Effects of polygenic risk score of type 2 diabetes on the hippocampal topological property and episodic memory

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Abstract
Type 2 diabetes is associated with a higher risk of dementia. The pathogenesis is complex and partly influenced by genetic factors. The hippocampus is the most vulnerable brain region in individuals with type 2 diabetes. However, whether the genetic risk of type 2 diabetes is associated with the hippocampus and episodic memory remains unclear. This study explored the influence of polygenic risk score (PRS) of type 2 diabetes on the white matter topological properties of the hippocampus among individuals with and without type 2 diabetes and its associations with episodic memory. This study included 103 individuals with type 2 diabetes and 114 well-matched individuals without type 2 diabetes. All the participants were genotyped, and a diffusion tensor imaging-based structural network was constructed. PRS was calculated based on a genome-wide association study of type 2 diabetes. The PRS-by-disease interactions on the bilateral hippocampal topological network properties were evaluated by analysis of covariance (ANCOVA). There were significant PRS-by-disease interaction effects on the nodal topological properties of the right hippocampus node. In the individuals with type 2 diabetes, the PRS was correlated with the right hippocampal nodal properties, and the nodal properties were correlated with the episodic memory. In addition, the right hippocampal nodal properties mediated the effect of PRS on episodic memory in individuals with type 2 diabetes. Our results suggested a gene-brain-cognition biological pathway, which might help understand the neural mechanism of the genetic risk of type 2 diabetes affects episodic memory in type 2 diabetes.

Keywords Type 2 diabetes · Polygenic risk score · hippocampus · Topological network · Episodic memory

Introduction
Type 2 diabetes is associated with accelerated brain aging and a higher risk of dementia in late life (Riederer et al., 2017). However, the underlying neural mechanisms responsible for cognitive decline in type 2 diabetes have not been fully elucidated. The pathogenesis of diabetes is complex. A better understanding of the factors associated with cognitive decline, including brain and genetic markers, will facilitate early clinical intervention to attenuate severe cognitive dysfunction or dementia.

The hippocampus is the most vulnerable brain region in individuals with type 2 diabetes (Sanjari Moghaddam, Ghazi Sherbaf, & Aarabi, 2019), and episodic memory impairment related to the hippocampus is the most prominent and specifically affected cognitive domain in individuals with type 2 diabetes (McCrinnon et al., 2012). Hippocampus atrophy has been frequently reported in individuals with type 2 diabetes with cognitive decline (Hempel et al., 2012; Milne et al., 2018; Zhang et al., 2014). Studies showed weaker functional connectivities between the hippocampus and other brain regions in individuals with type 2 diabetes, which correlated with memory performance (Sun et al., 2018; Zhou et al., 2010). In recent years, several diffusion tensor imaging (DTI) studies identified white matter (WM) alterations in the hippocampus and hippocampus-related WM fibers...
in individuals with type 2 diabetes (Qi et al., 2017; Sanjari Moghaddam et al., 2019). Of significant importance, by using a graph-theoretical approach (Xiong et al., 2020), the altered hippocampal topological properties were detected with a correlation with cognitive impairment in individuals with type 2 diabetes, suggesting that DTI topological network properties could be a sensitive marker of cognitive decline even when there is no sign of macrostructural gray matter (GM) volume abnormalities and atrophy of brain structures (Sanjari Moghaddam et al., 2019).

There is ample evidence that the individual risk of type 2 diabetes is strongly influenced by genetic factors, with a heritability of 26-69% depending on the age of onset (Padilla-Martínez et al., 2020). Over the past decades, more than a hundred genetic loci associated with type 2 diabetes risk have been discovered using genome-wide association studies (GWAS) (Spracklen et al., 2020). Although these variants have only a low or moderate impact on type 2 diabetes’ disease risk individually, combining multiple loci into a polygenic score may have significant predictive utility and potentially influence clinical management. Here we introduced a polygenic risk score (PRS), which accumulates the total risk of a phenotype in an individual based on variants present in their genome (Padilla-Martínez et al., 2020). In some cognitive changes-related diseases such as AD (de Rojas et al., 2021) and schizophrenia (Wimberley et al., 2017), the PRS of the disease has been proven to predict correlates of the disease risk and related brain structural perturbations. The type 2 diabetes’ PRS were reported to be linked to brain structural connectivity and cognition in patients with Major depressive disorder (Reppe et al., 2022). However, whether and how the type 2 diabetes’ PRS is related to the brain abnormality has not been documented in patients with type 2 diabetes.

