Neurosci Bull February 1, 2015, 31(1): 13–21. http://www.neurosci.cn
DOI: 10.1007/s12264-014-1489-1

·Original Article·

Altered functional connectivity networks of hippocampal subregions in remitted late-onset depression: a longitudinal resting-state study

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ABSTRACT

The regional specificity of hippocampal abnormalities in late-life depression (LLD) has been demonstrated in previous studies. In this study, we sought to examine the functional connectivity (FC) patterns of hippocampal subregions in remitted late-onset depression (rLOD), a special subtype of LLD. Fourteen rLOD patients and 18 healthy controls underwent clinical and cognitive evaluations as well as resting-state functional magnetic resonance imaging scans at baseline and at ~21 months of follow-up. Each hippocampus was divided into three parts, the cornu ammonis (CA), the dentate gyrus, and the subicular complex, and then six seed-based hippocampal subregional networks were established. Longitudinal changes of the six networks over time were directly compared between the rLOD and control groups. From baseline to follow-up, the rLOD group showed a greater decline in connectivity of the left CA to the bilateral posterior cingulate cortex/precuneus (PCC/PCUN), but showed increased connectivity of the right hippocampal subregional networks with the frontal cortex (bilateral medial prefrontal cortex/anterior cingulate cortex and supplementary motor area). Further correlative analyses revealed that the longitudinal changes in FC between the left CA and PCC/PCUN were positively correlated with longitudinal changes in the Symbol Digit Modalities Test (r = 0.624, P = 0.017) and the Digit Span Test (r = 0.545, P = 0.044) scores in the rLOD group. These results may provide insights into the neurobiological mechanism underlying the cognitive dysfunction in rLOD patients.

Keywords: remitted late-onset depression; hippocampal subregional network; functional connectivity; functional magnetic resonance imaging; cognitive dysfunction

INTRODUCTION

Depression remains to be a health-care risk factor for older adults and a major cause of disability[1]. A subset of elderly depression, late-onset depression (LOD), of which the first episode occurs later in life (usually after 60 years of age), exhibits certain unique clinical features; thus, LOD patients are more likely to have associated medical comorbidity, greater cognitive deficits, and an increased risk of dementia conversion compared with groups with early-onset depression[2]. LOD patients show cognitive deficits mainly in the processing speed and executive domains[3]. This cognitive impairment can persist even after the remission of

affective symptoms[4]. However, the mechanism underlying the persistent cognitive impairment in remitted LOD (rLOD) patients is still unclear.

The hippocampus is a critical neuronal substrate for memory and emotion processing. Altered hippocampal morphology plays an important role in the pathophysiology of elderly depression. Structural studies have reported decreased hippocampal volume in patients with elderly depression relative to healthy volunteers[5-8]. Moreover, hippocampal atrophy is associated with reduced cognitive performance in LOD patients[8]. Importantly, the hippocampus, as a heterogeneous area, can be parcellated into several subregions including the cornu ammonis (CA), the dentate gyrus (DG), and the subicular complex (SUB)[9]. Recent neuroimaging findings have indicated that these hippocampal subregions are differentially influenced in depression[2, 10-12]. For instance, Cole *et al.*[12] demonstrated significant deformations of the subiculum and CA1 subfield extending into the CA2–3 subfields in patients with major depression. Similarly, Ballmaier *et al.*[2] observed notable atrophy of the bilateral anterior CA1–CA3 subfields and the subiculum in LOD patients. Therefore, these findings support the hypothesis that the cognitive deficits of LOD patients may be associated with regionally specific hippocampal abnormalities. However, it remains unclear how the functional coupling of hippocampal subregions changes in LOD, especially when the affective symptoms are relieved.

Resting-state functional connectivity MRI (R-fMRI) is a promising tool for investigating the intrinsic functional connections among anatomically distinct brain regions within specific networks[13]. The intrinsic hippocampal functional connectivity (FC) networks have been identified using the R-fMRI method under normal and pathological conditions, including Alzheimer's disease (AD)[14-16] and amnestic mild cognitive impairment[14, 17]. Specifically, a recent R-fMRI study from our lab reported impaired hippocampal FC networks in rLOD[18]. Importantly, the extent of network alterations was linked to inferior cognitive performance in rLOD patients. Furthermore, depressive symptoms and cognitive dysfunction have interactive effects on the hippocampal FC networks[19]. These cross-sectional studies suggest that aberrant hippocampal FC networks might contribute to cognitive impairment in LOD patients even when the depressive symptoms have remitted. However, it is still unknown whether these aberrant networks can predict the progression of rLOD. Therefore, it is important to measure the longitudinal changes in intrinsic FC patterns of the hippocampal subregions in rLOD and to investigate their association with cognitive changes, considering the hippocampal heterogeneity and its association with LOD neuropathology.

