Aberrant temporal-spatial complexity of intrinsic fluctuations in major depression

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Abstract

Accumulating evidence suggested that the brain is highly dynamic, thus investigation of brain dynamics especially in brain connectivity would provide crucial information that stationary functional connectivity could miss. This study investigated temporal expressions of spatial modes within the default mode network (DMN), salience network (SN) and cognitive control network (CCN) using a reliable data-driven co-activation pattern (CAP) analysis. We found reduced number of CAPs, as well as transitions between different CAPs of the DMN and CCN, in patients with MDD. Results suggested reduced variability and flexibility of two brain networks in the patients. By contrast, we also found increased number of CAPs of the SN in the patients, indicating enhanced variability of the SN in individuals with MDD. In addition, the patients were characterized by prominent activation of mPFC and insula. More importantly, we showed that our findings were robust and reproducible with another independent data set. Our findings suggest that functional connectivity in the patients may not be simply attenuated or potentiated, but just alternating faster or slower among more complex patterns. The aberrant temporal-spatial complexity of intrinsic fluctuations reflects functional diaschisis of resting-state networks as characteristic of patients with MDD.

Keywords: major depressive disorder (MDD); resting-state functional networks; co-activation pattern analysis; brain network dynamic; temporal-spatial complexity of

intrinsic fluctuations

1. Introduction

Major depressive disorder (MDD) is a prevalent psychiatric disorder characterized by the symptoms of depressed mood, anhedonia, cognitive impairments and disturbed sleep or appetite [1–4]. Researchers have implicated aberrant resting-state functional intrinsic networks in the pathophysiology of MDD [5, 6]. Specifically, functional neuroimaging studies have highlighted the involvement of abnormal functional connectivity within the default mode network (DMN), cognitive control network (CCN) and salience network (SN), etc [7–10] in MDD. However, findings from previous studies have been mixed. For example, the majority of studies have reported elevated DMN connectivity in the patients [11, 12], while some studies also observed decreased DMN connectivity in MDD [13, 14]. These inconsistent findings undermine the potential usefulness of resting state fMRI as an endophenotype or biomarker for major depressive disorder.

One of the possible contributing factors to the contradictory results may be the non-stationary characteristic of brain connectivity [15–18]. Accumulating evidence have shown that the patterns of brain connectivity can change within time scales of seconds to minutes [16, 19, 20]. This kind of nonstationary phenomenon has been

consistently reported in unconscious anesthetized macaques, healthy controls, as well as patients with Parkinson's disease [21], autism [22], and depression [23]. Thus traditional (stationary) functional connectivity analysis which simply reports the averaged functional connectivity across the scanning session overlooks dynamics in brain connectivity, and hampers the capacity to capture the depression-specific alterations in brain dynamics.

Some attempts have been made to investigate temporal characteristics of functional connectivity among fixed predefined regions with the sliding-window algorithm which studies the temporal changes of functional connectivity in a truncated sequence of entire time series [20, 24, 25]. Altered variability of functional connectivity within the DMN and the frontoparietal network was observed in adults with depression [26]. Moreover, compared to healthy controls, patients with MDD exhibited similar functional connectivity states, but certain states were expressed for markedly different durations [27].

In addition to functional connectivity among fixed pre-defined regions, the spatial pattern that defines the intrinsic network is also highly dynamic. Recently, Liu et al. (2013) proposed the co-activation pattern (CAP) analysis, which provided a richer characterization of functional connectivity that may increase the sensitivity and specificity of dynamic functional network analysis [28, 29]. Most importantly, recent studies have shown that CAP analysis can establish the relationship between spatial

patterns and temporal changes within intrinsic brain networks, unlike the approach of the sliding-window [28, 30–32]. **So far, an increasing number of studies have begun to focus on exploring the dynamic properties of brain connectivity in patients with MDD using the CAP analysis [33, 34]. Kaiser et al. investigated the dynamic functional connectivity (DFC) of medial prefrontal cortical (mPFC) regions using the CAP analysis and found decreased DFC between mPFC and the parahippocampal gyrus within the DMN in the patients with MDD [33]. The authors further investigated dynamics of whole-brain states of spatial co-activation and reported abnormal frontoinsular dynamics which was associated with severity of symptoms in adolescent depression [34]. These studies have clearly shown that CAP analysis was a promising method to uncover the neural mechanisms of major depression.**

In the current study, we aimed to investigate the temporal changes in spatial patterns within three large-scale brain networks including the DMN, SN, and CCN in 158 patients with MDD. We proposed a revised CAP analysis algorithm (spCAP). Compared to the original algorithm in Liu et al. (2013), the spCAP is able to automatically determine the optimal number of the CAP maps instead of arbitrary setting it to 8 [28]. In addition, the spCAP employed a spectral clustering algorithm which could accommodate skewed distribution of the sample distance. This algorithm was then used to extract CAPs of the DMN, SN and CCN in patients with MDD. The features including numbers of CAP maps, occurrence rate, within-cluster similarity,

persistence and transitions of CAP maps were then compared between the MDD group and healthy controls. More importantly, these findings were reproducible and robust in another independent dataset.