Because the hippocampus is the most vulnerable target in type 2 diabetes, this study focused analyses on the hippocampus and its relationship with episodic memory performance. Genetic risk for type 2 diabetes was determined using a PRS that integrated 97 type 2 diabetes risk single-nucleotide polymorphisms (SNPs). We aimed to investigate whether and how the type 2 diabetes-related PRS affected the hippocampal topological network properties of the individuals with and without type 2 diabetes and to explore whether the PRS affected episodic memory by affecting the WM topological network properties of the hippocampus.

**Method**

**Participant**

In this study, the individuals with and without type 2 diabetes were recruited from the endocrinology department of Tianjin Medical University General Hospital and community recruitment, respectively, between 2018 and 2019. A total of 109 individuals with type 2 diabetes and 119 individuals without type 2 diabetes were initially recruited. Four individuals with type 2 diabetes and five without type 2 diabetes were excluded due to poor blood sample quality. Two individuals with type 2 diabetes and five without type 2 diabetes were excluded due to poor image quality. Finally, 103 individuals with type 2 diabetes and 114 well-matched individuals without type 2 diabetes were enrolled. Type 2 diabetes was diagnosed according to the 2010 criteria of the American Diabetes Association (ADA) (Association, 2010). Individuals with type 2 diabetes-related complications, including peripheral neuropathy, retinopathy, and nephropathy, were excluded from the study. None of the individuals had experienced severe hypoglycemia during the past two years. All the participants were right-handed. Exclusion criteria were: (1) previous history of brain disease, including stroke, epilepsy, trauma, or hemorrhage; (2) Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score <27; (3) psychiatric or neurologic disorders that may affect cognition; (4) alcohol or drug abuse; and (5) contraindications for MRI scan. All subjects underwent a series of standardized clinical evaluations.

All the participants were in Chinese Hans. Height, weight, and body mass index (BMI) were measured for each participant. The criteria for hypertension were systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, or taking antihypertensive medications. Fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) were measured via standard laboratory testing.

**Neuropsychological testing**

A battery of cognitive assessments was performed before MRI. General cognition was assessed with the MMSE (Folstein et al., 1975). Anxiety and depression were evaluated with the Self-Rating Anxiety Scale (Zung, 1971) and the Self-Rating Depressive Scale (Zung, 1965), respectively. Episodic memory was assessed by two tests: (1) The Rey-Osterrieth Complex Figure Test (ROCF) (Shin et al., 2006) which consists of three conditions: copy, immediate recall, and delayed recall. (2) The Chinese version of the Auditory Verbal Learning Test (AVLT) (Rosenberg et al., 1984) including short- and long-term memory.
**Image data acquisition**

All imaging data were obtained on a 3.0-T MR system (Discovery MR750; General Electric, Milwaukee, WI, USA), equipped with an 8-channel phase-array head coil. DTI images were acquired by a single-shot echo planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 7000ms; echo time (TE) = 95ms; flip angle (FA) = 12°; field of view (FOV) = 256 mm × 256 mm; matrix = 128 × 128; slice thickness = 3 mm, no gap; 48 axial slices; 64 encoding diffusion directions with b = 1,000 s/mm², and 12 non-diffusion b = 0 s/mm² images. The Sagittal T1-weighted images were obtained using a brain volume sequence, as follows: TR = 8.2ms, TE = 3.2ms, TI = 450ms, FA = 12°, matrix = 256 × 256, and 188 continued sagittal sections with section thickness of 1 mm.

