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# The trait and state negative affect can be separately predicted by stable and variable resting-state functional connectivity

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## Original Article

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## Abstract

**Background.** Many emotional experiences such as anxiety and depression are influenced by negative affect (NA). NA has both trait and state features, which play different roles in physiological and mental health. Attending to NA common to various emotional experiences and their trait-state features might help deepen the understanding of the shared foundation of related emotional disorders.

**Methods.** The principal component of five measures was calculated to indicate individuals' NA level. Applying the connectivity-based correlation analysis, we first identified resting-state functional connectives (FCs) relating to NA in sample 1 ($n = 367$), which were validated through an independent sample ($n = 232$; sample 2). Next, based on the variability of FCs across large timescale, we further divided the NA-related FCs into high- and low-variability groups. Finally, FCs in different variability groups were separately applied to predict individuals' neuroticism level (which is assumed to be the core trait-related factor underlying NA), and the change of NA level (which represents the state-related fluctuation of NA).

**Results.** The low-variability FCs were primarily within the default mode network (DMN) and between the DMN and dorsal attention network/sensory system and significantly predicted trait rather than state NA. The high-variability FCs were primarily between the DMN and ventral attention network, the fronto-parietal network and DMN/sensory system, and significantly predicted the change of NA level.

**Conclusions.** The trait and state NA can be separately predicted by stable and variable spontaneous FCs with different attentional processes and emotion regulatory mechanisms, which could deepen our understanding of NA.

## Introduction

Many different personality measurements reflect the structure of negative affects (NAs) including trait anxiety, neuroticism, general maladjustment, and repression sensitization (Watson & Clark, 1984). In a series of studies, Clark et al. showed that two emotional experiences, anxiety and depression, might differ with regard to their presentation modes among individuals under pressure but are both influenced by underlying NA together (Clark & Watson, 1991; Watson & Clark, 1984; Watson & Walker, 1996). Researchers also indicated the importance of attending to the NA common to many emotional experiences (Tackett, Waldman, Van Hulle, & Lahey, 2011); they might be even more important than their specific types (Andrews, 1996) because they help to reveal the common potential influencing factors associated with emotional experiences or emotional disorders and help explain the comorbidity patterns of multiple emotional disorders.

NA has the trait and state features. These features have different functions in physiological and mental health. Individuals with high NA across different situations are more likely to report discomfort, even when the current situation does not have an obvious source of stress (Watson & Clark, 1984). In addition, NA significantly affects the experience of pressure (Kong, Zhao, & You, 2012), health concerns, and the cognitive processing of unpleasant experiences (Jeronimus, Riese, Sanderman, & Ormel, 2014). The state feature usually refers to the temporary discomfort caused by uncertain events (negative stimulation or physiological situations) (Polk, Cohen, Doyle, Skoner, & Kirschbaum, 2005; Rutherford, MacLeod, & Campbell, 2004) and is the result of the interaction between many factors (specific feelings, physiological reactions, physical movements, ways of thinking, and experiences stored in memory) and the external environment (Berkowitz, 1994; Russell, 1980; Tepper, Duffy, Henle, & Lambert, 2006). Its major feature is that related NA experiences adapt with a change in the external environment and the internal physiological conditions of the individual, although these

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changes fluctuate around the baseline (i.e. trait) level (Mehra & Sah, 2002; Zelenski & Larsen, 2000). The current study sought to deepen the understanding of the potential influences of NA with regard to physiological and mental health based on the neural bases of state and trait NA as revealed by graph theory.

NA and related emotional disorders likely involve interactions among critical brain networks such as the fronto-parietal task control network (i.e. dorsolateral prefrontal cortex; right orbital and middle frontal gyrus), the default mode network (DMN) (i.e. medial prefrontal cortex, mPFC; anterior cingulate cortex, ACC), the dorsal/ventral attention network and subcortical structures. Individuals with high NA and/or related emotional disorders have weaker top-down (primarily from the frontal cortex to the limbic system/dorsal attention network) regulatory functions but stronger bottom-up driving functions (Pessoa, 2017; Savitz & Drevets, 2009). For example, the mPFC and the ACC connect up to the frontal cortex, parietal cortex, and sensorimotor area and down to limbic system structures and regions of ventral attention network (Pessoa, 2008, 2017), and they are involved in the appraisal and expression of negative emotion and the attention reorienting (Etkin, Egner, & Kalisch, 2011; Kaiser et al., 2015b; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015a). Studies of related emotional disorders have usually reported abnormal functional connectivity (FC) in these networks (Drevets, Price, & Furey, 2008; Etkin & Wager, 2007; Pizzagalli, 2011). Furthermore, the deregulation of frontoparietal functions can result in an excessively active, which produces uncontrolled negative emotions (Davidson, 2002). Abnormal FC presents with related emotional disorders and is considered as an important neural mechanism of pathological emotional affective disorders (Koenigs & Grafman, 2009).

