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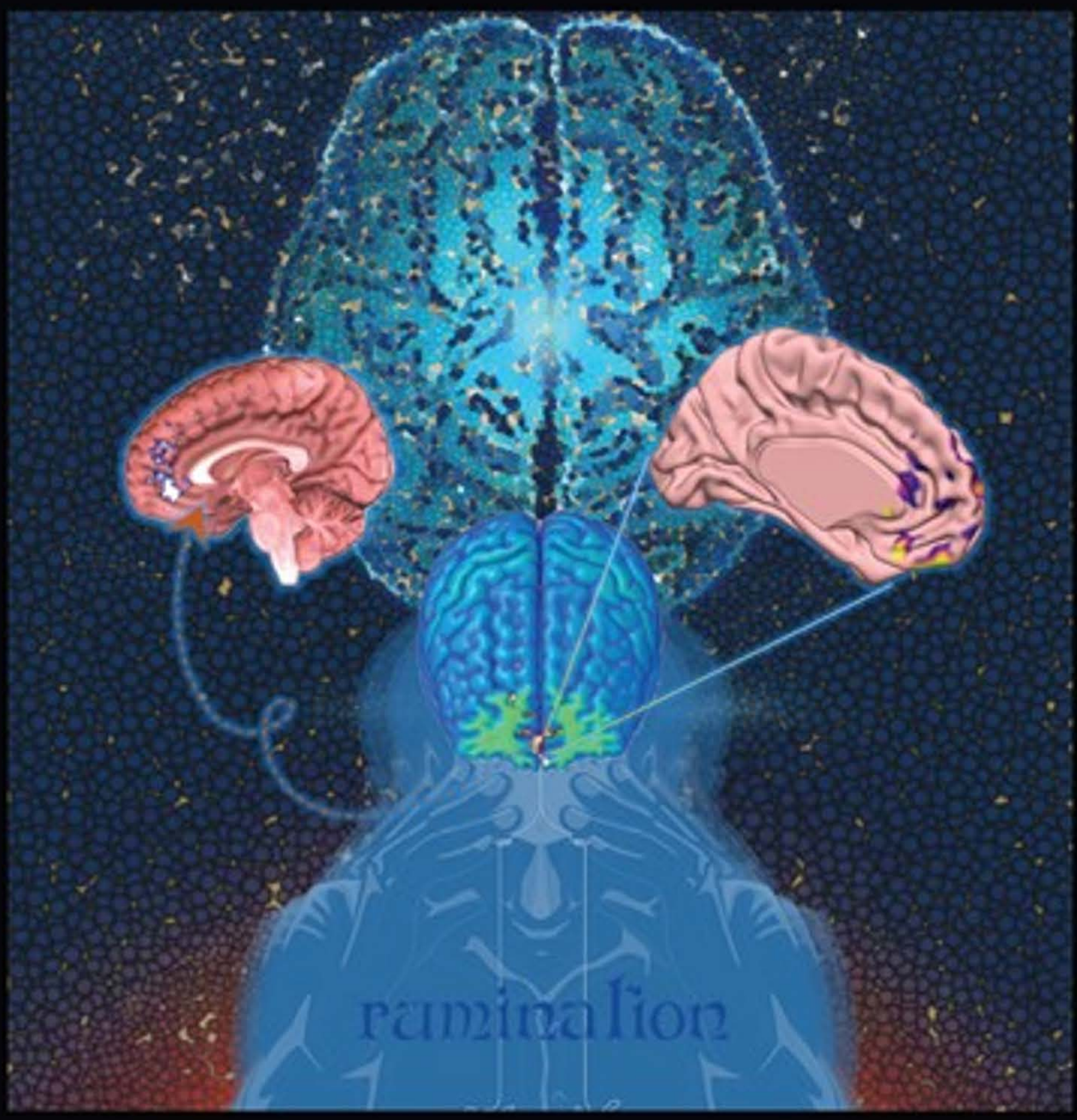

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Original Article

Temporal dynamic patterns of the ventromedial prefrontal cortex underlie the association between rumination and depression

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As a major contributor to the development of depression, rumination has proven linked with aberrant default-mode network (DMN) activity. However, it remains unclear how the spontaneous spatial and temporal activity of DMN underlie the association between rumination and depression. To illustrate this issue, behavioral measures and resting-state functional magnetic resonance images were connected in 2 independent samples ($N_{Sample1} = 100$, $N_{Sample2} = 95$). Fractional amplitude of low-frequency fluctuations (fALFF) and regional homogeneity (ReHo) were used to assess spatial characteristic patterns, while voxel-wise functional concordance (across time windows) (VC) and Hurst exponent (HE) were used to assess temporal dynamic patterns of brain activity. Results from both samples consistently show that temporal dynamics but not spatial patterns of DMN are associated with rumination. Specifically, rumination is positively correlated with HE and VC (but not fALFF and ReHo) values, reflecting more consistent and regular temporal dynamic patterns in DMN. Moreover, subregion analyses indicate that temporal dynamics of the ventromedial prefrontal cortex (VMPFC) reliably predict rumination scores. Furthermore, mediation analyses show that HE and VC of VMPFC mediate the association between rumination and depression. These findings shed light on neural mechanisms of individual differences in rumination and corresponding risk for depression.

Key words: rumination; depression; spatial patterns; temporal dynamics; VMPFC.

Introduction

Rumination has been conceptualized as a cognitive style marked by inflexible and repetitive patterns of thought and persistent, passive focus on negative self-relevant information. It has been considered one of the important cognitive risk factors of mood-related diseases (Huffziger et al. 2012; Olatunji et al. 2013) and is particularly involved in worsening depressive symptoms (Nolen-Hoeksema et al. 1993; Ciesla and Roberts 2007). Accumulating evidence from experimental and clinical studies have emphasized the role of rumination in the onset and maintenance of depressive symptoms and in the diagnosis of major depressive disorder (MDD) (Nolen-Hoeksema 2000; Spasojevic and Alloy 2001; Nolen-Hoeksema et al. 2008). Although rumination has been primarily examined with MDD, several studies indicated that levels of rumination could vary in both healthy and depressed individuals (Junkins and Haeffel 2017; Satyshur et al. 2018). Clarifying the neural mechanisms of rumination tendency in the healthy population may help shed light on important vulnerability factors implicated in depressive risk.