**Imaging preprocess and network construction**

The DTI data preprocessing steps were performed using a PANDA toolbox (Cui et al., 2013) based on FMRIB Software Library v5.0 (Jenkinson et al., 2012), briefly including brain extraction, realignment, eddy correct and motion artifact correction, fractional anisotropy calculation, and diffusion tensor tractography. An FA threshold of 0.2 and a turning angle threshold of 45° in the Fiber Assignment by Continuous Tracking (FACT) algorithm were set when tracking WM fibers. An estimate of head motion during the MRI scan was calculated using the output logfile of eddy correct. Rotation factor was not included as rotations and translations are highly correlated during the scanning (Rae et al., 2012).

An Automated Anatomical Labeling (AAL) atlas was used to parcellate each brain into 90 anatomical regions. For a detailed parcellation process, please see the Online Resource. Each AAL region was taken as a node, and interconnections between brain regions were taken as the edges of the structural network. Interconnections between brain regions were considered if at least three WM fibers were present between the regions, as in previous studies (Shu et al., 2012). Finally, a binary 90 × 90 matrix for each subject was obtained.

The nodal topological properties, including the nodal global efficiency (NGe), nodal local efficiency (NLe), nodal clustering coefficient (NCp), nodal shortest path length (NLp), and nodal degree (Nd), were calculated with the graph-theoretical network analysis toolbox (GRETNA; http://www.nitrc.org/projects/gretina). The explanation of these properties was documented in the Online Resource.

**Polygenic risk score**

After the strict QC and imputation process (for detailed steps, please see Online Resource), PRS was calculated. A recent meta-analyzed GWAS of type 2 diabetes in East Asian individuals (including 77,418 individuals with type 2 diabetes and 356,122 individuals without type 2 diabetes) (Spracklen et al., 2020) has identified 111 type 2 diabetes risk SNPs (adjusted for BMI), 97 of which were found in our imputed genotype dataset. The 97 risk SNPs were used for the calculation of PRS. The score was calculated on SNPs reaching genome-wide significance ($P = 5 \times 10^{-8}$). For each participant, the PRS was calculated by multiplying the number of risk alleles for each SNP by the weight for that SNP and then taking the sum across the 97 SNPs, according to the following formula (De Jager et al., 2009):

$$\omega_{ORi} = \ln(OR)$$

$$GRS = \sum_{i=1}^{I} \omega_{ORi}G_i$$

where $i$ was the SNP, $\omega_{ORi}$ was the weight for SNP $i$, and $G_i$ was the number of risk alleles. The weight was the natural log of the odds ratio (OR) value of each SNP, which was obtained from the above-mentioned type 2 diabetes GWAS research (Spracklen et al., 2020).

**Statistical approach**

**Demographic, clinical, behavioral data, PRS, and head motion**

Statistical analyses for demographic, clinical, behavioral data, PRS and headmotion were performed using Statistical Package for Social Sciences (SPSS, v. 23.0, IBM SPSS Statistics, IBM Corporation). The two samples T-test was used for continuous variables, and the Chi-square ($\chi^2$) test was used for categorical variables.
was used for categorical variables. The significant level was set at \( P < 0.05 \).

**PRS-by-disease interaction analysis**

The PRS-by-disease interactions on the bilateral hippocampal topological properties (NGe, NLe, NCp, NLp and Nd) were evaluated by analysis of covariance (ANCOVA) with the hippocampal topological property was treated as a dependent variable, diagnosis (individuals with type 2 diabetes vs. without type 2 diabetes), PRS, and their interaction as interesting independent variables, and age, gender, education years, BMI and head motion as confounding variables. Effect sizes were calculated using Cohen’s \( d \). When ANCOVA showed a statistically significant interaction effect after the Bonferroni correction, the post hoc correlation analyses were performed to test the relationship between the hippocampal topological properties and the PRS in the individuals with and without type 2 diabetes, respectively.

**Correlation analysis between hippocampal topological properties and episodic memory**

Partial correlation analyses were performed to test the correlation between the hippocampal topological properties and episodic memory tests after controlling for the age, gender, educational level, and BMI in the individuals with type 2 diabetes and those without type 2 diabetes. Statistical significance was set at \( P < 0.05 \). A false discovery rate (FDR) calculation was performed for the correction of multiple comparisons.

