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ORIGINAL RESEARCH

Altered functional connectivity of the posterior cingulate cortex in type 2 diabetes with cognitive impairment

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Abstract

The posterior cingulate cortex (PCC) has been suggested to be a cortical hub of the default mode network (DMN). Our goal in the current study was to determine whether there were alterations in the PCC's functional connectivity (FC) with whole brain regions in type 2 diabetes mellitus (T2DM) and to determine their relationships with cognitive dysfunction. In this study, the FC of the PCC was characterized by using resting-state functional MRI and a seed-based whole-brain correlation method in 24 T2DM patients and compared with 24 well-matched healthy controls. Spearman correlation analysis was performed to determine the relationships between the FC of the PCC and cognitive dysfunction. T2DM was associated with a significantly decreased FC of the PCC to widespread brain regions ($p < 0.05$, corrected for AlphaSim). We also found that the FC of the PCC in these brain regions was positively correlated with several neuropsychological test scores, such as the FC to the right angular gyrus (AnG) and the bilateral middle temporal gyrus (MTG) with the Auditory Verbal Learning Test (AVLT) and the FC to the bilateral inferior frontal gyrus (IFG) with the digit span test (DST). Moreover, the FCs of the PCC to the right superior parietal lobule (SPL), bilateral temporal lobes and left cerebrum were detected as negatively correlated with the Trail Making Test (TMT). No such correlations were detected in healthy controls. The present study provides useful information about the effect of the FC of the PCC on the underlying neuropathological process of T2DM-related cognitive dysfunction and may provide supporting evidence for further molecular biology studies.

Keywords Type 2 diabetes · Posterior cingulate cortex · Functional connectivity · Cognitive dysfunction

Introduction

Previous studies have revealed that T2DM is related to cognitive decrements, mainly including impaired visual construction, planning, visual memory and cognitive speed (Moran et al. 2013), and is a risk factor for dementia (Musen et al. 2012). However, the exact pathophysiological mechanisms of T2DM-related cognitive dysfunction are not very clear and hinder the development of preventive treatments.

The DMN contains several brain regions, including the PCC, anterior cingulate cortex, MTG, medial prefrontal cortex, and the medial, lateral, and inferior parietal cortex (Greicius et al. 2009; Anticevic et al. 2012), which are involved in constructing self-relevant mental simulation, such as remembering the past, thinking about the future and understanding the viewpoint of others (Li et al. 2014; Adrews-Hanna 2012). Previous studies have revealed that the DMN is associated with cognitive dysfunction in T2DM patients. Yang et al. (2016a, b) reported that the DMN was mainly involved in brain functional impairment in T2DM patients. Qi et al. (2017) revealed that T2DM patients performed poorly in episodic memory and showed aberrant DMN functional connectivity. Cui et al. (2015) found that the DMN connectivity was altered in T2DM patients, which was associated with impaired cognition and increased insulin resistance, while Musen et al. (2012) also showed that reduced functional connectivity in the DMN was associated with insulin resistance in selected brain regions in T2DM patients.

The PCC is a vital node of the DMN and has been reported to have altered functional activity and a close relationship with cognitive dysfunction. Leech et al. (2011) reported that the PCC and adjacent precuneus were highly heterogeneous and FC of the DMN occurred in response to changes in cognitive control. Buckner et al. (2008) showed that the PCC exhibited high metabolic activity at rest and during passive sensory processing tasks. Cui et al. (2014) found that the standardized

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ALFF and ReHo values in the PCC were significantly higher than the global mean values, which meant there was abnormal neural activity in the PCC in T2DM patients. Leech et al. (2012) suggested that the PCC has dense structural connectivity to widespread brain regions and is involved in internally directed thoughts and active control of cognition and behaviors by integrating information via directed brain activity. They also revealed that the PCC itself consists of functionally distinct areas, with highly heterogeneous functional organization and constant interaction with various brain regions. Recently, Yang et al. (2016a, b) applied magnetization transfer imaging to examine the biophysical integrity of macromolecular protein pools of the PCC and found that the degree of biophysical impairment of the PCC correlated with both hyperglycemia and vascular compromise in T2DM patients. These previous studies usually focused on the aberrant connectivity within the DMN. Since the PCC plays an important functional role in cognitive dysfunction, previous studies seldom set the PCC as the seed ROI to determine its relevant FC to whole brain regions in T2DM patients. Thus, alterations in FC of the PCC in T2DM patients and their relationships with cognitive dysfunction are still not very clear. Therefore, it will be interesting to learn more about the mechanism of the PCC's FC in mental disorders in T2DM patients.

