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Changes in default mode network connectivity in different glucose metabolism status and diabetes duration

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ABSTRACT

Aims/hypotheses: It is now generally accepted that diabetes increases the risk for cognitive impairment, but the precise mechanisms are poorly understood. In recent years, resting-state functional magnetic resonance imaging (rs-fMRI) is increasingly used to investigate the neural basis of cognitive dysfunction in type 2 diabetes (T2D) patients. Alterations in brain functional connectivity may underlie diabetes-related cognitive dysfunction and brain damage. The aim of this study was to investigate the changes in default mode network (DMN) connectivity in different glucose metabolism status and diabetes duration.

Methods: We used a seed-based fMRI analysis to investigate positive and negative DMN connectivity in four groups (39 subjects with normal glucose metabolism [NGM], 23 subjects with impaired glucose metabolism [IGM; i.e., prediabetes], 59 T2D patients with a diabetes duration of < 10 years, and 24 T2D patients with a diabetes duration of ≥10 years).

Results: Negative DMN connectivity increased and then regressed with deteriorating glucose metabolism status and extending diabetes duration. DMN connectivity showed a significant correlation with diabetes duration.

Conclusion/interpretation: This study suggests that DMN connectivity may exhibit distinct patterns in different glucose metabolism status and diabetes duration, providing some potential neuroimaging evidence for early diagnosis and further understanding of the pathophysiological mechanisms of diabetic brain damage.

1. Introduction

The human brain is one of the most metabolically-active organs in the body, so it follows that glucose metabolism dysregulation, a hallmark of diabetes, would cause a variety of deleterious effects on neural and cognitive processes. Previous studies have confirmed that type 2 diabetes (T2D) is associated with alterations in resting-state activity and connectivity in the brain. Resting-state functional magnetic resonance imaging (rs-fMRI) is generally considered a powerful tool for measuring brain functional connectivity. Recently, a number of studies used rs-fMRI to investigate the neuronal basis of cognitive dysfunction in T2D patients (Zhou et al., 2010; Musen et al., 2012; Cui et al., 2015; Chen et al., 2015; Xia et al., 2013). In particular, the default mode network (DMN) has been studied extensively. As a system of anatomically connected and functionally correlated brain regions, DMN exhibits elevated activity during undirected passive tasks (Andrews-Hanna, 2012). At the same time DMN is also related to "thinking about others", some goal-oriented tasks such as social working memory, executive

Abbreviations: ALFF, amplitude of low frequency fluctuation; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CSF, cerebrospinal fluid; DMN, default mode network; FA, flip angle; FDR, false discovery rate; FOV, field of view; FPG, fasting plasma glucose; 2hPG, 2-hour postprandial glucose; HbA_{1c}, glycosylated hemoglobin A_{1c}; HDL, high-density lipoprotein; HOMA2-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGM, impaired glucose metabolism; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; NEX, number of excitations; NGM, normal glucose metabolism; rs-fMRI, resting-state functional magnetic resonance imaging; SCr, serum creatine; SFG, superior frontal gyrus; T2D, type 2 diabetes; TG, triglyceride; TE, echo time; TR, repetition time; WM, white matter

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control, and DMN has been shown to be negatively correlated with other networks in the brain such as attention networks (Broyd et al., 2009; Andrews-Hanna, 2012), which can affect several mental disorders including bipolar disorder and schizophrenia as well (Zeng et al., 2012; Zeng et al., 2014a,b; He et al., 2016; Sui et al., 2018). DMN has also been involved with diabetes, so far the most consistent finding has been that T2D is associated with disrupted DMN connectivity (Macpherson et al., 2017). However, it remains unclear how DMN connectivity changes in the clinical progression of T2D.

Most cases of T2D undergo a gradual progression from normal glucose metabolism (NGM) to impaired glucose metabolism (IGM; i.e., prediabetes; including impaired fasting glucose [IFG] and impaired glucose tolerance [IGT]) and eventually to T2D. From the perspective of preventive medicine, it is more beneficial to explore brain alterations in different glucose metabolism status and diabetes severity than to focus only on the overall T2D. So the subjects in this study were divided into four levels according to glucose metabolism status and the duration of diabetes, including NGM, prediabetes, T2D patients with a diabetes duration of < 10 years, and T2D patients with a diabetes duration of ≥ 10 years.