Together, in this study, we first identified the FC patterns of the hippocampal subregions in rLOD patients and healthy controls using the R-fMRI approach. Then, longitudinal changes of the hippocampal subregional networks were compared between rLOD patients and healthy controls. Finally, we investigated whether longitudinal changes of the hippocampal subregional networks are associated with cognitive deficits in rLOD patients.

PARTICIPANTS AND METHODS

Participants

Nineteen rLOD patients and nineteen healthy controls were recruited from the Affiliated Brain Hospital of Nanjing Medical University, China. All rLOD patients met the following inclusion criteria: (1) they had previously met the criteria for major depressive disorder in DSM-IV and had remitted for > 6 months before enrollment; (2) the age at first depression onset was > 60 years; (3) Hamilton Depression Rating Scale scores < 7, and Mini-Mental State Examination (MMSE) scores > 24; (4) duration of illness < 5 years and a medication-free period > 3 months prior to the assessment; (5) absence of other major psychiatric disorders, including abuse of or dependence on psychoactive substances; (6) absence of primary neurological disorders, including dementia or stroke; (7) absence of a medical illness that impairs cognitive function; (8) no history of electroconvulsive therapy; and (9) no gross structural abnormalities on T1-weighted images, and no major white matter changes such as infarction or other vascular lesions on T2-weighted MRI. This study was approved by the Research Ethics Committee of the Affiliated ZhongDa Hospital of Southeast University and written informed consent was given by all participants. All participants completed a battery of neuropsychological tests that covered multiple cognitive domains, including the auditory verbal memory test-delayed recall (AVLT-DR),

trail-making tests A and B (TMT-A and B), the symbol digit modalities test (SDMT), and the digit span test (DST).

The follow-up study was performed at an average of 21 months (12–32 months) after baseline. During the follow-up period, 5 patients relapsed with an episode of depression/mania. One healthy control was excluded due to excessive motion artifacts. Hence, 14 rLOD patients and 18 healthy controls underwent baseline and follow-up MRI scans, and the two groups were matched for the follow-up period. In addition, the follow-up neuropsychological tests and MRI scan parameters were identical to those conducted at baseline.

Magnetic Resonance Imaging Data Acquisition

The participants were scanned by a General Electric 1.5 Tesla scanner (General Electric Medical Systems, Milwaukee, Wisconsin) with a homogeneous birdcage head coil. Axial R-fMRI data (no cognitive tasks were performed, eyes were closed, and ears were occluded) were obtained with a single-shot gradient-recalled echo-planar imaging sequence: TR = 3000 ms; TE = 40 ms; FA = 90°; acquisition matrix = 64 × 64; FOV = 240 mm × 240 mm; thickness = 4.0 mm; gap = 0 mm; and 3.75 mm × 3.75 mm in-plane resolution. The R-fMRI scan lasted 7 min and 6 s.

Functional Image Preprocessing

R-fMRI data analysis was carried out using the Statistical Parametric Mapping software (SPM8, www.fil.ion.ucl.ac.uk/spm). The first ten volumes were discarded and the remaining images were corrected for timing differences and motion effects. Participants with head motion > 3 mm maximum displacement in the *x*, *y*, or *z* direction or 3° of angular motion were excluded. The resulting images (both baseline and follow-up data) were spatially normalized into a standard stereotaxic space using a 12-parameter affine approach and an echo-planar imaging template, and then resampled to 3 × 3 × 3 mm^3 voxels. The obtained images were smoothed with a Gaussian kernel of 8 mm × 8 mm × 8 mm. Further preprocessing included linear de-trending and temporal band-pass filtering (0.01–0.08 Hz), which were used to reduce the effects of low-frequency drift and high-frequency physiological noise. Finally, several nuisance variables, including six head-motion parameters, global mean signal, white matter signal, and cerebrospinal fluid signal were regressed out from the data.