In the current study, the PCC was selected as the seed region to investigate the alterations of FC in T2DM patients. We also evaluated cognitive dysfunction of T2DM patients in order to investigate their relationships with the FC of the PCC.

Materials and methods

Participants

We enrolled 48 participants (24 T2DM patients and 24 healthy control subjects). Informed consent was obtained from each participant. T2DM was defined according to the latest criteria published by the American Diabetes Association: $HbA_{1c} \geq 6.5\%$ (48 mmol/mol); fasting blood glucose≥7.0 mmol/L (126 mg/dL); oral glucose tolerance test (OGTT) 2 h postprandial blood glucose≥1.1 mmol/L (200 mg/dL); symptoms of hyperglycemia or hyperglycemic crises and random blood glucose≥11.1 mmol/L (200 mg/dL), without symptoms of hyperglycemia, and the standard of 1 to 3 items was reviewed. Control participants were matched with T2DM patients with respect to age, sex and education, and the MoCA score was greater or equal to 26. Participants were excluded if they had a history of psychiatric diseases, stroke, epilepsy, head trauma, brain surgery, cerebrovascular accidents, or signs of impairment of cognitive function, or had severe liver, kidney or heart disease. A TIA attack in the past two years, alcohol or tobacco abuse, hypertension and contraindications to MRI were also exclusion criteria, as were specific brain abnormalities on conventional MR scans. Moreover, the T2DM patients were excluded if they had unstable blood glucose control, acute or chronic metabolic complications of clinical diabetes and severe hypoglycemia, or a history of ketoacidosis.

Medical history and biometric measurements

Medical history and medication use were recorded with a standardized questionnaire. Systolic and diastolic blood pressure were measured at three different time points during the day and biometric examinations, including those of averaged fasting glucose, HbA_{1c}, total cholesterol (TC), triglycerides (TG) and low density lipoprotein (LDL) were measured with standard laboratory testing. BMI was calculated as weight in kilograms divided by the square of height in meters.

Cognitive assessment

All participants underwent a series of neuropsychological tests that evaluated general cognitive function, memory, attention, executive function and visuospatial skills, including the Montreal Cognitive Assessment (MoCA, Beijing edition), AVLT, TMT-A and TMT-B, the Clock Drawing Test (CDT) and the DST. The Mini Mental State Exam (MMSE) was administered when the MoCA score was less than 26 to assess for possible dementia (Galea and Woodward 2005). The AVLT contains three parts, including immediate tasks, 5-min tasks and 20-min delayed recall tasks, which were used to assess short-term and delayed memory, and the DST was used as a simple method to assess immediate memory. The TMT-A and TMT-B were mainly used to evaluate attention and psychomotor speed. The CDT was used primarily to address executive function and working memory (Zhou et al. 2010). All of the tests took approximately 30 min to administer.

MRI data acquisition

The MR images were all acquired with a 3 T GE clinical scanner (SIGNA EXCITE GE Medical Systems, Milwaukee, WI, USA) with an 8-channel head coil. The conventional brain axial T_1-weighted, T_2-weighted, and FLAIR images were obtained for every subject to exclude organic disease and white matter hyperintensity (WMH) lesions. Subjects were instructed to keep their eyes closed but to remain awake and to keep their heads still during the scanning. Head motion was controlled as much as possible using foam padding and scanner noise was reduced using earplugs. Functional images were obtained using a gradient-echo planar sequence as follows: repetition time (TR) = 2000 ms; echo

time (TE) = 30 ms; slices =36; thickness = 3 mm; gap =0 mm; field of view (FOV) = 220 mm × 220 mm; acquisition matrix = 64 × 64; and flip angle (FA) = 90°. The resting state recording took 6 min and 10s. Structural images were acquired using a 3D magnetization-prepared rapid-acquisition gradient echo sequence with the following parameters: TR = 2000 ms, TE = 2.6 ms, inversion time = 450 ms, flip angle = 12°, matrix = 256 × 256, field of view = 250 mm × 250 mm, and 256 continuous sagital slices with a1mm thickness. The structural scan time is 4 min and 10s.

