

Abnormal functional connectivity of the posterior cingulate cortex is associated with depressive symptoms in patients with Alzheimer's disease

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Background: Depressive symptoms are significant and very common psychiatric complications in patients with Alzheimer's disease (AD), which can aggravate the decline in social function. However, changes in the functional connectivity (FC) of the brain in AD patients with depressive symptoms (D-AD) remain unclear.

Objective: To investigate whether any differences exist in the FC of the posterior cingulate cortex (PCC) between D-AD patients and non-depressed AD patients (nD-AD).

Materials and methods: We recruited 15 D-AD patients and 17 age-, sex-, educational level-, and Mini-Mental State Examination (MMSE)-matched nD-AD patients to undergo tests using the Neuropsychiatric Inventory, Hamilton Depression Rating Scale, and 3.0T resting-state functional magnetic resonance imaging. Bilateral PCC were selected as the regions of interest and between-group differences in the PCC FC network were assessed using Student's *t*-test.

Results: Compared with the nD-AD group, D-AD patients showed increased PCC FC in the right amygdala, right parahippocampus, right superior temporal pole, right middle temporal lobe, right middle temporal pole, and right hippocampus (AlphaSim correction; $P < 0.05$). In the nD-AD group, MMSE scores were positively correlated with PCC FC in the right superior temporal pole and right hippocampus (false discovery rate corrected; $P < 0.05$).

Conclusion: Differences were detected in PCC FC between nD-AD and D-AD patients, which may be related to depressive symptoms. Our study provides a significant enhancement to our understanding of the functional mechanisms underlying D-AD.

Keywords: Alzheimer's disease, depressive symptoms, resting-state functional MRI, PCC

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a decline in cognitive function, including the progressive loss of memory, reasoning, and language. Furthermore, almost all AD patients are affected by neuropsychiatric symptoms over the course of their illness.^{1,2} Depressive symptoms are very common and significant psychiatric complications are known to affect 30%–50% of AD patients.³ These complications can increase the burden upon AD patients and their caregivers, become a trigger for further disability, and shorten lifespan.^{3,4} However, little is known about the underlying mechanisms of depressive symptoms in AD patients.

Morphological studies of the brain, using magnetic resonance imaging (MRI), have revealed cortical thinning in the temporal, parietal,⁵ and frontal regions^{6,7} of AD patients with depressive symptoms (D-AD). Single photon emission computed tomography studies have also shown that the brains of people with D-AD exhibit hypoperfusion in the bilateral cingulate gyri and precuneus,⁸ left inferior frontal region,⁹

right orbitofrontal cortex, inferior frontal gyri,¹⁰ and the left frontal cortex.¹¹ Some positron emission tomography (PET) studies have also revealed hypo-metabolism in the dorsolateral prefrontal regions^{12,13} and in the left anterior cingulate cortices in D-AD patients.¹⁴ Furthermore, a PET-MRI study showed that, compared with non-depressed participants, β -amyloid-positive depressed mild cognitive impairment (MCI) patients had higher amyloid loading in the fronto-temporal and insular cortices, with coincident hyper-metabolism in the frontal cortices.¹⁵

Collectively, these studies indicate that the structure and function of the brain in D-AD patients is abnormal; however, these studies were limited to only a few specific brain regions. Recent network studies have demonstrated that normal global functional organization is disrupted in the AD brain, affecting both local connectivity and critical long-distance connections and specialized hub nodes.^{16–18} Resting-state functional MRI (fMRI) is a useful tool for studying intrinsic functional connectivity (FC). Using this approach, Guo et al observed reduced regional coherence in the right precentral gyri, right superior frontal gyri, right middle frontal gyri, and the right inferior frontal gyri in D-AD patients compared to non-depressed AD (nD-AD) patients.¹⁹ To investigate the intrinsic pattern of poor connectivity in whole-brain functional networks of D-AD patients, Guo et al used degree centrality at the voxel level. Their experiments found that D-AD patients possessed lower values in the right middle frontal, precentral, and postcentral gyrus, compared with nD-AD patients. Seed-based analysis, which is also based on abnormal degree centrality, further suggested that the connectivity between the precentral, postcentral, supplementary motor area, and the middle cingulum was reduced.²⁰