2. Methods and Materials

2.1. Participants

Principal Data Set

A total of 158 patients with major depressive disorder and 102 healthy controls participated in this study. All subjects were recruited from the Zhumadian Psychiatric Hospital. Patients with depression was clinically diagnosed using structural clinical interview for Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-4). The inclusion criteria for MDD groups were as follow: 1) a Hamilton Depression scale (HAMD, 24 items) score of more than 20; 2) no psychotropic medication for at least 2 weeks (6 weeks for fluoxetine) before inclusion. Exclusion criteria for both groups included current or history of systemic medical condition; brain injury; meeting the criteria of DSM-V alcohol/drug dependence in the past year, or meeting the criteria of DSM-V alcohol/substance abuse in the past 6 months; pregnant or **breast feeding** women; having used anticoagulants (heparin, warfarin, etc.), glucocorticoids or medications for thyroid diseases in the past 3 months; abnormal urine toxicology or thyroid screening results and significant current suicidal ideation or suicidal attempt.

Table 1 show the demographical and clinical characteristics of the principal data set.

Replication Data Set

A total of 99 subjects were recruited including 43 MDD patients and 56 healthy controls. All the subjects were informed about the study's aims and procedures – and signed informed consent. The experiment was conducted in accordance with the requirements of the Ethics Committee in Xi-jing Hospital. Patients with MDD were recruited from the Department of Psychiatry in Xi-jing Hospital. All 43 MDD patients conformed to the diagnostic criteria of DSM-IV for a current episode of MDD – as assessed by two experienced psychiatrists. The inclusion criteria were as follow: a Hamilton Depression scale (HAMD, 24 items) score of more than 18; a of Hamilton anxiety scale (HAMA) score of more than 12. Exclusion criteria included: **any the use of psychotropic medication**, demyelinating disorder, mild cerebral atrophy, previous history of encephalitis, past mental abnormality, vascular malformation, incomplete HAMD test, left handedness, imaging contraindications due to artificial teeth, deficient cerebellum in fMRI coverage, shadow in T1 image, or problems in spatial normalization, abnormal T1 segmentation and inappropriate head position. Table 1 show the demographical and clinical characteristics of the replication data set.

2.2. Data acquisition and preprocessing

Principal Data Set

Resting-state fMRI data and T1-weighted data were collected in Zhumadian Psychiatric Hospital using a GE Healthcare 3.0T MR scanner (Signa HDxt scanning, Milwaukee, WI). The subjects were asked to close their eyes, stay awake and lie still in the scanner without performing any explicit task during the fMRI scanning session. The head axis was aligned with the middle axle of MRI machine and two sponges were used to fix the subjects' head – in order to suppress head movement during the experiment. 180 functional images were collected for each subject with the following parameters: TR = 2000ms, TE = 30ms, flip angle = 90°, FOV = 220×220mm, slice thickness = 4mm, spacing = 0.6mm, matrix size = 64×64, number of slices = 33. The high-resolution 3D brain anatomical images using a T1-weighted BRAVO sequence were also collected with the following parameters: TR = 6.8ms, TE = 2.5ms, flip angle = 90°, slice thickness = 1mm, spacing= 0.0mm, matrix size = 256×256, FOV = 256×256mm, number of slices = 192, turnover time (TI) = 1100ms.

Resting state fMRI data were preprocessed using the graph theoretical network analysis (GRETNA) toolbox (https://www.nitrc.org/projects/gretna/). The first ten volumes of the functional fMRI data were discarded for magnetic saturation. Then, realignment was performed to correct for head motion between fMRI images at different time point by translation and rotation. The high-resolution structural

image was then co-registered with functional images and segmented into gray matter, white matter and cerebrospinal fluid (CSF). The deformation parameters from the structural image to the MNI (Montreal Neurological Institute) template were then used to normalize the resting-state fMRI images into a standard space. Additionally, a Gaussian filter with a half maximum width of 6 mm was used to smooth the functional images. Next, each participant's time series were band-pass filtered in the range of 0.01–0.08 Hz and we regressed out the effects of head motion, white matter and cerebrospinal fluid signals. **No significant differences in motion/outliers (framewise displacement) were observed.** Finally, the signal of each voxel was demeaned and then normalized by its standard deviation using the software of MATLAB (https://www.mathworks.com/).