Small-vessel disease assessment

Quantitative assessment of WMH and lacunar infarcts were performed on FLAIR and T2-weighted images with ARWMC Wahlund scoring rules (Wahlund et al. 2001) of five regions, including the bilateral frontal lobes, parietal and occipital lobes, temporal lobes, cerebellum and brain stem, and basal ganglia. All participants with a rating score > 2 were excluded. Two experienced raters blinded to group allocations performed the ratings independently.

Functional data analysis

Functional data were analyzed using DPARSF (Yan and Zang 2010), statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and REST (http://www.restfmri.net) on MATLAB software. The main procedure was conducted as follows: First, in pretreatment, any subjects with head motion >2.0 mm translation or > 2.0° rotation in any direction were excluded. Spatial normalization to the Montreal Neurological Institute template (resampling voxel size =3 × 3 × 3 mm^3) and smoothing with an isotropic Gaussian kernel (FWHM =6 mm), detrending and filtering (0.01–0.1 Hz) were performed in that order. Second, the PCC was defined as the seed regions of interest (ROI) using WFU_PickAtlas software (http://www.ansir.wfubmc.edu) in SPM8, but the seed ROI size was not suitable for further analysis and needed to be corrected by using REST software. The size was corrected to 3 × 3 × 3 mm^3. Third, correlation analysis was carried out between the PCC and every voxel of the whole brain, the significant FCs of the PCC to individual brain regions were calculated to compare T2DM and control group, and z-values were computed. Fourth, the significant brain regions were saved as a mask. Last, the FC of the PCC to the mask corresponding to neuropsychological test scores was calculated (significant thresholds were corrected to $p < 0.05$), a Fisher's z-transform was applied to improve the normality of the correlation coefficients, and then the significant brain regions were extracted. The individual mean z-values of the aberrant FC regions were calculated within every T2DM subject.

Statistical analysis

Demographic and clinical characteristics analysis

Statistical analysis was performed using SPSS software, version 20.0. Demographic and clinical variables were compared between the T2DM group and the control group. Continuous variables were tested by two-tailed *t*-tests, while sex differences were examined by Chi-square-tests.

The head motion analysis

Since previous studies revealed that head motion may have both noisy and neuronal effects on functional connectivity measures (Zeng et al. 2014a, b; Van Dijk et al. 2012), we compared the head motion parameters between the two groups by two-tailed t-test and the results are listed in Table 1.

Functional connectivity analysis

The FC analysis was conducted with the REST software. The z values of the two groups computed above (the third step in the functional data analysis) were obtained by using a one-sample t-test individually. Then, a two-sample t-test was performed using the SPM8 software to identify brain regions with a significant difference in connectivity to the PCC. Age, sex, education and BMI were included as covariates. The AlphaSim program for multiple comparisons correction was used and a P value <0.05 was considered statistically significant.

Correlation analysis

To investigate the relationship between altered FC of the PCC and cognitive performance, Spearman's correlation analyses were performed between the mean z-values and neuropsychological test scores and clinical variables. Partial Spearman's rank correlations were adjusted for the same covariates as those controlled in the FC analysis. The Bonferroni correction was used for multiple comparisons in the MoCA correlation analyses, and the FDR correction was used for the remaining correlation analyses. *Significant thresholds were corrected* $p < 0.05$.

Results

Demographic, clinical and cognitive characteristics

A total of 48 participants were recruited for this study, 24 T2DM patients and 24 healthy controls. The blood pressures of all T2DM patients were controlled within the normal range. No significant differences were identified in age, sex,

Table 1 The head motion parameters between the two groups

	T2DM ($n = 24$) (mean± SD)	Control ($n = 24$) (mean± SD)	p value
Mean Motion	0.288 ± 0.208	0.276 ± 0.169	0.839
Maximum Motion	0.642 ± 0.358	0.543 ± 0.296	0.323
Number of Movements	0	0	–
Rotation	0.172 ± 0.116	0.154 ± 0.090	0.007

educational level or diastolic blood pressure, while systolic blood pressure, HbA_{1c} level and BMI in patients with T2DM were significantly higher than those in the controls ($p < 0.05$). Moreover, T2DM patients had performed poorer scores in the MoCA (Table 2).

Functional connectivity results

The PCC was found to have weak FC to widespread brain regions in both groups, and the PCC also showed a strong FC to some brain regions, such as the occipital forceps (Fig. 1).

Compared to healthy controls, the PCC revealed weaker FC to several brain regions, including the frontal lobes, parietal lobes, temporal lobes, thalami, basal ganglia, cerebellar hemispheres and the brainstem, and stronger FC to the right occipital gyrus, the left IFG and the right insula in the T2DM group ($p < 0.05$) (Fig. 2).