To date, rumination is known to involve a wide range of affective and cognitive processes, such as self-referential processing and recall of autobiographical memories, which are related to the activation of the default-mode network (DMN) (Cooney et al. 2010). Moreover, rumination in depression is thought to involve excessive DMN spontaneous activity and a blunted ability to reduce DMN activity in response to external cues (Sheline et al. 2009). As such, neural network features of DMN during the resting-state provide a critical substrate for understanding ruminative features, relevant to depression. Numerous studies have found that rumination is associated with increased DMN hyperactivity and aberrant functional connectivity (Kühn et al. 2012; Giannis and Michèle 2016; Burkhouse et al. 2017). For example, several studies have indicated that rumination is associated with aberrant activity and connectivity of subcortical regions (e.g. the insula, hippocampus, and amygdala; Fabiansson et al. 2012; Murphy et al. 2016; Kaiser et al. 2019) as well as cortical regions [e.g. key nodes of the DMN including medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), and posterior

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cingulate cortex (PCC)] (Cooney et al. 2010; Hamilton et al. 2011; Wang et al. 2015; Apazoglou et al. 2019; Jacob et al. 2020). Moreover, meta-analytical findings demonstrate that increased functional connectivity between the DMN and subgenual prefrontal cortex predicts levels of rumination in adults (Hamilton et al. 2015). Furthermore, recent studies reported aberrant connectivity between cognitive control networks and the DMN during ruminative thought inhibition (Peters et al. 2016). Meanwhile, brain network analysis shows that MDD patients have deficient local information transfer and weakened functional connections within DMN (Jacob et al. 2020). Taken together, neural network features of the DMN provide a critical substrate for understanding rumination.

Investigating different dimensions of DMN features is important, as brain function may not only depend on the patterns of connectivity but also the power of local neuronal activity (Xia et al. 2017; Sun et al. 2018; Zhu et al. 2020). Recent studies investigating the network degeneration hypothesis have indicated that high-traffic network "hubs" are more likely to exhibit impaired network connectivity as a result of aberrant local neural activity (Seeley et al. 2009; Crossley et al. 2014; Gray et al. 2020). For example, a graph theory study of the DMN suggests that the precuneus exhibits hyperactivity resulting in an impaired ability to synchronize with the rest of the network, which may contribute to subsequent decreases in connectivity (Jacob et al. 2020). Thus, some local feature measures that depict spatial characteristic and alteration patterns of resting-state functional magnetic resonance imaging (rs-fMRI) metrics have been used to illustrate aberrant regional brain dysfunction, such as the fractional amplitude of low-frequency fluctuations (fALFF) and regional homogeneity (ReHo) (Späti et al. 2015; Egorova et al. 2017). FALFF is used to measure local fluctuations in neuronal activity and ReHo is used to measure the degree of functional synchrony of a given voxel with its neighboring voxels (Zang et al. 2004; Zou et al. 2008). Both fALFF and ReHo have been widely used to explore brain functional changes with depression (Iwabuchi et al. 2015; Zhou et al. 2017), and these rs-fMRI measures were used to explore the spatial characteristic patterns of DMN in this study.

In addition, researchers also sought to use the information contained within the variation of rs-fMRI measures over time to supplement temporal variability of the spontaneous neural activity, which were called dynamic measurements (Hutchison, Womelsdorf, Allen, et al. 2013a; Calhoun et al. 2014; Preti et al. 2017). Recent studies have applied some dynamic measurements to depict the temporal dynamic of rs-fMRI metrics, including the voxel-wise functional concordance across time windows (VC) and Hurst exponent (HE). Note that the concept "dynamic" here for VC and HE is not identical, but in function they both can be used to describe temporal variations of spontaneous brain activity during resting-state. The VC is used to measure temporal dynamics change consistency among multiple rs-fMRI metrics by computing the Kendall's coefficient of concordance (KCC) across all time windows (Zhu et al. 2018, 2019). The HE is used to measure the scale-free dynamics via describing the self-similarity of a time series, which can reflect temporal dynamics of the rs-fMRI blood oxygen level-dependent (BOLD) signal (Jing et al. 2017; Dong et al. 2018). Benefiting from the advantages of dynamic features, these temporal measurements facilitate the understanding of distinct aspects of rumination and depression, going beyond the static measurements (Wei et al. 2013; Zhu et al. 2019). For instance, a recent study proposed that the neural underpinnings of rumination can be characterized by the specific dynamic nature of DMN (Chen and Yan 2021). Moreover, recent studies have combined temporal dynamic approaches and the machine learning method to discriminate different subtypes of depression (Jing et al. 2017). Therefore, in this study, we use the VC and HE to explore the temporal dynamic of DMN, which facilitate the understanding of the relationship between rumination and depression.

Collectively, the spatial characteristic and temporal dynamic patterns of intrinsic neural activity provide complementary information about network integrity and have been found useful in characterizing spontaneous brain activity in depression. However, previous studies mostly focused on brain structure and inter-regional features that suggested aberrant function and connectivity between the DMN and other brain areas (Hamilton et al. 2011; Wang et al. 2015; Rosenbaum et al. 2017; Jacob et al. 2020). Although rumination and depression are believed to be related to the spontaneous brain activity of DMN, the intra-regional spatial and temporal feature abnormalities in DMN have not been well characterized. It is worthwhile to explore the neural network spatial characteristic and temporal dynamic patterns of rumination tendency for understanding depressive risk. Therefore, the present study aims to (i) characterize the spatial characteristic and temporal dynamic patterns of spontaneous brain activity in the DMN and (ii) clarify the neural mechanisms that underlie the relationship between rumination tendency and depressive risk.

In this study, we sought to explore the neural correlates between rs-fMRI spatial and temporal measures of the DMN and rumination tendency. On the one hand, given that rumination is considered as a perseverative process of negative thinking about personal concerns over time, we thought that rumination tendency would be more closely correlated with temporal dynamics compared to spatial characteristic patterns in the DMN. On the other hand, as the heterogeneity within DMN and its key nodes, such as the PCC and the MPFC, have been implicated in MDD (Lai 2018; Liu et al. 2019), we also extract these measures in subregions of the DMN and used machine learning to evaluate contributions of significant subregions to rumination tendency. Moreover, we further tested for

potential associations between rumination, spontaneous brain activity of DMN, and depression using mediation analyses. Additionally, given that the effect of machine learning regression algorithms is limited by sample size, the same procedure is administered to another independent sample to confirm the reliability and the consistency of the results in our study.

Methods

Participants and individual difference measures

The present study included 2 independent samples. For sample 1, 100 participants were recruited (51 males; age range: 18–28, $M = 23.36$, $SD = 3.11$). For the sample 2, 95 participants served as independent sample 2 (46 males; age range: 18–26, $M = 21.94$, $SD = 2.51$). Two participants were excluded from sample 1 and 3 from the sample 2 (excessive head movement, >2 mm). Both independent samples excluded subjects with any history of psychiatric or neurological illnesses. All participants gave written informed consent and were paid on an hourly rate for their participation. This study was approved by the local ethical committee and the Institutional Human Participants Review Board of the Southwest University Imaging Center for Human Brain Research.