Importantly, resting-state functional magnetic resonance imaging (fMRI) exhibits a rich source of information regarding the spontaneous (or intrinsic) activity of the brain (Buckner, Andrews-Hanna, & Schacter, 2008; Raichle, 2015) and its inner relationships with personality features (Scalabrini et al., 2017), subjectivity (Scalabrini et al., 2017), self (Northoff et al., 2006; Northoff & Bermpohl, 2004), and task-evoked activity (Scalabrini, Mucci, & Northoff, 2018; Viola et al., 2018). For instance, the correlation between spontaneous activity and neural activity of anticipating the animate target in anterior insula was mediated by individual personality features (Scalabrini et al., 2017). Moreover, the findings of revealing the correlations between disturbed resting-state activity and NA (Cui et al., 2016; Disner, Marquardt, Mueller, Burton, & Sponheim, 2018; Northoff, 2016) may bear important implications for understanding various emotional experiences. Specifically, the resting-state FC mode has both trait and state features. Although this mode largely remains stable (Cole, Bassett, Power, Braver, & Petersen, 2014; Tavor et al., 2016), it also undergoes a certain degree of adjustment as the individual's state changes (Laumann et al., 2015; Yeo, Tandi, & Chee, 2015), which reflects the variability of the resting-state. The variability of resting-state FC has attracted great attention due to its close relationship with various behaviors (Baldassarre et al., 2012; Douw, Wakeman, Tanaka, Liu, & Stufflebeam, 2016; Sun et al., 2019) and in serving as a sensitive biomarker for a number of mental disorders (Liu et al., 2017a; Magioncalda et al., 2015; Yu et al., 2015; Zhang et al., 2016). However, studies on the relationship between state-trait NA and the variability of resting-state FC are rare.

In the current study, we hypothesize that resting-state FC with different variability will correspond to NA with different characteristics. In other words, trait NA should correspond to relatively stable (low-variability) resting-state FC, whereas state NA should be associated with relatively variable (high-variability) FC. The purpose of this study was to use FC with different variability characteristics to predict the trait and state NA levels of individuals. First, the principal component score (PCS) of NA was obtained by a principal component analysis. The Pearson correlation between the resting-state FCs and the PSC was calculated in sample 1 ($n = 367$). The identified NA-related FCs were validated through an independent sample ($n = 232$; sample 2). Next, a community detection algorithm was applied to calculate FC variability. According to the median of the FC variability at the group level, the NA-related FCs were divided into high- and low-variability groups. Finally, FCs in different variability groups were separately applied to predict individuals' neuroticism level (which is assumed to be the core trait-related factor underlying NA), and the change of NA level (which represents the state-related fluctuation of NA).

## Methods

### Data collection

The Southwest University Longitudinal Multimodal Imaging (SLMI) Data Repository (Liu et al., 2017c) provided the data for this study. The SLMI was divided into three time points to longitudinally track the participants (the average time interval of the whole process was 515 days). Magnetic resonance imaging (MRI) multimodal brain imaging data were collected at all time points. In addition, various demographic, statistical, and physiological variables were collected at all time points.

The behavioral data were collected within 1–2 weeks of the MRI data acquisition. The NA-related measurements included were the State-Trait Anxiety Inventory (STAI), the Beck Depression Inventory (BDI-II) (Beck, Steer, & Brown, 1996); the Positive Affect and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988), and the Perceived Stress Scales (CPSS) (Yang & Huang, 2003). The STAI includes two subscales: the State Anxiety Inventory (SAI) and the Trait Anxiety Inventory (TAI). The Negative Affect Score (NAS) in the PANAS was included in the subsequent calculation. All subjects who completed the five questionnaires were divided into two samples. Sample 1 consisted of 385 subjects who completed five questionnaires at any one time point. Sample 2, a total of 236 people ($118 \times 2$), completed the five questionnaires at the 1st and 3rd time points.

Furthermore, the personality trait of neuroticism is closely related to negative emotionality (Jeronimus et al., 2014; Jeronimus, Kotov, Riese, & Ormel, 2016; Markon, Krueger, & Watson, 2005). These two have a stable relationship; the former is usually considered as an effective prediction factor for the latter (Jeronimus, Ormel, Aleman, Penninx, & Riese, 2013). Trait neuroticism can be understood as 'the sensitivity and activity of the negative affect system' (Henriques, 2011). Our study used neuroticism as a representative indicator of trait NA. Neuroticism was measured using the Revised Neuroticism Extraversion Openness Personality Inventory (NEO-PI-R) (Costa & McCrae, 1992).

The resting-state functional MRI imaging data were collected using a Siemens scanner (3.0-T Siemens Trio MRI) at the Brain Imaging Center of Southwest University, China. The resting-state scan used a gradient-echo EPI sequence to continuously collect 242 whole-brain resting-state 3D images within 8 min. The scanning parameters were as follows: repetition time (TR) = 2000 ms,

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echo time (TE) = 30 ms, flip angle (FA) = 9°, matrix = 64 × 64, field of vision (FOV) = 192 × 192 $mm^2$, slice = 32, thickness = 3 mm, distance between slice = 1 mm, and voxel size = 3.4 × 3.4 × 4 $mm^3$. After the resting-state data were collected, 3D structural imaging was performed using the magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence. The scanning parameters were as follows: TR = 1900 ms, TE = 2.52 ms, inversion time (TI) = 900 ms, FA = 9°, slice = 176, thickness = 1 mm, FOV = 256 × 256 $mm^2$, matrix = 256 × 256, and voxel size = 1 × 1 × 1 $mm^3$.

### Data preprocessing

(1) To ensure signal stability, the first 10 time points in the time sequence were deleted. (2) The remaining 232 time-points were subject to a slice-timing correction. In addition, head motion realignment was performed based on the displacement of the adjacent EPI data. (3) The EPI template (Ashburner & Friston, 1999) was used to map the data from the original space to the Montreal Neurological Institute (MNI) space with a voxel size of 3 × 3 × 3 $mm^3$. (4) The global signals, cerebrospinal fluid (CSF) signals, white matter signals, and 24 head motion parameters were used as covariates in the regression (Friston, Williams, Howard, Frackowiak, & Turner, 1996). (5) Waves (0.01–0.1 Hz) were filtered to remove the low-frequency signal drift and high-frequency physiological noise. (6) A 4-mm kernel was used for smoothing. EPI data with framewise-dependent (FD) values exceeding 0.5 (together with the data at the previous time point and the next two time points) were removed (Power et al., 2014). If more than 10% of the EPI data of one participant were excluded, then he or she was no longer included in the subsequent analysis. Based on this standard, sample 1 remained 367 subjects, and sample 2 remained 232 subjects. The above processing steps were competed using the DPABI toolbox (http://rfmri.org/dpabi).