Correlation analysis results

In T2DM patients, the weak FC of the PCC to several regions was found to be positively correlated with MoCA, AVLT and DST scores, and some negative correlations were identified between the TMT scores and certain regions (Table 3). In the memory tests, namely, AVLT and DST, the right AnG showed positive correlations with

Table 2 Demographic and clinical data

	T2DM ($n = 24$) (mean± SD)	Control ($n = 24$) (mean± SD)	p value
Age (years)	53.33 ± 8.86	51.29 ± 8.20	0.412
Sex (M/F) [a]	11/13	15/9	0.391
Education(years)	8.87 ± 5.06	10.17 ± 5.26	0.234
Fasting blood glucose (mmol/L) [b]	7.92 ± 3.86	4.90 ± 0.59	0.007
HbA_{1c} (%)[b]	7.82 ± 1.38	5.76 ± 0.23	0.000
HOMA-IR [b]	3.49 ± 3.67	–	–
Systolic blood pressure (mmHg) [b]	125.29 ± 11.39	118 ± 8.26	0.016
Diastolic blood pressure (mmHg)	79.54 ± 6.38	78.08 ± 3.78	0.455
TC (mmol/L)	1.84 ± 1.64	1.26 ± 0.26	0.131
TG (mmol/L)	4.25 ± 1.27	4.11 ± 0.64	0.659
LDL (mmol/L) [b]	3.02 ± 1.02	2.29 ± 0.85	0.013
BMI (kg/m^2)	24.33 ± 2.83	22.98 ± 2.09	0.069
Cognitive performance			
MMSE	26.67 ± 1.82	–	–
MoCA [b]	24.79 ± 3.65	27.12 ± 1.26	0.006
AVLT			
AVLT (immediate)	19.71 ± 5.59	21.57 ± 5.14	0.327
AVLT (5 min)	7.52 ± 2.20	7.85 ± 1.91	0.648
AVLT (20 min)	8.38 ± 2.85	7.93 ± 1.73	0.564
TMT			
TMT-A	67.45 ± 37.99	58.03 ± 22.56	0.428
TMT-B	55.15 ± 25.28	50.28 ± 20.15	0.564
CDT	3.00 ± 0.00	3.00 ± 0.00	–

Data are represented as Mean ± SD, n (%) or median (range). [a] The statistical analyses were performed by χ^2 test. [b] P value <0.05. HOMA-IR, homeostasis model assessment of insulin resistance

TC total cholesterol, *TG* triglyceride, *LDL* low density lipoprotein, *BMI* body mass index, *MMSE* mini-mental state examination, *MoCA* montreal cognitive assessment, *AVLT* auditory verbal learning test, *TMT* trail-making test, *DST* digit span test, *CDT* clock drawing test