There is also evidence that interventions involving physical activity and weight loss may affect brain functional connectivity. Recent studies have shown that increased physical activities have protective effects on the brain, including increases in the volume (Erickson et al., 2011) and blood flow (Burdette et al., 2010) to the hippocampus, and improved functional connectivity in the DMN (Burdette et al., 2010; Li et al., 2014). The importance of these findings is the implication that diabetes and related factors are modifiable, potentially permitting interventions to prevent or abate diabetic brain damage.

In this study, 39 subjects with NGM, 23 subjects with prediabetes, 59 T2D patients with a diabetes duration of < 10 years, and 24 T2D patients with a diabetes duration of ≥ 10 years were recruited. We used seed-based rs-fMRI analyses to investigate positive DMN connectivity (within-network correlations) in the four groups. We examined negative DMN connectivity (between-network anticorrelation) as well, as the previous studies suggest that the anticorrelation between the DMN and task-positive network (i.e., negative DMN connectivity) is associated with cognitive (dys)function (Di Perri et al., 2016). The purpose is to detect the changes of DMN functional connectivity in subjects with different glucose metabolism status and diabetes severity and to investigate the relationships between the strength of DMN functional connectivity and diabetes-related clinical variables.

2. Material and methods

2.1. Participants

In this cross-sectional study, based on the natural progression of T2D, we recruited 145 participants who met the criteria, including 39 subjects with NGM as controls, 23 subject with prediabetes, 59 T2D patients with a diabetes duration of < 10 years (here defined as early-stage T2D), and 24 T2D patients with a diabetes duration of ≥ 10 years (defined as later-stage T2D), between October 1, 2014 and October 31, 2016 from the Diabetes Outpatient Department and the Health Management Center at the Third Xiangya Hospital. All of the participants were selected according to the following criteria: (1) right-handed; (2) no visual, auditory and communication disorders; (3) no history of coronary disease, nephritis, tumors, gastrointestinal disease, or psychiatric illness; (4) able to meet the physical demands of the imaging procedure; (5) T2D was diagnosed using established criteria based on medical histories, medication use, fasting plasma glucose (FPG) levels ≥ 7.0 mmol/l or plasma glucose (PG) levels ≥ 11.1 mmol/l at any time; (6) IGM was diagnosed based on FPG levels of 6.1 to 7.0 mmol/l or a 2-h postprandial glucose (2hPG) level of 7.8 to 11.1 mmol/l; (7) NGM was diagnosed based on FPG levels < 6.1 mmol/l and 2hPG levels < 7.8 mmol/l. This study was approved by the Medical Ethical Committee of the Third Xiangya Hospital of Central South University. All participants gave written informed consent after a detailed description of the study.

2.2. Procedure and measures

Each subject provided a medical history and underwent a physical examination, during which clinical data were recorded or measured with standard laboratory tests, including sex, age, education, body mass index (BMI), blood pressure (BP), FPG, 2hPG, fasting insulin, fasting C-peptide, glycosylated hemoglobin A1c (HbA_{1c}), blood urea nitrogen (BUN), serum creatine (SCr), total cholesterol, triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL). The updated homeostasis model assessment of insulin resistance (HOMA2-IR) index was calculated using the HOMA2 Calculator v2.2.3 (http://www.dtu.ox.ac.uk/homacalculator/) from FPG and fasting insulin values to evaluate insulin resistance in the subjects without insulin treatment.

2.3. Image acquisition

The rs-fMRI scanning was performed on a 1.5-T scanner with a standard 8-channel head coil (Avanto, Siemens, Erlangen, Germany) for all subjects. For rs-fMRI, echo planar imaging (EPI) was employed with the following imaging parameters: repetition time (TR) = 2000 ms, echo time (TE) = 40 ms, flip angle (FA) = 90°, slice thickness = 4.0 mm, slice spacing = 1.0 mm, number of slices = 28, matrix size = 128 × 128, field of view (FOV) = 240 mm × 240 mm, number of excitations (NEX) = 1.0, scan time = 8 min 26 s, and scan range = 250.

