle, 2007; Bressler and Menon, 2010; Qin et al., 2012). Since its first use for mapping the somatomotor system (Biswal et al., 1995), intrinsic FC analysis has been used to characterize multiple brain systems, including those involved in sensory processing, language, emotion, and attention (Lowe et al., 1998; Hampson et al., 2002; Greicius et al., 2003; Fox et al., 2006). Previous studies have reported that both endogenous cortisol and pre-task baseline cortisol are related to the resting-state FC between brain areas (Veer et al., 2012; Vaisvaser et al., 2013). The relationship between the CAR in the early morning and the FC patterns of the brain a few hours later, however, has not been addressed.

In addition to a conventional seed-based correlation analysis of the resting-state FC, which did not take the possible functional role of regions outside a certain given seed and its variability into account (Gotts et al., 2012), there is a newly developed analysis method of global functional connectivity strength (FCS), which permits a comprehensive, whole-brain characterization for the FC property of each voxel across the whole brain. The global FCS is thought to be a measure of functional importance of a given voxel or region in support of information transferring in the whole brain (Jiang et al., 2004; Dai et al., 2012). It has also been found that global FCS is related to physiological indices such as cerebral metabolic rate of glucose (CMRGlu; Tomasi et al., 2013) and regional cerebral blood flow (rCBF; Liang et al., 2013). Brain regions with high global FCS have been regarded as functional hubs in large-scale brain networks, including regions in the default mode such as mPFC, posterior cingulate cortex (PCC)/retrosplenial cortex, and inferior parietal lobule, regions in the salience and sensory-perceptual networks such as insula and visual regions (Buckner and Carroll, 2007; Liang et al., 2013).

In the present study, we used resting-state fMRI to test whether and how CAR predicts large-scale intrinsic functional networks in the afternoon of the same day. We computed the FCS for each voxel to identify the connection property of each voxel with voxels across the whole brain and then computed the correlation of each voxel's FCS with each participant's CAR. The CAR has been analyzed using different approaches. Broadly speaking, there are two basic methods: total cortisol secretion over the waking period, often measured by the area under the curve with reference to the ground (AUCg); and the change of cortisol levels (typically increase) from the level recorded upon waking, often measured by area under the curve with respect to the increase (AUCi) or by absolute increase of cortisol (Pruessner et al., 2003; Chida and Steptoe, 2009). Based on the knowledge of the overlap between the brain areas with higher GR concentrations and higher FCS, and the slow effects of corticosteroids on brain (Henckens et al., 2010, 2011), we predicted that a high CAR would be associated with increased FCS in the mPFC. Furthermore, we used the mPFC as a seed region to examine the relationships between the CAR and FC between the mPFC and other brain regions.

Materials and methods

Participants

Fifty-seven healthy right-handed male undergraduates were recruited (mean age, 21.75 ± 0.98 years). The inclusion criteria included the following: no history of neurological or psychiatric disorders, no current illness, such as cold, periodontitis, or other acute inflammation, no current medication use within one week of participation in the study, no irregular sleep/wake cycles, and no excessive nicotine consumption (more than five cigarettes a day). Students with psychiatric disorders were excluded preliminarily by self-report on the telephone and then screened by the SCL-90 (Derogatis, 1977; Wang, 1984). As sex differences in the HPA axis activity have been reported (Kudielka and Kirschbaum, 2005), we only recruited male volunteers in our study. Eight participants were excluded from the analyses: three for incomplete saliva samples, three for excessive head motion during scanning, and two for abnormal global FC patterns (see Supplementary material, Fig. S1). All participants provided written informed consent and were paid for their participation. The study protocol was approved by the Ethics Committee of Human Experimentation at the Institute of Psychology, Chinese Academy of Sciences.