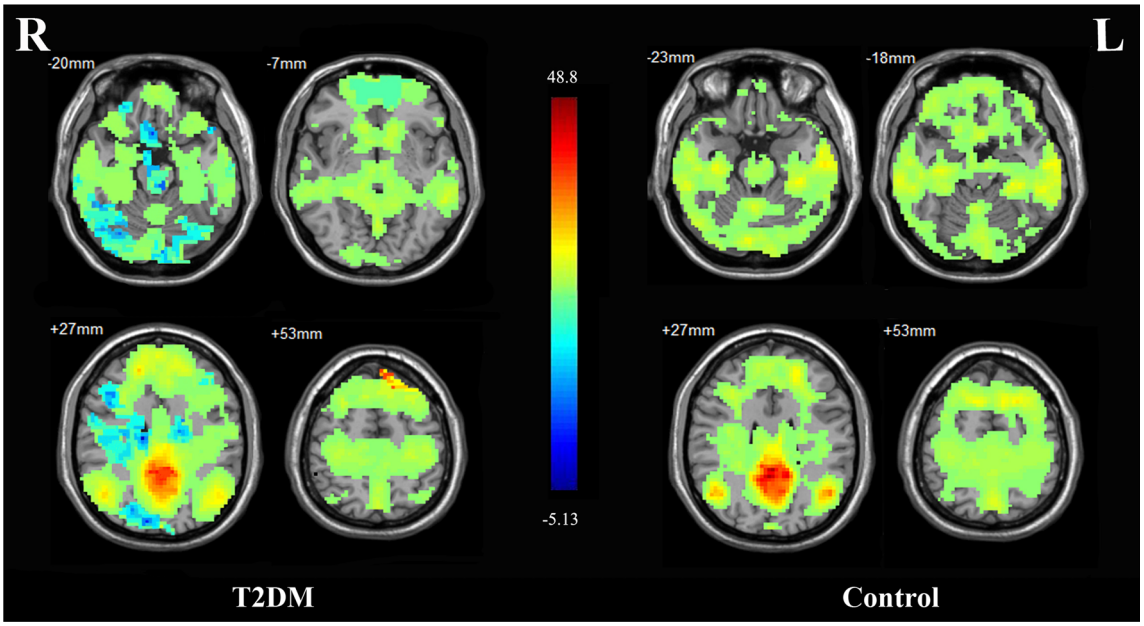

Fig. 1 Maps of the FC of the PCC obtained in both groups using a one-sample t-test. Thresholds were set at a corrected $p < 0.05$, as determined by Monte Carlo simulation. The color bar indicates the t scores. Green and blue indicate weak FCs of the PCC, and red and yellow indicate strong FCs of the PCC. Note that the left side corresponds to the right hemisphere

the immediate and 5-min AVLT but not with the 20-min AVLT, and the bilateral IFG showed positive correlations with the DST. The temporal lobes and left cerebrum were negatively correlated with the TMT. No such correlations were detected in the healthy controls. Moreover, we found a negative correlation between the FC of the PCC to the left MTG and HbA_{1c} (Fig. 3).

Discussions

In the current study, we set the PCC as a seed ROI to investigate disrupted FC in diabetic brains and found weak FC to widespread brain regions, suggesting that whole brain spontaneous nerve activity is decreased in T2DM patients. However, we also found a strong FC in several regions, such

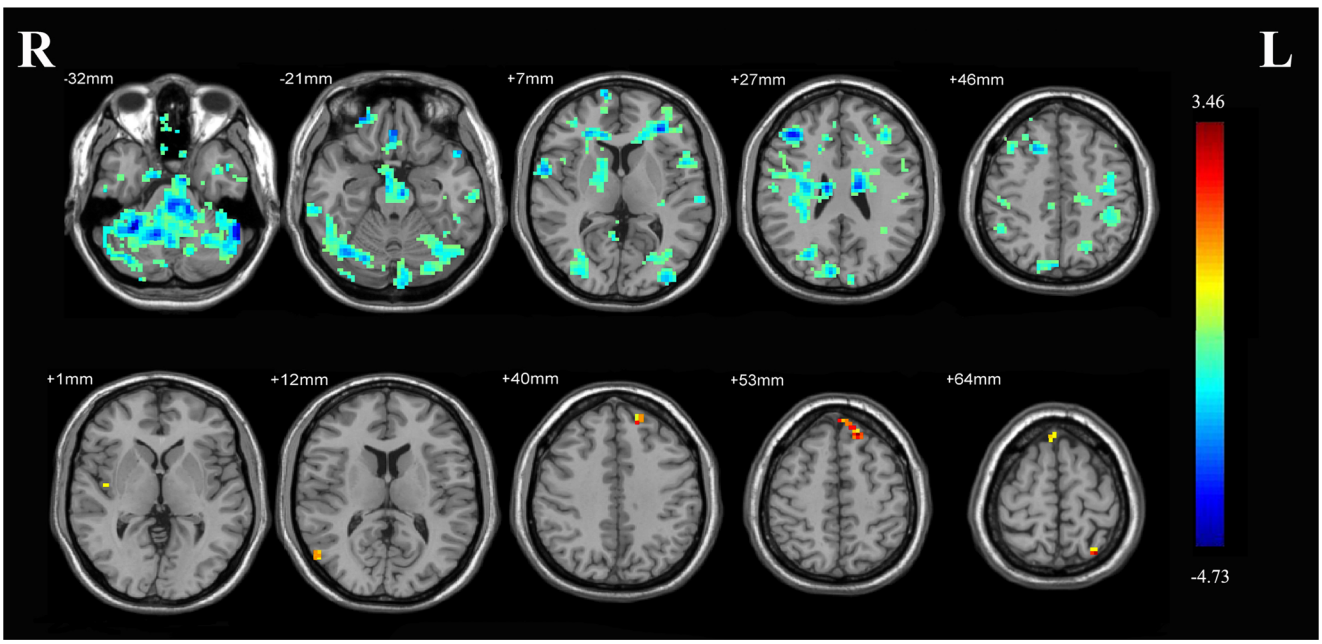

Fig. 2 Significant differences in FC of the PCC between T2DM patients and healthy controls. Thresholds were set at a corrected $p < 0.05$, determined by Monte Carlo simulation. The color bar indicates the t scores. The upper row shows the weak FCs of the PCC, and the lower row shows the strong ones. Note that the left side corresponded to the right hemisphere