The Rumination Response Scale (RRS) is used to assess the level of rumination because it is a reliable and valid measure of rumination tendency among healthy and depressed individuals (Luminet 2004; Fawcett et al. 2015). Participants recorded their responses on a 1- to 4-point scale (almost never to almost always; 22 items), with higher RRS scores indicating generally more frequent ruminative thoughts and behaviors. The Beck Depression Inventory (BDI-II) (Beck et al. 1961) was used to assess the level of depressive risk in this study. The BDI-II consists of 21 items, and each item has a 4-point scale ranging from 0 to 3, assessing the severity of various cognitive, behavioral, and physiological symptoms associated with depression. The BDI-II can not only assess the intensity of depression but also detect possible depression in the general population, and it has a high validity and internal consistency (Wang and Gorenstein 2013). In addition, measures of possible control variables include (i) the Chinese version of 48-item Neuroticism questionnaire of the Neuroticism-Extraversion-Openness Five-Factor Personality Inventory (McCrae and Costa Jr 2004), which assesses individual's preference to experience psychological distress; (ii) the State–Trait Anxiety Inventory (STAI), which assesses individual differences in trait anxiety (Barnes et al. 2002).

Imaging data acquisition and preprocessing

RS-fMRI data of 2 independent samples were acquired with the General Electric Discovery MR750 scanner of 3 Tesla (GE Healthcare, Milwaukee, Wisconsin) and the Siemens Trio MRI scanner of 3 Tesla (Siemens Medical Department, Erlangen, Germany), respectively. Before the scanning, all subjects were instructed to keep their eyes closed, move as little as possible, and not fall asleep during the scans. Functional scanning used echo-planar imaging sequence in sample 1 [time repetition (TR), 2,000 ms; time echo (TE), 30 ms; flip angle, 90°; field of view, 224 mm; in-plane resolution, 64×64; voxel size, $3.5 \times 3.5 \times 3.5$ mm^3] and sample 2 (TR, 1,500 ms; TE, 30 ms; flip angle, 77°; field of view, 192 mm; in-plane resolution, 64×64; voxel size, $3 \times 3 \times 3$ mm^3). Anatomical images with $1 \times 1 \times 1$ mm^3 resolution were obtained by a T1*-weighted 3-dimensional magnetization-prepared rapid gradient echo sequence (more details see in Supplement Materials).

Preprocessing was performed using statistical parametric mapping (SPM12) tools (www.fil.ion.ucl.ac.uk) implemented in DPARSF (V4.3_170105, Yan et al. 2016). The first 10 volumes of each dataset were discarded to allow the T1 signal to reach equilibrium and the participants to adapt to the scanning noise. The remaining images were corrected for slice timing differences; then, realignment was performed to correct the motion between time points. Head motion parameters were computed by estimating the translation in each direction and the angular rotation on each axis for each volume and used to exclude individuals with significant motion (2 mm or 2°). Several covariates (the estimated motion parameters based on the Friston-24 model, the linear drift, the white matter signal, and the cerebrospinal fluid signal) were regressed out from the data. We also calculated the frame-wise displacement (FD) and regressed out spike volumes when the FD of the specific volume exceeded 0.5, because the signal spike caused by head motion significantly contaminated the final rs-fMRI results even after regressing out the linear motion parameters (Power et al. 2012). In the normalization step, each anatomical image was co-registered with the mean functional image and then was segmented and normalized to the Montreal Neurological Institute (MNI) space. Finally, each filtered functional volume was spatially normalized to MNI space using the deformation parameters estimated during the above step and resliced into a 3-mm cubic voxel. After preprocessing, we used a series of analyses as follows (Fig. 1A).

DMN identification

After rs-fMRI data preprocessing, we performed group independent component analysis (ICA) to identify the DMN and select the DMN mask from all participants as has been recently suggested (Guo et al. 2017; Lei et al. 2017). Three steps, including data reduction, independent component separation, and back reconstruction, were conducted with the toolbox GIFT (http://mialab.mrn.org/software/#gica). After data reduction by principal component analysis, ICA decomposition was performed on concatenated datasets using the Extended Infomax algorithm. DMN masks of the 2 samples are shown in Fig. 1B.