Procedure

Participants' saliva samples were collected at four time points: immediately after awakening, 15, 30, and 60 min after awakening in the morning of the scanning day. On average across participants, the first saliva sample was collected at 7:02 AM, and the fourth saliva sample was collected at 8:02 AM. During the 1 h of saliva sampling after awakening, participants were asked to complete the sleeping quality questionnaire. On the afternoon of the same day, participant came to fMRI laboratory. Before scanning, another sample of saliva was collected. All participants were scanned in the afternoon, approximately 7 h on average after saliva collecting. During resting-state fMRI scanning which lasted 6 min, participants were instructed to stay relaxed and awake with their eyes fixated on a white cross on the screen. The scans were performed using a Siemens TRIO 3-Tesla scanner (Erlangen, German) at the Neuroimaging Center in the State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University.

Questionnaires

A sleep quality questionnaire was completed during the saliva collection period after awakening. The questionnaire included seven items, and each item had five response options: (1) how did you sleep (very poorly, 1 to very well, 5); (2) did you feel refreshed upon waking (not at all, 1 to completely, 5); (3) how deeply did you sleep last night (very lightly, 1 to very deep, 5); (4) did you sleep for the entire time allocated for sleep (woke up much earlier, 1 to slept for the whole night, 5); (5) how easy was it for you to wake up (very easy, 1 to very difficult, 5); (6) how easily did you fall asleep last night (very easily, 1 to very difficult, 5); and (7) how many dreams did you have last night (no dreams, 1 to many dreams, 5). The scores of items 6 and 7 were inverted. The total sleep quality score was calculated by adding the scores for each item.

Salivary cortisol sampling and analysis

Saliva samples were collected using Salivette collection devices (Sarstedt, Nümbrecht, Germany). Participants were asked to wake up between 06:00 and 08:00 and were asked to stay in bed until all four saliva samples were obtained. However, they were allowed to read quietly as well as to go to the bathroom if necessary. To avoid saliva contamination, participants were asked not to brush their teeth, drink, eat or smoke before completing the saliva sampling procedures. They were also required to refrain from alcohol and nicotine consumption as well as excessive exercise on the day before saliva sampling. The participants were asked to record when each sample was taken to assure adherence to the timing protocol. The participants were told the importance of adhering to the sampling instructions and were asked to follow the instructions carefully, and each participant was given a copy of the instruction sheet to increase compliance. After collection, participants were instructed to return the samples back to the laboratory where they were kept frozen (−20 °C) until the assay. One saliva sample was also collected before the imaging session to assess the baseline level of cortisol. The cortisol level from this sample was used as a covariate in data analysis.

After thawing and centrifuging at 3200 rpm for 10 min, the samples were analyzed using an electrochemiluminescence immunoassay (ECLIA, Cobas e601, Roche Diagnostics, Mannheim, Germany). Two scoring methods were used to compute the CAR: (1) AUCg = (S (sample) 1 + S2) × 0.25/2 + (S2 + S3) × 0.25/2 + (S3 + S4) × 0.5/2, an estimate of the total cortisol secretion over the first hour after awakening, and (2) AUCi = AUCg − S1 × (0.25 + 0.25 + 0.5), a measure of the dynamics of the cortisol awakening response that emphasizes changes over time (Pruessner et al., 2003; Clow et al., 2004). Note that S1 to S4 represent the single measurements of cortisol, and 0.25 and 0.5 (hours) denote the time intervals between the measurements, i.e., 15 min between S1 and S2, and between S2 and S3, and 30 min between S3 and S4. The distribution of the cortisol data was examined by the Kolmogorov–Smirnov test, and a z-transformation was applied to the cortisol data which were not normally distributed.

Image data acquisition

Whole-brain functional images were collected using an echoplanar imaging sequence with the following parameter settings: axial slices, 33; slice thickness, 4 mm; gap, 0.6 mm; TR, 2000 ms; TE, 30 ms; flip angle, 90°; voxel size, 3.1 × 3.1 × 4.6 mm; FOV, 200 × 200 mm; and 180 volumes. Moreover, high-resolution structural images were acquired through a 3D sagittal T 1-weighted magnetization-prepared rapid gradient echo, with the following parameter settings: 192 slices; TR, 2530 ms; TE, 3.45 ms; slice thickness, 1 mm; voxel size, 1.0 × 1.0 × 1.0 mm; flip angle, 7°; inversion time, 1100 ms; and FOV, 256 × 256 mm.