2.4. Image processing

All of the rs-fMRI data were preprocessed by using previously described procedures (Zeng et al., 2014a,b; Zeng et al., 2018) with SPM (SPM8, http://www.fil.ion.ucl.ac.uk/spm). For each subject, the first ten frames of the scanned data were discarded for magnetic saturation. Slice-timing and head motion correction were performed in which the remaining images were realigned to the first volume within a run for the correction of interscan head motions. All of the participants in this study had < 2 mm translation and 2° of rotation in any of the x-, y-, and z-axes. Next, spatial normalization, spatial smoothing and temporal filtering were performed with the images normalized (3 mm isotropic voxels) to the standard EPI template in the Montreal Neurological Institute (MNI) space, spatially smoothed with a Gaussian filter kernel of 6 mm full-width half-maximum and temporally filtered with a Chebyshev bandpass filter (0.01–0.08 Hz). Finally, we removed the signals which are unlikely to reflect neuronal activity from the filtered images by multiple regression, including three mean signals from the white matter (WM), cerebrospinal fluid (CSF) and whole brain and six parameters obtained from head motion correction, as well as their first-order derivative terms. The residuals of the regression were used for further analysis.

To examine the differences in rs-fMRI functional connectivity among the four groups, we performed a seed-based correlation analysis based on the images of residual. In our research, two seeds were defined as spheres with a 5-mm radius around the peak coordinates of the two main DMN nodes (i.e., the medial prefrontal cortex [−1, 54, 27] and the posterior cingulate cortex [0, −52, 27]) (Raichle, 2011; Di Perri et al., 2016). The time series from the voxels in each seed region were extracted and then averaged together. For each individual, we obtained functional connectivity maps by calculating Pearson's correlation coefficients between this averaged signal and the time series of each voxel in the entire brain. The functional correlation r between a voxel and the given seed is defined as $r = cov(V, R)/(\sigma(V) * \sigma(R))$, where V denotes the time series of this voxel, R denotes the averaged signal of the seed, and $cov(\cdot)$ and $\sigma(\cdot)$ denote the covariance and standard

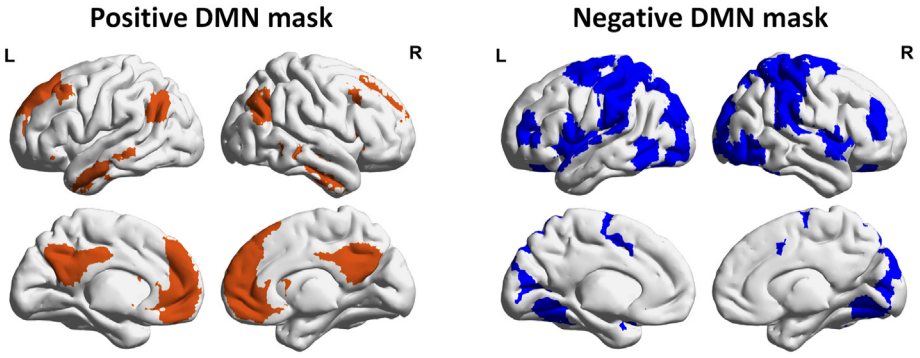

Fig. 1. Functional connectivity masks of DMN from all subjects (one-sample *t*-tests, FDR, $p < .005$, cluster size > 30). (Left) The regions in orange showed significant positive functional connectivity with the seeds of DMN. (Right) The regions in blue showed significant negative functional connectivity with the seeds of DMN.

deviation, respectively. It should be noted that roughly averaging the time series from the voxels of spatially separated ROIs may cause possible problems in the calculation of functional connectivity. But we averaged the time series from the voxels of the posterior cingulate cortex and medial prefrontal cortex here because of the high temporal correlation between the two critical DMN nodes, as the previous studies (Di Perri et al., 2016). Subsequently, Fisher's r-to-z transformation was applied to the resulting maps to improve normality.