**Mediation analysis**

The PROCESS macro version 3.4 implemented in IBM SPSS was adopted to perform the mediation analyses to examine whether the hippocampal topological properties mediated the association between the PRS and the episodic memory, with the PRS as the independent variable, the hippocampal topological property as the mediation variable, and the episodic memory as the dependent variables. The age, gender, education years, and BMI were controlled. During the mediation analysis, ordinary least squares regression was used to calculate statistics for specific paths, and 5000 bias-corrected bootstrap resamples were conducted to generate a CI for the mediation effect (Preacher & Hayes, 2008). 95% CI and effect size for relative indirect effect was reported for our mediation analysis. When the 95% CI does not contain zero, it is considered a significant mediation effect.

### Table 1 Demographics, clinical Data, neuropsychological, episodic memory and head motion assessment

| Characteristics | Type 2 Diabetes \((n = 103)\) | No Diabetes \((n = 114)\) | Statistical value | \( P \) value |
|-----------------|-----------------------------|---------------------------|------------------|----------------|
| **Demographics** |                             |                           |                  |                |
| Age (years)     | 60.15 ± 6.72                | 58.56 ± 7.53              | 1.629\(^a\)      | 0.105          |
| Gender (Man/ Woman) | 54/49                       | 53/61                     | 0.763\(^b\)      | 0.382          |
| Education (years) | 10.87 ± 2.52                | 10.89 ± 3.11              | -0.032\(^a\)     | 0.975          |
| **Clinical Data** |                             |                           |                  |                |
| Weight (kg)     | 72.94 ± 10.94               | 67.64 ± 10.38             | 3.658\(^*\)      | < 0.001\(^*\) |
| Height (cm)     | 167.02 ± 8.25               | 165.80 ± 7.46             | 1.141\(^a\)      | 0.255          |
| BMI (kg m\(^{-2}\)) | 26.03 ± 2.70                | 24.62 ± 2.90              | 3.702\(^a\)      | < 0.001\(^*\) |
| BP (Hypertension/ Normotension) | 53/50 | 47/67 | 2.278\(^b\) | 0.137 |
| FBG (mmol L\(^{-1}\)) | 9.25 ± 3.63                | 6.20 ± 1.21               | 8.453\(^*\)      | < 0.001\(^*\) |
| HbA1c (%)       | 7.29 ± 1.43                 | 5.67 ± 0.45               | 11.467\(^a\)     | < 0.001\(^*\) |
| HbA1c (mmol L\(^{-1}\)) | 56.15 ± 15.61              | 38.53 ± 4.86              | 11.455\(^*\)     | < 0.001\(^*\) |
| **Neuropsychological Test** |               |                           |                  |                |
| MMSE            | 27.95 ± 1.67                | 27.88 ± 1.86              | 0.293\(^a\)      | 0.770          |
| SAS             | 36.80 ± 9.11                | 35.37 ± 7.28              | 1.281\(^a\)      | 0.202          |
| SDS             | 37.83 ± 10.75               | 37.25 ± 8.34              | 0.447\(^a\)      | 0.655          |
| **Episodic Memory** |                             |                           |                  |                |
| ROCF Immediate Recall | 17.05 ± 6.52              | 18.64 ± 6.41              | -1.816\(^a\)     | 0.071          |
| ROCF Delayed Recall | 16.64 ± 6.33              | 19.00 ± 6.47              | -2.703\(^a\)     | 0.007\(^*\)   |
| AVLT Short-term Memory | 41.39 ± 8.36 | 44.00 ± 9.94 | -2.083\(^a\) | 0.038\(^*\)    |
| AVLT Long-term Memory | 8.45 ± 2.63 | 9.39 ± 2.87 | -2.528\(^b\) | 0.012\(^*\) |
| **Head motion** | 0.724 ± 0.211               | 0.676 ± 0.154             | 1.919\(^a\)      | 0.056          |

\(^\text{a}\)Significant level \( P < 0.05 \). \(^\text{b}\)presents T values, \(^*\)presents \( \chi^2 \) values. Values are mean ± standard deviation or number of subjects. AVLT, Auditory Verbal Learning Test; FBG, fasting blood glucose; MMSE, mini-mental state examination; ROCF, Rey–Osterrieth Complex Figure Test; SAS, self-rating anxiety scale; SDS, self-rating depression scale.