Image preprocessing

Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI (Yan and Zang, 2010) were used to preprocess the brain imaging data. The first 10 volumes of the functional images were discarded for signal equilibrium and participants' adaptation to scanning noise. Then, the images were corrected for slice-timing and realigned for head movement correction. Three participants were excluded under the criteria, with head motion exceeding 2.5 mm maximum translation or 2.5° rotation throughout the course of scans. Table S1 of Supplementary material reports the root mean square for all the six head motion parameters for 49 participants. After that, participants' structural brain image was coregistered to their mean functional image, then all participants' functional images were normalized into the standard Montreal Neurological Institute space (MNI template, resampling voxel size was 3 × 3 × 3 mm). Subsequently, the linear trend of the time courses was removed, and band-pass filtering (0.01–0.1 Hz) was performed on the time series of each voxel to reduce the effect of low-frequency drifts and high-frequency physiological noise. Then, the images were spatially smoothed using a Gaussian filter (4 × 4 × 4 mm FWHM (Wei et al., 2012)) to decrease spatial noise. Finally, six head-motion parameters, global mean signal, white matter signal, and the cerebrospinal signal were regressed out.

Global FCS analysis and FCS–CAR correlation analysis

Whole-brain global FCS analysis was performed. First, we created a brain gray-matter mask ($N_{voxel} = 45{,}381$) by selecting a threshold of 0.2 on the gray-matter probability map in SPM8 and excluding cerebellar regions (#91–#116) in the Automated Anatomical Labeling template (Tzourio-Mazoyer et al., 2002) for signal distortion in the cerebellum. A whole-brain FC matrix for each participant was obtained by computing the correlation (Pearson's r) of the time series between all of the pairs of brain voxels in the brain mask and storing the mean correlation back in each voxel. Taking the removal of global mean signal into account, negative correlations were left out of consideration and put to zero (Hagmann et al., 2008; Buckner et al., 2009). The correlation strength (i.e. FCS) of each voxel was defined as $S_{voxel}(i) = \frac{1}{N-1}\sum_{j\neq i} R_{ij}$, where R_{ij} is the correlation coefficient between a voxel and voxel and N is the number of voxels. FCS measures the average correlation extent of a given voxel with all of the other voxels.

To determine the relationship between FCS and CAR indicators, voxel-based Pearson's correlation analyses were separately conducted on individual FCS maps for z scores of AUCg and AUCi. The cortisol level before scan and the sleep quality score were regressed out from the correlation analysis. We calculated correlations at both the r_{peak} (correlation coefficient between the FCS in the peak coordinate and CAR indicators) and $r_{cluster}$ (correlation coefficient between the averaged FCS within the significant ROI and the CAR indicators) levels.

AlphaSim was used to correct for multiple comparisons (originally in AFNI software and implemented in Resting-State fMRI Data Analysis Toolkit, http://www.restfmri.net), and the statistical significance threshold was set as a combination of a voxel-wise p value of <.05 and a cluster size of >66 voxels (1782 mm^3), resulting in an overall corrected significant level of $p < .05$.

Correlation analysis between CAR and MPFC-based connectivity networks

Based on the results of global FCS analyses, we further examined whether CAR is associated with the relationships among the activity of core networks. Therefore, we created spherical seed ROIs (radius, 4 mm) that centered on the coordinates of the peak point of mPFC (which we detected in the FCS–CAR correlation analysis), calculated the mean time series of the seed ROI and correlated the seed time series

