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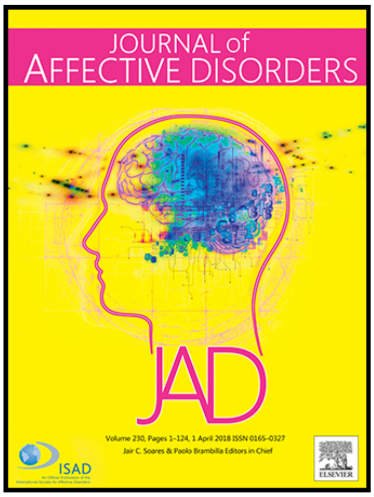

Personality traits are related with dynamic functional connectivity in major depression disorder: a resting-state analysis

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Highlight

- The advantages of this study are mainly reflected in following aspects.
- Firstly, we used a large sample in this study to avoid the problems in previous MDD researches with small sample.
- Besides, the practice combining personality traits with psychiatric disease in research keeps with current idea that diseased people and healthy people should not be seen as separate, but as different location on a same spectrum. Consistent with this idea, the results of this study support the potential of personality as an important factor affecting depression and as a therapeutic target.
- Moreover, we used DFNC method, which was more sensitive to overall mental state and could catch more instantaneous difference so we could get some information that is not available with traditional static FC analysis.

Title: Personality traits are related with dynamic functional connectivity in major depression disorder: a resting-state analysis

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ABSTRACT

Background: Major depressive disorder (MDD) is one of the most well-known psychiatric disorders, which can be destructive for its damage to people's normal cognitive, emotional and social functions. Personality refers to the unique and stable character of thinking and behavior style of an individual, which has long been thought as a key influence factor for MDD. Although some knowledge about the common neural basic between MDD and personality traits has been acquired, there are few studies exploring dynamic neural mechanism behind them, which changes brain connectivity pattern rapidly to adapt to the environment over time.

Methods: In this study, the emerging dynamic functional network connectivity (DFNC) method was used in resting-state fMRI data to find the differences between healthy group (N=107) and MDD group (N=109) in state-based dynamic measures, and the correlations between these measures and personality traits (extraversion and neuroticism in Eysenck Personality Questionnaire, EPQ) were explored.

Results: The results showed that MDD was significantly less than the health control group in dwell time and fraction time of state 4, which was positively correlated with extraversion score and negatively correlated with neuroticism score. Further exploration on state 4 showed that it had low modularity, hyper-connectedness of sensory-related regions and DMN, and weak connections between cortex and subcortical areas, which suggested that the absence of this state in MDD might represent a decrease in activity and positive emotions.

Conclusion: We found the dynamic functional connectivity mechanism underlying

MDD, confirmed our hypothesis that there existed the interacted relationship between trait, disease and the brain's dynamic characteristic, and suggested some reference for treatment of depression.

Keywords: DFNC, major depression disorder, personality trait, EPQ, FC state

Introduction

Major depressive disorder (MDD) is one of the most well-known psychiatric disorders characterized by a long period of low mood, anhedonia, pessimism, lack of initiative and dysfunction of neuro-vegetative system (Iwabuchi et al., 2015; Lux & Kendler, 2010; L. Wang, Hermens, Hickie, & Lagopoulosn, 2012). Compared with other mental health problems, MDD is quite common (it is estimated that 11.2% of individuals affected by MDD at some time point in their lives) and can damage people's normal cognitive, emotional and social function in multiple aspects (C, A, & P, 2015), so it is important to determine the key psychological and neural factors affecting the generation, development and treatment of MDD. Personality refers to the unique and stable character of thinking and behavior style of a person, which is considered to be closely associated with a variety of psychiatric disorders, including depression and anxiety (Bienvenu et al., 2004; Lux & Kendler, 2010), and the personality traits most widely studied have been neuroticism and extraversion. Extraversion is characterized by being talkative and outgoing, having more positive affect, and seeking external stimulation; neuroticism or emotionality is characterized by more negative affect such as observed in depression and anxiety (Eysenck & Eysenck, 1975). In previous studies, neuroticism was shown to be a risk factor for depression, while extroversion was seen as a protective factor against MDD (Grav, Stordal, Romild, & Hellzen, 2012; Kendler, Gatz, Gardner, & Pedersen, 2006). Studies of patients with depression suggested that individuals with high neuroticism and/or low extraversion tended to show more severe depressive symptoms, and they were found more difficult to recover from depression and benefit less from psychological treatment or medication (Bagby, Joffe, Parker, Kalemba, & Harkness, 1995; Bienvenu et al., 2004; Jylha, Melartin, Rytsala, & Isometsa, 2009; Kudo et al., 2017; Quilty et al., 2008). Recently, there had been a consensus in academia that abnormalities in various mental disorders and psychiatric function might be distributed on a continuous spectrum, and the new research paradigm, Research Domain Criteria (RDoC) project, was proposed to promote cross-disease research (BJ et al., 2013; T. Insel, Cuthbert, Garvey, Heinssen, & Pine, 2010; T. R. Insel, 2014; Lilienfeld, 2014). Personality, as a stable cognitive and behavioral trait across individuals, could serve as a bridge between diseased and normal function, which highlights the necessity of combining personality measures with MDD in research.