However, to date, there have been no studies of the default mode network (DMN) characteristics of D-AD patients. The DMN includes the medial prefrontal cortex, medial temporal lobes, dorsolateral prefrontal cortex, posterior cingulate cortex (PCC), and inferior parietal lobes.^{21,22} The DMN is considered to be involved in the process of self-referential processing, affective cognition, and emotion regulation. Poor functional connectivity in the DMN has been widely reported in a variety of mental disorders, including major depressive disorder (MDD).²³ In MDD patients, it has also been reported that during emotional processing, several sub-regions of the DMN show significant reductions in negative blood oxygenation level-dependent responses, which correlate with the severity of depression and feelings of hopelessness.²⁴ A resting-state FC study demonstrated that the FC between the PCC and the right medial temporal

lobe were significantly stronger during rest, but significantly weaker during task performance, in remitted late-onset depression (rLOD) patients.²⁵ Accordingly, it is possible that the DMN may be the primary neural network underlying the complex relationships between depressive symptoms.

We hypothesized that depressive symptoms can affect FC of the DMN in AD patients. Zhong et al reported that the PCC is a convergence center and may represent the only convergence region receiving interactions from other regions in the DMN.²⁶ Therefore, we employed resting-state fMRI to explore differences in FC between D-AD and nD-AD patients, with PCC as the specific region of interest (ROI). This study will help to contribute to our wider understanding of the mechanisms underlying D-AD.

Materials and methods

Participants

In total, 32 patients, aged between 65 and 80 years, were recruited between February 2013 and December 2014 from Tongde Hospital in Zhejiang Province, China. All participants were right-handed and had received more than 6 years of schooling. All participants met criteria for the diagnosis of probable AD according to the recommendations of the National Institute on Aging-Alzheimer's Association workgroup's diagnostic guidelines for Alzheimer's disease:²⁷ a score of 20–24 on the Mini-Mental State Examination (MMSE), and a score of 1 on the Clinical Dementia Rating scale. Depressive symptoms met the *Diagnostic and Statistical Manual of Mental Disorders* (4th Edition),²⁸ which meant that all D-AD patients had one or more of the two core criteria (depressed mood and loss of interest or pleasure), for a duration of at least 2 weeks. The severity of depressive symptoms was assessed by the 17-item Hamilton Depression Rating Scale (HAM-D-17).²⁹ The Neuropsychiatric Inventory (NPI) is a valid and reliable instrument for measuring the non-cognitive symptoms of dementia^{30,31} and was used to examine other neuropsychiatric conditions aside from depression:³⁰ D-AD scored 1 on the depression domain, and scored 0 on each of the other eleven NPI domains. The total score on the depression domain of the NPI (D-NPI) represents the product of the frequency (scores 1–4) and severity (scores 1–3). Based on recommendations for clinical trial entry criteria, D-NPI scores of ≥ 4 indicate clinical significance.³² All of these cases were assigned by trained neuropsychologists.

Patients with a history of significant visual or hearing impairments were excluded, since this rendered interview participation difficult. Participants with a history of other neurological disorders, mental illnesses, or significant alcohol,

psychotropic medications, and/or other substance abuse, were also excluded. We also excluded subjects whose dual-echo MR images showed two or more hyper-intense lesions with diameters ≥ 5 mm, or more than four hyper-intense lesions with diameters between 0 and 5 mm.

MRI data acquisition

All participants were scanned using a 3T Siemens scanner (Magnetom Verio; Siemens, Erlangen, Germany) with a 12-channel head coil. Resting-state functional images were acquired with a gradient-echo echo-planar imaging (EPI) sequence: repetition time (TR)/echo time (TE)=2,000/30 ms, flip angle =90°, 33 axial slices, thickness/gap =4.8/0 mm, matrix =64×64, and field of view (FOV) =200×200 mm². Each condition consisted of 200 functional volumes. Subsequently, high-resolution structural images were obtained using a magnetization-prepared rapid gradient-echo sequence: TR/TE/inversion time (TI)=1,900/2.48/900 ms, flip angle =9°, 128 sagittal slices, slice thickness/gap =1/0 mm, matrix =512×512, and FOV =256×256 mm². The participants were informed to lie quietly, keep their eyes closed, and not to fall asleep. Scanner noise was attenuated with earplugs and head motion was restricted with foam padding around the head.