with other voxels in the gray matter mask to obtain an r map for each participant. After that, we transformed the correlation coefficients into z scores (Fisher z-transformation) for each voxel in our gray mask and performed one-sample t tests on these z-FC maps to identify the regions displaying significant (non-zero) functional connectivity with the seed(s). AlphaSim with threshold of $p < .05$ and cluster size >66, reaching an overall significant level of $p < .05$ was used to correct for multiple comparisons. For the same reason as the FCS calculation, we created a mask in which only voxels that have a significant positive connectivity with the mPFC seed(s) were included (26,248 voxels in this mask). Finally, for each voxel in this mask, we performed across-subject correlation analyses between its functional connectivity (z score) with the seed(s) and the participant's CAR measures. This approach is adopted from previous studies examining neural networks (Gotts et al., 2012; Wei et al., 2012; Liang et al., 2013) to find a CAR-related network. Similarly, the participants' cortisol level before the scan and sleep quality were regressed out from the correlation analysis. AlphaSim was used to correct for multiple comparisons with a combination of voxel-wise threshold $p < .05$ and cluster size >43, resulting in an overall threshold of $p < .05$.

Results

CAR

Fig. 1A shows the raw cortisol results for four time points. The cortisol levels increased from awakening point (13.92 ± 6.49 nmol/L), then peaked at 15–30 min after awakening (19.28 ± 6.97 nmol/L and 18.89 ± 7.26 nmol/L, respectively), and showed a decline at 60 min (15.22 ± 8.29 nmol/L) (Fig. 1A). The mean AUCg was 17.45 ± 5.82 nmol/L, and the mean AUCi was 3.53 ± 5.53 nmol/L (Fig. 1B).

Global FCS analysis and FCS–CAR correlation analysis

The global FCS results indicated that the mPFC (peak activation coordinates: −9, 57, −6; 140 voxels, 3780 mm^3; Fig. 2A) was positively correlated with the participants' AUCg ($r_{peak} = 0.57$; $r_{cluster} = 0.63$; $p < .001$; Fig. 2B represents the scatter plot of the simple correlation between AUCg and FCS in mPFC). Table 1 reports the significant correlations between the AUCg and FCS in other regions, including the right and left middle cingulate cortices, right and left dorsolateral prefrontal cortices, right angular gyrus, precentral gyrus (PrCG), left postcentral gyrus (PoCG), left middle temporal gyrus, left superior parietal gyrus (SPG), and middle occipital gyrus.

No significant correlations were found between the AUCi and FCS of the mPFC. AUCi was negatively correlated with the FCS of the middle occipital gyrus (peak coordinates: −30, −84, −15, 78 voxels, 2106 mm^3; $r_{peak} = -0.49$, $p < .001$; $r_{cluster} = -0.46$, $p < .01$) and was positively correlated with the FCS of the right PrCG (peak coordinates: 48, −15, 36, 68 voxels, 1836 mm^3; $r_{peak} = 0.42$, $p < .01$; $r_{cluster} = 0.46$, $p < .01$).

Correlation analysis between CAR and MPFC-based connectivity networks

Due to our main interest in the region of mPFC, we next performed a voxel-wise correlation analysis between the mPFC region found in the above-reported analysis and all of the other voxels in the brain and correlated the obtained significant positive connectivity coefficients (z scores) with the AUCg scores across participants. The results revealed that the AUCg is positively associated with the strength of FC between the mPFC and PCC/precuneus, left and right angular gyri, left and right middle temporal gyri, the mPFC, and left and right parahippocampal gyri, which are considered components of the default mode network (DMN, Binder et al., 1999; Buckner and Carroll, 2007; Fig. 3, Table 2). Another region whose FC to the seed(s) positively correlated with the AUCg scores was the left insula.

Discussion

In this study, we investigated whether the CAR is predictive of the intrinsic FC of the brain in the afternoon of the same day. As predicted, the cortisol secretion within the first hour after morning awakening (i.e., AUCg) positively predicted the FCS across a set of widely distributed brain regions at rest, including the primary region of interest in this study, the mPFC. Further analyses revealed that a higher AUCg predicted the strength of the positive FC between the mPFC and DMN regions.