In early studies, due to the limitations of technology, the temporal attributes of brain activity were always ignored, and most studies focused on functional spatial localization in the brain. However, the temporal attribute is quite significant; for example, maintaining depressive mood for more than two weeks is one of the core diagnostic criteria for MDD (Lux & Kendler, 2010; US, 2013). A common paradigm for considering time information is the functional connectivity (FC) method, which focuses on synchronous activity between two brain regions (Bastos & Schoffelen, 2016; Biswal, Yetkin, Hyde, & Haughton, 1996; Mp & Hulshoff Pol, 2010), and since its birth, it has been widely used to study MDD, neuroticism and extraversion. In previous studies, MDD was suggested to be associated with multiple functional networks, mainly including the default mode network (DMN), control executive network (CEN), salience network (SN) and the subcortical limbic system. The DMN is one of the most frequently reported networks in MDD studies. MDD patients were usually reported to have stronger connectivity within the DMN, but there have also been inconsistent results, which some researchers thought was caused by the heterogeneity of the DMN (Bohr et al., 2012; Brakowski et al., 2017; Gudayol-Ferre, Pero-Cebollero, Gonzalez-Garrido, & Guardia-Olmos, 2015; Ma et al., 2012; Sacchet et al., 2016; Sexton et al., 2011; Xueling Zhu et al., 2012). The CEN, the network associated with cognitive control and attention, and its essential hub the dorsolateral prefrontal cortex (dlPFC) showed reduced connectivity with other brain regions, especially with parts of the DMN (Crowther et al., 2015; He et al., 2016; Klauser et al., 2015; Ye et al., 2012). The SN was thought to be responsible for the switching between the DMN and CEN, and some studies showed that MDD patients had stronger connectedness with the anterior cingulate cortex (ACC) and weaker connectedness with the bilateral insula (Andrei et al., 2013; Goulden et al., 2014; Tahmasian et al., 2013). In addition, the subcortical limbic system, represented by the basal ganglia, amygdala and hippocampus, is considered to be significant in MDD. The amygdala was reported to be less connected with other brain regions, except the temporal lobe, and the basal ganglia typically showed lower connectivity in MDD (Cullen et al., 2014; Gabbay et al., 2013; Klauser et al., 2015; Lui et al., 2011; Peng et al., 2014; Taylor et al., 2014). Personality neuroscience research has shown that there are plentiful overlapping neural mechanisms among neuroticism, extraversion and MDD. For example, neuroticism was thought to be associated with higher DMN, SN and amygdala activity, as well as the lack of CEN activity (Aghajani et al., 2014; Hsu, Rosenberg, Scheinost, Constable, & Chun, 2018; Michelle N. Servaas et al., 2017; Servaas et al., 2015), and extroversion was thought to be associated with higher basal ganglia activities and lower amygdala activity (Aghajani et al., 2014; Hsu et al., 2018; Lei, Yang, & Wu, 2015; Lei, Zhao, & Chen, 2013). However, FC studies use the time series from an entire scanning period to calculate the correlation coefficients, which leads to the loss of information on the micro-time scale.

In recent years, many studies have shown that the brain is not immutable but rather a dynamic complex system that constantly changes itself for adapting to the environment on a micro-time scale (Deco & Kringelbach, 2014; Preti, Bolton, & Van De Ville, 2017). Dynamic methods, represented by the sliding time window method, have been widely used in studies of cognitive function, mental illness and lifelong development and other fields (Allen et al., 2014; Gonzalez-Castillo & Bandettini, 2017; Marusak et al., 2017; Sakoglu et al., 2010; Young et al., 2017). Along with the development of dynamic methods, growing research interest on the brain's temporal properties emerged, in which dynamic functional network connectivity (DFNC) is a promising research direction. The DFNC method focuses on the dynamic FC patterns that occur within and between all functional networks, which contain a reoccurring network configuration (Calhoun, Miller, Pearlson, & Adali, 2014; R. M. Hutchison et al., 2013). The recurring states of activation or FC, that is, the chronnectome, might represent a certain state of arousal or consciousness level, and information related to development, learning, and training as well as individual differences could be acquired by measuring the temporal characteristics of certain FC states (Calhoun et al., 2014). As a new method, DFNC had demonstrated its effectiveness in a variety of diseases and conditions, such as schizophrenia (Damaraju et al., 2014; Shen et al., 2014), bipolar disorder (Rashid, Damaraju, Pearlson, & Calhoun, 2014), autism spectrum disorder (Lacy, Doherty, King, Rachakonda, & Calhoun, 2017) and mild traumatic brain injury (Mayer et al., 2015), but there is no systematic study on MDD to explore its dynamic FC characteristics.

Therefore, the goal of this research was to explore abnormalities in the dynamic FC characteristics of MDD and to identify whether personality traits had a significant relationship to these dynamic characteristics. We used group-level independent component analysis (group ICA) to divide the brain into eight functional networks and built DFNC frameworks for all MDD patients and participants in the healthy control group. Then, k-means clustering was used to detect the relatively stable FC states. For all identified states, the time-frequency attributes were determined and compared between groups. The correlation coefficients between dynamic measures and personality traits was also calculated. Based on prior FC studies of MDD, we hypothesized that there existed one or more critical FC states with different time attributes between the MDD and control groups, which might show abnormalities in regions that were related to both MDD and personality, such as the DMN and limbic system, and was likely to be under the influence of specific personality traits.

Methods and materials

Participants

A total of 383 patients and 260 healthy people were enrolled in the outpatient department of the First Affiliated Hospital of Chongqing Medical School in Chongqing, China. For all patients, there were two psychiatrists providing independent diagnoses according to the Structured Clinical Interview for the DSM-IV by to exclude patients with other disorders, such as bipolar depression (BP). Each patient was asked to complete a series of questionnaires, including the Beck Depression Inventory (Parker Jones, Voets, Adcock, Stacey, & Jbabdi), Hamilton Depression Rating Scale (HAMD), Symptom Checklist 90 (SCL-90), Short Ruminative Responses Scale (SRRS) and Eysenck Personality Questionnaire [EPQ, 85-question Adult Edition, translated into Chinese by Chen et al. (Chen & Al, 1983)]. Clinical information, such as illness duration and current medications, were also collected.

Healthy individuals matched with the patients for sex, age and education level were selected as the healthy control group (HC group) and completed the same EPQ questionnaire. The HC group did not complete the clinical questionnaire. For the HC group, to exclude subjects with potential mental disorders, two well-trained and experienced graduate students in the school of psychology performed the Structured Clinical Interview for the DSM-IV. All subjects included in the HC group did not meet the DSM-IV criteria for psychiatric disorders and did not use drugs that could affect brain function (including antidepressant drugs).In addition, a self-report checklist was used for both the MDD group and HC group to exclude participants who satisfied any of the following criteria: serious brain trauma, substance abuse, hypertension or cardiovascular disease. To decrease extraneous variability, underage

(<18) and overage (>75) participants were also removed. Finally, 226 participants (114 patients and 112 healthy controls) were included in the analysis. The subject exclusion process is shown in Fig 1.

INSERT FIGURE 1 HERE

This study was approved by the Research Ethics Committee of the Brain Imaging Center of Southwest University and First Affiliated Hospital of Chongqing Medical School. Before MRI scanning, all participants completed an informed consent form.

To detect differences between the groups in basic demographic variables, we performed independent samples t-tests, and the results are shown in Supplemental Materials.