For the z-value maps of the four groups, one-sample *t*-tests ($p < .005$, false discovery rate [FDR]-corrected) were conducted first to identify the brain regions showing significant positive and negative functional connectivity, respectively, with the DMN. By combining the binary spatial maps of the four groups, we obtained a positive spatial mask and a negative spatial mask (Fig. 1). Within these two masks, averaged positive and negative DMN functional connectivity were calculated for each subject. Finally, group-to-group two-sample t-tests were performed to identify between-group differences in positive and negative DMN connectivity. Pearson correlation analyses were performed among all patients with T2D to assess the relationship between DMN connectivity and diabetes-related clinical variables.

In addition, to further examine the changes of the spatial functional pattern of DMN, the voxel-based comparison was also performed among the four groups. Specifically, repeated measures analyses of variance (ANOVAs, $p < .005$) were performed on the individual z-maps in a voxel-wise manner by applying the spatial positive and negative masks, respectively.

3. Results

The demographic and clinical characteristics of the four groups are summarized in Table 1. The groups differed significantly in HbA_{1c}, FPG, 2hPG, TG and HDL (Table 1, $p < .05$).

Negative DMN connectivity was increased in subjects with early-stage T2D compared with controls ($p < .05$). Individuals with later-stage T2D had lower negative DMN connectivity than those with early-stage T2D ($p < .01$). Negative DMN connectivity did not differ between individuals with prediabetes and those with early-stage T2D or NGM ($p > .05$). Therefore, in the different glucose metabolism status and diabetes duration, negative connectivity appears to increase and then regress instead of following a linear pattern (Fig. 2A).

Positive DMN connectivity was not significantly altered in subjects with prediabetes or early-stage T2D compared with controls ($p > .05$). Patients with later-stage T2D had significantly lower positive DMN connectivity than those with early-stage T2D ($p < .05$). Positive connectivity followed a similar overall trend to negative connectivity, increasing and then regressing (Fig. 2B).

Correlation analyses indicated that both negative and positive DMN connectivity were correlated with diabetes duration ($r = 0.32$, $p < .01$ and $r = -0.26$, $p = .02$, respectively; Fig. 2C,D).

ANOVAs indicated that some regions exhibited the significant changes of positive functional connectivity with the DMN, including the bilateral superior frontal gyrus and right caudate. The significant changes of negative functional connectivity were observed between the DMN and the right middle temporal gyrus, the left precentral gyrus as well as the right superior parietal gyrus (Table 2 and Fig. 3).

4. Discussion

In the current study, we observed that negative connectivity increases and then decreases as a parabolic relation instead of following a simple linear pattern in different glucose metabolism status and diabetes duration. The magnitudes of both the positive and negative DMN connectivity values are correlated with diabetes duration. To the best of our knowledge, this cross-sectional study is the first to examine the positive and negative DMN connectivity of groups with NGM, prediabetes and T2D with different diabetes duration, especially from the perspective of T2D development and the severity of diabetes (here assessed by diabetes duration).

Patients with early-stage T2D had significantly increased negative connectivity and slightly increased positive connectivity. Some previous studies have suggested that between-network anticorrelations reflect an effective ability to switch between internal thoughts and perception of the external world (Fransson, 2005). Previous studies have also shown that early-stage type 1 diabetes patients had enhanced functional connectivity (Van Duinkerken et al., 2012; Saggar et al., 2017). Moreover, similar findings were found in patients with early-stage multiple sclerosis and mild cognitive impairment (Roosendaal et al., 2010; Celone et al., 2006). This phenomenon may be a result of the loss of local inhibitory neurons, leading to the augmentation of long-distance neuronal activation which, in turn, would lead to an increase in the functional connectivity of the brain (de Haan et al., 2012). This enhancement could also be a reaction to a loss of connectivity that could inhibit the lower-order cognitive networks (Seeley, 2011). Another theory interprets the increase in functional connectivity as a sign of functional reorganization (Schoonheim et al., 2010) in response to early, mild brain damage. Compensatory mechanisms, such as the functional reorganization of networks, may play a role in counteracting the slight decrements in cognitive performance among participants with prediabetes and early-stage T2D before the onset of clinically apparent cognitive deterioration (van Bussel et al., 2016). Then, when the functional reorganization fails, functional networks become disrupted and cognitive decrements become identifiable in the later stages of diabetes. This decompensation may be why patients in our study with later-stage T2D had lower connectivity than those with early-stage T2D. Furthermore, this disruption of functional networks may explain the increased risk of developing mild cognitive impairment and

Table 1
Demographic and clinical characteristics of all subjects.