The mPFC has been consistently identified as a key region of the default network and an important hub in functional brain networks. It is believed to be critical for transferring information across regions during both resting and task states (Buckner et al., 2008, 2009; Liang et al., 2013). Research in animals has also established the mPFC as a brain area with a high concentration of GRs (Diorio et al., 1993). The mPFC region we detected here is similar to the cortical hub region identified by previous research (Buckner et al., 2009) and that found in the mPFC-amygdala FC and baseline cortisol level correlation (Veer et al., 2012). The results in the current study suggest that higher levels of cortisol in the early morning are associated with stronger global intrinsic FC between the mPFC and other regions.

In conjunction with the global FC of the mPFC, we further used mPFC as a seed region and found that a higher AUCg predicted a stronger positive FC between the mPFC and other regions within the DMN, such as the PCC/precuneus, right and left middle temporal gyri, right and left

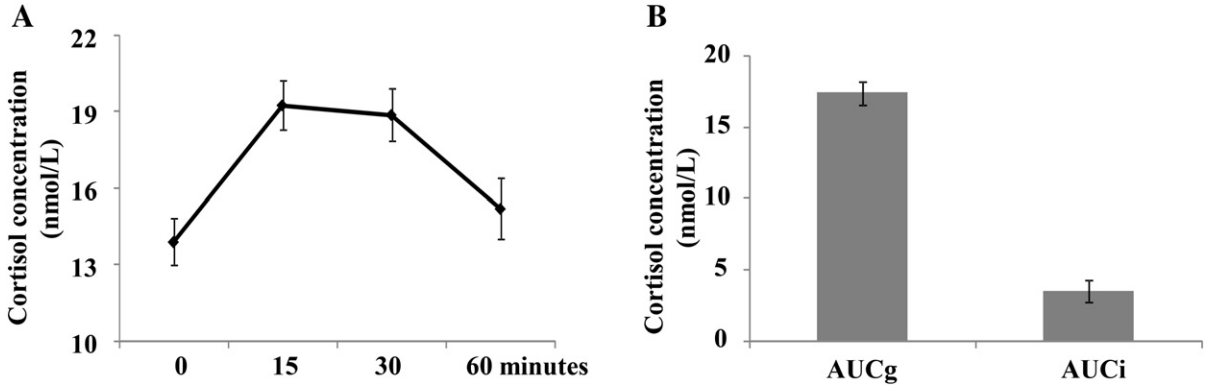

Fig. 1. Mean awakening cortisol levels. (A) The x-axis represents the time points of saliva sampling, and the y-axis represents the averaged original cortisol levels. Error bars represent the standard error of the mean. (B) Values of two different cortisol awakening response (CAR) measures. The graph shows the mean values, with the error bars representing the standard error of the mean.