### Construction of the resting-state FC matrix

(1) The Power-264 template defined based on the meta-analysis of task-based fMRI studies and resting-state fMRI data was selected (Power et al., 2011). This template provides near whole-brain coverage with greater specificity than most atlases and accurately divides nodes into communities to enable us to investigate canonical functional networks. Moreover, the homogeneity of the nodes is superior to most parcellations (Gordon et al., 2016) and they do not share physical boundaries, which will not overestimate the local connectivity of regions. Furthermore, this template has been widely used in FC studies (Cole, Ito, Bassett, & Schultz, 2016; Doré et al., 2019; Yang et al., 2018), and there is evidence to suggest that this template yields superior predictive features that are strongly related to behavioral measures (Plitt, Barnes, & Martin, 2015), thus this approach may be well suited for predicting. Therefore, considering the above advantages and our research aim of predicting NA using resting-state FC, we selected the Power-264 template. (2) The average blood oxygenation level-dependent (BOLD) time sequence was extracted from 264 cortical and subcortical brain regions (nodes). (3) Four cerebellum nodes, 11 nodes with a signal-to-noise ratio smaller than 100 (primarily including regions in the orbitofrontal cortex, temporal pole, and inferior temporal gyrus), and 21 nodes with unclear attributions in the brain network were excluded. Finally, 228 nodes were included as regions of interest (ROIs). (4) The Pearson's correlation coefficients between any two ROI time sequences were calculated, and the values were converted into *z*-scores using Fisher's *r*-to-*z* transformation to define the strength of the FC among ROIs and ultimately construct the 228 × 228 resting-state FC matrix.

### Data analysis

#### Identification of NA-related FCs

*Principal component analysis*. All subjects in samples 1 and 2 who completed the five NA measures (TAI, SAI, BDI, NAS, and CPSS) were included in the principal component analysis (the scores of the same participant at different time points were viewed as independent data points). The Kaiser-Meyer-Olkin (KMO) and Bartlett's sphericity test were used to examine whether the above data were suitable for principal component analysis. Specifically, we generated 1000 of 5 (measure) × 621 (subjects) random data matrices and calculated the average eigenvalue. Then the principal components were extracted according to the principle that the eigenvalue of real data should be greater than that of random data, and the corresponding factor score was multiplied by the square root of the variance to obtain the standardized principal component score of negative affect (NA-PCS).

*FC-based correlation analysis*. The following analysis steps were performed: (1) identify the FC related to NA: the Pearson correlation between the resting-state FC matrices and the NA-PCS was calculated across all individuals in sample 1, with age, sex being regressed out. (2) Feature selection: edges of a significance threshold at $p < 0.05$ were selected as input features. (3) Model fitting: to enhance the robustness of our conclusions, kernel ridge regression (KRR) algorithms combined with a five-fold cross-validation procedure were adopted to prediction analysis. Kernel method is a classical machine learning approach and minimizes the estimation error in the training data and model complexity. The KRR has received considerable attention among kernel-based methods due to its non-iterative approach of learning ability and efficient way for predicting behavioral phenotypes in individuals using resting-state fMRI (He et al., 2020; Kong et al., 2018). In this step, the KRR assumes a linear relationship between the selected edges (independent variable) and the NA-PCS values (the dependent variable) in a training set (80% of the sample). In each five-fold cross-validation, 80% of the sample was used for training and 20% for testing. (4) Evaluation of the predictive model: after predicting the NA-PCS values for all subjects in the testing set, statistical significance for the correlation between predicted and observed values were assessed using permutation testing (1000 iterations). Furthermore, to cross-validate the findings from sample 1, we masked the individual connectivity matrices with edges selected in step 2 among an independent set (sample 2), and then we repeated steps 3 and 4.

### Calculation of the resting-state FC variability

In sample 2, the participants with NEO-PI-R were included in the analysis of calculating variability and predicting trait and state NA. A total of 184 people (92 × 2) provided excellent imaging data. To detect the variability of the resting-state FC, we first applied the community detection algorithm for each participant's resting-state FC matrix at different time points to generate the node-affiliation matrix. In this matrix, if two nodes belong to the same network, their edge assignment is 1; otherwise, 0. Then, on this basis, the variability matrix (VM) is generated

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by examining how possible each link changes its network affiliation among the node-affiliation matrices at different scanning time points. Because this study only focused on the variability of specific connections under the general level, the mean of the variability matrices of all participants was obtained to generate the VM at the group level to determine whether the connection relationship was relatively stable or variable. The specific procedures were as follows: (1) the network structure of resting-state FC was detected using the multilayer Louvain community detection algorithm (Mucha, Richardson, Macon, Porter, & Onnela, 2010). Briefly, this algorithm performs repetitive iterations of the community structure until the maximum modularity ($Q$) is obtained. Gamma ($\gamma$) and omega ($\omega$) are two important parameters. Respectively, they define the expected community size (larger values denote more communities and more scattered nodes) and the connectivity strength of the same node at different levels (i.e. time points; higher values denote stronger connectivity between levels). The formula of this algorithm was as follows:

(Formula 1)

$$Q = \frac{1}{2\mu}\sum_{ijlr}\{(A_{ijl} - \gamma_l P_{ijl})\delta_{lr} + \delta_{ij}\omega_{jlr}\}\delta(g_{jl}, g_{jr})$$

In the above formula, $i$ and $j$ indicate different nodes in the FC matrix; 1 and $r$ indicate different layers (time points); $A_{ij}$ indicated the FC matrix; $P_{ijlr}$ indicates the Newman-Girvan null model; $\gamma_l$ indicates the structure analysis parameters in one layer; $\omega_{jlr}$ indicates the coupling parameter of node $j$ between the $l$ and $r$ layers. When node $j$ at the $l$ and $r$ layers belong to the same community, $\delta(g_{jl}, g_{jr})$ is 1; otherwise, it is 0. Based on previous studies (Mantini, Corbetta, Romani, Orban, & Vanduffel, 2013), $\gamma$ and $\omega$ parameters were both set as 1. This algorithm was involved in the null model, and a certain degree of randomness was present; therefore, each data point was simulated 100 times using this algorithm. (2) After the community detection of the FC matrix at different time points, the 100 node relation matrices were generated based on the community division results. In addition, the variability of the specific FC was calculated based on the relation matrix at any two time points to further generate the VM. The calculation formula was as follows:

(Formula 2)

$$Variability(V) = \frac{1}{N}\sum\nolimits_{i=1}^{N} f_i$$

In the above formula, $N$ indicates the theoretic variability of the relationship between any two nodes, and $\sum_{i=1}^{N} f_i$ indicates the actual variability of the relationship between these two nodes. We extend the node variability (Bassett et al., 2011) to FC variability within and between resting-state networks, and that reflects the rapid adaptation and continuous evolution of the temporal scales in the brain networks, and the indicator is sensitive to both intraindividual and interindividual temporal variability (Reddy et al., 2018; Sun et al., 2019). Because 100 community detection simulations were executed, the variability of each detection result was calculated. The final variability at the individual level was the average value after 100 iterations, and the variability at the group level was the mean variability (mV) of all participants. The above analytic process enabled the calculation of the mV from different levels (sides, nodes, and network), where the mV of one node was the mean of the mV of all sides of that node. The mV of the whole network was the mean of the mV of all sides in the network. Finally, through the median of the FC variability at the group level, the NA-PCS-related FC was divided into two components: relatively stable [variability lower than the median, the stable connectivity component (SCC)] and relatively variable [variability higher than the median, the variable connectivity component (VCC)].

### Predictive analyses of state and trait NA

Prediction of trait NA: (1) Neuroticism was used as a representative indicator of trait NA. (2) The SCC and VCC were inputted as features which masked by the edges selected in step 2 (see '*FC-based correlation analysis*' section) to predict neuroticism. And the same predictive procedure (steps 3 and 4 of the above '*FC-based correlation analysis*' section) was performed. Prediction of state NA: (1) the difference in subjects' NA-PCS (NA-PCSD) values was calculated between two time points as an indicator of the change of state NA. (2) The difference between SCC and VCC (ΔSCC, ΔVCC) between two time points (3rd time point and 1st time point) was calculated as an indicator of the FC change of NA level. Note that, the trait NA might be strongly correlated with state NA, and that in its phenomenology people with higher scores of neuroticism might be more prone to state NA and its features of variability across time. Therefore, covariates of neuroticism scores, as well as sex and age, were regressed out from every participants' FCs by removing values of each link on covariates to obtain residuals as final values. (3) The ΔSCC and ΔVCC which masked by the edges selected in step 2 (see '*FC-based correlation analysis*' section) were used as features to predict the NA-PCSD. And the same predictive procedure (steps 3 and 4 of the above '*FC-based correlation analysis*' section) was performed.

### Global signal

Previous researches have shown that global signal is associated with non-neuronal activity, such as respiration and cardiac rhythms (Liu, Nalci, & Falahpour, 2017b; Power, Plitt, Laumann, & Martin, 2017), and therefore global signal regression (GSR) is highly effective at removing global artifacts arising from these physiological sources. Moreover, this recent research suggests that some behavioral phenotypes exhibit greater improvement in prediction accuracy after GSR (using kernel regression) (Li et al., 2019b). Consequently, given the absolute importance of the prediction analysis to the current study, we mainly focus on results with GSR. However, the global signal is not only mere noise but also an important source of information (Li et al., 2019a). Therefore, we repeated the same prediction analyses based on the corresponding FC features without GSR, which can serve as a control analysis for the FCs identified in our study and may provide complementary insights.

## Results

The principal component analysis included 621 participants (342 females; mean ± s.d. age, 20.7 ± 1.4 years, ranging from 17 to 27 years). Common factors were observed between the matrices suitable for principal component extraction (KMO = 0.837, $p <$ 0.001). Based on the parallel analysis principle, one principal component was extracted. This principal component explained 62.4% of the total variation of the variables (Table 1).