Replication Data Set

Resting-state fMRI data were collected in Xi-jing Hospital using a GE Discovery MR750 3.0 T MRI system. 210 resting-state fMRI images were collected for each subject with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, field of view (FOV) = 240×240 mm, matrix size = 64×64, number of slices = 45, slice thickness = 3.5 mm, spacing= 0.0 mm. A high-resolution structural image was also collected with the following parameters: TR = 8.2 ms, TE = 3.2 ms, FOV = 256×256 mm, matrix= 256×256, flip angle = 12°, slice thickness = 1 mm, spacing = 0.0 mm.

Resting state fMRI data were preprocessed using the graph theoretical network analysis (GRETNA) toolbox (https://www.nitrc.org/projects/gretna/). The first ten volumes of the functional fMRI data were discarded for magnetic saturation. The remaining functional fMRI data had been preprocessed for slice timing, correcting for head movement, normalization, smoothing (**6mm**), temporally filtering (0.01–0.08 Hz) and head motion, white matter and CSF regression. **No significant differences in motion/outliers (framewise displacement) were observed.** Finally, the signal of each voxel was demeaned and then normalized by its standard deviation using the software of MATLAB (https://www.mathworks.com/).

2.3. Group independent component analysis (GICA)

We used group independent component analysis of fMRI Toolbox (GIFT, http://mialab.mrn.org/software/gift/index.html, v3.0b) to decompose the fMRI images into spatially independent components. The number of independent components was first estimated using the minimum description length (MDL) criterion and we then decomposed the fMRI images into the estimated number of spatially independent components. Finally, the SN, DMN, left and right CCN were identified according to the resting-state network templates created by Smith [35].

2.4. Spontaneous co-activation pattern analysis

Workflow of spontaneous co-activation pattern analysis

Spontaneous activity in resting-state networks – including DMN, SN and bilateral CCN – were investigated using the co-activation pattern (CAP) analysis [28]. Figure 1 shows the workflow of the spontaneous co-activation pattern analysis. In this study, the spontaneous co-activation pattern analysis is mainly divided into five steps: first, we extracted time courses of region of interest (ROI) (Figure 1A). Second, we computed the optimal threshold to select the supra-threshold frames (Figure 1B). Third, the spectral clustering algorithm was applied to cluster the supra-threshold frames (Figure 1D). Fourth, we determined the optimal number of the clusters to obtain CAP maps. Fifth, we compared the temporal properties of CAP maps in both groups. Finally, we further extracted the overall dominant CAP maps (dCAP) within resting-state networks and compared the spatial expressions of dCAP in both groups (Figure 1E).

Extraction of time courses of ROI

For each network, we specified a 6mm-sphere ROI centered on the peak seed locations for the DMN, SN, LCCN and RCCN according to GICA analysis. Time courses from these 4 ROIs were extracted (Figure 1A).

1. Computing the optimal threshold

According to a previous study [28], we computed the optimal threshold. Firstly, the spatial correlation (Pearson's correlation coefficient) between the average of the first n% (threshold) frames of each ROI and corresponding independent components using GICA was computed, resulting in a distribution of the spatial correlation *M*

according to the different threshold. Then we computed the gradient vector *G* of *M*:

$$G(i)=\begin{cases} M(2)-M(1) & i=1 \\ \dfrac{M(i+1)-M(i-1)}{2} & 1<i<n \\ M(n)-M(n-1) & i=n \end{cases}$$

Finally, we computed the optimal threshold n% based on the variation of *G*. According to the above procedures, we obtained the optimal thresholds of DMN, SN, LCCN and RCCN which included 12.9%, 7.6%, 11.2% and 10% for the principal data set (Figure 3-6A). In the replication data set, the optimal thresholds of DMN, SN, LCCN and RCCN including8%, 5%, 7% and 5% were selected (Supplementary Figure 1-4A).

2. Spectral clustering algorithm

Figure 1C showed data distribution of patients with MDD in the principal data set using the principal component analysis (PCA). Importantly, we observed that the distance among frames in the principal data set may exhibit skewed distribution which is consistent with previous study [36]. Since the spectral clustering method is independent on the explicit estimation of data distribution [37], we selected the spectral clustering to cluster and pool the supra-threshold frames. The steps of spectral clustering are as follows:

Firstly, a cross-correlation matrix *J* was obtained by calculating the Pearson correlation coefficient between each pair of fMRI frames. A distance matrix *S* denoted

as 1-J was then used to represent the distances among the supra-threshold frames.