Functional Connectivity Analyses

The six hippocampal subregions (bilateral CA, DG, and SUB; Fig. 1)[20] were defined using the Anatomy Toolbox in SPM. Basically, the Anatomy Toolbox provides a maximum

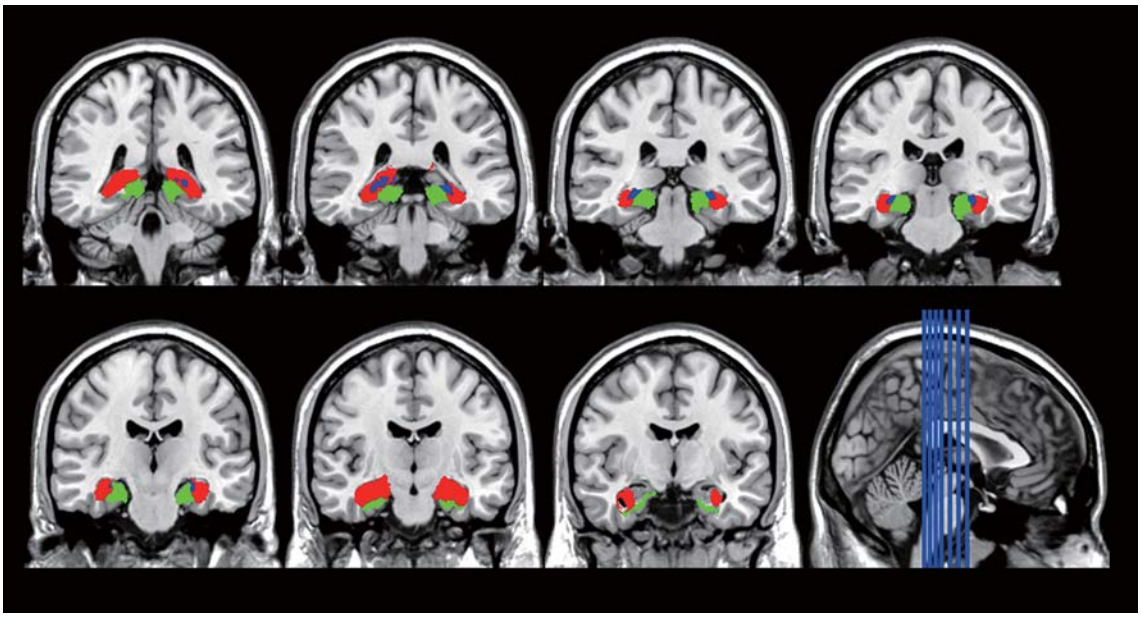

Fig. 1. Locations of hippocampal subregions. Red: CA (CA1-CA3); Blue: DG (fascia dentata and CA4); Green: SUB.

probabilistic map of each hippocampal subregion[21, 22]. This is a summary map of the hippocampal subregions that attributes each voxel to the most likely subregion with no less than 40% likelihood of cytoarchitectonic probability[21]. Then, the whole-brain FC maps for each subregion were computed as the Pearson correlation coefficients between the mean time course in the subregion and the time-course of every voxel of the whole brain. Fisher's *z*-transform was further applied to improve the normality of the correlation coefficients[23]. These analyses were performed using the Resting State fMRI Data Analysis Toolkit (REST) software (available at: http: //www.restingfmri.sourceforge. net).

Group-Level Analysis

Within-group: To determine the FC patterns of the hippocampal subregions in each of the four groups (baseline rLOD and healthy control groups and their follow-up), the FC maps were gathered in each group separately for random effect analysis using the one-sample *t*-test, corrected by the AlphaSim program based on Monte Carlo simulation (α = 0.05, single-voxel *P* value = 0.01, FWHM = 8 mm, with grey matter mask). To avoid potential interpretational confounds related to apparently negative connectivity resulting from correction for global signal changes[24], only positive functional connectivity was examined. Further, for each hippocampal subregion, we added the within-group FC patterns of the four groups together to produce a mask for between-group comparisons.

Between-groups: To determine whether the longitudinal changes in the FC strength of hippocampal subregions were significantly different between rLOD patients and healthy controls, a direct comparison between the change estimates (the FC maps at follow-up subtracted from those at baseline) between the rLOD group and the control group was conducted (networks of CA, DG, and SUB were performed separately). Multiple comparisons were corrected by the AlphaSim program (α = 0.05, single-voxel *P* value = 0.01, FWHM = 8 mm, with mask). These group-level analyses were performed using the REST software.