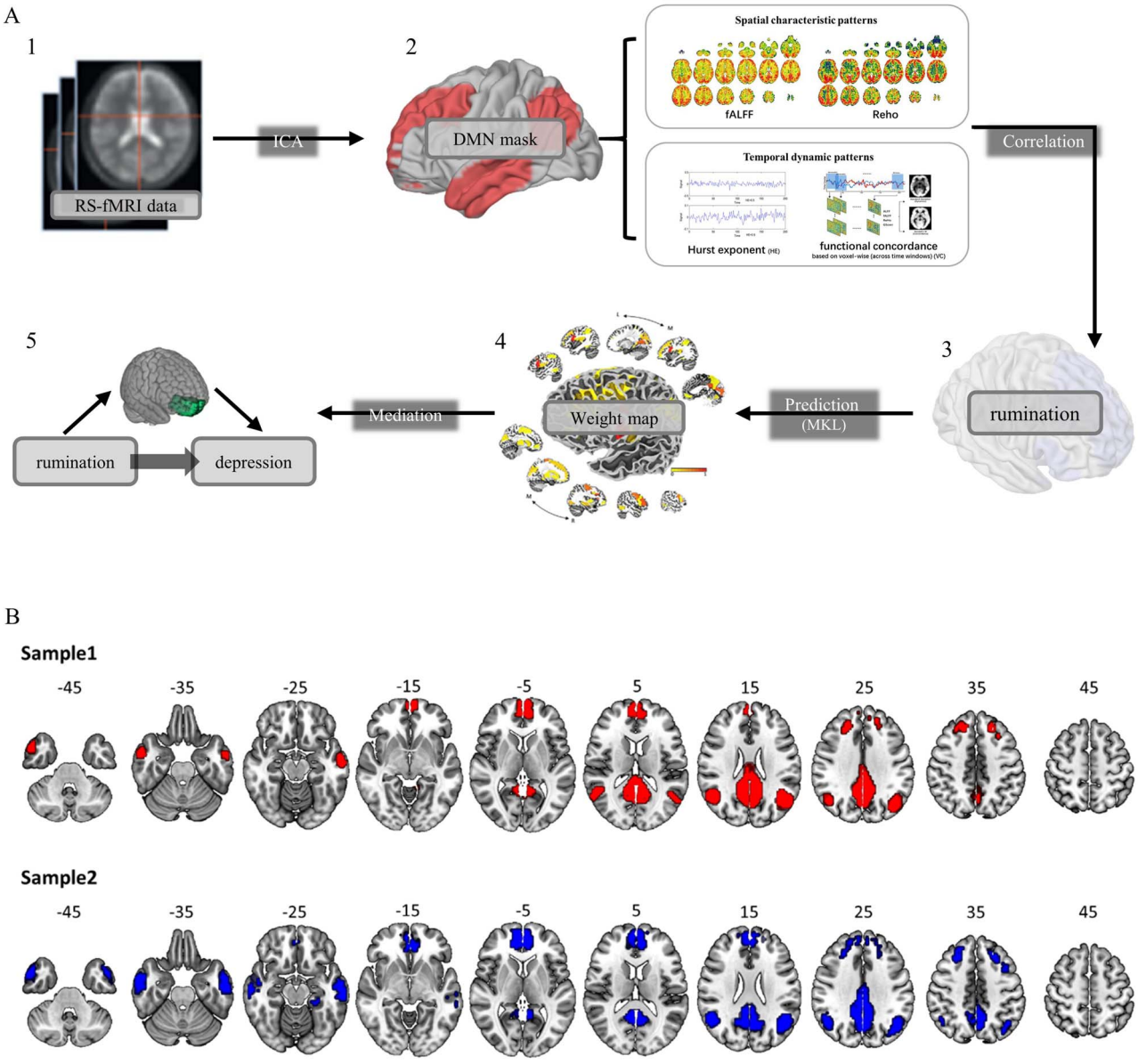

Fig. 1. A) Flowchart of the study. (1) Resting-state fMRI images preprocessing. (2) We identified DMN masks by using ICA and extracted spatial characteristic and temporal dynamic measures of DMN. (3) We calculated correlations between spatial characteristic and temporal dynamic and rumination in DMN and its subregions. (4) Prediction analysis of rumination and weight map show the contribution of the different brain regions. (5) Mediation analysis between rumination and depression. B) DMN masks generated from all participants by group ICA.

Calculation of spatial characteristic patterns

The BOLD time course was transformed to the power spectrum using fast Fourier transform. FALFF represents the relative contribution from low-frequency fluctuation based on the ratio of the power spectrum in the low-frequency band (0.01–0.08 Hz) to that in the entire frequency range (Zou et al. 2008). For standardization, the normalized fALFF was then generated based on the ratio of fALFF value at each voxel to the global mean fALFF value. On the assumption that neural activity would more likely occur in a cluster than in a single voxel, ReHo can be used to measure the degree of regional neural activity coherence. Individual ReHo maps were generated by calculating KCC of the time series of the 27 nearest neighboring voxels in a voxel-wise manner (Zang et al. 2004). For standardization purposes, the individual ReHo maps were divided by their global mean values. Previous studies indicated that the functional concordance analysis depends on rs-fMRI indices (i.e. fALFF, ReHo, VMHC, DC, and GSCorr) (Yan et al. 2017). Given that fALFF and ReHo showed sensitivity and specificity in detecting spontaneous brain activity and were involved in MDD studies (Egorova et al. 2017; Sun et al. 2018), we chose fALFF and ReHo to calculate the VC.

Calculation of temporal dynamic patterns

To characterize temporal dynamic patterns of spontaneous brain activity in the DMN, we calculated the HE, which measures long-range correlations of a time series and can effectively examine the temporal complexity of a

time series. The calculation of HE was conducted in Matlab 11.0 (Math Works, Natick, MA) by using the WLBMF toolbox (https://www.irit.fr/~Herwig. Wendt/). The scale parameters were chosen to correspond to a frequency range of (0.016, 0.063) Hz (Ciuciu et al. 2012) and the linear slope (B) of the log–log scale plot of the power spectra is used to calculate the HE by the formula $H = (B - 1)/2$ (Lei et al. 2013). The VC was also utilized to characterize their temporal dynamic patterns. Specifically, hamming windows with window size = 30 TR and window step = 1 TR were applied to each participant's preprocessed functional images to obtain a series of BOLD signal windows and rs-fMRI measures were calculated for each window. Kendall's W was used to measure voxel-wise concordance since this nonparametric statistic has no assumptions of the distribution and is insensitive to differences in scale among these rs-fMRI measures (Yan et al. 2017). For each participant, Kendall's W of these rs-fMRI measures was calculated across all voxels within the whole gray matter for each time window. Temporal concordance was computed as Kendall's W of these rs-fMRI measures across all time windows, resulting in a dynamic voxel-wise concordance map for each participant. Window size of 40 TRs and 60 TRs were also tested; results are shown in Supplementary Materials (Supplementary Tables S2 and S3).

Statistical analysis

First, we performed correlation analysis to verify the relationship between rumination scores and depression scores. Subsequently, we used a hierarchical regression analysis to exclude the possible impact of confounding variables such as neuroticism and trait anxiety. Then, we explored the association between rumination tendency and the spontaneous brain activity of DMN (spatial characteristic and temporal dynamic patterns). Both demographic variables and other possible control variables were included as covariates in our analyses. Given that increasing evidence suggested that the DMN is a heterogeneous brain system composed of at least 3 separable subnets including MPFC, PCC, and medial temporal lobe (MTL) (Roy et al. 2009; Fingelkurts et al. 2016). Therefore, we also examined the association between rumination tendency and the spontaneous brain activity of DMN at the subregion level. We divided the DMN into 3 key nodes by the "Free ROI" toolbox (http://freeroi.brainactivityatlas.org) that comprises a set of interconnected brain regions (MPFC, PCC, and MTL) (Wu et al. 2020); these spatial and temporal pattern images of DMN sub-regions were involved in our subsequent analyses. To correct for multiple comparisons in our study, we used Bonferroni–Holm correction for multiple testing ($\alpha = 0.05$, $P = 0.008$, 2-tailed) (Holm 1979). Moreover, to ensure reliable results, we only showed the results, which were found significant in 2 samples.

Prediction analysis

Pattern regression analyses were applied to explore the relationship between rumination tendency and spontaneous brain activity of DMN subregions. To determine different contributions of DMN subregions to rumination tendency, we extracted the spatial and temporal measures of MPFC, PCC, and MTL and calculated the correlation between these measures and rumination scores. Subsequently, to test the robustness of the brain–behavior relationship in this study, we performed pattern regression analyses based on the multiple kernel learning (MKL) (using PRoNTo v2.1; Schrouff et al. 2013; Weichwald et al. 2015; Oliveira et al. 2019). Prediction regions were defined using significant brain regions based on the correlation analysis. A linear kernel was computed for prediction regions based on the regional pattern of activation containing all voxels within the region. These kernels were normalized and mean-centered using standard kernel operations implemented in PRoNTo. A nested 5-fold cross-validation procedure was used to train the model for rumination scores, with the same cross-validation scheme for the internal and external loop. The model performance is evaluated using two metrics to measure the agreement between the predicted and the actual rumination scores: Pearson's correlation coefficient (r) and mean squared error (MSE). In the second sample, the same analysis was performed. Age and gender were included as covariates in the whole prediction analysis.