	NGM (n = 39)	Prediabetes (n = 23)	T2D		p-Value
			Duration < 10 years (n = 59)	Duration ≥ 10 years (n = 24)	
Age (years)	57.0 ± 8.2	58.3 ± 6.9	55.5 ± 7.4	59.7 ± 6.5	0.10[a]
Sex (male/female, n)	18/21	11/12	35/24	13/11	0.58[b]
Education (years)	11.6 ± 3.5	11.9 ± 3.5	12.0 ± 3.7	12.2 ± 3.6	0.93[a]
BMI (kg/m^2)	24.5 ± 2.4	25.8 ± 3.3	25.3 ± 3.1	24.8 ± 2.2	0.30[a]
Systolic BP (mmHg)	125.2 ± 18.6	131.2 ± 13.3	132.7 ± 15.6	130.0 ± 15.4	0.16[a]
Diastolic BP (mmHg)	75.8 ± 12.3	79.6 ± 10.5	79.9 ± 9.6	74.5 ± 10.4	0.08[a]
Total cholesterol (mmol/l)	5.2 ± 0.9	5.1 ± 0.9	5.0 ± 1.1	4.7 ± 1.0	0.33[a]
TG (mmol/l)	1.6 ± 0.7	2.6 ± 2.4	2.6 ± 2.3	1.7 ± 1.5	0.03[a,*]
HDL (mmol/l)	1.7 ± 0.4	1.7 ± 0.4	1.4 ± 0.4	1.5 ± 0.4	0.005[a,*]
LDL (mmol/l)	2.9 ± 0.7	2.4 ± 0.9	2.7 ± 0.8	2.6 ± 0.8	0.12[a]
BUN (mmol/l)	4.7 ± 1.1	5.1 ± 0.8	5.2 ± 1.4	5.2 ± 1.6	0.35[a]
SCr (μmol/l)	64.5 ± 13.3	66.5 ± 15.8	65.7 ± 21.3	65.0 ± 16.2	0.98[a]
FPG (mmol/l)	5.3 ± 0.4	5.7 ± 0.6	8.3 ± 2.6	7.8 ± 2.2	< 0.001[a,*]
2hPG (mmol/l)	6.2 ± 0.9	7.7 ± 1.6	14.0 ± 5.2	13.4 ± 4.2	< 0.001[a,*]
Fasting insulin (μU/ml)	10.2 ± 5.8	13.2 ± 5.3	12.5 ± 8.4	11.5 ± 8.4	0.34[a]
Fasting C-peptide(ng/ml)	2.1 ± 0.8	2.5 ± 0.6	2.3 ± 0.9	1.9 ± 0.7	0.05[a]
HbA_{1c} (mmol/mol [%])	38 ± 4.4 (5.6 ± 0.4)	41 ± 6.6 (5.9 ± 0.6)	58 ± 16.4 (7.5 ± 1.5)	58 ± 14.2 (7.5 ± 1.3)	< 0.001[a,*]
HOMA2-%β	91.2 ± 35.9	69.3 ± 35.4	79.3 ± 46.3	85.3 ± 42.2	0.22[a]
HOMA2-IR	1.3 ± 0.7	1.7 ± 0.7	1.8 ± 1.2	1.6 ± 1.2	0.15[a]

All data are expressed as the mean ± standard deviation (SD) unless otherwise indicated.
NGM, normal glucose metabolism; BMI, body mass index; BP, blood pressure; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BUN, blood urea nitrogen; SCr, serum creatine; FPG, fasting plasma glucose; 2hPG, 2-h postprandial glucose; HbA_{1c}, glycosylated hemoglobin A1c; HOMA2-%β, updated homeostatic model assessment of beta-cell function; HOMA2-IR, updated homeostatic model assessment of insulin resistance.
[*] Indicates a significant difference between groups (p-value < .05).
[a] ANOVA test.
[b] Pearson's chi-squared test.