Statistical Analysis

One-way analysis of variance (ANOVA) was used to compare the neuropsychological performance among groups with statistical significance of $P < 0.05$. *Post-hoc* tests by Bonferroni correction were used to reveal the source of ANOVA difference. Further correlative analysis between R-fMRI data and neuropsychological performance was performed. First, the mean FC strengths of the clusters showing significant between-group differences were extracted for rLOD patients. Then, Pearson's correlation analysis between the extracted FC strength and neuropsychological performance was performed to investigate the cognitive significance of the altered FC strength in the rLOD group.

RESULTS

Sample Description

The demographic and neuropsychological characteristics for each group are shown in Table 1. The four groups did not differ significantly in terms of age, years of education, gender, and MMSE score (all $P > 0.05$).

Neuropsychological Data

Significant differences among the four groups were found in the scores on AVLT-DR, TMT-A, TMT-B, and DST (Table 1). *Post-hoc* tests further revealed that the rLOD patients had poorer performance in AVLT-DR, TMT-A, and DST than healthy controls at baseline. At follow-up, the performance in AVLT-DR and DST by rLOD patients was still worse than that by healthy controls. Moreover, from baseline to follow-up, the performance in TMT-A and -B improved significantly in the rLOD patients.

Functional Connectivity Patterns of Hippocampal Subregions

Each hippocampal subregional network involved diffuse subcortical, medial frontal, temporal, parietal, and cerebellar regions in both the control and rLOD groups at baseline and follow-up ($P < 0.05$, AlphaSim-corrected, Fig. 2). These FC patterns are similar to those in previous studies using the whole hippocampus as the seed region[14-16]. However, at both baseline and follow-up, nearly all hippocampal subregional seeds showed significantly stronger and more diffuse FC with regions typically located in the parietal cortex in the control group (Fig. 2); these parietal regions showed weaker FC with hippocampal subregions in the rLOD group. Further, in the rLOD group from baseline to follow-up, nearly all hippocampal subregions showed

Table 1. Demographic and neuropsychological data for all participants (mean ± SD)

	Baseline		Follow-up		F or χ^2	P^*
	rLOD (n = 14)	HC (n = 18)	rLOD (n = 14)	HC (n = 18)		
Age (years)	67.6 ± 4.0	71.4 ± 3.8	69.8 ± 3.9	73.2 ± 3.8	-	-
Education (years)	14.4 ± 2.1	15.2 ± 2.8	14.4 ± 2.1	15.2 ± 2.8	-	-
Gender (male/female)	7/7	10/8	7/7	10/8	-	-
Mean age at onset (years)	64.7 ± 4.1	-	64.7 ± 4.1	-	-	-
MMSE score	28.6 ± 1.9	28.3 ± 1.3	27.8 ± 4.0	28.6 ± 1.8	0.421	0.739
AVLT-DR[a,b]	5.9 ± 2.5	8.1 ± 1.9	5.0 ± 2.8	8.6 ± 2.7	7.837	0.000
TMT-A[a,c]	133.5 ± 96.7	70.0 ± 28.7	70.4 ± 25.5	75.7 ± 25.5	5.401	0.002
TMT-B[c]	237.7 ± 138.4	139.3 ± 39.2	157.7 ± 36.9	138.8 ± 55.5	5.935	0.001
SDMT	25.0 ± 15.0	34.3 ± 8.7	27.1 ± 15.8	33.2 ± 12.8	2.038	0.118
DST[a,b]	11.7 ± 2.1	13.2 ± 1.8	11.7 ± 2.1	13.6 ± 2.6	3.704	0.016

**P* values were obtained by one-way analysis of variance (ANOVA) analysis.

[a]*P* <0.05, baseline rLOD *vs* baseline HC; [b]*P* <0.05, follow-up rLOD *vs* follow-up HC; [c]*P* <0.05, baseline rLOD *vs* follow-up rLOD.

AVLT-DR, Auditory Verbal Learning Test-delayed Recall; DST, Digit Span Test; HC, healthy controls; MMSE, Mini Mental State Exam; rLOD, remitted late-onset depression; SDMT, Symbol Digit Modalities Test; TMT-A, Trail-making Test A; TMT-B, Trail-making Test B.