MRI Data Acquisition and Preprocessing:

All subjects underwent MRI scanning at the Brain Imaging Center of Southwest University. Resting-state image data were acquired using a 3.0-T Siemens Trio MRI scanner with a 16-channel whole-brain coil (Siemens Medical, Erlangen, Germany). For each participant, 242 functional images were acquired with a gradient echo type echo planar imaging (EPI) sequence [echo time (TE)=30 ms; repetition time (TR)=2000 ms; flip angle=90 degrees; slice thickness=3.0 mm; slices=32; resolution matrix=64×64; voxel size=3.4×3.4×3 mm]. All subjects were asked to stare at a white fixation point on a dark background and keep their head still throughout the scan.

Preprocessing was performed by Data Processing Assistant for Resting-State fMRI (DPARSF; http://rfmri.org/DPARSF), which is a toolbox based on the SPM12 software package (Chao-Gan & Yu-Feng, 2010). To reduce equilibration effects, the first 10 volumes were discarded. The remaining images underwent slice timing correction, motion correction to reduce displacement between volumes, spatial normalization toward standard Montreal Neurological Institute (MNI) space and spatial smoothing (6 mm full width half maximum). To eliminate the influence of motion on DFNC, participants with a maximum displacement of >2 mm and maximum rotation of >2 degrees were excluded before further analysis. Ten participants' data were discarded, and the basic demographic information of the 216 remaining participants is listed in Table 1.

INSERT TABLE 1 HERE.

Group ICA and component selection:

The pipeline of the ICA basically followed the steps described in the classic article by Allen and his colleagues (Allen et al., 2014). A relatively high model order (number of components=100) group-level spatial ICA was implemented to decompose the signal into compositions of functional networks using the GIFT toolbox (http://mialab.mrn.org/software/gift/). Before ICA, a subject-specific principal component analysis (PCA) was performed in which 150 principal components remained using standard economy-size decomposition. Then, the group data were further reduced to 100 independent components (IC) using the expectation-maximization algorithm. Aggregate spatial maps were constructed using the Infomax algorithm in ICASSO, and this process was repeated 10 times. Using the GICA1 back reconstruction, time courses (TCs) and spatial maps (SM) of each individual were estimated.

We characterized 75 of 100 ICs to perform further analysis, and 25 other ICs were discarded as physiological noise, movement signals, or artifacts of the scanner. To determine whether a component was noise was based on the following characteristics: peaks were in a gray matter area, had low spatial overlap with vascular regions, or were due to cerebrospinal fluid (CSF) or head motion artifacts (Cordes et al., 2000). The remaining ICs were assigned into 8 functional networks based on visual identity. The distribution of these networks was consistent with the findings of Allen et al.; in addition, the salience network (SN) was added to this study for its essential role in a variety of psychiatric and mental disorders. All 8 functional networks shown in Fig 2.

INSERT FIGURE 2 HERE.

Postprocessing and dynamic FC construction:

The sliding time window method was used to construct dynamic functional connectivity. Before dividing the sliding windows, additional postprocessing was performed for TCs of all components to regress out the remaining noise sources. Processing at this step mainly included (1) detrending linear, quadratic, and cubic trends, (2) regressing the 6 parameters of head movement, (3) regressing of outliers, (4) low-pass filtering (cutoff=0.15 Hz) and (5) normalizing the variance of each TC.

Because previous studies have suggested that the best window size settings should be between 30 ~ 60 s (R. M. Hutchison et al., 2013; Preti et al., 2017), we chose the 30-TR window (60 s). We used a Gaussian (σ=3 TRs) function to create a tapered window, slid in steps of one TR every time, and then computed the covariance matrices in every slide window.

Clustering Analysis and state-based measures

A k-means clustering was performed to detect specific FC patterns to the windowed covariance matrices, and the dynamic measures for each subject were calculated.

In k-means clustering, we use the Manhattan distance to measure the similarity between different time windows. In previous work, we suggested that in high-dimensional data, the Manhattan distance might be more effective than the Euclidean distance (Aggarwal, Hinneburg, & Keim, 2001). To select an optimal number of clusters (k), we performed the analysis setting k from 2 to 10 and used the "elbow method" to find that the inflection of the ratio between the mean distance between the clusters and the mean distance within the clusters as the optimal k value. In this analysis, the best k value was 4. To avoid cost function convergence to the local optimal solution, all clustering analyses were iterated 5 times, and the best result was kept. The centroids of 4 clusters are shown in Fig 3 representations of 4 FC states.

INSERT FIGURE 3 HERE

According to the clustering results, we calculated the dynamic measures for each individual, including (1) fraction of the total time, which means the proportion of the number of time windows belonging to a certain state to the total number of windows; (2) mean dwell time, which means the mean length of time that a certain state occurs; (3) number of transitions, which means the number of state transitions throughout the entire scan (Rashid et al., 2014).

Cross- group difference comparison

Because of the nonnormality of the dynamic measures, the Mann-Whitney U test, a nonparametric test, was used in this study to detect the difference between MDD and HC. To keep the type I error low, the false discovery rate (FDR) correction was used for each analysis. The Mann-Whitney U test was performed using Statistic Package for Social Science (SPSS).

Correlation analysis

To further explore the relationship between depression, personality and brain dynamic connectivity characteristics and to determine the intrinsic meaning of these connectivity states, we calculated the Spearman rank correlation between behavior scales and dynamic measures within the MDD patient group. To keep the type I error low, the false discovery rate (FDR) correction was used for each analysis. The analysis within the HC group was also performed with the same methods as the MDD group. All correlation analyses were performed using the built-in function *corr* provided by MATLAB.

Exploring the meaning of dynamic FC states

The interpretation of the meaning of FC states is essential in dynamic studies. In this study, we describe two aspects of the 4 states: the global integration level and the connection characteristics of each functional network.

We used the modularity index Q to describe the integration level of each FC state, and a normal Louvain community detection algorithm was performed to find the potential functional communities that might exist. The Brain Connectivity Toolbox (BCT, http://www.brain-connectivity-toolbox.net/) was used to perform the community detection algorithm and calculate the Q value. Modularity Q is defined as the fraction of edges that fall within group 1 or 2 minus the expected number of edges within groups 1 and 2 for a random graph with the same node degree distribution as the given network. The formulation of Q is as follows (Yue et al., 2017):

$$Q=1/2m\sum_{vw}(A_{vw}-k_v k_w/2m)\delta_{vw}$$

Considering a graph with n nodes and m links, A_{vw} represents the real edge between node v and w, the expected number of edges between them is $k_v k_w/2m$, and δ_{vw} is equal to 1 when v and w belong to a community; otherwise, it is equal to 0. The larger the Q value, regions of the brain are more likely to aggregate into different functional modules; smaller Q values represent a brain that tends to integrate into a generally connected, inseparable whole. The results of community detection are shown in Fig 4.

