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Research article

Aberrant topographical organization of the default mode network underlying the cognitive impairment of remitted late-onset depression

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HIGHLIGHTS

- rLOD patients showed decreased FC of DMN.
- Patients' DMN showed abnormal small-world properties.
- Abnormal small-world properties significantly correlated with the episodic memory.

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ABSTRACT

To investigate the alteration of resting-state functional connectivity (FC) and topological organization of the default mode network (DMN), and their contribution to the cognitive impairment in remitted late-onset depression (rLOD) patients. Thirty-three rLOD patients and thirty-one healthy controls underwent clinical and cognitive evaluations as well as resting-state functional magnetic resonance imaging (R-fMRI) scans. The FC networks were constructed by thresholding Pearson correlation metrics of the DMN regions, and their topological properties were analyzed using graph theory-based approaches. Nonparametric permutation tests were further used for group comparisons of topological metrics. Finally, multiple linear regression analyses were performed to examine the relationships between the network measures and cognitive performances. Patients displayed universally decreased FC of DMN and abnormal global topology of the DMN (i.e., increased characteristic path length L_p and reduced global efficiency E_{glob}) compared with healthy controls. According to the distance-dependent FC results, the long-distance connections were mainly involved in the connectivity between anterior and posterior hubs, and the short-distance connections were primarily located in the frontal lobe. There were significant correlations between the global topology and the episodic memory performance in rLOD patients. In conclusion, the present study indicated that the disrupted topological organization of the DMN might be considered as a potential biomarker of the episodic memory deficits in rLOD patients.

1. Introduction

Substantial evidence suggests that late-onset depression (LOD) is both a risk factor and a prodrome of dementia, approximately doubling the risk of subsequent Alzheimer's disease (AD) [1,2]. Moreover, remitted LOD (rLOD) displayed a great majority of commonalities in the topological patterns of white matter structural networks with amnestic mild cognitive impairment (aMCI) which is a primary prodromal syndrome of AD [3]. Importantly, residual cognitive impairments in rLOD probably contribute much to the progress to AD [4,5]. Therefore, it is necessary to get to the bottom of the pathophysiology underlying the cognitive impairments in rLOD.

Converging findings from previous neuroimaging studies have suggested the default mode network (DMN) as a potentially useful biomarker for major depressive disorder [6–8]. The DMN is a large-scale network that encompasses a specific set of brain regions, including posterior cingulate cortex/precuneus (PCC/Pcu), medial prefrontal cortex, and medial, lateral, and inferior parietal regions,

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which indeed demonstrate a consistent pattern of deactivation during the initiation of task-related activity [9]. This network is suggested to mediate internally generated thought process, episodic memory [10], and attention [11]. Therefore, the DMN is considered as an important candidate network which may take part in the cognitive modulating. Investigations of DMN properties are typically conducted during resting state to avoid cofounds from task-related effort and performance. Our previous work has discovered a certain association between resting state functional connectivity (FC) of the DMN and cognitive impairments in rLOD [12]. However, the changes of resting-state DMN FC reported from the previous studies as well as ours were quite discrepant. While a wide array of studies have reported increased neural activity and FC of the DMN [6,8,13,14], others also showed decreased FC of the DMN [15]. Moreover, a recent study found increased FC in the anterior DMN but reduced FC in the posterior aspects of the DMN in major depression [7]. The observed heterogeneity, possibly attributing to different neural underpinnings of various subtypes of depression, also indicates that the DMN changes in depression may present in a complex way, not in a pure increased or decreased model [16,17]. Mounting evidence has attested small-world properties is an efficient hallmark of the whole-brain as well as sub-brain functional networks [18]. Previous publications have suggested that brain disorders are associated with an altered topological architecture of a disrupted network of brain regions. For instance, patients with rLOD showed a disrupted topological organization in a large-scale brain network [3]. The dysfunctional topological organization of the brain network probably results from the damaged FC and has a more consistent performance in a specific disease than FC.

According to our accumulated findings [12,19,20], in the current study, we focused exclusively on both FC and topological organization of the DMN in rLOD and hypothesized that the cognitive impairment in rLOD might be ascribed to the disrupted topological configuration which probably resulted from the decreased resting-state FC of the DMN.