Alzheimer's disease in the later stages of T2D.

Furthermore, we found some regions exhibited the significant diabetes-related functional connectivity changes within the DMN, such as the bilateral superior frontal gyrus (SFG), right middle temporal gyrus (MTG), left precentral gyrus, right superior parietal gyrus, et al. The structural and functional changes of these brain regions have been reported in the diabetic population. Significantly increased connectivity was found in the bilateral SFG in T2D patients (Cui et al., 2015). The pooled and subgroup meta-analyses found that T2D patients showed robustly reduced gray matter in the MTG, medial SFG, et al. (Liu et al., 2017). Compared with healthy controls, T2D patients had significantly decreased amplitude of low-frequency fluctuation (ALFF) values in the bilateral MTG, et al.; and increased ALFF values in both the bilateral cerebellum posterior lobe and right cerebellum culmen (Xia et al., 2013).

In addition, we identified no evident alteration of brain DMN function connectivity in prediabetes. Previous studies in prediabetes patients have focused mostly on changes in brain morphometry (Schneider et al., 2017; Markus et al., 2017). No consistent results were obtained, likely because the neuroimaging methods and the characteristics of the subjects differed from study to study. Therefore, it is necessary to conduct further research in a large sample and expand into longitudinal, multimodal studies.

Moreover, we observed that DMN connectivity in patients with T2D was significantly correlated with disease duration. The longer the diabetes duration was, the weaker the average positive and negative connectivity would be. A dynamic equilibrium of interaction within the DMN and between the DMN and other brain systems, such as the task-positive network, is very important for the maintenance of normal cognitive function (Uddin et al., 2009). The reduced between-network anticorrelations indicate that the effective capacity to switch between internal thoughts and perception of the external world may be impaired. Thus, one may conclude that the impairment of cognitive function becomes more serious as the duration of diabetes prolong, which is consistent with previous findings (Schneider et al., 2017; Yang et al., 2016).

This study has some limitations that should be noted. First, this experiment has a cross-sectional design and a relatively small sample; therefore, a longitudinal study with a large sample is needed to confirm the findings. Second, the effects of glucose-lowering treatments on functional connectivity were not taken into account. Third, this study did not include cognitive assessments to examine the relationship between brain connectivity changes and cognitive deficits; such assessments could be carried out in the future. In addition, another limitation of this study is the use of 1.5-T MRI scanner for data acquisition, as the signal-to-noise ratio of 1.5-T MRI is slightly lower than 3.0-T MRI. With the wide availability of higher field strength MRI scanners, this may not be conducive to future longitudinal comparison studies. Nevertheless, the current findings provide new insights and prompt new questions for future studies to further understand the pathophysiology of diabetic brain damage.

5. Conclusions

In conclusion, we detected the impairment of connectivity patterns in subjects with different glucose metabolism status and diabetes severity. No evident alteration of positive or negative DMN connectivity was observed in prediabetes, and compensatory enhancement of negative DMN connectivity was displayed in patients with a diabetes duration of < 10 years, while decompensatory reductions were found in patients with a longer duration of diabetes (≥10 years). The DMN connectivity of T2D patients was associated with illness duration. Overall, T2D is associated with disrupted DMN functional connectivity. DMN connectivity may exhibit distinct patterns in different glucose metabolism status and diabetes duration, providing some potential neuroimaging evidence for early diagnosis and further understanding of the pathophysiological mechanisms of diabetic brain damage.