Image analysis

Image pre-processing

Resting-state fMRI data were processed using Statistical Parametric Mapping 8 (SPM, <http://www.fil.ion.ucl.ac.uk/spm>) and Data Processing Assistant for Resting-State fMRI (<http://www.restfmri.net>).³³ The procedure included the following pre-processing steps: 1) removal of the first ten volumes of functional images because of the instability of the initial signal and to allow participants to adapt to the scanner environment; 2) slice timing for acquisition delay between slices; 3) head motion correction, with all participants having <1.5 mm maximum displacement in x, y, or z planes and 1.5° of angular motion during the entire fMRI scan; 4) spatial normalization (realigned functional data were normalized to the standard EPI template in the Montreal Neurological Institute space by using 12 parameter affine transformation and non-linear deformation) and resampling of functional images to 3 mm isotropic voxels; 5) removal of linear trends within the time series; and 6) band-pass filtering (0.01–0.08 Hz) to reduce low-frequency drift and physiological high-frequency respiratory and cardiac noise. Finally, several sources of spurious variances were removed by linear regression, including six head motion parameters, along with average signals from cerebrospinal fluid and white matter.³⁴

Analysis of functional connectivity

We selected the bilateral PCC, consisting of Brodmann areas 29, 30, 23, and 31, as the template ROI using Wake Forest University Pick Atlas software.^{35,36} In order to perform ROI-based correlation analysis, the mean PCC signal intensity was calculated by averaging the time series of all voxels within a selected ROI. The resulting time course was then used to perform Pearson linear correlation analysis with all voxels of the brain data.^{37,38} A Fisher z-transformation was applied to improve normality of the correlation coefficients.^{34,37}

Statistical analysis

Differences in demographic and clinical data between the D-AD and nD-AD groups of patients were analyzed using two-sample Student's *t*-tests and χ^2 -tests.

To investigate differences in PCC connectivity between the two groups of patients, two-sample *t*-tests were performed using REST (<http://www.restfmri.net>). AlphaSim, a program based on Monte Carlo simulation and implemented in Analysis of Functional Neuro Images (<http://afni.nimh.nih.gov>), was used for multiple comparison correction. Monte Carlo simulations determine the random cluster size distribution for a given per voxel threshold.³⁹ According to this distribution, a corrected *P*-value less than 0.05 had obtained a combination criterion of voxels with a *P*-value ≤ 0.05 and a cluster size ≥ 198 voxels within the intersection mask.

We then investigated correlations between PCC FC and clinical symptoms. Correlation analyses were then performed between the two groups of patients in terms of PCC FC and MMSE, NPI, and HAMD scores. The threshold for statistical significance was set at false discovery rate corrected $P < 0.05$ in SPM8.

Results

Demographics and neuropsychological tests

There was no significant difference between the D-AD and nD-AD groups in terms of age, sex distribution, and levels of education. The MMSE was not statistically different between the groups and no subjects were excluded by our exclusion criteria. As expected, there was a significant difference in HAMD and D-NPI scores when compared between the two groups. Further details are presented in Table 1.

Between-group analyses of PCC connectivity

Between-group analyses were carried out using REST two-sample *t*-tests ($P < 0.05$, AlphaSim corrected; Table 2).

Table 1 Demographic and clinical characteristics of the study participants

	D-AD (mean ± SD)	nD-AD (mean ± SD)	t/ χ^2	P-value
Age (years)	73.5±4.73	75.8±3.75	-1.564	0.128
Sex, N (M:F)	15 (6:9)	17 (8:9)	0.161	0.735
Educational level (years)	8.6±1.83	8.5±1.84	0.211	0.835
HAMD	13.9±2.31	2.82±1.91	14.872	0.000
D-NPI	6.6±1.92	0	14.206	0.000
MMSE	19.6±2.20	21.0±2.09	-1.845	0.075

Abbreviations: D-AD, Alzheimer's disease patients with depressive symptoms; nD-AD, non-depressed Alzheimer's disease patients; M, male; F, female; HAMD, Hamilton Depression Rating Scale; D-NPI, depression domain of the Neuropsychiatric Inventory; MMSE, Mini-Mental State Examination.