INSERT FIGURE 4 HERE.

Given the significant role of subcortical regions such as the hippocampus, thalamus and ventral striatum (VS), we computed a common graph theory measure, degree, to explore the connectedness of these three components. Degree was calculated by counting the numbers of connections between these areas and other regions of the entire brain separately. We used the Graph thEoreTical Network Analysis (GRETNA; https://www.nitrc.org/projects/gretna) toolbox to calculate the degree (J. Wang et al., 2015). To avoid the influence of threshold, we used sparsity thresholds from 0.05 to 0.4 with a step of 0.01 to acquire multiple measures of degree and draw the receiver operating characteristic curve (ROC curve). The area under the curve (de Moor et al.) was used as the final measure of degree.

Validation analysis

To ensure the validity of the results, different window sizes (20 TRs, 40 TRs) were used to systematically replicate the analysis. In addition, to control the effects from nuisance variables, we repeated the correlation analysis using the Spearman partial correlation method, controlling for head motion and other demographics (age, gender and education years) as covariates. All partial correlation analyses were performed using the built-in function *partialcorr* provided by MATLAB.

Results

Cross-group difference comparison

At the behavioral level of analysis, we found that the extroversion of the MDD group was significantly lower than that of the HC group, whereas the neuroticism of the MDD group was significantly higher than that of the HC group. At the brain image level of analysis, we found in state 4 that patients had significantly lower fraction and mean dwell time than the HC group (for fraction, Mann-Whitney U=6824, p=0.006; for mean dwell time, Mann-Whitney U=6869, p=0.004; $p_{FDR}<0.05$). No significant result was found in other states.

Correlation analysis

In state 4, both fraction and mean dwell time showed positive correlations with extroversion (for fraction, r=0.292, p=0.002; for mean dwell time, r=0.29, p=0.002; $p_{FDR}<0.05$) and showed negative correlations with neuroticism (for fraction, r=-0.23, p=0.016; for mean dwell time, r=-0.23, p=0.016; $p_{FDR}<0.05$); in addition, there were also negative correlations with the SCL-90 measures of phobic anxiety (for fraction,

$r=-0.241$, $p=0.012$; for mean dwell time, $r=-0.232$, $p=0.016$; $p_{FDR}<0.05$) and "additional items" (assesses other aspects of the patients' symptoms such as poor appetite; for fraction, $r=-0.196$, $p=0.042$; for mean dwell time, $r=-0.195$, $p=0.043$; $p_{FDR}<0.05$). Regarding the other states, state 1 exhibited a positive covariant relationship with extroversion and a negative relationship with scores on the BDI scale; state 2 exhibited a negative correlation relationship with extroversion and a positive correlation with the depression evaluation dimension of the SRRS; state 3 and transition times did not show any significant correlations with the behavioral measures. In addition, no dynamic measure was significantly correlated with age and education years. See Table 3 for more details about the correlation analyses for all dynamic measures.

For the HC group, there were no significant results that survived under the FDR correction except that the neuroticism score was significantly correlated with the mean dwell time of state 4 when the window size was 30 TR ($r=-0.263$, $p=0.006$; $p_{FDR}<0.05$) and the fraction of state 4 when the window size was 40 TR ($r=-0.281$, $p=0.003$; $p_{FDR}<0.05$). It is worth noting that while there were not many significant results following the multiple comparison correction, the HC group showed the same trend of correlation as the MDD group in state 4: more state 4 tended to be associated with higher extroversion scores and lower neuroticism scores. The information about correlation analysis within the HC group can be found in the Supplemental Materials.

Exploring the meaning of dynamic FC states

State 1 and state 4 tended to have lower Q, and in particular, there were only two functional modules in state 4 rather than three observed in other states. A large cluster that stretched across the anterior joint area and the posterior sensory cortex existed in state 4, which was always separated into an anterior part and a posterior part in other states.

The average connection strength in all 8 networks between each network and between other regions of the entire brain was calculated. State 4 showed the strongest connection inside and outside of the auditory network (AN), sensory motor network (SMN) and visual network (VN), while showing the weakest links inside and outside of the subcortical area (SC). In addition, state 4 showed relatively strong connections in the CEN, DMN and SN. Regarding the other states, state 1 showed a similar pattern as state 4, but it showed the strongest connectivity inside and outside the CEN, SN, AN and SC, as well as the cerebellum (CB); state 2 exhibited the weakest connectivity of the CEN, SN and SMN; and state 3 exhibited the weakest connectivity of the DMN and VN. For the subcortical regions, state 4 showed the lowest connectedness with other regions in the hippocampus and VS (shown in Fig 4).

Based on the analysis above, we defined two low-modularized states, state 1 (with global strong connectivity) and state 4 (with strong connectivity in sensory regions and the DMN, but weak links between cortex and subcortical regions), and two high-modularized states, state 2 (with global weak connectivity) and state 3 (a globally modularized state).

Validation analysis

In the validation analysis, all other parameters remained unchanged except the window size, and all the dynamic measures were calculated separately. To ensure the consistency of multiple clustering results, we calculated the Pearson correlation coefficient between the cluster centroids under different window sizes and defined the states with the highest correlation coefficient as the same state. The average r value between FC centroids identified as the same state in different window sizes was 0.953, and the average r value between centroids defined as different states was 0.652. All cross-group analyses and the correlation analyses were repeated using different window sizes. Most of the main results could be repeated successfully, except for the correlation between state 2 and the depression evaluation (window size=40 TR). In addition, the fraction of state 2 was higher in the MDD group than in the HC group when the window size=40 TR, and a negative correlation was reported for state 4 with the anxiety dimension assessed by the SCL-90 (window size=40 TR).

For the partial correlation analysis, most of the extroversion results were repeated successfully, while the neuroticism score only correlated significantly with the mean dwell time of state 4 ($r=-0.258$, $p=0.007$; $p_{FDR}<0.05$). Additionally, the results of the BDI score and the anxiety score from the SCL-90 were only repeated when the window size=40 TR. Detailed validation information can be found in the Supplemental Materials.