Table 3 Significant correlation between the FC of the PCC and neuropsychological tests and clinical variables in T2DM patients

	Brain regions	Hemisphere	r	p
MoCA	Inferior temporal lobe	L	0.576	0.003
	Precentral gyrus	R	0.624	0.001
	Parietal lobe	R	0.513	0.01
AVLT				
AVLT (immediate)	Angular gyrus	R	0.498	0.022
	Middle temporal lobe	L	0.568	0.007
	Middle temporal lobe	R	0.685	0.001
AVLT (5 min)	Angular gyrus	R	0.525	0.015
	Middle temporal gyrus	L	0.639	0.002
	Middle temporal gyrus	R	0.665	0.001
AVLT (20 min)	Inferior frontal gyrus	L	0.610	0.003
	Middel temporal gyrus	R	0.624	0.002
	Superior frontal gyrus	R	0.707	0.000
TMT				
TMT-A	Inferior temporal lobe	L	−0.641	0.002
	Superior parietal lobe	R	−0.641	0.002
TMT-B	Cerebrum	L	−0.478	0.033
	Middle temporal gyrus	L	−0.559	0.01
	Middle temporal gyrus	R	−0.636	0.003
	Superior temporal gyrus	R	−0.47	0.033
DST	Inferior frontal gyrus	L	0.640	0.002
	Inferior frontal gyrus	R	0.721	0.000
HbA_{1c}	Middle temporal gyrus	L	−0.534	0.007

MoCA montreal cognitive assessment, *AVLT* auditory verbal learning test, *TMT* trail making test, *DST* digit span test, *L* left, *R* right

as the right occipital gyrus, left superior frontal gyrus and right insula, which may reflect the compensation for the maintenance of whole-brain nerve activity at the normal level. Furthermore, the weak FC of the PCC to brain regions correlated with impaired cognitive performances. Our findings provide novel insight into how the FC of the PCC affect the underlying neuropathological process in diabetic brains and T2DM-related cognitive dysfunction. Our study also indicated that abnormalities of the PCC's FC may serve as evidence for further molecular imaging studies and provide more information about the neural mechanisms of diabetes-related cognitive decline.

We found aberrant FC of the PCC to several brain regions associated with memory decline, such as the right AnG, MTG, IFG, the right SPL, and the left cerebrum. In our study, the memory task for memory recollection required the retrieval of the integrated word-voice context. It was interesting to find that the FC of the PCC to the right AnG was positively correlated with immediate and 5-min AVLT scores but not with 20-min AVLT scores. Thakral et al. (2017) found that the AnG was critical for episodic simulation and memory. Our result suggests that the aberrant FC of the PCC to the AnG was more associated with short-term memory functional decline than with long-term decline in T2DM patients. Moreover, the AnG was also closely associated with complex language functions, such as content and episodic memories (Seghier 2013). Binder et al. (2009) revealed that the AnG was more important for semantic rather than perceptual features and may be a key region for semantic processing. Bravo et al. (2017) reported that the AnG was implicated in mental state attribution and attention reorienting processes. Therefore, we assumed that the T2DM patients lacked the attention to comprehend the words that the researcher spoke and had short-term memory dysfunction, leading to poor performance in repeating the words because the connection route of the PCC to the right AnG was disrupted.

Another short-term memory test, the DST showed different results. The FC of the PCC to the IFG was found to be weak and positively correlated with DST scores. The IFG is an area of the frontal gyrus that is close to the precentral gyrus. Previous studies showed that this region is not only related to memory but also participates in language processing (Liakakis et al. 2011). Chen et al. (2014) reported that T2DM patients exhibited reduced activation in the left IFG under different working memory loads. Costafreda et al. (2006) revealed that the left IFG was associated with both phonologic and semantic operations in functional neuroimaging studies. Liakakis et al. (2011) demonstrated that one of the clusters in the IFG was