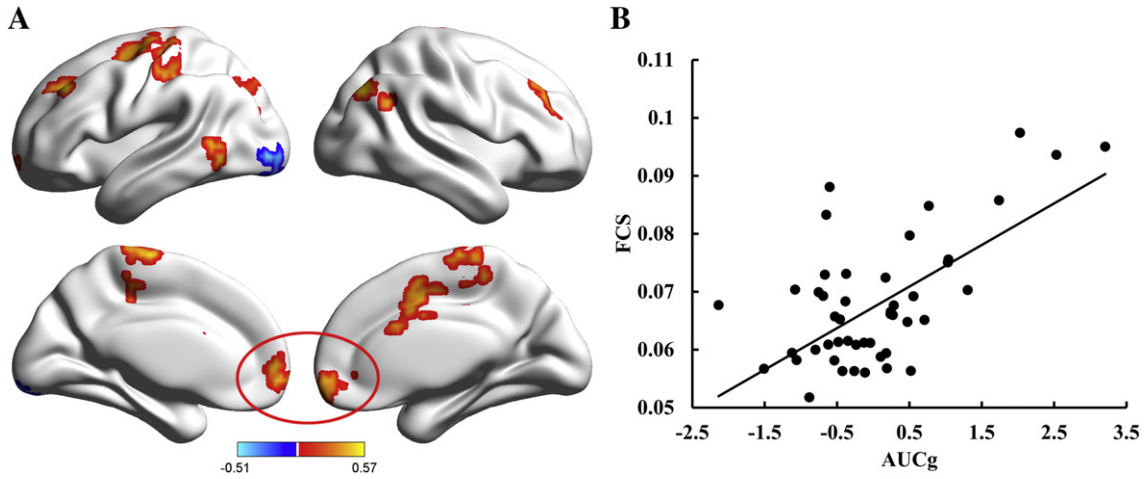

Fig. 2. Global functional connectivity strength (FCS)–AUCg correlation analysis. (A) Statistical map for the correlation between FCS and z scores of AUCg. The correlation value is indicated using the color scale at the bottom of the figure. The red circle indicates the significant region in the medial prefrontal cortex (mPFC). The statistical threshold of voxel wise $p < .05$ and cluster size >66 was applied for display purposes. (B) The scatter plots (which serve illustrative purposes only) of simple correlation analysis show the positive correlation between the z scores of AUCg and averaged FCS in the mPFC region marked in the left figure. Each dot represents data from one participant. The results were mapped on the cortical surface using the BrainNet Viewer (http://www.nitrc.org/projects/bnv/; Xia et al., 2013).

angular gyri, and left and right parahippocampal gyri. Notably, as one of the possible adaptive functions of the DMN, the spontaneous activity within the default network is to support a broad low-level exploratory state which is maintained in an unfocused manner "that provide a means to anticipate and evaluate upcoming events before they happen" (Buckner et al., 2008).

We emphasize that no causality can be attributed to the observed association between the CAR and resting-state FC of the brain. There are three possible interpretations of these results. Firstly, the CAR may exert a slow effect on brain functional connectivity. Although a number of studies have revealed that stress and stress hormone have an acute effect on brain function and functional connectivity (Wang et al., 2005; Pruessner et al., 2008; Wager et al., 2009; Qin et al., 2009; Hermans et al., 2011; Ossewaarde et al., 2011; Veer et al., 2011), previous studies have also demonstrated that corticosteroids enhance PFC function (Henckens et al., 2011) and increase the coupling between the amygdala and the mPFC (Henckens et al., 2010) by slow, genomic changes that manifest themselves several hours after exogenous administration. These pharmacological studies, however, are not an exact copy of naturally occurring circumstances. In our results, we focus on naturally secreted cortisol (i.e., CAR) instead of exogenous cortisol administration, and the results suggest that the higher HPA activity in the morning is associated with stronger intrinsic functional connectivity of the mPFC with other brain regions several hours later.

Secondly, the resting-state FC characteristics of the brain could also be the cause of alterations in the CAR. The mPFC is known for its regulatory role in HPA axis responsivity (Diorio et al., 1993; Radley et al., 2004; Kern et al., 2008; Buchanan et al., 2010). Although the specific contribution of the mPFC to the CAR is unknown, the mPFC and its connectivity might also be involved in maintaining homeostasis in response to the elevation of cortisol after awakening (Fries et al., 2009; Frokjaer et al., 2013). Although the current study focused on state measures of CAR, the CAR of a single day to a lesser extent also reflects a trait (Hellhammer et al., 2007), which could be affected by the functional state of the mPFC.

The third possibility underlying the association between CAR and resting-state FC is that there is a common factor that may shape both CAR and FC measured in the present study. Several studies have demonstrated an increased CAR on days with greater demands compared to days with lesser demands (Kunz-Ebrecht et al., 2004; Schlotz et al., 2004; Rohleder et al., 2007). Findings such as these have led to the speculation that the CAR reflects the expectations of stress or challenge in the day to come (Fries et al., 2009). Increased appraisals of the intensity of daily stressors may also shape the FC between mPFC and other regions (Eryilmaz et al., 2011; Kim et al., 2011; Muscatell et al., 2015). For example, those who feel most challenged upon awakening by the anticipation of being scanned, are also likely to experience the scanning as more of a stressor or challenge (see Muehlhan et al., 2011), thus the scanning as a stressor may create a link between CAR and FC.