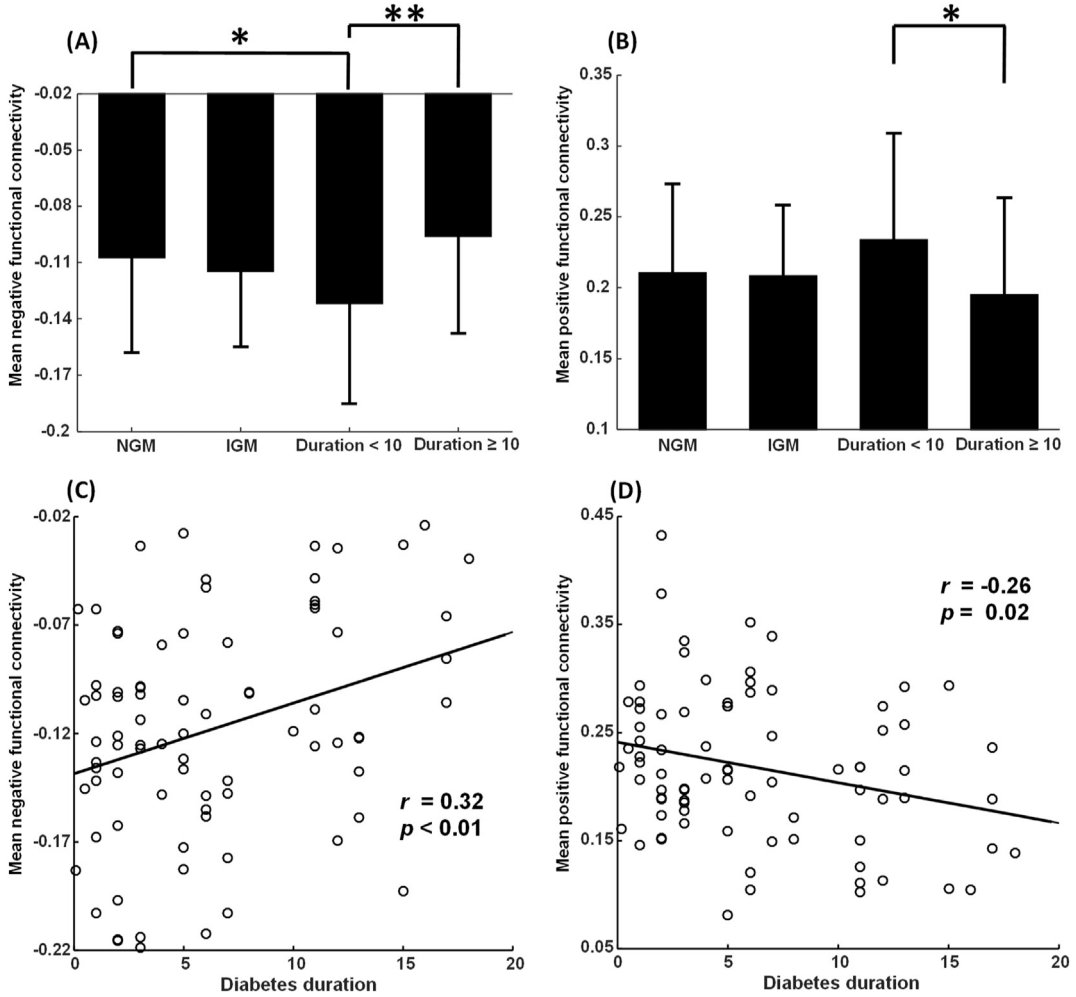

Fig. 2. (A) Between-group differences in mean negative DMN functional connectivity. Negative connectivity did not differ between subjects with prediabetes and those with a diabetes duration of < 10 years, and no significant differences between subjects with prediabetes and controls were observed ($p > .05$). Negative DMN connectivity was significantly increased in patients with a diabetes duration of < 10 years compared with controls ($*p < .05$). The patients with a diabetes duration of ≥10 years had lower negative connectivity than those with a duration of < 10 years ($**p < .01$). (B) Between-group differences in mean positive DMN functional connectivity. Positive connectivity was not significantly different among controls, subjects with prediabetes, and those with a diabetes duration of < 10 years ($p > .05$). The patients with a diabetes duration of ≥10 years had significantly lower positive DMN connectivity than those with a duration of < 10 years ($*p < .05$). (C) A significant positive correlation between negative DMN functional connectivity and diabetes duration. NGM, normal glucose metabolism; IGM, impaired glucose metabolism; Duration < 10, diabetes duration of < 10 years; Duration ≥10, diabetes duration of ≥10 years. (D) A negative correlation between positive DMN functional connectivity and diabetes duration.