Next, adjacency matrix W was constructed based on S:

$$W(i, j) = \exp(\frac{-S(i, j)^2}{2\sigma^2}),$$

where σ denotes the width parameter of the gaussian kernel function and is set to 0.1. We then defined the degree matrix D which is a diagonal matrix:

$$D(i, j) = \sum_{j=1}^{n} W(i, j),$$

and constructed the Laplacian matrix $L=D^{-1/2}WD^{1/2}$. The eigenvalues of L were calculated, and the eigenvalues were then sorted in descending order. We obtained the first k (the number of clusters) eigenvalues and calculated corresponding eigenvectors $U = [u_1, u_2 \ldots u_k]$. Finally, the K-means algorithm was applied to cluster these frames according to the U matrix.

3. Determination of the optimal number of the clusters

Moreover, we adopted the Calinski Harabasz' (CH) index to identify the optimal number of the clusters [38]. CH is defined as:

$$CH = \frac{SS_B}{k-1} / \frac{SS_W}{n-k},$$

where n denotes the total number of frames, k denotes the number of clusters, SS_W denotes the overall within-cluster variance and SS_B denotes the overall between-cluster

variance.

Based on a previous study [28], the optimal number of the clusters is not more than 20. Thus, the spectral clustering approach was repeated with k=2, ..., 20, and the optimal number of the clusters was selected on the basis of the highest Calinski Harabasz' values. Finally, the CAP maps were generated through averaging the frames assigned to the same cluster (Figure 1D).

4. The temporal properties of CAP maps

We compared the temporal properties of CAP maps including the occurrence rate of distinct CAPs, within-cluster similarity of CAP maps in both groups. The occurrence rate is defined as the proportion of the number of different CAP maps to the total number of frames in a subject and within cluster similarity is defined as the average of the Pearson correlation coefficient between each fMRI frames and corresponding CAP in a subject. We also compared the transitions of CAP maps: total frequency of CAP-to-CAP transitions from one frame to the next.

To compare between groups on temporal characteristics on each CAP network state, we further re-analyzed CAP analysis with the pooled MDD and HC sample and calculated measures of distinct CAP maps dominance and transitions including overall dwell time in a CAP map, persistence of a CAP maps and total frequency of CAP-to-CAP transitions for each participant. Overall dwell time is defined as the total proportion of frames of different CAP maps to the total

number of frames in a subject and persistence is defined as the total frame-to-frame maintenance in a CAP map. Furthermore, we also compared total frequency of CAP-to-CAP transitions from one CAP map to the other CAP maps. More details were described in previous study [34]**.**

The spatial expression of the overall dominant CAP maps

To select the most reproducible pattern of CAP maps, the overall dominant CAP maps (dCAP) within resting-state networks were extracted (Figure 1E). Firstly, we computed the temporal fractions (TF) and distinct CAP maps were then sorted in descending order according to TF. The TF is defined as the proportion of the number of fMRI frames assigned to the same cluster to the total number of fMRI frames. Next, the series of temporal frames averages S_m was computed:

$$S_m = \sum_{1 \le i \le m} SM_i \times TF_i$$

where SM_i is the spatial map of CAP^i. Then we calculated the Pearson correlation coefficient r_si between SM_i and the overall average of all frames. Finally, to remove miscellaneous CAPs, we selected the overall dominant CAP maps (SM_i) through comparing r_si greater than the fixed threshold, where the fixed threshold was chosen as 0.95 according to a previous study [30].

2.5. Statistical test

Permutation test was used to assess the statistical significance of the number of

CAP maps within three networks in both groups. In permutation testing, the class labels were randomly shuffled across participants 1,000 times (the principal data set and the replication data set) when guaranteeing the number of participants in each cohort invariant. Each time, the spontaneous co-activation pattern analysis was repeated, gaining the changes of number of CAP maps within three networks in both groups. The *p* value was then defined as the proportion of the changes of number of CAP maps that were greater than the changes of number of CAP maps without permutation.

In addition, Wilcoxon rank-sum tests ($p<0.05$) were applied to determine whether the temporal properties of CAP maps were significantly different between patients with MDD and healthy controls, after the effects of age, gender, and education were regressed out.

Finally, the relationship between temporal properties of CAP maps and HAMD scores were assessed for the participants with MDD using the Pearson correlation method.