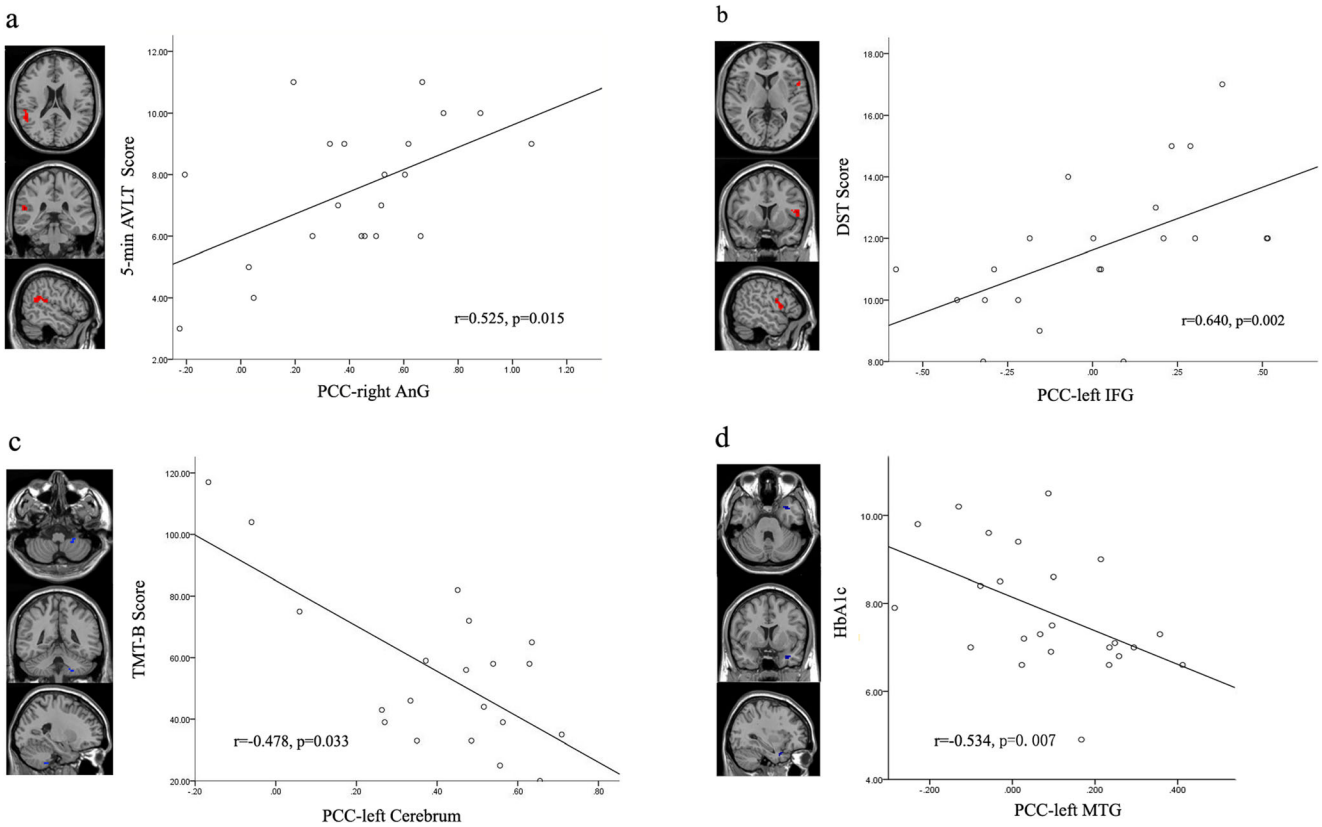

Fig. 3 Significant correlations between FC of the PCC and neuropsychological performances in T2DM patients. a Correlation between the FC of PCC- to the right AnG and the 5-min AVLT score. b Correlation between the FC of PCC- to the left IFG and the DST score. c Correlation between the FC of PCC- to the left cerebrum and the TMT-B Score. d Correlation between the FC of PCC- to the left MTG and HbA_{1c} levels. The red color represents a positive correlation, and the blue color represents a negative correlation. PCC, posterior cingulate cortex; AnG, angular gyrus; IFG, inferior frontal gyrus; SPL, superior parietal gyrus; AVLT, auditory verbal learning test; DST, digit span test; TMT-B, trail-making test B

involved in memory. Our results suggested that the FC of the PCC to the IFG is another connection route associated with short-term memory. However, since the DST examines the numerical memory, we hypothesized that numeral figures and words may involve different connection routes and the FC of the PCC to the IFG may be associated with the former, while the right AnG may be associated with the latter in T2DM patients. However, more studies comparing numerical and word memory are needed. Previous studies showed that the middle temporal gyrus (MTG) plays a vital role in memory tasks, verbal functions, verbal fluency, language processing and speech production (Pihlajamaki et al. 2000; Wood et al. 2016), and we also found the FC of the PCC to the MTG associated with memory test scores and HbA_{1c} levels, our results are consistent with the previous studies.