Mediation analysis

To further explore the potential association between rumination scores, the spontaneous brain activity of DMN, and depression scores, mediation analysis was performed using the PROCESS macro (http://www.processmacro.org/) developed by Hayes (2012). Mediation analysis calculates a bootstrap estimate of the indirect effect between the independent variable and dependent variable, an estimated standard error, and 95% confidence intervals (CIs) for the population value of the indirect effect. In the mediation analysis model, all paths were reported as unstandardized ordinary least squares regression coefficients, namely the total effect of X on Y (c) = indirect effect of X on Y through M ($a \times b$) + direct effect of X on Y (c'). The significance analysis was based on 5,000 bootstrap realizations and the significance of indirect effects was assessed by applying bootstrap method to calculation of 95%CI. Before conducting analyses, all variables were z-scored to produce standardized β weights. In this study, only variables significantly related to rumination scores in prediction analysis can be considered as mediating variables.

Results

Relationship between rumination tendency and depressive risk

The sample of participants had an average total RRS scores ($M_{\text{sample 1}} = 50.83$, SD = 11.74; $M_{\text{sample 2}} = 50.98$, SD = 9.12) and BDI scores ($M_{\text{sample 1}} = 15.60$, SD = 5.97; $M_{\text{sample 2}} = 14.25$, SD = 7.78). The correlation analysis

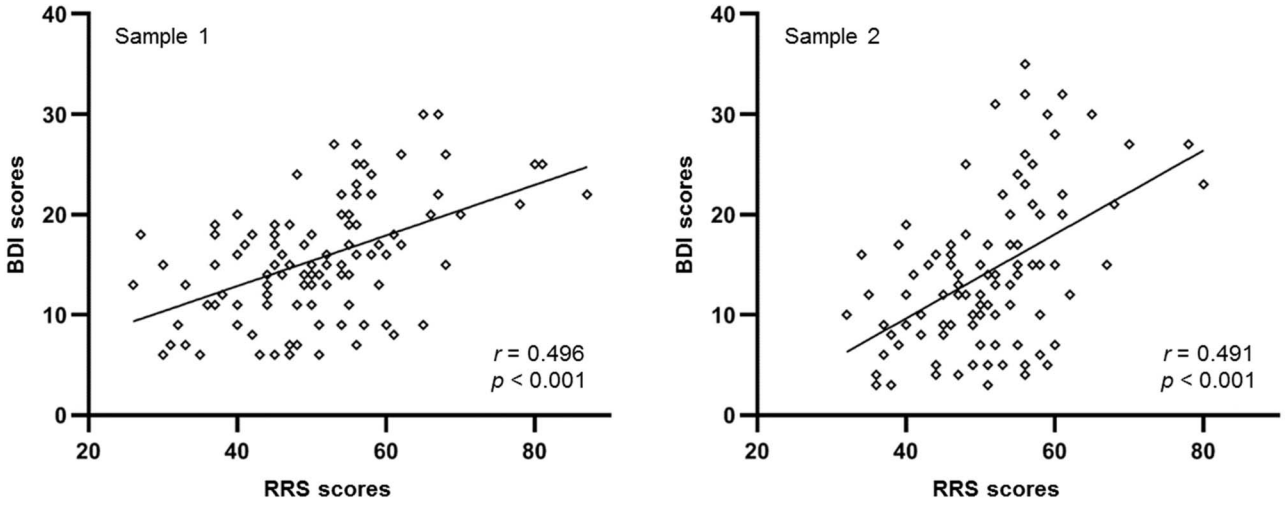

Fig. 2. The correlation and scatterplots displaying the relationship between the scores of rumination and depression scores.

Table 1. Regression coefficients (R^2, ΔR^2) and statistical results of hierarchical linear regression analyses on depression with respect to the influence of rumination, neuroticism, and trait anxiety are shown.

Step	Depression (sample 1)				Depression (sample 2)			
	Beta	R^2	ΔR^2	P	Beta	R^2	ΔR^2	P
Rumination alone	0.252	0.246		0.001	0.419	0.241		0.001
Rumination added first	0.238	0.246		0.001	0.404	0.241		0.001
Neuroticism added second	0.177		0.035	0.035	0.249		0.042	0.025
Rumination added first	0.236	0.246		0.001	0.396	0.241		0.001
Neuroticism added second	0.174		0.035	0.035	0.215		0.042	0.050
TA added third	0.169		0.030	0.044	0.236		0.032	0.044

TA, trait anxiety. Probability values are 2-tailed. R^2 illustrates the regression model, whereas ΔR^2 illustrates the improvement of the regression model when additional independent variables are considered.

showed a significant positive correlation between RRS and BDI scores (sample 1: $r = 0.496$; $P < 0.001$; sample 2: $r = 0.491$; $P < 0.001$) (Fig. 2). Consistent with previous studies, our results show that individuals with higher rumination scores have higher depression scores (Spasojevic and Alloy 2001; Ciesla and Roberts 2007; Berman et al. 2011). Moreover, we used a hierarchical regression analysis to exclude the possible impact of confounding variables such as neuroticism and trait anxiety, which were associated with depression (Table 1). Rumination captured 23.6% in sample 1 and 39.6% in sample 2 of the variance while the addition of trait anxiety and neuroticism to the equation did not result in a significant increment of R^2 ($P < 0.01$). These findings indicated that the relationship between rumination tendency and depressive risk was not due to individual difference in personality characteristics.

Correlations between rumination and the spatial and temporal measures of DMN

Rumination scores showed significant positive correlations with the HE (sample 1: $r = 0.279$, $P = 0.005$; sample 2: $r = 0.275$, $P = 0.008$) and VC (sample 1: $r = 0.267$, $P = 0.008$; sample 2: $r = 0.284$, $P = 0.006$) of DMN. These results exclude the possible impact of confounding variables (for more details, see Supplementary Materials). The correlation results indicated that higher rumination scores were associated with higher HE and VC values, reflecting more consistent and regular temporal dynamic patterns of the DMN. However, we found that rumination scores have no statistical significant correlations with the fALFF (sample 1: $r = 0.179$, $P = 0.077$; sample 2: $r = 0.203$, $P = 0.052$) and ReHo (sample 1: $r = 0.182$, $P = 0.073$; sample 2: $r = 0.181$, $P = 0.083$) of DMN. Moreover, given that some recent studies suggest that the DMN exhibits heterogeneous functional components (Zhang et al. 2020; Zhou et al. 2020), it is necessary to examine the spontaneous brain activity of DMN subregions. The further subregion analysis showed that the fALFF of PCC and the HE and VC of MPFC were significantly correlated with rumination scores in both samples (Table 2). These results indicated that the spatial characteristic and temporal dynamic patterns of DMN subregions make contributions and may have different sensitivity to rumination tendency.