3. Results

3.1 Spatial patterns of the resting-state networks and the time courses of regions of interest (ROIs)

Thirty independent components were obtained by the GICA analyses. The DMN, bilateral CCN and SN were identified according to the spatial maps provided in Smith

et al. 2009 [35]. The spatial patterns of these networks are shown in Supplementary Figure 1A. The coordinates of the peak seed locations (the left precuneus (MNI coordinates: 0, -60, 15), the left middle cingulum (MNI coordinates: 0, 24, 36), the left middle frontal gyrus (-36, 21, 51), the right middle frontal gyrus (39, 21, 51)) are shown in Supplementary figure 1A. More details are listed in supplementary materials (Supplementary Table 1).

3.2 Temporal expression of the CAP maps within three networks

In this study, we examined the temporal properties of CAP maps within DMN, SN, LCCN and RCCN by computing the number of clusters, the occurrence rate of distinct CAP maps, transitions of CAP maps and within-cluster similarity of CAP maps **for analysis with MDD and HC sample separately**. Figure 6-7 and supplementary figure 2-3 depict the spatial patterns and the temporal properties of CAP maps within DMN, SN, LCCN and RCCN in both groups.

Figure 6-7 B and supplementary figure 2-3 B demonstrated that MDD patients differed significantly from healthy controls in the number of associated clusters. By CAP analysis, we observed that the DMN pattern was decomposed into 2 CAP maps in patients with MDD, while that of healthy controls was decomposed into 4 CAP maps (Figure 6B). Permutation test was further applied to assess the statistical significance of the number of CAP maps within DMN. We found significantly attenuated number of CAP maps within DMN in patients with MDD compared with healthy controls

(permutation testing using 1,000 permutations, p<0.001).

By examining the spatial patterns of the CAP states and the IC map for the DMN (see Figure 8 of the supplementary materials), we can clearly see that one advantages of the new CAP analysis is that it can provide detailed dynamic properties of spatial modes of the DMN compared with ICA. The DMN component obtained by the traditional ICA was actually highly dynamic and switch between DMN-CAP1 and DMN-CAP2. In addition, the CAP analysis could also provided detailed information on the dwell time, persistence, and numbers of transitions of the CAP states.

Furthermore, SN, LCCN and RCCN were further analyzed: the SN pattern was decomposed into 9 SN-CAP maps in patients with MDD, while the SN pattern of healthy controls was decomposed into 2 CAP maps (permutation testing using 1,000 permutations, p<0.001, Figure 7B), the LCCN pattern was decomposed into 2 LCCN-CAP maps in patients with MDD and healthy controls (permutation testing using 1,000 permutations, p=0.007, Supplementary Figure 2B) and the RCCN pattern was decomposed into 2 RCCN-CAP maps in patients with MDD, while the RCCN pattern of healthy controls was decomposed into 3 CAP maps (permutation testing using 1,000 permutations, p<0.001, Supplementary Figure 3B). Enhanced number of clusters within SN and attenuated number of clusters within DMN and LCCN indicated abnormal dynamic activation of spatial organization.

In addition, we also examined measures of distinct CAP maps dominance and transitions within DMN, SN, LCCN and RCCN by computing overall dwell time in a CAP map, persistence of a CAP map and total frequency of CAP-to-CAP transitions for analysis with the pooled MDD and HC sample. Figure 2-5 depict the spatial patterns and the temporal properties of CAP maps within DMN, SN, LCCN and RCCN in both groups. By CAP analysis, we observed that the DMN pattern was decomposed into 2 CAP maps (Figure 2), the SN pattern was decomposed into 3 CAP maps (Figure 3), the LCCN pattern was decomposed into 2 CAP maps (Figure 4) and the RCCN pattern was decomposed into 2 CAP maps (Figure 5). Increased total frequency of CAP-to-CAP transitions of CAP 3 within SN in the patients compared with healthy controls were observed in the principal data set (p=0.028, uncorrected, Figure 3).

Finally, we calculated the correlations between temporal properties of CAP maps and HAMD scores for the participants with MDD. However, no significant associations between temporal properties of CAP maps and HAMD scores were observed in the principal data set.

3.3 Spatial expression of the overall dominant CAP maps

In addition, we further investigated spatial expression of the overall dominant CAP maps to select the most reproducible pattern of CAP maps. Specifically, the overall dominant CAP, which is the CAP of the maximum temporal fractions, is able to reflect

the most repeated spatial pattern dominating the brain repertoire [30]. Figure 6 depicts the spatial expression of the overall dominant CAP maps within distinct resting-state networks. Apparently, their overall dominant CAP maps within resting-state networks are similar (Figure 6C).