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**Table 1.** The eigenvalues and variance contribution rates of all components

| Component | Eigenvalue | % of Variance | Cumulative % |
|---|---|---|---|
| 1 | 3.122 | 62.44 | 62.4 |
| 2 | 0.648 | 12.95 | 75.4 |
| 3 | 0.483 | 9.65 | 85.0 |
| 4 | 0.464 | 9.28 | 94.3 |
| 5 | 0.284 | 5.68 | 100.0 |

We first confirmed the resting-state FC related to the NA-PCS at the $p < 0.05$ level in sample 1. As the prediction analyses showed, these FCs significantly predicted the NA-PCS in sample 1. The correlation between the real value ($Y$) and the predicted $Y$ was 0.72 (Fig. 1*b*), and the permutation test (1000 iterations) showed that the prediction function was significant ($p < 0.001$). Using the independent dataset (sample 2), these FCs still predicted the NA-PCS based on the permutation test with $p = 0.003$. And the correlation between $Y$ and the predicted $Y$ reached 0.24 (Fig. 1*c*). We sorted all nodes by the total number of its functional connectivities and the FCs of the top 25 nodes were presented in Fig. 1*a*. Based on the classical functional network defined in previous studies (Power et al., 2011), Fig. 1*a* showed the positive and negative FCs mainly involved the DMN, frontoparietal task control network (FPN), the attention system (dorsal/ventral attention network), and the sensory system (visual network, auditory network, sensory-somatomotor network). The results of the same prediction analyses using preprocessing data without GSR were showed in the online Supplementary material, which indicated the FCs also predicted the NA-PCS in sample 1 and sample 2. Please see the online Supplementary material for details.

According to the median of the FC variability at the group level, the NA-PCS-related FCs were divided into relatively stable FCs and relatively variable FCs. Figure 2*a* shows the FCs of the top 12 nodes in SCC. These connections were mostly positive and mainly within DMN or between the DMN and the dorsal attention network/sensory system. Figure 3*a* shows FC of the top 13 nodes in VCC, and the connections were primarily between the DMN and the ventral attention network, the FPN and the DMN/sensory system. Specifically, ΔSCC did not show a predictive function with regard to the NA-PCSD. The correlation between the $Y$ and the predicted $Y$ was 0.06 (see Fig. 2*b*). The permutation test (1000 iterations) showed that the prediction function was not significant ($p = 0.488$). In contrast, a significant predictive function regarding SCC and neuroticism was presented with $r = 0.22$ (see Fig. 3*a*) and $p = 0.005$. The ΔVCC predicted the NA-PCSD, the correlation between the $Y$ and the predicted $Y$ was 0.34 (Fig. 3*b*), and the permutation test (1000 iterations) showed that the prediction function was significant ($p = 0.026$). No prediction function was found with regard to VCC and neuroticism based on $r = 0.11$ (Fig. 3*c*) and $p = 0.091$. The details of the same prediction analyses using preprocessing data without GSR were presented in the online Supplementary material.

## Discussion

In the current study, we used FC with different variabilities to predict the trait and state NA among individuals. Firstly, we identified the resting-state FC which predicted NA. And then the FC was divided into high- and low-variability groups to predict trait and state NA. Finally, we found that the low-variability FCs significantly predicted neuroticism (trait) rather than NA-PCSD (state), and high-variability FCs significantly predicted NA-PCSD, not neuroticism. Specifically, the relatively stable (low-variability) FCs were primarily within DMN or between DMN and the dorsal attention network/sensory system. The relatively variable (high-variability) FCs were primarily between the DMN and the ventral attention network, the FPN and the DMN/sensory system. These results suggest that the trait and state NA can be separately predicted by stable and variable resting-state FC which may involve in different attentional processes and emotion regulatory mechanisms.

We found that the stable FCs, which were positively correlated with NA and within the DMN or between the DMN and the sensory system/dorsal attention network, were sensitive to trait rather than state NA. Firstly, the DMN is involved in affective regulation and internal mental thoughts (i.e. mind wandering, self-referential processes) (Christoff, Gordon, Smallwood, Smith, & Schooler, 2009; Davidson, 2000; Sheline et al., 2009). Our results of intranetwork FC in the DMN positively related to NA might indicate that individuals generate internally focused spontaneous thoughts which bias toward NA and self-focused, which has found in NA-related mental disorders. For instance, the abnormally increased FCs within the DMN have found in depression (Anand et al., 2005; Liu et al., 2012) as well as ultra-high risk for psychosis relative to healthy individuals (Shim et al., 2010). Regarding the sensory system, as the center of sensory processing and motor functions (Huang et al., 2015), it is important for the psychomotor dimension (Martino et al., 2016). We found the connections between the DMN and the sensory system might suggest the internally oriented cognition for NA interact with the psychomotor behaviors. As recent evidence further shows that the DMN/sensorimotor networks in depression exhibited interaction between excessive internally directed thoughts and fluctuating psychomotor (Martino et al., 2016).

The results also indicated that the increased connections between the DMN and the dorsal attention network were correlated with increased trait NA. Briefly, the dorsal attention network has been suggested to generate and maintain voluntary attention by biasing processing based on internal goals or expectations (top-down orienting) (Corbetta, Patel, & Shulman, 2008). Our result is consistent with previous researches showing that weakened anti-correlations between the DMN and the dorsal attention network are involved in worse clinical status (De Havas, Parimal, Soon, & Chee, 2012; Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). Indeed, the greater connectivity between the DMN and the dorsal attention network predicts poorer distractor suppression (Poole et al., 2016) and shows increased levels of rumination in healthy subjects (Lois & Wessa, 2016). Taken together, our findings may support the idea that the DMN provides sustained internally concerned negative experiences indicating where, when, or to what individuals should orient their attention. Importantly, the dynamic characteristic of the connectivities identified to predict trait NA are stable, which indicates these FCs maintain community allegiance during the resting-state, and this is an important attribute for predicting trait rather than state. The previous researches suggest that static aspects of FC may simultaneously capture individuals' disposition about stably inherent traits (Cole, Yarkoni, Repovš, Anticevic, & Braver, 2012; Finn et al., 2015). Combining with our results, the DMN might provide sustained internally directed negative cognition