Results of prediction and mediation analysis

The MKL model computes 2 sets of weights, the kernel weights and the voxel weights. The kernel weights represent the contribution of each region (region weights) to the predictive model, and the voxel weights represent the contribution of each voxel within the regions to the

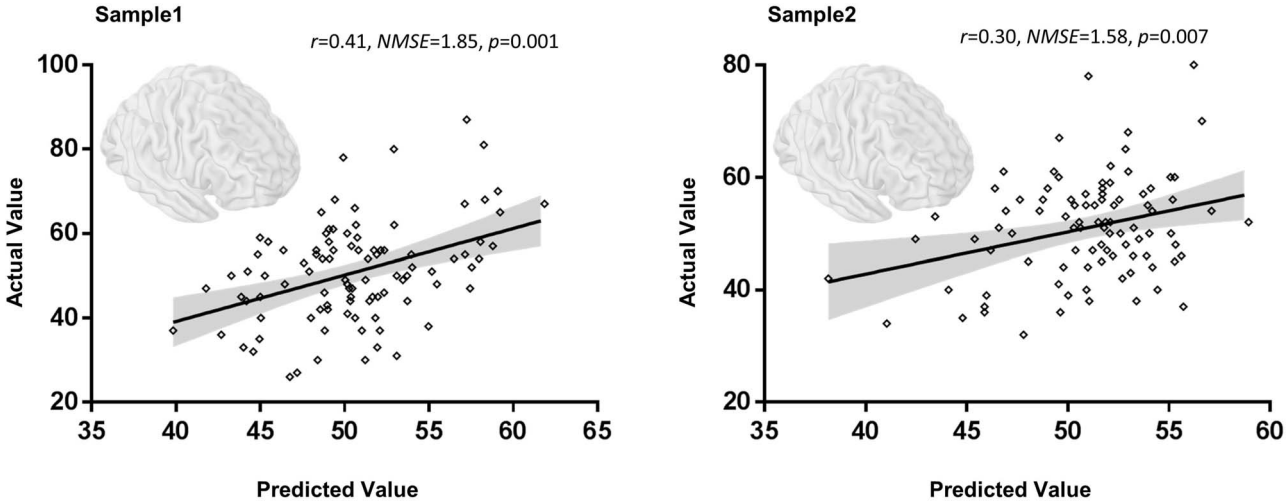

Fig. 3. The correlation between the actual value and predicted value of rumination scores (RRS). NSME, normalized mean square error.

Table 2. Correlations between rumination scores (RRS) and the spatial and temporal measures of DMN subregions.

	Sample1 rumination scores *r* (*P*)	Sample2 rumination scores *r* (*P*)
fALFF of MPFC	0.074 (0.471)	0.165 (0.116)
fALFF of PCC	0.331 (0.001)[a]	0.295 (0.004)[a]
fALFF of MTL	0.160 (0.115)	0.178 (0.090)
ReHo of MPFC	0.006 (0.955)	0.078 (0.460)
ReHo of PCC	0.291 (0.004)	0.226 (0.031)
ReHo of MTL	0.203 (0.045)	0.137 (0.192)
HE of MPFC	0.291 (0.004)[a]	0.321 (0.002)[a]
HE of PCC	0.168 (0.098)	0.122 (0.246)
HE of MTL	0.256 (0.011)	0.180 (0.087)
VC of MPFC	0.274 (0.006)[a]	0.319 (0.002)[a]
VC of PCC	0.181 (0.074)	0.123 (0.242)
VC of MTL	0.164 (0.106)	0.135 (0.201)

[a]P values withstand multiple test correction in both samples.

predictive model. Both sets of weights can be explicitly computed and plotted as brain images. The kernel or region weights thus enable interpretation of the predictive model in terms of contributions of DMN subregions. Our results showed that the MKL regression models predicted rumination scores, only from temporal dynamic patterns of the MPFC (sample 1: $r = 0.41$, NMSE = 1.85, $P = 0.001$; sample 2: $r = 0.30$, NMSE = 1.58, $P = 0.007$) (Fig. 3). In both samples, we found that the neural region with the higher contribution was the VMPFC. Figure 4A displayed the corresponding voxel weights map showing the contribution of different regions in the MPFC to the MKL predictive model. These results suggest that temporal dynamic patterns of the VMPFC may have sensitivity in predicting rumination tendency.

In mediation analysis, we used an independent mask of VMPFC based on prior studies (Bhanji et al. 2019). The mediation analysis is based on a standard 3-variable path model with a bootstrap test for the statistical significance of the indirect effect. Results showed a significant indirect effect between rumination and depression scores through the HE and VC of VMPFC (see Fig. 4B). These results indicate that temporal dynamic patterns in the VMPFC explain a part of the rumination and depression association. A CI that does not contain zero indicates that there is a significant mediation effect for the proposed mediating factor. Several studies of functional neuroimaging with CI lower values also indicated convincing mediation effects (Wager et al. 2008; Menatti et al. 2015). Therefore, our current mediation effects are significant though CI lower values are small. Details about the mediation analysis are shown in Table 3.

Discussion

Rumination is a major contributor to the development and maintenance of depression and has been linked to abnormal spontaneous brain activities of DMN. An increasing body of evidence suggests that the intraregional alteration features of DMN are implicated in depression. However, how DMN spontaneous alteration features underlie the association between rumination and depression remains elusive. To this end, we examined the roles of the spatial and temporal alteration patterns of DMN in rumination tendency and depressive risk. Our findings indicate that (i) individuals with higher rumination tendency have higher depressive risk; (ii) increased rumination tendency is associated with more consistent and regular temporal dynamic patterns of DMN (higher HE and VC values); (iii) the spatial and temporal measures of DMN subregions have different contributions and sensitivity to rumination tendency; (iv) higher HE and VC values of VMPFC predict higher individual rumination scores; (v) temporal dynamic patterns of VMPFC play a mediator between the association of rumination and depression. These findings suggest that temporal dynamic patterns of VMPFC serve as important biomarkers for individual difference in rumination and its close association with the risk of depression.