We found that the right SPL and left cerebrum connected to the PCC were negatively correlated with TMT scores in this study and that these regions were associated with motor, attention and spatial orientation. The TMT examines visual conceptual and visuo-motor tracking. Previous studies reported that the SPL and its FC to other regions was aberrant on fMRI. Liu et al. (2017) revealed a weaker FC between the right insula and the SPL and between the right straight gyrus and right SPL in T2DM patients than in healthy patients. Liang et al. (2012) also revealed decreased connectivity between the straight gyrus and the SPL in patients with mild cognitive impairment, which was related to attention regulation impairment. Bledowski et al. (2004) showed that activation of the SPL was correlated with attention switching ability in a distractor condition. Our study suggested that this FC route of the PCC to the right SPL is associated with attention and spatial orientation. T2DM patients may lack attention and usually needed more time to finish a task, indicating a decline in spatial orientation function. Previous studies have demonstrated matter integrity damage in the cerebellum, and in our previous studies (Hsu et al. 2012; Reijmer et al. 2013; Frøkjær et al. 2013), we used DTI and found damaged fibers across the cerebrum and decreased anatomical connections in the cerebellar and cerebro-cerebellar circuits of T2DM patients (Fang et al. 2017; Tan et al. 2016). Seldom have studies reported on aberrant functional connectivity of the cerebrum. The FC to the left cerebrum was the only connection we found from the PCC to the infratentorial region. The cerebellum plays an important role in motor control and may also be

involved in some cognitive functions such as attention, coordination and precision (Strick et al. 2009; Ivry et al. 2002). It receives input signals from the spinal cord and other parts of the brain and integrates these inputs to elicit motor activity. In our previous studies, we used DTI and found damaged fibers across the cerebrum and decreased anatomical connections in the cerebellar and cerebro-cerebellar circuits of T2DM patients We supposed that T2DM patients may have dysfunction in the circuit that accepts and generates signals outside of the DMN and that several FC routes of the PCC (the region within the DMN) to brain regions outside of the DMN may be responsible for this circuit.

T2DM was demonstrated to be closely related to depression which was associated with functional connectivity alternations of the DMN. It is necessary to discuss the potential relationship between DMN and depressed T2DM symptoms. Previous studies showed that alterations of some regions associated with DMN may play important roles in memory dysfunction and emotional deficits in depression. For example, the dorsal nexus had increased connectivity to DMN and patients showed decreased attention (Sheline et al. 2010). The hippocampus had abnormal connectivity to the amygdala and orbitofrontal cortex, which may be related to deficits in emotion-mediated memory (Savitz and Drevets 2009). The cerebellum had alternate connections to the limbic regions and was involved in mood regulation (Zeng et al. 2012; Sheline et al. 2009). Based on these findings, previous studies also developed classification of major depression (Zeng et al. 2014a, b, 2012) and regarded these regions as biomarkers. In our current study, we also found abnormal functional connectivities of the DMN that were related to memory and attention deficits in T2DM patients. Our findings indicated potential relationships between depression and T2DM. We supposed that DMN may be the key network and may have an effect on depressed symptoms with the development of T2DM. More accurate evaluations of depressed symptoms in T2DM patients should be included in further studies.

In conclusion, a weak FC of the PCC to several brain regions was associated with cognitive dysfunction in T2DM patients. These FC routes of the PCC may serve as biomarkers to further reveal the biological mechanism in the underlying neuropathological process of T2DM-related cognitive dysfunction and may provide evidence for further molecular biology studies.

Limitations

The current study has several limitations. First, the T2DM patients were taking various anti-diabetic medications that could have affected neural activities. Future studies should include medication-naïve subjects to avoid this possible bias. Second, the relatively small sample size in the current study may have reduced our ability to detect altered FC of the PCC and its relationship with neurocognitive performance. Therefore, future studies with larger sample sizes are required. Moreover, none of the T2DM patients in our study had high blood pressure, but almost all of them had higher systolic blood pressures than the controls, which could have affected the results.

Compliance with ethical standards

Conflicts of interest We declare that we have no conflict of interest.

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