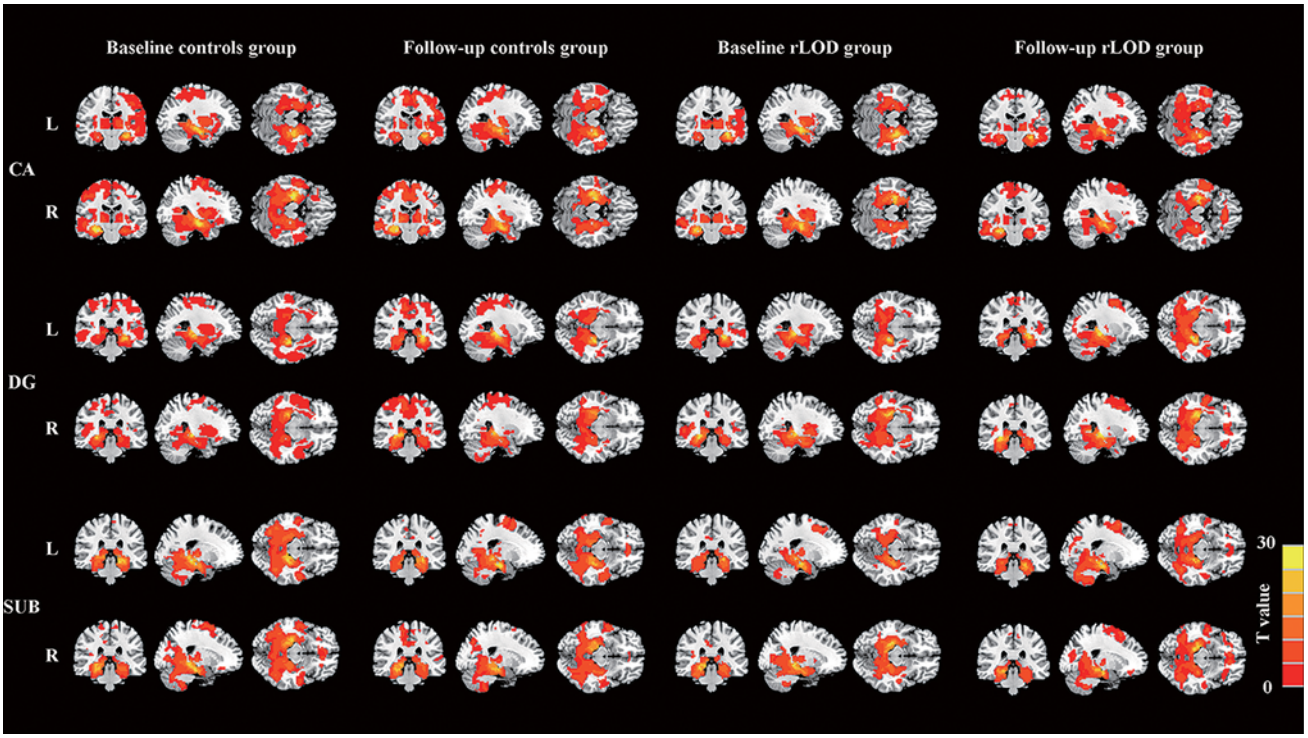

Fig. 2. Resting-state functional connectivity maps of the hippocampal subregions. Thresholds were set at *P* <0.05, corrected by Monte Carlo simulation.

stronger FC with regions mainly located in the frontal cortex.

Between-Group Differences in the Longitudinal Changes of Hippocampal Subregional Networks

With regard to the left hippocampal subregional networks, the rLOD group showed greater longitudinal deficits in the left CA network integrity, including connections with the bilateral posterior cingulate gyrus/precuneus (PCC/PCUN), compared with the control group (Fig. 3A). However, longitudinal changes in the left DG or SUB network did not show a significant between-group difference. Furthermore, within the rLOD group, longitudinal changes in the FC between the left CA and PCC/PCUN were positively correlated with the longitudinal changes in the SDMT and DST scores (Fig. 3B).

On the contrary, longitudinal changes in the right three subregional networks all showed significant differences between the rLOD and control groups. For the right three subregions (CA, DG, and SUB), the rLOD group showed greater increases in network strength, including connections with the frontal cortex (bilateral medial prefrontal cortex/anterior cingulate cortex, and supplementary motor area) compared with the control group (Fig. 3C1–3).