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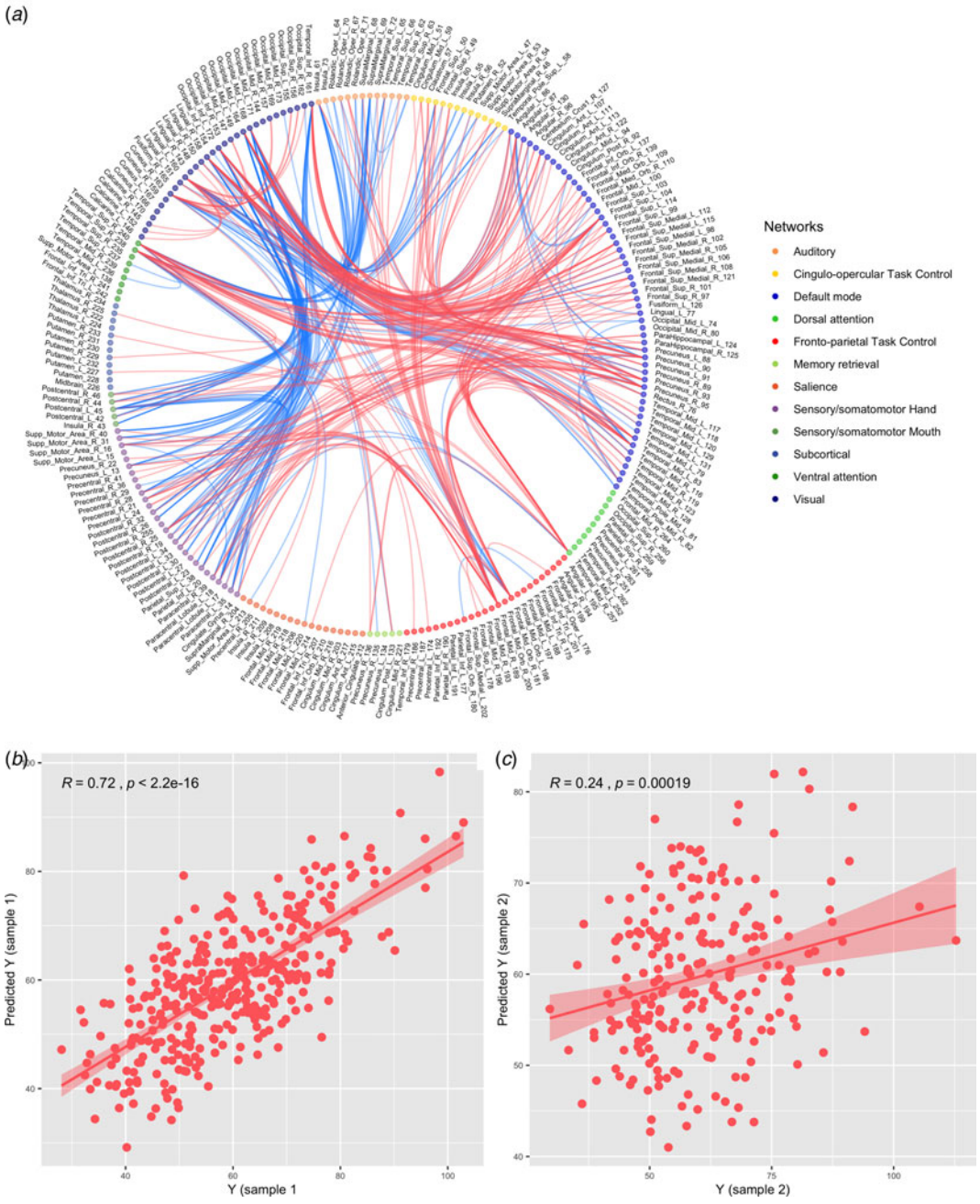



**Fig. 1.** (*a*) Functional connectivities (the functional connectivity of the top 25 nodes were presented) associated with the NA-PCS at the $p < 0.05$ level in sample 1. (*b*) The prediction effect of the NA-PCS-related functional connectivities in sample 1. (*c*) The prediction effect of the NA-PCS-related functional connectivities in sample 2. Red: increased functional connectivity, Blue: decreased functional connectivity.

coupling with the sensory system (psychomotor function) and the dorsal attention network (top-down orienting) to predict trait NA in a stable modular manner.

On the other hand, we found the changing level of the variable FCs, which were positively correlated with NA and between the DMN and the ventral attention network, were sensitive to the change of state rather than trait NA. In contrast to the dorsal attention network which supports top-down orienting, the ventral attention network is primarily involved in bottom-up stimulus-driven which re-orienting attention toward salient external stimuli (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). Our result is consistent with the previous evidence, which shows that, in response to negative emotional distractors, subclinical depressive individuals are associated with hyperconnectivity between brain regions responsive to salience and regions related to internal mentation (Kaiser et al., 2015b). In this study, the findings of the connections between the DMN and the ventral attention network might suggest the bottom-up processing of negative cues that correspond to the content of internal thoughts. Crucially, the high level of variability of these connections indicates that the FC constantly shifts allegiance, which appears to characterize the frequently regulating focus of external stimuli (Vartanian, 2009) or