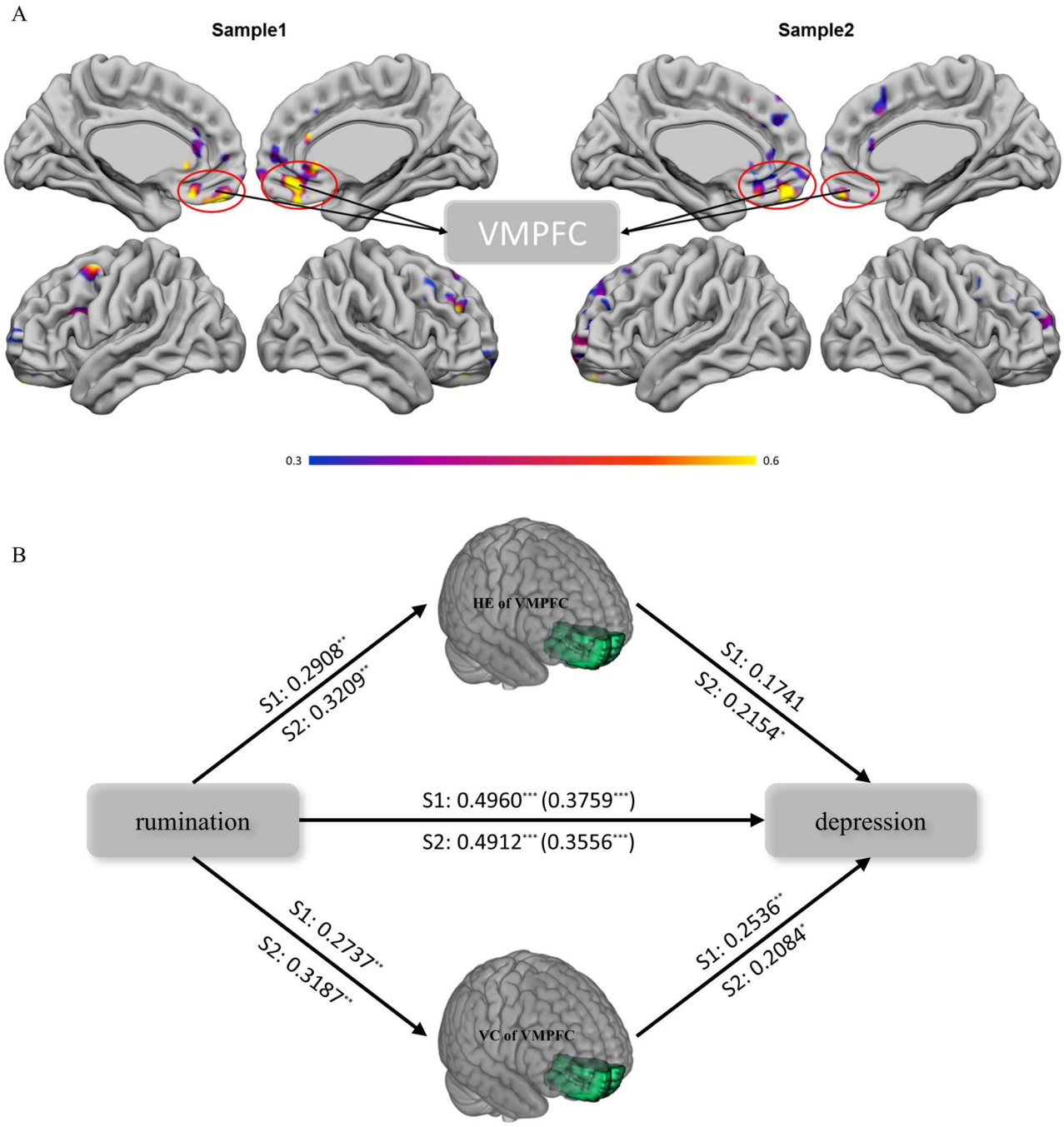

Fig. 4. A) Weight map showing the contribution of the different brain regions for predicting RRS scores from temporal dynamic patterns of MPFC. The region with the highest contribution according to the multiple kernel learning predictive model was the ventromedial prefrontal cortex. B) The relationship between rumination and depression scores was mediated by the HE and VC of VMPFC. S1 = sample 1, S2 = sample 2. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

In this study, our results indicate that the temporal dynamic but not spatial characteristic patterns of DMN are associated with rumination. One possible explanation is that rumination is a perseverative process over time, which would be more closely correlated with temporal dynamics of DMN. We found higher rumination scores are associated with higher HE and VC values of DMN, which reflect more consistent and regular temporal dynamic patterns. These results might be attributed to impaired cognitive flexibility in ruminative individuals. Previous studies suggest that rumination reduces cognitive flexibility, by placing additional demands on a resources-limited system (Nolen-Hoeksema et al. 2008; Watkins 2008; Kühn et al. 2012). Several studies have indicated that people who ruminate also have difficulty in cognitive flexibility (Whitmer and Banich 2007; Beckwe et al. 2014). Recent studies also found that people who ruminate show deficits in cognitive flexibility by finding it difficult to maintain their concentration, focus, and cognitive control (Whitmer 2009; Joormann and Vanderlind 2014). Cognitive flexibility is closely associated with information processing efficiency, which can affect the

Table 3. The indirect effects of rumination scores (RRS) on depression scores (BDI) through the HE and VC of VMPFC.

	Mediator	Indirect effect	SE	95% CI (BC)	
				Lower	Upper
Sample 1					
	HE of VMPFC	0.0506	0.0280	0.0063	0.1161
	VC of VMPFC	0.0694	0.0375	0.0085	0.1540
Sample 2					
	HE of VMPFC	0.0691	0.0342	0.0065	0.1411
	VC of VMPFC	0.0664	0.0287	0.0145	0.1259

Notes: Number of bootstrap resamples = 5,000. CI(BC), bias corrected confidence interval.

ability to adjust one's emotional, cognitive, and behavioral responses to a situation based on new input information (Diamond 2013; Vries et al. 2015). Moreover, prior studies suggest a close association between temporal dynamic patterns of the DMN and one's cognitive flexibility (Blackwell et al. 2009; Ragozzino et al. 2012; Gao et al. 2018). The temporal dynamic patterns of DMN are correlated with online information-processing efficiency and the change of the established cognitive schema over time, as reflected by cognitive flexibility (Yang et al. 2013; Vatansever et al. 2016). Based on these studies, we consider that higher HE and VC values reflecting more consistent and regular temporal dynamic patterns of the DMN may correspond to lower cognitive flexibility (worse online information processing). More importantly, several studies suggest that cognitive dysfunctions are psychological characteristics of MDD patients, and cognitive inflexibility may play an important role in the relationship between rumination and depression (Davis and Nolen-Hoeksema 2000; Gu et al. 2008; Cooney et al. 2010; Murphy et al. 2012). Therefore, our findings indicate that the temporal dynamic patterns of DMN during resting state provide a critical substrate for understanding ruminative features that are relevant to depression.