3.4 Reproducible test

In the replication data set, we also used the GICA analyses to obtain twenty-seven independent components. Similarly, the spatial patterns of these networks are shown in Supplementary Figure 1B. The coordinates of the peak seed locations (left cuneus (MNI coordinates: 0, -72, 33), left anterior cingulum (MNI coordinates: -3, 27, 27), left middle frontal gyrus (MNI coordinates: -39, 27, 39) and right middle frontal gyrus (MNI coordinates: 39, 27, 39)) for the three resting-state networks are also shown in the figure 1B. More details are available in supplementary materials (Supplementary Table 2).

To test the reproducibility of findings from the principal data set, we further repeated the spontaneous co-activation pattern analysis on the replication data set. Similar observations of the number of clusters were observed in the replication data set: the DMN pattern was decomposed into 2 DMN-CAP maps in patients with MDD, while the DMN pattern of healthy controls was decomposed into 3 CAP maps (permutation testing using 1,0000 permutations, $p<0.0001$, Supplementary Figure 4B); the SN pattern was decomposed into 3 SN-CAP maps in patients with MDD, while the SN

pattern of healthy controls was decomposed into 2 CAP maps (permutation testing using 1,0000 permutations, $p<0.0001$, Supplementary Figure 5B); the LCCN pattern was decomposed into 2 LCCN-CAP maps in patients with MDD, while the LCCN pattern of healthy controls was decomposed into 3 CAP maps (permutation testing using 1,0000 permutations, $p<0.05$, Supplementary Figure 6B) and the RCCN pattern was decomposed into 2 RCCN-CAP maps in patients with MDD, while the RCCN pattern of healthy controls was decomposed into 2 CAP maps (permutation testing using 1,0000 permutations, $p<0.05$, Supplementary Figure 7B). These results further supported our main findings: MDDs are characterized by enhanced number of clusters within SN and attenuated number of clusters within DMN and RCCN.

In addition, similar findings were observed in the results of occurrence rate and within-cluster similarity, DMN-CAP was detected to occur more frequently in healthy controls compared to patients with MDD ($p<0.0001$, uncorrected, Supplementary Figure 4C) and SN-CAP was observed to occur more frequently in MDD subjects ($p<0.0001$, uncorrected, Supplementary Figure 5C). However, results that significantly reduced within-cluster similarity of the DMN was observed in patients with MDD in the principal data set ($p=0.0079$, uncorrected, Supplementary Figure 4C), were missing from the replication data set. Moreover, increased transitions of CAP maps ($p<0.0001$, uncorrected, Supplementary Figure 5B) within SN in patients with MDD were also observed in the replication data set. **For analysis with the pooled MDD and HC sample, decreased persistence of CAP 3 within DMN in the patients with MDD**

compared with healthy controls were observed in the replication data set (p=0.0294, uncorrected, Figure 3). We also analyzed the spatial expressions of the overall dominant CAP maps within different resting-state networks in both groups. Similar spatial expressions of the overall dominant CAP maps of three networks were detected in the replication data set (Figure 8).

Moreover, correlation analysis showed that longer persistence of CAP 1 within RCCN was related with decreased HAMD scores (r = -0.31, p = 0.04, Figure 9) in the replication data set. In addition, the association between higher frequency of transitions of CAP 2 within RCCN and enhanced HAMD scores was significant (r = 0.32, p = 0.04, Figure 9) in the replication data set.

4. Discussion

In this study, we investigated how temporal expressions of spatial modes were altered in patients with MDD through the CAPs analysis. We found reduced number of CAPs, of the DMN and CCN in subjects with MDD, which suggested reduced variability in dynamic configuration of these two networks. In addition, the number of transitions between different CAPs was also significantly decreased in the patients, indicating reduced flexibility of the DMN and CCN in the patients. However, the variability and flexibility of brain dynamics of another core brain network (the SN) was increased in the patients, suggesting enhanced spatial complexity of intrinsic fluctuations. More importantly, with another independent data set, we showed that our

results were robust and reproducible.

The number of CAPs reflects the spatial complexity of temporal changes in resting-state intrinsic functional networks. Our findings of reduced number of CAP maps within DMN and CCN in patients with MDD suggested reduced variability in dynamic configuration of these two networks. These findings are in line with previous studies using sliding-window approach that have reported reduced dynamic functional connectivity among PFC subregions [39], or between the CCN and DMN [40], or reduced variability in dynamic functional network connectivity between the DMN and right CEN (rCEN) in patients with MDD [23]. Using a data-driven approach, our study further confirmed that variability of the DMN and CCN was disrupted in patients with MDD as reflected by decreased number of recurring coactivation maps. More importantly, our reproducible test with another independent data set showed that reduced number of CAPs may serve as a robust neuroimaging biomarker in the patients.