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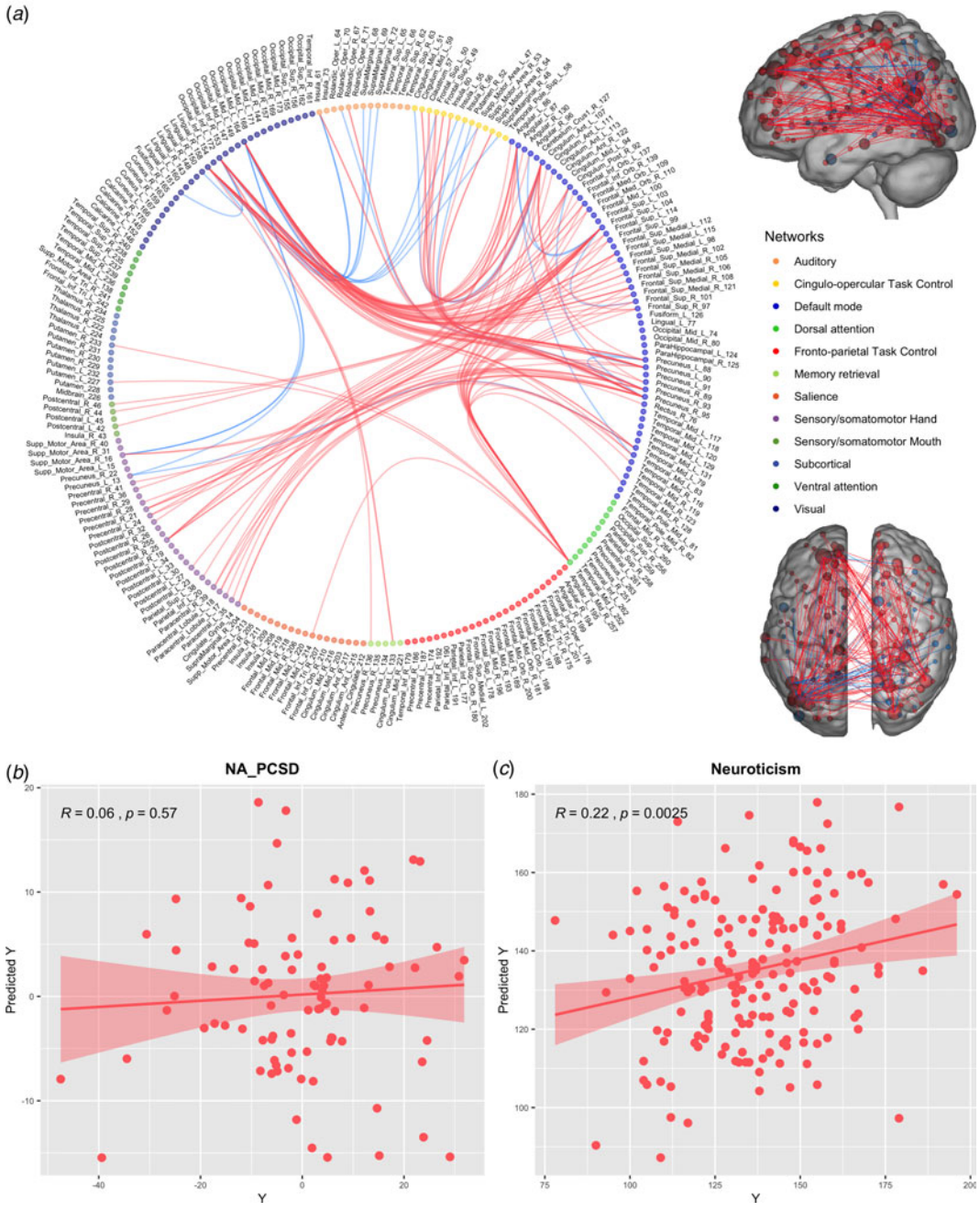



**Fig. 2.** (*a*) Functional connectivities of the top 12 nodes in SCC. Red: increased functional connectivity, Blue: decreased functional connectivity. (*b*) The prediction effect of the ΔSCC on the NA-PCSD. (*c*) The prediction effect of the SCC on neuroticism. SCC: the stable connectivity component. NA-PCSD: the difference in subjects' principal component score of negative affect.

shifting of the focus of mental thoughts (Kucyi, Esterman, Riley, & Valera, 2016). The regulating or shifting of connections between the DMN and the ventral attention network thus may influence the level of NA.

Moreover, the findings indicated that the increased connectivity between the FPN and DMN/sensory system predicted greater state NA. The FPN is typically involved in the executive, top-down regulation of attention and emotion (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008), and the abnormal activity within the FPN may reflect deficits in cognitive control (Kaiser et al., 2015b). Previous researches show that the FPN and the DMN positively couple during internal attention-oriented processing such as self-referential processing (Spreng, 2012) and mind-wandering (Fox, Spreng, Ellamil, Andrews-Hanna, & Christoff, 2015). Furthermore, allocating too many resources toward the internally oriented processing at the cost of engaging with external attention may lead to hyperconnectivity between the two networks. For example, the increased connectivity between the FPN and the DMN is observed in major depressive disorder (Whitton et al., 2018). This evidence suggests that aberrant communication between the two networks may reflect ongoing rumination or an underlying bias for control systems (Kaiser et al., 2015b). Combining with our results, the communication between the two networks may contribute to certain