This allowed us to determine the between-group difference in PCC connectivity. We then compared the D-AD group with the nD-AD group and showed that connectivity between the PCC and the right amygdala, right parahippocampal gyri, right superior temporal pole, right middle temporal lobe, right middle temporal pole, and right hippocampus was increased in the D-AD group (Table 2, Figure 1).

Correlations between PCC FC and clinical symptoms

Regarding the D-AD patients, a correlation analysis between the PCC FC of the right amygdala, right parahippocampal gyri, right superior temporal pole, right middle temporal lobe, right middle temporal pole, right hippocampus, and the MMSE, NPI, and HAMD scores suggested that the MMSE scores of the nD-AD group were positively correlated with PCC FC in the right superior temporal pole and right hippocampus (Table 3). There were no significant correlations between the PCC FC of the right amygdala, right

Table 2 Brain regions with significantly increased functional connectivity in the D-AD group compared with the nD-AD group (AlphaSim correction, $P < 0.05$)

Brain regions	BA	Vols	Stereotaxic Coordinates, mm			Peak intensity
			x	y	z	
R Amygdala	34/36	18	27	3	-27	4.7771
R Parahippocampal	28/36	34	28	3	-29	4.22891
R Temporal_Pole_Sup	21/38/48	46	47	7	-14	2.82391
R Temporal_Mid	21	31	50	-1	-14	2.37799
R Temporal_Pole_Mid	21	31	47	7	-22	2.36318
R Hippocampus	20	35	33	-23	-8	2.31557

Abbreviations: D-AD, Alzheimer's disease patients with depressive symptoms; nD-AD, non-depressed Alzheimer's disease patients; BA, Brodmann area; Vols, number of voxels; R, right.

parahippocampal gyri, right superior temporal pole, right middle temporal lobe, right middle temporal pole, or right hippocampus and NPI and HAMD scores in the nD-AD group (Table 3). Furthermore, there were no significant correlations between the PCC FC of the right amygdala, right parahippocampal gyri, right superior temporal pole, right middle temporal lobe, right middle temporal pole, right hippocampus and MMSE, NPI, and HAMD scores in the D-AD group (Table 4).

Discussion

In this exploratory study, we employed resting-state fMRI to investigate different levels of FC in D-AD patients compared with nD-AD patients using the bilateral PCC as an ROI. Our results showed that in D-AD patients, compared with nD-AD patients, there was an increase in resting-state FC between the PCC and the right hippocampus, right parahippocampal gyri, right amygdala, and right temporal pole.

The hippocampus is the main structural substrate for episodic memory deficits^{40,41} and is among the first regions targeted by AD pathology.^{42,43} The hippocampus demonstrates predominantly diminished FC with other regions as AD progresses.⁴⁴ As a core region in the limbic system, the hippocampus is involved in not only cognitive functions such as learning and memory,⁴⁵ but also the regulation of motivation and emotion.^{46,47} Specifically, the hippocampus may potentially mediate the relationship between helplessness and depression by regulating gene expression.^{48,49} Altered FC in the hippocampus may be related to the deficits in emotion-mediated memory formation observed in depression.^{50,51} In this study, compared with nD-AD patients, the FC of the PCC and the hippocampus in D-AD patients was increased, which may reflect how a reduced ability to form memories arises from the effects of depressive symptoms. A previous neuropathological study also showed that D-AD leads to increased hippocampal plaques and tangles, and a more rapid cognitive decline, compared to nD-AD patients.⁵² This further suggests that the reduced ability to form memories arises from the effects of depressive symptoms in D-AD patients.

In our study, we found increased FC between the PCC and the right parahippocampal gyrus in D-AD patients. The parahippocampal gyrus is an important region of the limbic system and a key region in the episodic memory network.^{53,54} Imaging findings have consistently identified abnormal changes in the right parahippocampus, such as gray matter atrophy,⁵⁵ reduced cortical thickness,⁵⁶ and hypoperfusion,⁵⁷ which are all related to cognitive degradation in AD patients. Chen et al also found that the right parahippocampal gyrus