### Results

**Demographic, clinical, cognitive characteristics, and head motion**

Participant demographic, clinical, cognitive characteristics, and head motion are shown in Table 1. The individuals with type 2 diabetes and those without type 2 diabetes were matched for age, gender and education. There were no difference in head motion between the two groups. The weight, BMI, FBG, and HbA1c were significantly higher in the individuals with type 2 diabetes than those without type 2 diabetes (\( P < 0.05 \)). The ROCF delayed recall score and
the AVLT short- and long-term memory scores were significantly lower in individuals with type 2 diabetes than those without type 2 diabetes \((P<0.05)\).

### PRS-by-disease interaction on WM topological network properties of the hippocampus

There were significant PRS-by-disease interaction effects with medium to strong effect sizes on three topological properties of the right hippocampus after multiple comparison correction, including the NGe \((F=11.799, P<0.001\), Cohen’s \(d=0.801)\), NLp \((F=11.390, P<0.001,\) Cohen’s \(d=0.773)\) and Nd \((F=11.463, P<0.001, Cohen’s d=0.778)\). Detailed statistic results were listed in Table 2. The post hoc analyses identified significant correlation between the PRS and the three right hippocampal nodal properties in the individuals with type 2 diabetes (NGe: \(r=0.366, P<0.001\); NLp: \(r=-0.366, P<0.001\); Nd: \(r=0.320, P=0.001\)), while no such correlation was observed among individuals without type 2 diabetes. Please see Fig. 1. Since the correlations between PRS and hippocampal nodal properties were found to be significant only in the individuals with type 2 diabetes, the follow-up analyses mainly focused on the individuals with type 2 diabetes.

### Correlation analysis

In the individuals with type 2 diabetes, the PRS was positively correlated with the NGe and the Nd, while negatively correlated with the NLp, of the right hippocampus.
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Mediation analysis

In the individuals with type 2 diabetes, mediation analysis showed significant indirect effects from the PRS to episodic memory mediated by the NGe/ NLp of the right hippocampus. (PRS-NGe-ROCF_Imediate Recall: 95% CI, 0.283–2.382; effect size = 1.111; PRS-NGe-A VLT_Long-term Memory: 95% CI, 0.145–1.126; effect size = 0.524; PRS-NLp-A VLT_Long-term Memory: 95% CI, 0.143–1.146; effect size = 0.536.) These three confidential intervals did not contain zero and therefore confirmed the existence of a mediation effect of the NGe/ NLp of the right hippocampus on the association between the PRS and episodic memory. Please see Figs. 3 and 4.

Additionally, the NGe of the right hippocampus was positively correlated with three episodic memory test performances, including the ROCF immediate recall score, the ROCF delayed recall score, and the long-term memory score. The NLp of the right hippocampus was negatively correlated with three episodic memory test performances, including the ROCF immediate recall score, the ROCF delayed recall score, and the long-term memory score. After FDR correction, the NGe of the right hippocampus was positively correlated with the ROCF immediate recall score ($r = 0.252, P_{(FDR)} = 0.048$) and the long-term memory score ($r = 0.268, P_{(FDR)} = 0.042$). The NLp of the right hippocampus was negatively correlated with the long-term memory score ($r = 0.273, P_{(FDR)} = 0.042$). Please see Fig. 2.