For the results that temporal but not spatial patterns are associated with rumination, the heterogeneity of DMN may be another explanation. We noticed that both spatial characteristic ($P < 0.05$, not withstand multiple test correction) and temporal dynamic are correlated with rumination, but these correlations happen in different brain regions (fALFF and ReHo in PCC; VC and HE in MPFC). We thought the different rumination correlation can be attributed to different brain region's function. As a part of archicortex, the contributions of PCC to rumination can be directly reflected by spatial characteristic patterns. As a part of neocortex which takes charge of more complex psychological processes, the function of MPFC needs more temporal dynamics to provide complementary information. Indeed, subregion analysis showed a positive relationship between rumination and the abnormal fALFF of PCC, which is consistent with previous studies. There is considerable evidence that the increased activity of PCC may be related to autobiographical memory search and retrieval processes (Mantani et al. 2005; Addis et al. 2007; Mason et al. 2007; Leech and Sharp 2014). Several studies also indicate that the PCC is reliably involved in pathological rumination and self-focused attention in depression (Fransson and Marrelec 2008; Granados-Domínguez et al. 2013). More recently, a study suggests that the lateral orbitofrontal cortex-posterior cingulate cortex circuit is related to the enhanced bias towards rumination with negative self-focused memories (Cheng et al. 2018). Moreover, it has been demonstrated that rumination is closely linked to maladaptive and perseverative negative thinking, including excessive negative self-focused thoughts and autobiographical memories retrieval (Davis and Nolen-Hoeksema 2000; Nolen-Hoeksema et al. 2008; Koval et al. 2012). Our results support the notion that increased fALFF of PCC might be involved in the retrieval of negative autobiographical memories, reflecting a highly maladaptive self-focused state in rumination.

Our subregion analysis found that higher rumination tendencies were associated with higher HE and VC values of the MPFC, which might be explained by the persistence and regularity of long-range memory in rumination. Resting-state spontaneous brain activity can be conceptualized as a multistable dynamic process wherein multiple distinct states recur over time (Hutchison, Womelsdorf, Allen, et al. 2013a; Hutchison, Womelsdorf, Gati, et al. 2013b). Prior studies have demonstrated that spontaneous brain activity exhibits scale-free dynamics, and researchers quantify the temporal dynamics based on HE, because HE can reflect the property of scale-free dynamics via describing the self-similarity of time courses (Aguirre et al. 1997; Ciuciu et al. 2012). The HE, as an index ranging from 0 to 1, has been utilized to assess pathological and physiological conditions (Wink et al. 2006; Lai et al. 2010; Gentili et al. 2015). The HE closer to 0.5 indicates more randomness or chaos (e.g. Brownian motion), whereas the HE value closer to 1 indicates more regular or persistent fluctuations (e.g. Euclidian order). Existent evidence indicated that the brain network with a higher value of HE is related to deficits in online information processing and persistent in long-range memory (Yang et al. 2013; Yang and Tsai 2013). Similarly, the VC provides an approach to quantitatively describe the consistency across time among a set of base metrics (Yan et al. 2017). Several studies have used VC to determine how the consistency

of different metrics is related to their variation from one state to the next, which may reflect consistent temporal dynamic patterns (Zhu et al. 2018, 2019). Taken together, our results suggest that higher HE and VC values of the MPFC might reflect the persistent and regular self-relevant processing and long-range memory associated with rumination.

Further mediation results show that the temporal dynamic patterns of VMPFC mediate the relationship between rumination and depression, which might be attributed to the VMPFC involved in both cognitive flexibility and self-referential processing (Lemogne et al. 2012; Hang et al. 2016; Hernandez et al. 2016). The VMPFC is critical in internal, self-referential processing (Northoff et al. 2006) and has been suggested to play an important role in self-referential processing in MDD (Lemogne et al. 2010, 2012). Lemogne et al. (2012) provided compelling evidence for the role of increased VMPFC activities in the depressive self-focus, which is associated with acute depressive states and with an increased risk of depressive relapse through ruminative processes. A recent study found that the VMPFC might contribute to self-referential processing by representing the subjective value of the contents of imagined or recollected scenarios (Lin et al. 2016). On the other hand, previous studies have shown that successful performance of cognitive flexibility depends on the normal structure and function of VMPFC (Dalley et al. 2004; Hang et al. 2016). For instance, Morris and colleagues found that VMPFC-striatal connectivity plays an important role in cognitive–behavioral flexibility and goal-directed behaviors (Morris 2016). Several studies show that both lesions in VMPFC and alterations of the level of VMPFC dopamine have been found to induce disturbances in cognitive flexibility (Logue and Gould 2014; Hernandez et al. 2016). In this regard, our findings suggest that lower temporal dynamics of VMPFC may reflect decreased cognitive flexibility and more rumination on self-referential memories, which causes increased depressive risk.

There are several limitations that necessitate further investigation. Firstly, this study used 2 samples of Chinese college students and only healthy subjects were involved. Further work is needed to examine whether our conclusions can be generalized to other age groups. Besides, representativeness and generalizability of our findings should be tested in a clinical sample and be considered in different socio-demographic backgrounds. Secondly, it has been reported that gender moderates the tendency of rumination, with women scoring higher than men on rumination in general (Johnson and Whisman 2013). Though we controlled the effects of gender in data analysis, it is still necessary to examine potential gender effects with rumination in future studies. Additionally, a recent study has found that the HE phenomenon is a sufficient condition to prove long-range memory only in the stationary fractional Gaussian noise process (Von Wegner et al. 2018). Thus, the interpretation that the long-range memory can be predicted by HE correctly should be more cautious, and future study should apply multiple approaches to delineate brain network temporal dynamics, like co-activation pattern analysis (Chen et al. 2015) and multi-layered dynamic analysis (Raz et al. 2012). Finally, previous studies show that individuals' rumination processes are not equivalent to resting state (Berman et al. 2014). Although rumination was regarded as a personality trait in the current study, future studies should adopt an induced rumination task to explore real rumination processes and replicate our findings.

Conclusion

In summary, this study contributes to the current understanding of the relationship between rumination and depression by elucidating the spatial and temporal spontaneous brain activity of the DMN. We show that rumination is associated with temporal dynamic but not spatial characteristic patterns, which may be attributed to DMN subregions possessing different contributions and sensitivity to rumination. It provides important neuroimaging evidence that individuals with rumination tendency have higher HE and VC values of the DMN (reflecting more consistent and regular temporal dynamic patterns). Moreover, temporal dynamic patterns of the VMPFC play a key role in mediating the association between rumination and depression, which underscore the function of VMPFC in both cognitive flexibility and self-referential processing. These findings suggest that temporal dynamic patterns of VMPFC serve as potential biomarkers of individual difference in rumination tendency and the risk of depression.

Supplementary material

Supplementary material is available at *Cerebral Cortex Journal* online.

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