Distinct CAP maps correspond to distinct spatial coactivation patterns which are reflective of synchronization of fMRI signals [28]. **The CAPs mode of the DMN that recurred most frequently in patients with MDD was the principal CAP map which showed more prominent activation in mPFC than other DMN-CAPs.** This CAP had the maximum temporal fractions of 83.98%, reflecting the most repeated spatial pattern dominating the brain repertoire [30]. **When re-performing the CAP analyses with the pooled HC and MDD samples, we observed similar results. The patients appeared**

to mainly stay in a CAP state with prominent activity of the mPFC while the controls showed longer persistence of another CAP state with prominent activity of the parietal cortex. These findings were in line with previous studies including our own that have reported increased activity or functional connectivity of the mPFC in patients with depression.

The mPFC is a core region of the anterior subnetwork of the DMN. This region has been shown to be associated with social cognition involving the monitoring of one's own psychological states, and mentalizing about the psychological states of others [41, 42]. Thus more prominent mPFC activation and prolonged expression of **the principal CAP map** in MDD subjects may account for maladaptive rumination- the process of repetitively and passively thinking about one's negative feelings, possible causes, and consequences in the patients [43, 44]. **As a matter of fact, recent studies have started to directly investigate association between the temporal patterns of brain activity and depressive symptomatology in patients with MDD. Goodman and co-authors found that increased depressive symptoms were correlated with enhanced frequency and dwell time of the DMN** [50]**. In addition, another study reported that elevated dynamic functional connectivity between regions of the DMN and LCCN was associated with more severe symptomatology in depressed patients** [33]**. In the current study, we observed that persistence and frequency of transitions within RCCN which was generally involved in cognition control was correlated with the severity of depression. These findings suggested that investigation of**

dynamic properties of CAP states may provide useful information for our understanding of the symptomatology in depressed patients.

In addition to reduced number of CAPs, we also observed fewer transitions between these CAP modes in the patients, suggesting reduced flexibility of the DMN in MDD subjects. Transitions between CAPs are reflective of transitions between different brain states. Thus, our results suggested that the brain of the patients tend to stay longer of recurred more frequently in a brain state with prominent mPFC activation, and less frequently switched to other brain states. Considering that the mPFC is generally associated self-focus, fewer switching between **the principal CAP map** and other CAPs may result in the risk of deficits in the patients' ability to distinguish between the internal world and external environment [45, 46].

When the CAP analyses were performed separately within the HC or MDD group, we observed different numbers of CAP patterns in the patients and controls. Specifically, increased number of CAP patterns within the SN was found in the patients. Interestingly, when we re-analyzed the data with the pooled HC and MDD samples and obtained the same number of CAP states in both groups, we found significantly increased number of state transitions in the patients. Thus, the analyses separately performed on different subject group and with pooled data consistently suggested enhanced spatial-temporal complexity of intrinsic fluctuations of the SN in the MDD patients.

Limitations

There are some limitations in this work. In the current study, we were interested in three intrinsic brain networks that have consistently been reported to be involved in MDD. Our study demonstrated deficits in brain dynamics of the DMN, SN and CCN. In future studies, we would extend our analysis to other resting-state brain networks such as the attention network, the motor network, and the visual network, etc. Recent studies showed that the functions supported by these networks were also damped in patients with MDD as well [51–53]. However, it is not clear whether brain coactivation patterns would also be impaired in the patients. In addition, the subject in the current study were adults between the ages of 18 and 61. Although the results are robust in another independent data set, whether our findings are also reproducible in adolescent with MDD or patients with late onset MDD remains unknown. Our future work will further test the consistency of our findings in different age groups. **Finally, we collected the data with traditional rs-fMRI acquisition which could only provide lower temporal resolution of images and limited quality of evaluations of brain dynamics, advanced multiband multi-echo imaging acquisition will be adopted in our future studies to improve the robustness and repeatability of CAP method** [54]**.**

Conclusions

In conclusion, these results suggest abnormally temporal and spatial changes of functional networks that standard (stationary) functional connectivity could miss;

functional connectivity in the patients may not simply attenuated or potentiated, but just alternating faster or slower among more complex patterns. An abrupt switch of brain patterns may lead to significant considerable variations of standard functional connectivity, which may be a crucial reason for the contradictory results reported in previous studies. The aberrant spatial complexity of intrinsic fluctuations reflects functional diaschisis of resting-state networks as characteristic of patients with MDD.

Declarations

Ethics approval and consent to participants

This study was approved by the Ethics Committee in Zhumadian Psychiatric Hospital and Xi-jing Hospital. All subjects gave informed consent before participating in this study.

Consent for publication

Last version of the manuscript was approved by the authors before the submission.

Availability of data and code

The data that support the findings of this study as well as code used during the current study are available from the corresponding author upon reasonable request.