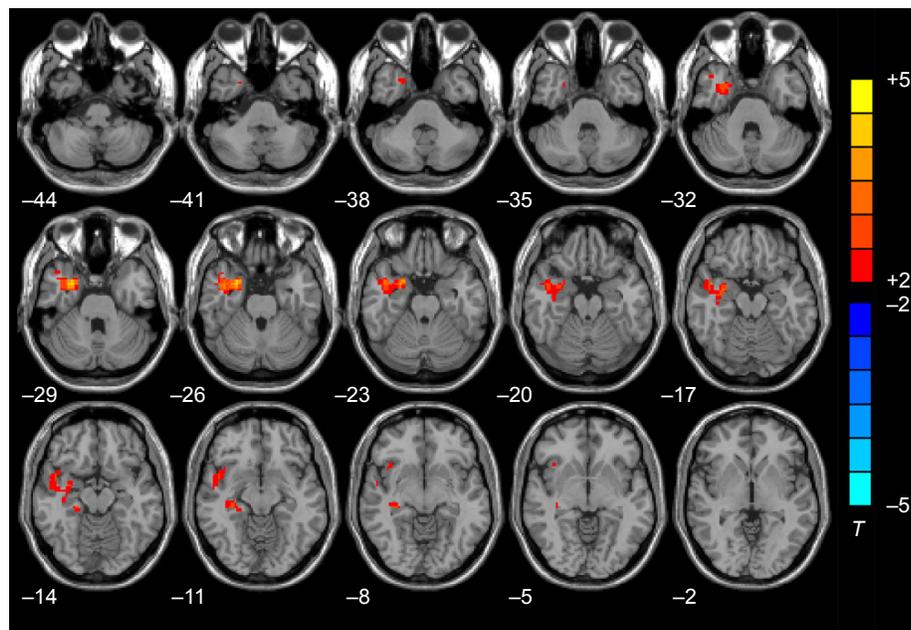


Figure 1 Brain regions showing increased PCC FC in the nD-AD group compared with the D-AD group on an axial map ($P < 0.05$, AlphaSim corrected).

Note: T-value scale is to the right of the image.

Abbreviations: PCC, posterior cingulate cortex; FC, functional connectivity; nD-AD, non-depressed Alzheimer's disease patients; D-AD, Alzheimer's disease patients with depressive symptoms.

showed imbalanced bidirectional effective connections in AD patients, which received weaker input connections from the neocortices, although output connections were significantly increased.⁵⁸ The FC between the parahippocampal gyrus and the PCC is known to be reduced in AD patients and becomes more severely damaged as the disease progresses.⁵⁹ Conversely, previous studies have detected gray matter reduction and diffusion tensor MRI abnormalities in the right parahippocampal gyrus in MDD.^{60,61} Remitted depressed participants are also known to show increased connectivity between the PCC and the parahippocampal gyri, compared with healthy controls.⁶² These studies indicate that the

structure and function of the parahippocampus are abnormal in both MDD and AD patients. Our present study showed increased FC between the PCC and the right parahippocampal gyrus in D-AD patients compared with nD-AD patients. In combination, these studies reflect the difference in changes of brain function between D-AD and nD-AD patients. This may represent the underlying reason for the deterioration of episodic memory in D-AD patients, which may be further affected by depressive symptoms.

The amygdala and temporal poles are important parts of the affective network, which includes the amygdala, orbitofrontal cortex, temporal cortex, pallidum, and insular cortex.⁶³ These regions are involved in mood regulation and affective processing.^{64,65} It is believed that depressive mood might be correlated with the affective network.⁶⁶ Dolan et al demonstrated responses of the amygdala and temporal poles to the activation of an emotional memory retrieval task.⁶⁷ The amygdala is the most important area of the human brain for forming emotional memories and modulating emotional response and is considered to be a key brain region in relation to stress reactivity and vulnerability for depressive disorder.⁶⁸ Increased activity of the amygdala has been reported in response to negative emotional signals (eg, faces, pictures, and words) in MDD.^{69,70} Ramasubbu et al found that the intrinsic connectivity of the amygdala with the temporal poles was increased in adults with MDD and that increased FC was

Table 3 Correlation between FC and MMSE, NPI, and HAMD in the nD-AD group (FDR corrected $P < 0.05$)

Brain regions	MMSE		D-NPI ^a		HAMD	
	r	P-value	r	P-value	r	P-value
R Amygdala	0.1400	0.5920	–	–	0.3789	0.1337
R Parahippocampal	0.1187	0.6501	–	–	0.4055	0.1064
R Temporal_Pole_Sup	0.4980	0.0419	–	–	0.2322	0.3699
R Temporal_Mid	0.4165	0.0963	–	–	0.0638	0.8079
R Temporal_Pole_Mid	0.4252	0.0899	–	–	0.2520	0.8079
R Hippocampus	0.5334	0.0275	–	–	0.4574	0.0649

Note: ^aBecause all the NPI scores were 0 in nD-AD group, the correlation analysis was unable to be performed.