Law et al. (2013) reviewed studies about the day-to-day variation in the CAR and offer the possibility of the relationship between the CAR and daily functioning. Interestingly, a more recent behavioral study by Moriarty et al. (2014) found that CAR AUCg (but not AUCi) has an inverted U-shaped relationship with working memory performance which occurred on the afternoon of the day on which the CAR samples were collected. Our study, although no overt tasks were probed, further suggest that AUCg (but not AUCi) predicts the resting-state functional connectivity of the medial prefrontal cortex in the afternoon of the same day.

Previous studies have also reported an association between pre-task baseline cortisol levels and brain activity/FC during both the task and resting-state (Tops et al., 2006; Tops and Boksem, 2011; Veer et al., 2012). For example, higher pre-test cortisol level is predictive of the resting-state functional coupling between the amygdala and mPFC (Veer et al., 2012). Our results extend the results of these studies and

Table 1
Regions in which functional connectivity strength (FCS) correlated significantly with the AUCg.

Brain regions	Peak MNI coordinates					
	BA	x	y	z	r (peak)	Cluster size
Medial prefrontal cortex	11	−9	57	−6	0.57**	140
Right middle cingulate gyrus	6	12	6	51	0.49**	89
Left middle cingulate cortex		−12	−24	51	0.48**	73
Right dorsolateral prefrontal cortex	46	33	30	33	0.50**	82
Left dorsolateral prefrontal cortex	9	−30	33	42	0.51**	117
Right angular gyrus	19	42	−75	36	0.52**	93
Precentral gyrus	6	3	−18	69	0.53**	118
Left postcentral gyrus	3	−39	−24	51	0.55**	312
Left middle temporal gyrus	37	−48	−51	−3	0.54**	83
Left superior parietal gyrus	7	−21	−69	36	0.53**	84
Middle occipital gyrus	18	−42	−90	0	−0.51**	70

Note: BA, Brodmann Area.
** $p < 0.001$.
* $p < 0.01$.

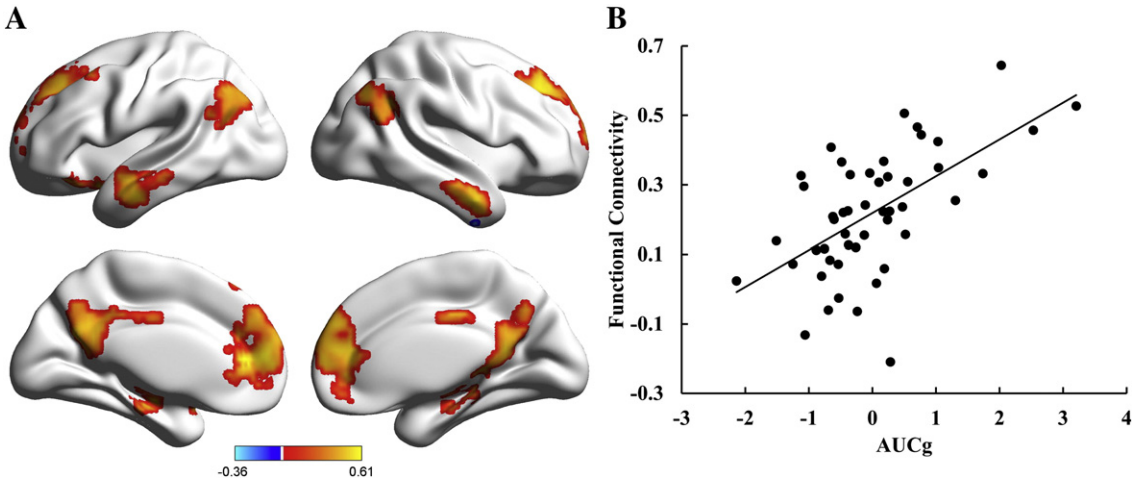

Fig. 3. (A) Statistical map for the correlation between functional connectivity (FC) analysis using the medial prefrontal cortex (mPFC) as a seed and the z scores of AUCg. The correlation value is indicated using the color scale at the bottom of the figure. The statistical threshold of $p < .05$ and cluster size > 43 was applied for display purpose. (B) The scatter plots (which serve illustrative purposes only) show the results of simple correlation between the z scores of AUCg and the average FC of the mPFC and regions in the default mode network. Each dot represents data from one participant.

hint that higher CAR might be a predictive biomarker of brain activity throughout the day. Notably our results were achieved by regressing out the effects of baseline cortisol level before resting-state scanning.