Competing Interests

All authors declare that they have no competing interests.

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Author's contributions

All authors contributed to the study conception and design. Data collection was performed by the prof. Lingjiang Li and Dr. Kaizhong Zheng. The first draft of the manuscript was written by Dr. Kaizhong Zheng and Prof. Baojuan Li. All authors commented on previous versions of the manuscript. Dr. Kaizhong Zheng, Prof. Badong Chen and Prof. Dewen Hu reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

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Not applicable.

Compliance with Ethical Standards

Not applicable.

Research involving Human Participants and/or Animals

Human and human samples were used in the current study.

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Tables and Figures Legends

Table 1. Demographic and Clinical Characteristics of the participants.

	Principal Data Set			***Replication Data Set***		
	MDD (n=158)	HC (n=102)	P value	MDD (n=43)	HC (n=56)	P value
Age (years)	36.1 (10.0)	32.5 (8.3)	0.003[a]	35.2 (11.2)	32.3 (10.8)	0.19[a]
Age range(years)	18-58	18-50	—	17-61	20-61	—
Gender	(68M/90F)	(58M/44F)	0.0315[b]	(13M/30F)	(30M/26F)	0.02[b]
Education (years)	10.1 (3.3)	11.7 (3.5)	<0.01[a]	11.4 (3.3)	15.8 (4.3)	<0.01[a]
Handedness	(158R/0L)	(102R/0L)	0[b]	(43R/0L)	(56R/0L)	0[b]
HAMD	**31.4 (7.3)**	—	—	**23.4 (3.3)**	—	—
HAMD range	**19-50**	—	—	**18-32**	—	—

Notes: Demographic information for each variable is expressed as mean (standard deviation) or count. MDD: Major depressive disorder; HC: Healthy controls; F, female; M, male; R, right handedness; L, left handedness.

[a] represents P values for two sample t-test and [b] represents P values for $\chi 2$ test.

Figure 1 Workflow for spontaneous co-activation patterns (CAPs) analysis using the default

mode network (DMN) as an example. A, A 6mm-sphere region of interest (ROI) centered on the peak seed locations (left cuneus (MNI coordinates: 0, -72, 33)) for the DMN was specified. B, Time points (fMRI frames) in the time course of posterior cingulate cortex (PCC) in DMN were selected when their BOLD signals were greater than a preset threshold. The spatial correlation (Pearson's correlation coefficient) between the average of the selected time frames and DMN templates using all time frames increases quickly when including more frames by lowering the threshold. C, Data distribution of patients with MDD in the principal data set using the principal component analysis (PCA). The data was reshaped to a two-dimensional matrix. Then the two-dimensional matrix was descended dimensions using PCA. The first three eigenvectors were selected and displayed. D, the extracted fMRI frames were further classified into 5 groups using the spectral clustering method. Next, the DMN-CAP of each group was generated by averaging all subjects within groups. E, the workflow for extracting the overall dominant CAP maps using DMN-CAPs.

Figure 2 Results of spontaneous co-activation pattern analysis within DMN using the pooled MDD and HC sample in both datasets.

Figure 3 Results of spontaneous co-activation pattern analysis within SN using the pooled MDD and HC sample in both datasets.

Figure 4 Results of spontaneous co-activation pattern analysis within LCCN using the pooled

MDD and HC sample in both datasets.

Figure 5 Results of spontaneous co-activation pattern analysis within RCCN using the pooled MDD and HC sample in both datasets.

Figure 6 Results of spontaneous co-activation pattern analysis within DMN in both groups (The principal data set). A, the optimal threshold of DMN was 12.9%. B, The DMN pattern was decomposed into 2 DMN-CAP maps in patients with MDD, while that of healthy controls was decomposed into 4 DMN-CAP maps. C, significantly attenuated occurrence rate of distinct CAP maps and number of transitions of CAP maps were detected in patients; *** $P< 0.001$.

Figure 7 Results of spontaneous co-activation pattern analysis within SN in both groups (The principal data set). A, the optimal threshold of SN was 7.6%. B, The SN pattern was decomposed into 9 SN-CAP maps in patients with MDD, while that of healthy controls was decomposed into 2 SN-CAP maps. C, significantly enhanced occurrence rate of distinct CAP maps and number of transitions of CAP maps were detected in patients; *** $P< 0.001$.

Figure 8 Spatial expression of distinct overall dominant CAP maps of A, DMN, B, SN, C, LCCN and D, RCCN in both groups (The principal data set and the replication dataset).

Figure 9 Correlation between clinical scores on the depression and temporal properties of CAP maps in the replication data set.