Abbreviations: FC, functional connectivity; MMSE, Mini-Mental State Examination; D-NPI, depression domain of the Neuropsychiatric Inventory; HAMD, Hamilton Depression Rating Scale; nD-AD, non-depressed Alzheimer's disease patients; D-AD, Alzheimer's disease patients with depressive symptoms; R, right.

Table 4 Correlation between FC and MMSE, NPI, and HAMD in the D-AD group (FDR corrected $P < 0.05$)

Brain regions	MMSE		D-NPI		HAMD	
	r	P-value	r	P-value	r	P-value
R Amygdala	-0.3896	0.1512	0.3209	0.2435	0.3568	0.1917
R Parahippocampal	-0.3762	0.1670	0.3104	0.2602	0.3175	0.2489
R Temporal_Pole_Sup	-0.1437	0.6095	0.2111	0.4501	0.1007	0.7211
R Temporal_Mid	-0.1073	0.7035	0.3105	0.2599	0.2459	0.3769
R Temporal_Pole_Mid	-0.0659	0.8156	0.2317	0.4061	0.3002	0.2771
R Hippocampus	0.1663	0.5536	0.1617	0.5647	0.1709	0.5426

Abbreviations: FC, functional connectivity; MMSE, Mini-Mental State Examination; D-NPI, depression domain of the Neuropsychiatric Inventory; HAMD, Hamilton Depression Rating Scale; D-AD, Alzheimer's disease patients with depressive symptoms; FDR, false discovery rate; R, right.

inversely correlated with symptom severity.⁷¹ Another two studies also showed increased amygdala resting-state FC with the dorsal mid-insular cortex⁷² and the sub-genual anterior cingulate cortex in patients with depression.⁷³ Longitudinal alteration of amygdala FC with regions of the DMN which are involved in MCI were reduced, which was significantly correlated with cognitive ability.⁷⁴ In AD, the strengthening effect of emotion on memory is impaired, and the level of damage is associated with the level of amygdala damage and emotional projections.⁷⁵ Yao et al found that reduced FC in AD patients was mainly located between the amygdala and the regions that were included in the DMN. Importantly, the reduced level of FC between the amygdala and some of the identified regions positively correlated with MMSE scores, which indicated that the impairment of cognitive function was related to alterations in the FC of the amygdala.⁷⁶ The fact that our current study identified increased resting-state FC between the PCC and the amygdala in D-AD patients may, in part, be the basis for the differential clinical scenarios between D-AD and nD-AD patients. The more severe clinical condition of D-AD may partly arise from depressive symptoms affecting the amygdala and consequential modulation of emotional responses.

The temporal pole is the anterior-most portion of the temporal lobes and is considered to be part of an extended limbic system due to its location lateral to the amygdala, posterior to the orbital frontal cortex, and heavily interconnected to the limbic and paralimbic regions.⁷⁷ The temporal pole is involved in numerous aspects of emotional processing, including the subjective perception of affect,^{78,79} as well as anxiety and stress.^{80,81} The function of the temporal pole is abnormal in MDD patients. Activation of the right anterior temporal pole in depressed individuals is increased when they attempt to voluntarily downregulate sad feelings.⁸² Guo et al directly examined cerebellar-DMN connectivity in drug-naive MDD patients by using the cerebellum Crus I as an ROI, and observed significantly increased FCs between the

right Crus I and the superior temporal pole.⁸³ Liu et al also demonstrated that depressed patients showed significantly increased FC between the cerebellum and the temporal poles.⁸⁴ Meanwhile, significantly reduced intrinsic connectivity in the anterior temporal pole was found in amnesic MCI patients,⁸⁵ which reflected the effect of the temporal pole in cognition. The anterior temporal pole has also been associated with emotional memory retrieval.⁶⁷ Our present results show that the resting-state FC of the right temporal pole, and the PCC in D-AD patients, was increased compared with nD-AD patients. Based on these findings, we may assume that dysfunction of the temporal pole leads to abnormal emotional processing, which may further lead to depression and worsened emotional memory retrieval in D-AD patients. Our study therefore provides significant insight into the important effects of depressive symptoms on emotional processing in the right temporal pole in AD.