**Fig. 2** Correlations between the nodal properties of the right hippocampus and the episodic memory tests in the individuals with type 2 diabetes. The NGe of the right hippocampus was positively correlated with the ROCF immediate recall ($r = 0.252, P = 0.048$ after FDR correction) (a), and the AVLT long-term memory ($r = 0.268, P = 0.042$ after FDR correction) (b) in the individuals with type 2 diabetes. The NLp of the right hippocampus was negatively correlated with the AVLT long-term memory ($r = -0.273, P = 0.042$ after FDR correction) (c) in the individuals with type 2 diabetes. AVLT, Auditory Verbal Learning Test; NGe, nodal global efficiency; NLp, nodal shortest path length; R right; ROCF, Rey-Osterrieth Complex Figure Test.
The individuals with type 2 diabetes with higher PRS showed higher NGe and Nd, while lower NLp of the right hippocampus. Second, the NGe of the right hippocampus showed higher NGe and Nd, while lower NLp of the right hippocampus.

**Discussion**

In this study, there were three main findings. First, significant PRS-by-disease interaction effects on three topological network properties of the right hippocampus were found. The individuals with type 2 diabetes with higher PRS showed higher NGe and Nd, while lower NLp of the right hippocampus. Second, the NGe of the right hippocampus showed higher NGe and Nd, while lower NLp of the right hippocampus.

**Fig. 3** Mediation model of the PRS, the NGe of the right hippocampus, and episodic memory in individuals with type 2 diabetes. A significant direct effect was detected from the PRS to the NGe of the right hippocampus; and from the NGe of the right hippocampus to the episodic memory tests (ROCF immediate recall score, AVLT long-term memory) in individuals with type 2 diabetes. A significant indirect effect was also found from the PRS to the episodic memory tests (ROCF immediate recall score, AVLT long-term memory) mediated by the NGe of the right hippocampus. AVLT, Auditory Verbal Learning Test; NGe, nodal global efficiency; R right; ROCF, Rey-Osterrieth Complex Figure Test.

**Fig. 4** Mediation model of the PRS, the NLp of the right hippocampus, and episodic memory in individuals with type 2 diabetes. A significant direct effect was detected from the PRS to the NLp of the right hippocampus; and from the NLp of the right hippocampus to the AVLT long-term memory tests (ROCF immediate recall score, AVLT long-term memory) in individuals with type 2 diabetes. A significant indirect effect was also found from the PRS to the AVLT long-term memory mediated by the NLp of the right hippocampus. AVLT, Auditory Verbal Learning Test; NLp, nodal shortest path length; R right.
was positively correlated with episodic memory, while the NLp of the right hippocampus was negatively correlated with episodic memory performance. Finally, in the individuals with type 2 diabetes, significant indirect effects from the PRS to episodic memory mediated by the NGe and NLp of the right hippocampus were also found.

Normally, the NLp estimates the potential for functional integration between brain regions, with shorter paths implying the greater potential for integration. The average inverse NLp is defined as the NGe. Both the NGe and NLp are measures of integration and reflect the global information transmission capability of the network (Rubinov & Sporns, 2010). Therefore, the short NLp and high NGe of hippocampal nodes can ensure effective integrity or prompt transfer of information between the hippocampus and other brain regions, which is the basis of cognitive processes (Sporns & Zwi, 2004). The Nd equals the number of links connected to the node, that is, the number of neighbor nodes directly connected to the node. The Nd value reflects the importance of a node in the network. Therefore, a node with higher Nd usually has stronger information interactions with other brain regions.

We observed a combination of higher Nd, higher NGe, and lower NLp in the right hippocampal node in patients with higher PRS of type 2 diabetes. It suggested that the patients with a higher genetic risk of type 2 diabetes have more links (integration) and stronger information interaction between the right hippocampal node and other brain regions. The hippocampus is a key brain region involved in cognitive functions such as learning and memory. Previous studies have identified the hippocampus as a hub node in normal human brain networks, with ascending and descending pathways responsible for transmitting and regulating memory signals (Li et al., 2020). Our results appeared contradictory given the known negative effects of type 2 diabetes on cognition. However, this seemingly better-organized brain network in patients with high PRS may be a sign of changes in the early stages of brain injury; that is, the complex brain network may regulate the separation and integration of information processing by changing the properties of important nodes, thereby achieving compensatory network reorganization to maintain normal brain cognitive function. Similar brain network compensation has been reported in previous studies of functional graph networks in patients with type 2 diabetes (van Bussel et al., 2016; Xiong et al., 2020). Considering that the individuals with type 2 diabetes in our study did not have clinical complications, their brain networks might remain capable of compensatory reorganization. We speculated that, in our study, the compensatory brain network reorganization was mainly manifested in the forced excessive participation of the right hippocampal node in the integration of information processing to counteract the negative impact of early brain damage on cognition. Moreover, our patients showed a significant correlation between the right hippocampal nodal properties and episodic memory performance, further supporting the interpretation of the compensatory mechanism. However, the compensation is limited to maintaining general cognition (MMSE) levels. Higher-level cognition functions such as episodic memory declined in patients with type 2 diabetes mellitus. We speculated that as the disease progressed, the load on the right hippocampal node would continue to increase until it eventually decompensate, and cognitive function would decline significantly. On the contrary, no correlation between hippocampal nodal properties and cognitive performance was found among the individuals without type 2 diabetes, suggesting no such compensation happened.