2. Materials and methods

2.1. Participants

Thirty-three rLOD patients and thirty-one healthy controls (HCs) were recruited in the present study. Patients were recruited from Affiliated Brain Hospital of Nanjing Medical University. HCs were recruited through community health screening. All rLOD patients met the following inclusion criteria: (1) they had previously met the major depression disorder in DSM-IV criteria and remitted for more than 6 months before the enrollment; (2) the age of first depressive onset was over 60 years; (3) Hamilton Depression Rating Scale (HDRS) scores were lower than 7, and Mini-Mental State Examination (MMSE) scores were higher than 24; (4) duration of illness must be less than 5 years and a medication-free period for all patients was longer than 3 months prior to the assessment; (5) absence of other major psychiatric disorder, including hidden abuse or dependence of psychoactive substances; (6) absence of serious physical ailments, primary neurological illness, organic brain disease (e.g. former stroke, cerebral vascular malformations, or epilepsy), and former brain injury; (7) absence of dementia based on semi-structured interview with the patient according to DSM-IV; (8) no history of electroconvulsive therapy; (9) no gross structural abnormalities on T1-weight images, and no major white matter changes such as infarction or other vascular lesions on T2-weight MRI. All participants were aware of the purpose of the study before participating in this study and signed an informed consent form approved by the Ethics Committee of ZhongDa Hospital Affiliated to Southeast University.

2.2. Neuropsychological tests

All participants were administered a battery of neuropsychological tests that covered multiple cognitive domains such as episodic memory, working memory, visuospatial, perceptual speed and executive, including the Auditory Verbal Learning Test–20 min delayed recall (AVLT-DR), Rey-Osterrieth Complex Figure Test (CFT) and its 20min-delayed recall (CFT-DR), Clock Drawing Test (CDT), Trail-Making Tests A and B (TMT-A and TMT-B), Digit Span Test (DST) and Symbol Digit Modalities Test (SDMT).

2.3. Image acquisition

All participants were scanned using a 1.5-T MRI scanner (General Electric Medical Systems, USA) with a standard head coil. During the scanning, participants were instructed to lie still with their eyes closed and not to fall asleep. Functional images were obtained axially using a single-shot, gradient-recalled echo-planar imaging sequence parallel to the line of the anterior-posterior commissure. The following parameters were applied for functional imaging: 142 whole-brain volumes; repetition time = 3000 ms; echo time = 40 ms; flip angle = 90°; acquisition matrix = 64 × 64; field of view = 240 mm × 240 mm; thickness = 4.0 mm, without gap. High-resolution 3-dimensional T1-weighted MRIs were acquired using a high-resolution spoiled gradient-recalled echo 3D axial images (repetition time (TR)/echo time (TE) = 2530 ms/3.34 ms; flip angle (FA) = 7°; acquisition matrix = 512 × 512; field of view (FOV) = 256 × 256 mm^2; thickness = 1.33 mm).

2.4. Image preprocessing

All imaging preprocessing steps were conducted using Data Processing Assistant for Resting-State fMRI (DPARSF, http://www.restfmri.net/forum/dparsf). The first ten volumes were discarded for scanner stabilization and participants adaption to the scanning noise. The remaining images were corrected for acquisition delay between slices and for head motion. Participants should have no more than 3 mm maximum displacement in *x*, *y*, or *z* or and 3° of angular motion during the scan acquisition. Subsequently, the resulting images were spatially normalized into the Montreal Neurological Institute (MNI) echo-planar imaging template and resampled to 3 × 3 × 3 mm^3. Following this, temporal filtering (0.01 Hz < f < 0.08 Hz) was applied to the time series of each voxel to reduce the effect of low-frequency drifts and high-frequency noise. Any linear trend was then removed. Finally, the nuisance signals involving six head motion parameters, global mean signal, cerebrospinal fluid signal, and white matter signal were regressed out from the data.

2.5. Network construction

A whole-brain parcellation scheme was recently created based on a large meta-analysis of fMRI studies combined with the whole brain FC mapping [21]. This set of 264 putative functional regions was shown to more accurately represent the information present in the network (i.e., it was better at detecting previously characterized functional networks such as dorsal and ventral attention subnetworks, and DMN) relative to voxel-wise and atlas-based parcellation approaches. Therefore, in the present study, we focused on the DMN and chose a set of 58 regions of interest (ROIs) for DMN parcellation. The subgraph (i.e., DMN) derived using these ROIs show substantial agreement with task-dependent functional neural system defined previously [21]. For each subject, we then computed Pearson correlation coefficients between the mean time courses of all possible pairs of 58 ROIs, yielding a 58 × 58 correlation matrix.