Discussion

This study used the DFNC method to depict the difference in brain dynamic FC characteristics between MDD patients and healthy participants and explored the effect of two essential personality traits, extraversion and neuroticism, on the dynamic characteristics. Four reoccurring FC states were defined using the hard clustering algorithm, in which state 4 exhibited a significant difference between the MDD and HC groups and was associated with extraversion and neuroticism. Quantitative analysis of all states found that state 4 has the following particular characteristics: extensive integration among the entire brain, especially the frontal part and the posterior part; increased covariation between sensory-related regions and the DMN with themselves and other areas; and decreased connectivity linking the cortex and subcortical areas, such as hippocampus and VS. In addition, we validated the analysis with different conditions to ensure stable results.

Different dynamic FC states between MDD and HC

In this study, our primary goal was to identify the differences between the MDD and HC groups. We found in MDD patients that there was a significant lack of state 4, a relatively low-modularized state, in which all parts of the brain tended to communicate with each other and the information processing tendency might represent a higher level of integration. For state 4, an interesting feature was that stronger links existed widely among multiple networks, especially for sensory-related regions and the DMN. Findings that involve sensory-related areas have been relatively rare in previous FC studies of depression, although several studies have reported decreases in connectivity in sensory areas in MDD (Ben-Shimol, Goelman, Sartorius, & Gass, 2014; Benshimol, Gass, Vollmayr, Sartorius, & Goelman, 2015; Cullen et al., 2014; Liu et al., 2016; Veer et al., 2010). In previous behavioral studies, depressive individuals exhibited anhedonia, emotional indifference and lack of emotional expression (Liss, Mailloux, & Erchull, 2008; Liss, Timmel, Baxley, & Killingsworth, 2005; Rottenberg, 2010), while individuals with high emotional expression showed a strong tendency of sensation seeking (Carton, Jouvent, Bungener, & Widlöcher, 1992). Given the association at the behavioral level, we thought our results were consistent, and this lack of state 4 in MDD might represent a deficit in the processing of sensory stimuli, which might lead to the failure of producing sufficient mood change. The reason why sensory regions were rarely found in previous studies might be that the FC changes in these areas occurred over a relatively short timescale, and static analyses might obscure the variation by treating the entire scan as a whole. In addition, the high connectedness of the DMN was another feature of state 4. Many studies have supported functional and structural abnormalities in the DMN as being important neural mechanisms of MDD, especially for rumination (Baune, Fuhr, Air, & Hering, 2014; Brakowski et al., 2017; Gong & He, 2015). In the work of Zhu et al., in patients with first episode MDD, decreased internetwork connectivity among subsystems of the DMN was observed, and this decrease was positively correlated with depressive rumination (X. Zhu, Zhu, Shen, Liao, & Yuan, 2017). In addition, a study reported that the cognitive emotion regulation state significantly increased the interaction across functional networks of the brain, especially with the DMN and amygdala (Brandl et al., 2017). Taken together, it could be speculated that a wider connection might mean more effective regulation, and the lack of state 4 in MDD might reflect a deficiency of an intrinsic emotional regulation ability.

Another noticeable characteristic of state 4 was the lowest connectedness of the hippocampus and VS. The hippocampus has been thought to be closely associated with emotional learning, episodic memory and neural plasticity, and functional and structural abnormalities of this area have often been reported in MDD (Fatemi, Earle, & Mcmenomy, 2000; Lee, Ogle, & Sapolsky, 2015; MERVAALA et al., 2000; Peng et al., 2014; Rouach & Nicoll, 2015; Sapolsky, 2000; Taylor et al., 2014). Zhang et al. reported that the degree of the hippocampus was increased in MDD patients compared with healthy people (Zhang et al., 2012). The VS is part of the reward circuit, and its dysfunction has often been associated with low activity and anhedonia in MDD (Avissar et al., 2017; Furman, Hamilton, & Gotlib, 2011; Gabbay et al., 2013; Manelis et al., 2016; Pan et al., 2017; Phillips et al., 2015). Some studies reported a decline of connectivity in the VS region in patients with depression (Furman et al., 2011; Gabbay et al., 2013; Kenny et al., 2010; Kerestes et al., 2015), which was consistent with our results. Given the evidence above, low connectivity of the two emotion-related regions in state 4 might represent less negative emotions and higher activity, and MDD patients lacking this state might have a deficiency in decreasing negative emotions and getting pleasure from rewards.

Dynamic FC states and personality traits

We found that in the MDD group several FC states were correlated with personality traits. Extraversion scores showed positive correlations with fraction time and dwell time in state 4 and state 1 (with global strong connectivity), while there was a negative correlation with state 2 (with global weak connectivity). Generally, high extraversion individuals display more positive affect, high sensation seeking, high sociability and higher willingness to engage the external world (Eysenck & Eysenck, 1975; JanWacker & Smillie, 2015; Lei et al., 2015). Interestingly, a state with global weak connectivity was proven to be associated with an autistic trait in previous DFNC studies investigating autistic spectrum disorder. Although our results were not completely consistent with those findings, the general conclusion was convergent: increasing a highly connected state might increase an individual's sociability. In addition, studies on DFNC proved that there were lower levels of a highly connected state in conditions of low arousal or unconsciousness (Allen et al., 2014; Barttfeld et al., 2015; Hutchison, Womelsdorf, Gati, Everling, & Menon, 2013; Kucyi & Davis, 2014; Young et al., 2017), which indicated that the highly connected states might also represent a basic energy level and that individuals with greater levels of these highly connected states might tend to have higher energy and less fatigue.

For state 4, individuals with high neuroticism tended to show higher fraction time and longer dwell time. High neuroticism individuals usually exhibited attention and processing biases toward negative emotional stimuli, lower tolerance to stress, and greater negative emotional experiences (Canli, 2004; Eysenck & Eysenck, 1975), and high neuroticism was always thought to have many overlapping neural mechanisms with MDD (de Moor et al., 2015; Jylha et al., 2009; Quilty et al., 2008). In individuals with high neuroticism, dysfunction of the hippocampus was often reported and was suggested to be associated with negative emotional learning and maladaptive stress responses (Montag et al., 2013; M. N. Servaas et al., 2017; Servaas et al., 2013). In patients with high neuroticism, the lack of this state 4 reflected the excessively strong connectivity between the hippocampus and other regions, which might make individuals more sensitive to negative stimuli and more difficult to get rid of negative emotions. In addition, studies have shown that high neurotic individuals showed weak whole brain connectivity and decreased global efficiency (Servaas et al., 2015), which was consistent with our results.