Here we noticed that the interactive effect was only found in the right hippocampus, suggesting that the PRS had more pronounced effects on the right hippocampus of the patients. In previous studies, hippocampal asymmetry has been discovered in all kinds of individuals, while with controversial findings. The current consensus is that people with normal cognition usually show that the right hippocampus is larger than the left hippocampus (Pedraza et al., 2004). The right hippocampus plays the dominant role in encoding visual-spatial memory (Burgess et al., 2002; Iaria et al., 2003; Iglói et al., 2010; Maguire et al., 1998). In AD patients, world list recall scores were positively correlated with the right hippocampal deformation. Topological network analysis by Li et al. (Li et al., 2020) found that only the right hippocampus became the brain hub node, but not the left. And the hub node of the right hippocampus was lost in individuals with type 2 diabetes. In animal studies, the dominance of the right hippocampus in spatial memory was also found in rats (Klur et al., 2009; Shinohara et al., 2012). Moreover, spatial learning-related gene expression changes were nearly 10 times richer in the right hippocampus than in the left in rats (Klur et al., 2009). Our study was consistent with these results and suggested that the right hippocampus was more likely to play a stronger role in early compensation than the left hippocampus.

The mediation analysis further revealed that right hippocampal nodal properties mediated the effect of PRS on episodic memory in individuals with type 2 diabetes. These results provided a gene-brain-cognition pathway that helps understand how the PRS affects episodic memory in individuals with type 2 diabetes.

Some limitations need to be addressed. First, this study is a cross-sectional study. Thus, dynamic changes cannot be obtained. The current results are only applicable to individuals in a specific stage of the disease. Second, individuals with type 2 diabetes received various medications that may have produced confounding effects on cognition. Further
Quality control and imputation

Quality control (QC) steps were applied at the sample- and SNP-specific level before applying imputation approaches. Sample-level QC included filtering out samples with incorrect sex assignment, missing genotyping rate greater than 0.02, possible relative relationships, population outliers identified by multidimensional scaling (IBD > 0.1875), and abnormal heterozygosis (more than three times of average heterozygous ratio). SNP-level QC included filtering out SNPs with missing call rate greater than 0.01, minor allele frequency less than 0.05, and significant deviation from Hardy-Weinberg equilibrium (P < 1 × 10^{-6}). Imputation was performed using IMPUTE version 2 with a reference panel of 1KG Genome Phase three and the pre-phasing algorithm of SHAPEIT. Imputation information score (info score > 0.8)

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Authors' contributions
Y.Z. and Q.Z. designed research; Y.Z., X.D., Y.F., Q.Z., W.Q. and Q.Z. performed research; Y.Z., X.D., W.Q., and Q.Z. analyzed data; Y.Z. and Q.Z. wrote the paper. Q.Z. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and material
The data sets generated during and/or analyzed during the current study are not publicly available because they are under construction but are available from the corresponding author upon reasonable request. No applicable resources were generated or analyzed during the current study.

Declarations
Conflict of interest
No potential conflicts of interest relevant to this article were reported.

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of Tianjin Medical University General Hospital, with written informed consent from all subjects.

Consent for publication
Not applicable.

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