Increased FC has been noted between the PCC and the right medial temporal lobe, which contains parts of the hippocampus, parahippocampal gyrus, amygdala, and uncus during resting state in rLOD patients, and became significantly weaker during task performance.²⁵ Previous studies of AD patients showed a correlation between episodic memory decline and abnormal structure and function of the medial temporal lobe.^{86,87} Our current results indicated that the increased resting-state FC between the PCC and right hippocampus, right parahippocampal gyri, right amygdala, and right temporal pole, may underlie the defects in memory and cognitive function in D-AD patients. This may result from the decline of information relating to memory, episodic memory, emotional response, and emotional processing, which may be associated with the depressive symptoms.

The MMSE scores of the nD-AD group in our study were positively correlated with the PCC FC in the right superior temporal pole and the right hippocampus, which further indicates that the FCs of the PCC, the hippocampus, and the temporal lobe are associated with memory loss in AD.⁸⁸

However, in the D-AD group, there were no significant correlations between the PCC FC of the right amygdala, right parahippocampus, right superior temporal pole, right middle temporal lobe, right middle temporal pole, and right hippocampus and the symptoms. This may be related to our small sample size, or it may reflect the differential pathogenic mechanisms of D-AD and nD-AD, which require further research.

Limitations and future directions

Although the results of this study provide new knowledge, limitations remain regarding our small sample size. According to Eklund et al⁸⁹ our primary *P*-value, which we set for between-group analysis, was too stringent. When we utilized a voxel *P*-value of $P < 0.001$, there were no significant differences identified between groups. This may have been due to our relatively small sample size. Consequently, in future studies, it may be wiser to use a less stringent *P*-value. However, reducing the stringency of our primary threshold may lead to false positive findings. Consequently, further studies are now needed to examine the reproducibility of the current study.

It is also possible that scanner variability had an effect upon our data. Some types of physiological noise, such as cardiac and respiratory rates, can affect the low-frequency domain of fMRI signals.^{90,91} However, cardiac and respiratory rates were not recorded during the scans in this study. Additional neuroimaging evidence, such as structural abnormalities, are now needed as a synthesized biomarker to ensure a more reliable clinical diagnosis of this complex disorder.

Furthermore, it is important to note that although neuropsychiatric symptoms are not required for the diagnosis of AD, they represent a major clinical feature and contribute to the distress of both patients and caregivers. Currently, there is no gold standard source of information for the assessment of these conditions. In the current study, we employed the informant-based NPI to measure neuropsychiatric symptoms because of its long-standing use in the dementia literature, ease of administration, and good validity and reliability.⁹² However, it has been shown that the educational level and the psychological state of AD patients, and the attitude of their caregivers toward the disease, may influence the results of this inventory.⁹³ These factors may introduce some degree of bias into our assessment by the over-reporting or under-reporting of symptoms, or variations in perception of behavior.^{93,94} Finally, we did not acquire pathological confirmation of our clinical diagnosis of early AD, although our diagnosis was based on detailed clinical examination,

extensive neuropsychological testing, and structural imaging, and has been shown to achieve an accuracy of 85%–95%.⁹⁵

Conclusion

To our knowledge this is the first study to report differences in the resting-state FC of D-AD patients compared with nD-AD patients using the bilateral PCC as the ROI. We identified abnormal FC in both the limbic system and the affective network of D-AD patients, which may have arisen from depression. Our study provides a significant step forward in our understanding of the neural mechanisms of D-AD.

Ethics approval and consent to participate

All participants (or their legal representatives) provided informed written consent. The research protocol was approved by the Ethics Committee of Tongde Hospital in Zhejiang Province.

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Disclosure

The authors report no conflicts of interests in this work.

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