The results indicated that only AUCg predicted FCS in the mPFC, but no significant correlation was found between the AUCi and the FCS of the mPFC, although the correlation between AUCi and the FCS of small neural regions, including the middle occipital gyrus and right PrCG, reached significance. Previous studies have also found that the AUCi and AUCg are differentially associated with variable mental and physical factors (e.g., Edwards et al., 2001; Pruessner et al., 2003; Rane et al., 2012; Lamers et al., 2013). The mechanisms underlying the difference between the predictive value of AUCg and AUCi are largely unknown. AUCi is a measure of the dynamics of the CAR that emphasizes changes over time, and is somewhat distinct from the circadian rise in HPA activity in the morning hours (Pruessner et al., 2003; Clow et al., 2004; Wilhelm et al., 2007). AUCg, however, is an estimate of the total cortisol secretion over the short period (e.g., 1 h) after awakening (Pruessner et al., 2003). One study demonstrated that AUCg (but not the AUCi) predicts mean cortisol concentration throughout the following 12 h (Edwards et al., 2001). These neuroendocrinological and behavioral findings (Moriarty et al., 2014) together with our current functional neuroimaging data suggest that AUCg may have a closer association with diurnal cortisol concentrations and is a better metric to assess the relationship between CAR and brain functioning of the same day. More studies are necessary to support this temporal assumption.

In addition to the mPFC, our results also found that the AUCg displays positive associations with FCS in other brain areas, including the angular gyrus, middle temporal gyrus, and SPG. These areas are considered parts of the DMN (Binder et al., 1999; Damoiseaux et al., 2008; Mormino et al., 2011). The positive association between AUCg and FCS in these areas suggests that HPA activity after awakening can predict the FCS of the broad default mode network and even some brain regions of the non-DMN. More studies are necessary to investigate the associations between the CAR and resting-state FC between brain areas, in addition to the mechanism behind these associations.

Our research has some limitations that should be mentioned. First, our study only focused on male university students. It is possible that the association between AUCg and the intrinsic FC of the mPFC observed in this study might not be generalizable to a female sample or non-university student sample. Second, our study measured resting-state brain activity without any task and behavioral data, thus more research that includes overt tasks and measures of performance is necessary to test whether the findings in the present study can extend the relationship between the CAR as a state and functions of the mPFC.

Table 2
Regions in which functional connectivity (FC) using the medial prefrontal cortex (mPFC) as a seed correlated significantly with the AUCg.

Brain regions	Peak MNI coordinates					
	BA	x	y	z	r (peak)	Cluster size
Medial prefrontal cortex	32	−9	39	9	0.61**	1566
Posterior cingulate cortex/precuneus		0	−60	39	0.57**	575
Left angular	39	−51	−66	21	0.43*	232
Right angular	39	48	−69	39	0.53**	237
Left middle temporal gyrus	21	−51	−6	−15	0.52**	204
Right middle temporal gyrus	21	57	−3	−27	0.53**	176
Left parahippocampal gyrus	20	−30	−15	−15	0.48**	53
Right parahippocampal gyrus	35	21	−18	−15	0.52**	62
Left insula	38	−30	9	−15	0.52**	44

Note: BA, Brodmann Area.
** $p < 0.001$.
* $p < 0.01$.

Conclusions

Our study demonstrates that the total cortisol secretion after awakening is predictive of the resting-state FCS of the mPFC on the afternoon of the same day. Further analysis using the mPFC as a seed suggests that a higher CAR predicts enhanced positive FC between the mPFC and brain regions within the DMN.

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Conflict of interest

The authors report no financial conflict of interest with regard to the content of this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.08.016.

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