In addition, we found that the correlations between dynamic connectivity states and personality was weak in the HC group but strong in the MDD group, so there might exist intergroup interactions in the relationship between individual personality and dynamic indicators, but the direction of causality among MDD, personality and dynamic measurements are still not clear. State 4 shows a certain consistency in the two groups, which might indicate that state 4 is relatively unaffected by personality. With the increase of depression, the change of personality may show a developmental process (extroversion is decreasing while neuroticism is increasing), while the continuous decrease of state 4 might play an essential role in this process.

Additional considerations

In previous dynamic studies, the focus has usually been on cognitive function or physiological attributes of dynamic FC, such as level of consciousness, daydreaming, and attentive function (Barttfeld et al., 2015; Kucyi & Davis, 2014; Kucyi, Hove, Esterman, Hutchison, & Valera, 2017). In this study, the dynamic characteristics of the functional connections showed associations with both a disease and general personality traits, which suggested that the dynamic properties of the brain might contain information about general psychological variables. Based on previous studies, similar dynamic states of the brain have been shown to exist widely in both normal and diseased populations. In a repetitive study, data from 7500 subjects were used to verify the validity of the DFNC method; state 3 in that study and state 4 in the present study were relatively similar in both the activation patterns and the proportion of the total time (9%) (Abrol et al., 2017). In addition, in studies of populations with various disease states, the FC pattern of state 4 was often similar to patterns in other studies, such as states 2 and 3 in Damaraju et al. (Damaraju et al., 2014) and state 2in Rashid et al. (Rashid et al., 2014). Those results illustrated the universality and stability of the states, and proved that state-based measures have the potential as an important indicator of individual differences.

The advantages of this study are mainly reflected in the following aspects. First, we used a large sample in this study to avoid the problems in previous MDD studies with small samples. In addition, the practice of combining personality traits with research in psychiatric disease is consistent with the current idea that diseased people and healthy people should not be seen as separate but as points in different locations on the same spectrum. Consistent with this idea, the results of this study support the potential of personality traits as an important factor affecting depression and as a therapeutic target. Moreover, we used the DFNC method, which was more sensitive to the overall mental state and could identify more instantaneous differences, so we could obtain information that is not available with traditional static FC analysis.

There are also unsolved limitations to this study. In the current DFNC study based on

ICA technology, the selection of IC is subjective and much depends on the researchers, which results in difficulty comparing between different studies. In addition, the age effect observed in previous DFNC studies (Faghiri, Stephen, Wang, Wilson, & Calhoun, 2018) was not found in this study. We hypothesize that this may be related to the interaction effect between sample and age, but the actual effect still needs to be explored. Finally, we cannot determine the causal direction of the interactions between personality, MDD symptoms and dynamic FC states, so additional studies based on longitudinal data are necessary.

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Figures

Figure 1. The pipeline of excluding subjects.

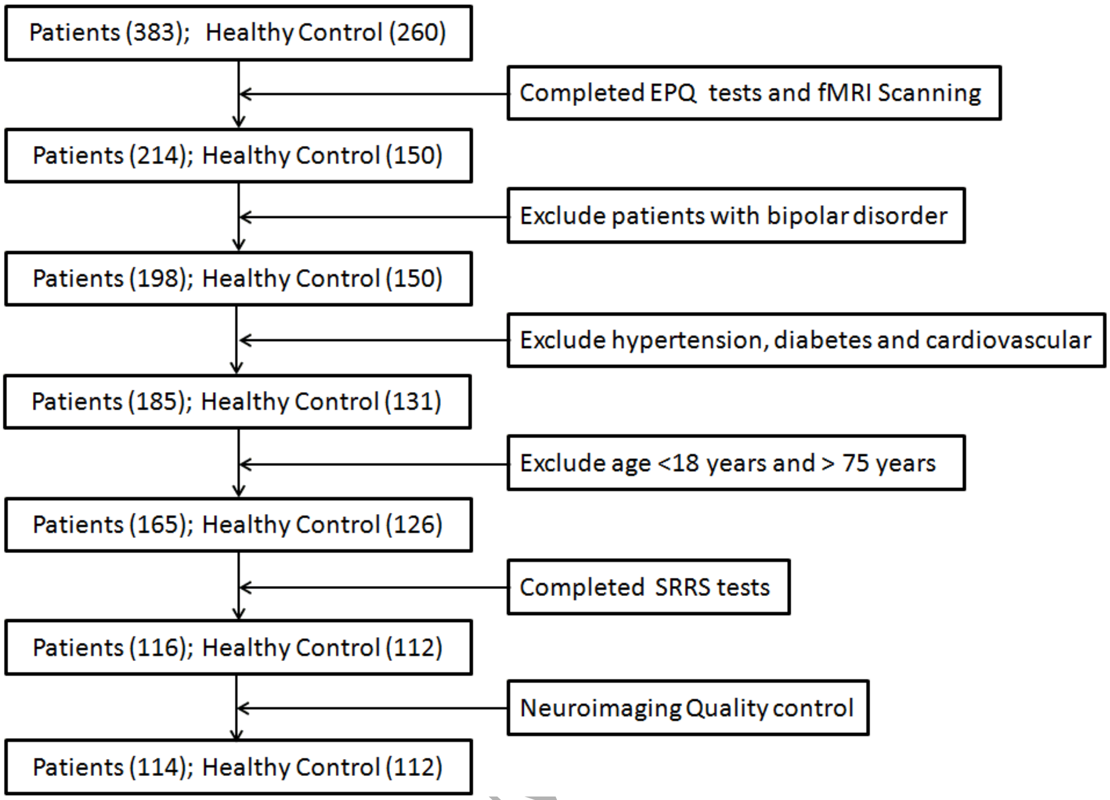


Figure 2. A. Resting-state networks. 75 independent components were selected and divide into eight functional networks. The IC network from top to bottom is default mode network (DMN), control executive network (Fox et al.), salience network (SN), auditory network (AN), sensory motor network (SMN), visual network (VN), subcortical area (SC) and cerebellum (CB). B. The pipeline of DFNC method. This figure comes from Damaraju et al. (Damaraju et al., 2014). C. Mean functional connectivity matrix of healthy control and MDD group.