DISCUSSION

Using the R-fMRI approach, in this study we demonstrated altered hippocampal subregional networks during rLOD progression. From baseline to follow-up, the rLOD group showed greater decreases in the FC between the left CA and bilateral PCC/PCUN, but increased connectivity in right hippocampal subregional networks with the frontal cortex (bilateral medial frontal gyrus/anterior cingulate cortex, and supplementary motor area). Importantly, the impaired intrinsic connectivity was positively correlated with the deficits in cognitive performance within the rLOD group. These results may provide insight into the neurobiolgical

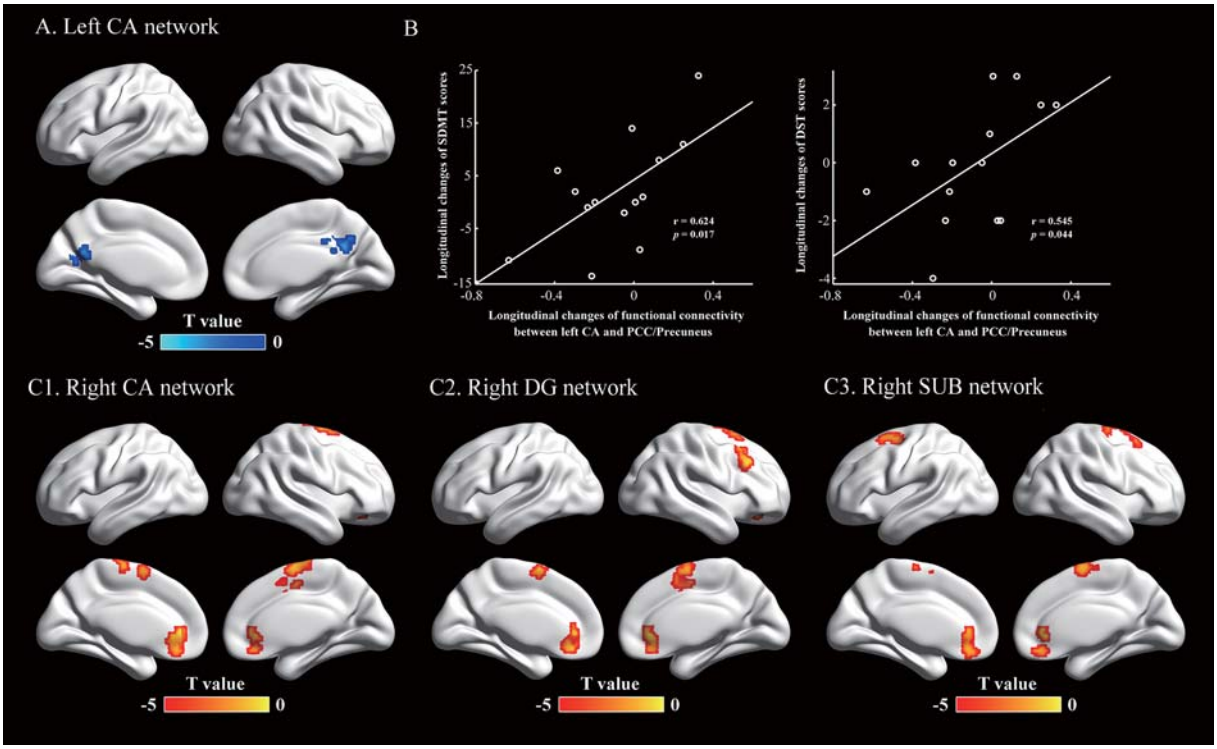

Fig. 3. Longitudinal changes in rLOD patients *versus* controls. Thresholds were set at P <0.05, AlphaSim-corrected. (A) Left CA network; (C1) right CA network; (C2) right DG network; (C3) right SUB network. (B) In the rLOD group, longitudinal changes in functional connectivity between the left CA and PCC/PCUN were significantly correlated with the longitudinal changes in the SDMT and DST scores.

mechanisms underlying the cognitive dysfunction in rLOD patients.