Table 2
Significantly altered spatial patterns of positive and negative DMN functional connectivity were observed among the four groups.

Target region	Side	BA	Cluster size	MNI coordinates	F-value
			(voxels)	(*x*, *y*, *z*)	F(3,141)
Positive DMN FC					
Medial Superior Frontal Gyrus	L	10	12	−9, 48, 12	5.71
Superior Frontal Gyrus	R	9	10	12, 48, 30	6.25
Caudate	R		17	12, 15, 21	6.73
Negative DMN FC					
Middle Temporal Gyrus	R	21	23	33,-66,27	8.55
Precentral Gyrus	L	6	13	30,-15,54	6.33
Superior Parietal Gyrus	R	7	10	15,-54,72	5.17
Cerebellum Posterior Lobe	R		10	27,-51,39	6.34

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Duality of interest

The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement

H.H.L. designed the experiment, collected the data, performed the analysis and wrote the manuscript. J.L. designed the experiment, collected the data and revised the manuscript. L.M.P. performed the data analysis and wrote the Methods section. Z.C.F., L.C., H.S.L., H.S. and D.W.H. contributed to the discussion and manuscript revision. L.L.Z.

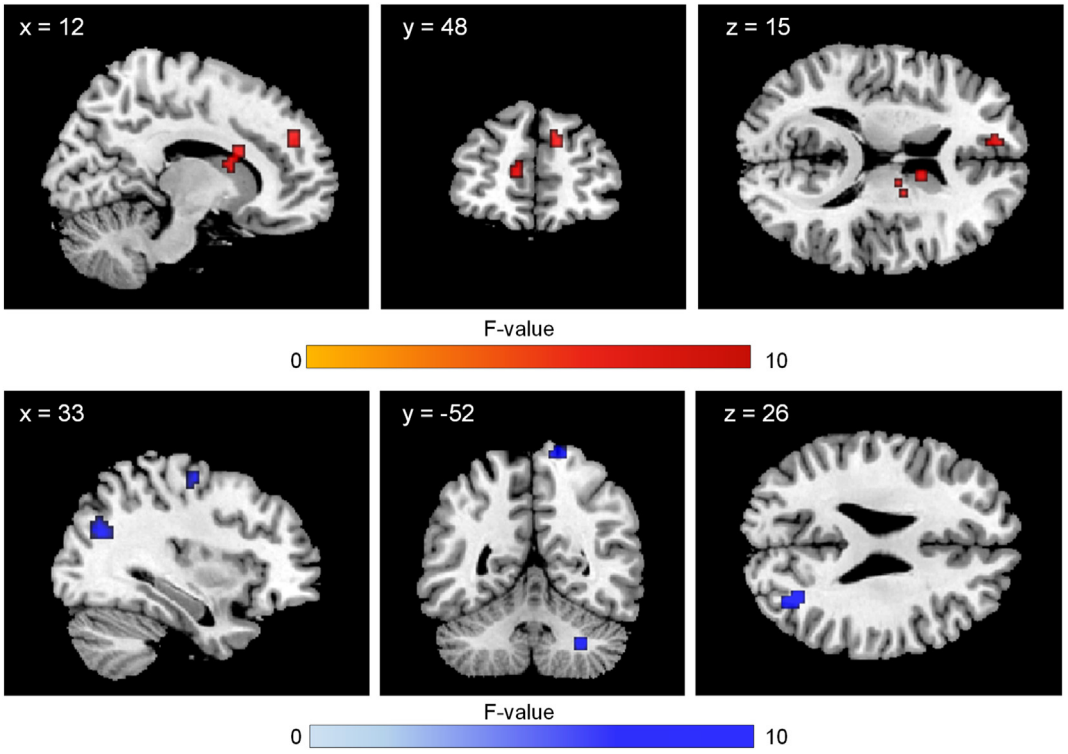

Fig. 3. Comparison of the positive and negative DMN functional connectivity patterns among the four groups.

and W.W. made contributions to the design of the experiment and revised the manuscript. Both L.L.Z. and W.W. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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