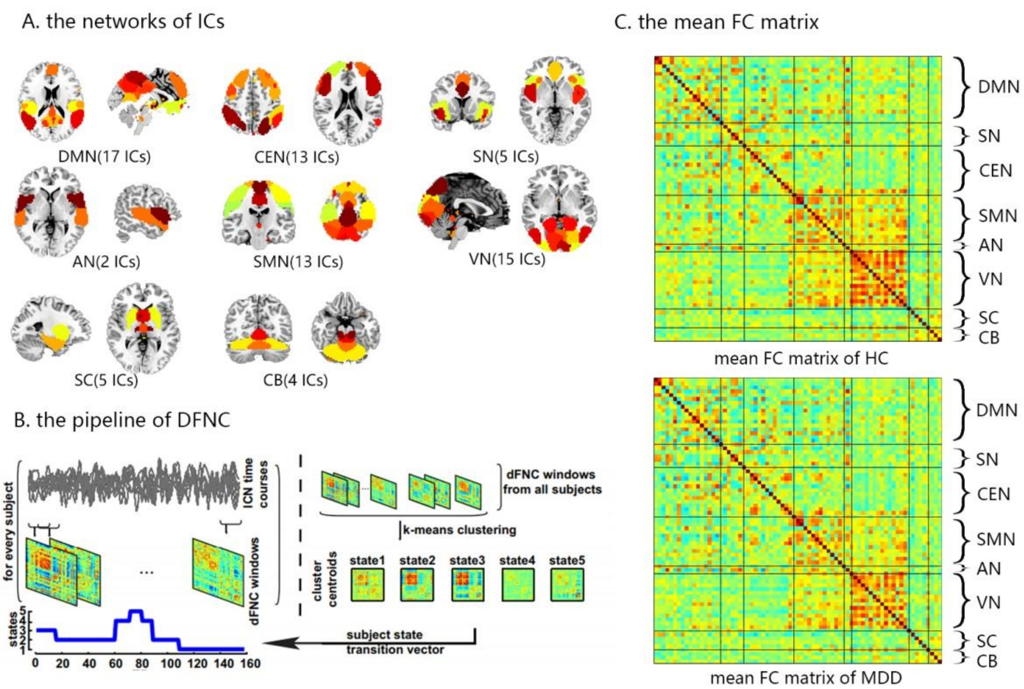


Figure 3. The dynamic FC states and their modular distribution. Using k-means clustering method, 4 FC states were extracted from dynamic FC data and the centroids of them were displayed. State 1 accounted for the largest proportion of the participants; it had the lowest modularity Q and was characterized by a wide range of positive connectivity. State 2 had the extensive weak connectivity among whole brain and high modularity. State 3 was highly segregated and had plenty of negative connectivity. In state 4, there existed lots of strong connectivity between and within sensory motor network, auditory network and visual network and only two large modules unlike the three modules in all other states; besides, the DMN region showed strong connectivity with other regions.

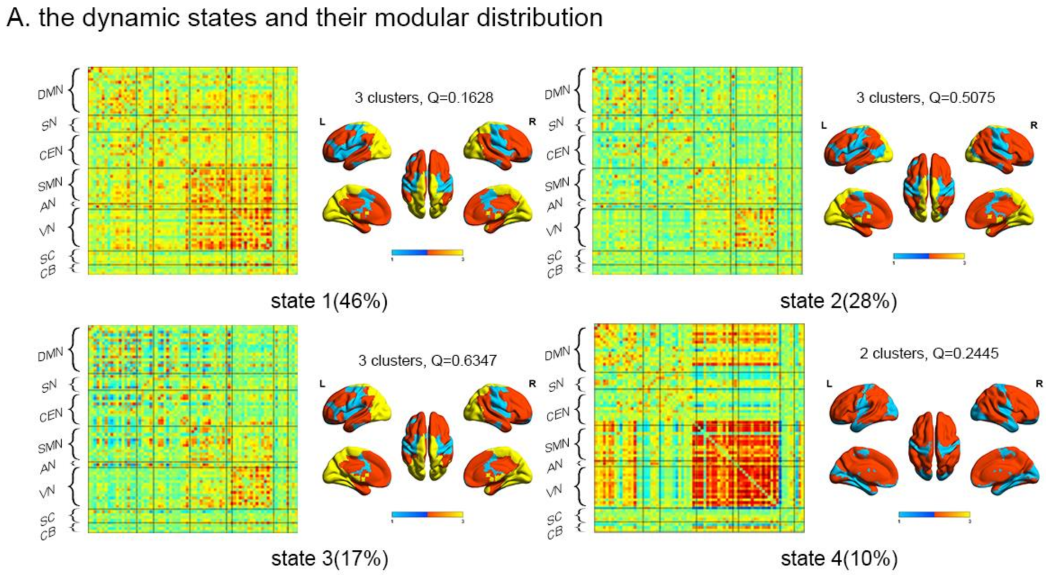
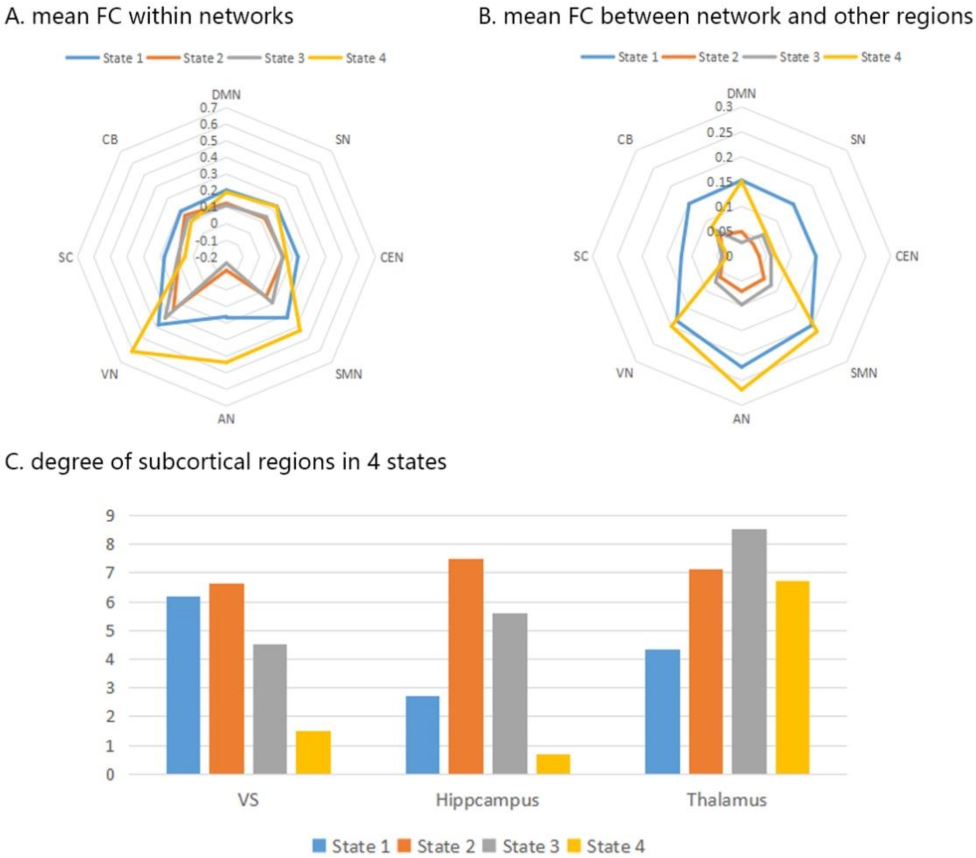