First, multiple domains of cognitive impairment in rLOD patients were detected at baseline. After follow-up, these patients still demonstrated significantly worse episodic memory (indicated by AVLT-DR) and attention (indicated by DST) than healthy controls. This is consistent with prior reports that remitted depression patients show persistent cognitive impairment[25, 26]. There is also supportive evidence that persistent cognitive impairment or a significantly elevated incidence of AD occurs in remitted depression patients[27], although we found that the rLOD patients showed greater improvement in executive function (indicated by TMT-A and -B) from baseline to follow-up. Furthermore, rLOD patients showed increased connectivity in the right hippocampal subregional networks from baseline to follow-up. Consistent with this finding, a previous study from our group using the same dataset observed increased right hippocampal volumes in rLOD patients from baseline to follow-up[28]; the lateralized enlarged volumes were positively correlated with increased SDMT scores. Therefore, given that antidepressant treatment may have a neuroprotective effect on the hippocampus[29-31], we speculate that the improvement in cognitive function (i.e., TMT-A and -B) and increased connectivity in the right subregional networks in rLOD patients may be, at least partly, associated with this neuroprotective effect. Further, this effect might be prolonged and so may postpone or even reverse hippocampal deterioration and its related cognitive deficits. As no rLOD patients took antidepressants during the follow-up period, future studies are essential to test this speculation.

Second, the rLOD group showed a greater decline in connectivity of the left CA to bilateral PCC/PCUN from baseline to follow-up. Previous postmortem studies have revealed complex neuronal abnormalities in distinct layers of the hippocampal subfields in depression, with the greatest changes in CA1, followed by CA2 and CA3[32]. Recent studies also reported subtle deficits in hippocampal subregions in LLD patients through shape analysis, i.e. deformations in CA (CA1–3)[12]. These data suggest that the CA subregion may be more sensitive to neuroplastic changes in depression. Furthermore, the PCC/PCUN has been considered an anatomical hub in the resting-state brain[33]. Structural and functional MRI studies have demonstrated that the PCC/PCUN is closely connected with medial temporal lobe structures (e.g. the hippocampus)[34-36]. Previous neuroimaging studies have revealed abnormalities of the PCC/PCUN in depressed patients, i.e., reduced fractional anisotropy in the PCC[37], hypoactivity in the PCUN[38], and decreased FC in the PCC/PCUN[39]. More importantly, a recent study reported that elderly patients with depression show widespread abnormalities, especially in the hippocampal cingulum tract connecting the hippocampus and the PCC/PCUN[40]. The authors also found that the abnormality of the hippocampal cingulum was associated with lower episodic memory scores. Interestingly, the greater longitudinal deficits (left CA-PCC/PCUN) were associated with greater impairment in cognitive function (indicated by SDMT and DST scores) in rLOD patients. The performances in SDMT and DST are specifically associated with activity in the medial temporal lobe as well as in frontal and parietal areas involved in associative recognition, visual-verbal memory and selective attention, and working memory[41]. Therefore, these findings suggest that altered functional coupling between the hippocampus and PCC/PCUN might be an important contributor to cognitive impairment in elderly depression, indicating their important role in the progression of connectivity disturbances in rLOD.

Third, interestingly, we found left-lateralized deficits of hippocampal subregional networks in rLOD patients. However, the mechanism is unclear. Previous studies using structural MRI have shown that decreased left hippocampal volume is significantly associated with later dementia onset among older depressed patients[42]. Therefore, it may be important to determine whether the left-lateralized deficits are associated with dementia onset, particularly in AD.

Several issues need to be further addressed. First, this longitudinal study had a relatively small sample size, so the findings cannot be considered categorical. Second, given that all patients had received various antidepressant treatments, the results could not exclude a potential medication effect. Third, magnetic resonance imaging was performed with a 1.5-Tesla scanner, which may not be suitable for subfield-level analysis. Thus, high-resolution 3T scanning would be necessary to validate our findings in future. Finally, it is necessary to validate these findings in a large cohort, as previous studies suggested only moderate test-retest reliability of R-fMRI measures.

In summary, in the present study we explored the longitudinal changes in the functional connectivity pattern of hippocampal subregions in rLOD patients, and these may have important clinical implications. Our findings suggest that the altered functional connectivity pattern of hippocampal subregional networks may be an important indicator for monitoring the progression of this disease.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (30825014, 81061120529, 30970814, 81371488, 91132727 and 30830046), and the Key Program for Clinical Medicine and Science and Technology, Jiangsu Provincial Clinical Medical Research Center, China (BL2013025).

Received date: 2014-07-05; Accepted date: 2014-11-06

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