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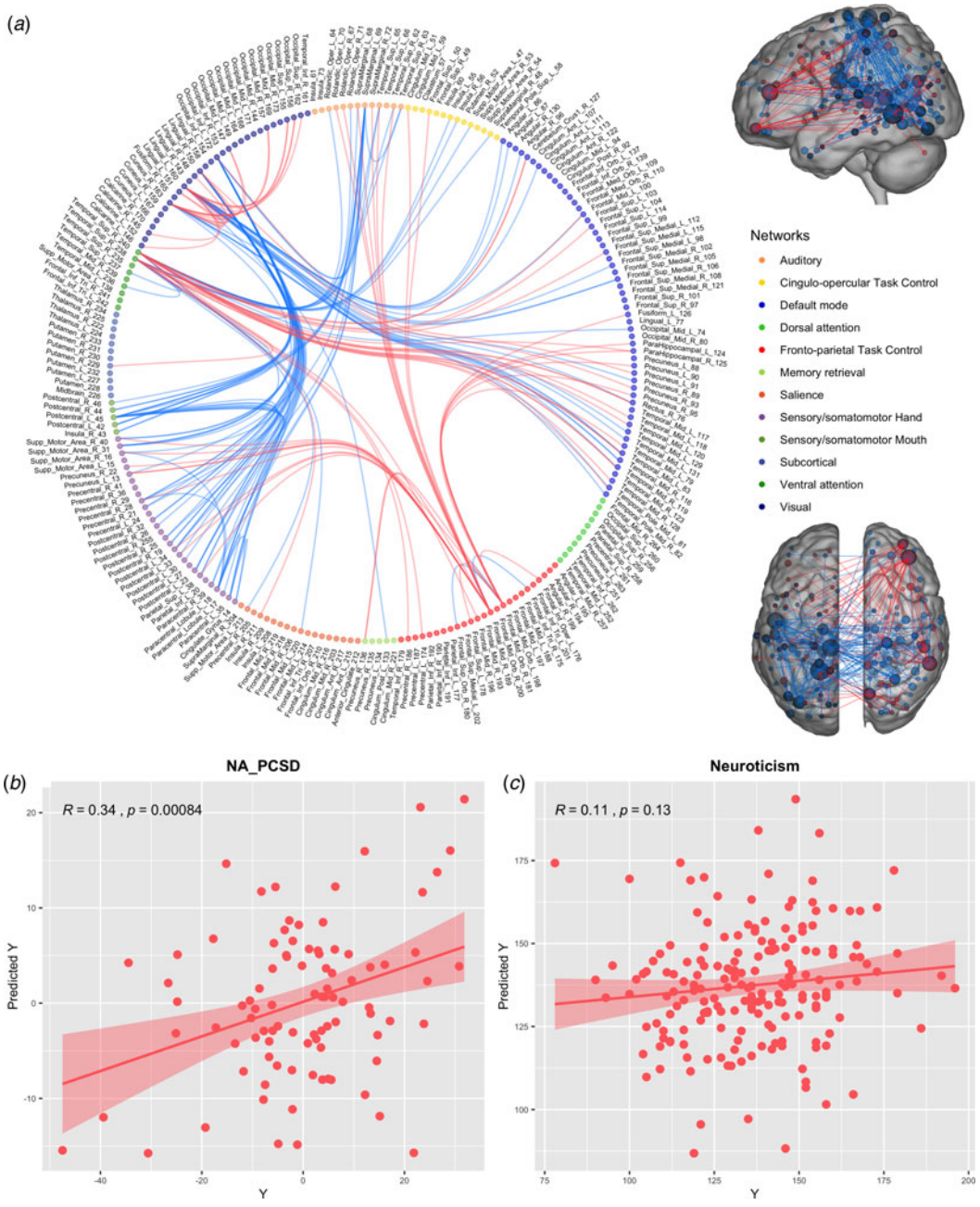



**Fig. 3.** (*a*) Functional connectivities of the top 13 nodes in VCC. Red: increased functional connectivity, Blue: decreased functional connectivity. (*b*) The prediction effect of the ΔVCC on the NA-PCSD. (*c*) The prediction effect of the VCC on neuroticism. VCC: the variable connectivity component. NA-PCSD: the difference in subjects' principal component score of negative affect.

patterns in cognitive and affective functioning that are considered to underlie state NA. In addition to the sensory system, the FPN may positively couple with it for use of sensory computational resources (Anticevic et al., 2012) according to task demands which may be associated with the level of NA. Specifically, the above connections constantly shifted among modular structures. This high-variability pattern within FPN or between FPN and other networks (i.e. DMN, sensory system) has been reported in previous studies, which shows that the dynamic FC of FPN, as a flexible hub of cognitive control, is related to the state-dependent variability (Betzel, Satterthwaite, Gold, & Bassett, 2017; Douw et al., 2016; Zanto & Gazzaley, 2013). Therefore, this pattern may facilitate dynamic cognitive regulation for internal-oriented processing or transformations of sensory manifestation of psychomotricity, and thus be related to the change of NA.

To summarize, the current study combines FC strength with variability to distinguish trait and state NA. The low-variability with the attribute of maintaining community allegiance may provide implications for understanding individuals' personality trait or a disposition to retain NA. In contrast, the high-variability with the attribute of shifting allegiance frequently may play an important role in the fluctuation of NA. And the FCs correlated with trait and state NA were involved in different networks,

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such as DMN-dorsal attention network *v.* DMN-ventral attention network, within DMN *v.* FPN-DMN, which suggests that trait and state NA are specifically subserved by the intrinsic brain activities with different attentional processes and emotion regulatory mechanisms. This study supports the hypotheses of previous studies regarding the important neural mechanisms of NA. Furthermore, the variability of the intrinsic activity was adopted to obtain additional unique NA-related brain imaging mode which previous studies have rarely used to predict the trait and state NA separately. The current study deepens our understanding of NA and provides new thinking and references for future studies.

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