Figure 4. A. The radar maps of the mean FC within networks for all states. State 1 and state 4 displayed higher internetwork connectivity than state 2 and state 3. In addition, state 4 showed the lowest connectivity in SC and the highest connectivity in three sensory related networks (SMN, AN, VN). B. The radar maps of the mean FC between network and other regions for all states. State 1 showed the strongest connectivity inside and outside of CEN, SN, SC and CB; state 2 exhibited the weakest connectivity inside and outside of CEN, SN and SMN; state 3 exhibited the weakest connectivity inside and outside of DMN and VN; state 4 showed the strong connection inside and outside of DMN, AN, SMN and VN, meanwhile showing the weakest link outside of subcortical area (SC). C. The degree of subcortical regions for all states. State 4 showed the lowest centrality degree in hippocampus and ventral striatum (Cole et al.).


A. mean FC within networks
State 1 State 2 State 3 State 4
DMN
SN
CEN
SMN
AN
VN
SC
CB
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
B. mean FC between network and other regions
State 1 State 2 State 3 State 4
DMN
SN
CEN
SMN
AN
VN
SC
CB
0.3
0.25
0.2
0.15
0.1
0.05
0
C. degree of subcortical regions in 4 states
9
8
7
6
5
4
3
2
1
0
VS
Hippcampus
Thalamus
State 1 State 2 State 3 State 4

Tables

Table 1. The basic information of participants.

Characteristic	Major Depression Disorders (N=109)								Healthy Control Subjects(N=107)	
	First episode (N=91)		Recurrent (N=18)		With anxiety (N=27)		Medicated MDD (N=50, >3 months)			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age(years)	39.61	12.72	36.84	13.15	37.57	11.9	38.98	11.6	37.12	13.27
Education(years)	11.77	3.52	12.74	3.86	12.06	3.54	11.74	3.04	13.48	4.18
Durations of illness(months)	41.99	59.92	98.53	57.21	51.23	55.84	77.4	72.23	/	/
HAMD	8.91	4.51	9.32	4.73	8.48	4.81	8.34	4.71	/	/
BDI-II scores	12.8	7.63	12.53	4.66	12.34	7.71	11.4	6.7	/	/
Neuroticism	15.05	5.3	18	4.14	16.2	4.8	17	5	13.17	3.66
Extroversion	9.03	4.69	8.26	4.48	9.4	4.71	7.62	4.48	8.18	4.65
Gender										
Female	61	67.03%	11	61.11%	17	62.96%	32	64%	69	64.49%
Male	31	34.44%	7	38.89%	10	37.03%	18	36%	39	36.45%

Table 2. The results of Mann-Whitney U Test

	Mann-Whitney U	Wilcoxon W	Z	SSE	p
Fraction					

State1	6207.5	11985.5	0.828	454.02	0.408
State2	5267.5	11045.5	-1.228	459.221	0.219
State3	5750.5	11528.5	-0.177	458.82	0.86
State4	6824	12602	2.754	360.439	0.006**
Dwell time					
State1	6312.5	12090.5	1.059	454.01	0.289
State2	5453	11231	-0.824	459.23	0.41
State3	5943.5	11721.5	0.244	458.8	0.807
State4	6869	12647	2.878	360.44	0.004**
Transition	6298	12076	1.023	456.2	0.307

Note: one asterisk (*) means $p < 0.05$, FDR correction; two asterisks mean $p < 0.001$, FDR correction.

Table 3. The results of correlation analysis.

		E	N	BDI	Depression evaluation (SRRS)	Phobic anxiety (SCL-90)	Additional items (SCL-90)	Age	Education years
Fraction									
State1	r	0.32	-0.07	-0.23	-0.07	-0.18	-0.03	0.17	0.03
	p	0.001**	0.4	0.015*	0.45	0.07	0.8	0.082	0.73
State2	r	-0.31	0.16	0.08	0.242	0.15	0.14	-0.1	0.08
	p	0.001**	0.1	0.4	0.011*	0.12	0.14	0.32	0.41
State3	r	-0.04	0.08	0.07	-0.14	0.12	-0.03	-0.09	-0.18

	p	0.69	0.4	0.5	0.14	0.23	0.73	0.38	0.07
State4	r	0.292	-0.23	0.03	-0.15	-0.241	-0.196	0.02	0.17
	p	0.002**	0.016*	0.7	0.13	0.012*	0.042*	0.83	0.074
Dwell time									
State1	r	0.28	-0.06	-0.23	-0.09	-0.13	-0.02	0.165	0.02
	p	0.003**	0.54	0.015*	0.35	0.17	0.825	0.09	0.9
State2	r	-0.28	0.1	0.02	0.175	0.13	0.11	-0.05	0.05
	p	0.003**	0.27	0.81	0.07	0.18	0.26	0.62	0.6
State3	r	-0.04	0.08	0.06	-0.1	0.06	-0.12	-0.09	-0.18
	p	0.7	0.42	0.5	0.33	0.526	0.23	0.35	0.06
State4	r	0.29	-0.23	0.04	-0.147	-0.232	-0.195	0.02	0.18
	p	0.002**	0.016*	0.72	0.13	0.016*	0.043*	0.85	0.07
Transition	r	0.176	0.067	-0.02	-0.104	-0.103	0.023	0.007	0.02
	p	0.067	0.53	0.8	0.28	0.3	0.81	0.94	0.9

Note: one asterisk (*) means $p < 0.05$, FDR correction; two asterisks mean $p < 0.001$, FDR correction.