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Structural and functional brain abnormal alteration in patients with type 2 diabetes mellitus: A coordinate-based meta-analysis

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BACKGROUND: Type 2 diabetes mellitus (T2DM) is a prevalent chronic condition associated with a range of abnormalities in both the functional and structural aspects of the brain. However, existing studies have produced inconsistent results due to disease heterogeneity and small sample size. Therefore, we aim to examine common functional and structural alterations in patients with T2DM.

METHOD: We searched PubMed, Web of Science, and Embase (published before July 2023) and included a total of 52 valid studies (58 datasets), which have 2160 patients with T2DM and 2124 healthy controls (HCs). Then, we used the anisotropic effect size seed-based d mapping (AES-SDM) to examine changes in neural activity and grey matter volume (GMV) in patients with T2DM. To validate the findings of the AES-SDM results, two additional meta-analyses were performed using activation likelihood estimation (ALE) and multilevel kernel density analysis (MKDA).

RESULTS: The results showed that patients with T2DM exhibited abnormal neural activity, functional connectivity of default mode network, and GMV in brain regions related to visual processing, such as the occipital lobe, lingual gyrus, and Heschl's gyrus. In addition, functional or structural alterations were also found in other sensory-motor, cognitive, and attention-related brain regions in patients with T2DM. The results of ALE and MKDA fundamentally confirmed the findings of the AES-SDM analysis.

CONCLUSION: These findings offer robust neural markers and deepen our understanding of the neurobiological underpinnings of T2DM.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most prevalent metabolic diseases in the world and its incidence is still increasing globally [1, 2]. T2DM is primarily attributed to insufficient insulin secretion and insulin resistance, leading to elevated blood glucose levels [3], which affects the ability to conduct nerve signals and process information, and subsequently affects the patients' many areas of functioning, including cognitive, mood, awareness, and behavior [4, 5]. In recent years, more and more studies have shown that alterations in brain function and structure are related to the pathological mechanisms of T2DM, suggesting that it is important for us to explore the neural mechanisms of T2DM in depth with the help of neuroimaging tools.

Resting-state functional magnetic resonance imaging (rs-fMRI), which measures spontaneous brain activity by detecting low-frequency blood oxygen level-dependent (BOLD) signal changes, is an important tool for exploring the mechanisms of T2DM [6, 7]. Functional connectivity (FC) is one of the most commonly used methods for rs-fMRI, which is a measure of synchronized activity between different brain regions that helps us to understand the exchange of information and synergy between brain regions [8, 9]. In most of the available studies, FC changes in patients with T2DM have been explored to find evidence of altered neural networks in

patients with T2DM [10, 11]. Among the many brain networks, the default mode network (DMN), one of the most important resting-state brain networks, is characterized by high activity when the brain is not engaged in specific tasks and low activity when the brain is focused on the external environment [12]. Marder et al. [13] found that people with T2DM exhibited reduced FC in DMN, and were associated with an increased risk of cognitive impairment. However, FC can only respond to the correlation of activity between brain regions and does not directly identify which brain region is at fault [14]. In contrast, local metrics can examine brain areas with abnormal spontaneous neural activity, and the combination of FC and local metrics can help to assess the functional state of the brain more comprehensively and provide more clues for the diagnosis and treatment of T2DM [15–18].

In the analysis of regional spontaneous brain activity, three common local metrics are amplitude of low-frequency (ALFF), fractional amplitude of low-frequency fluctuation (fALFF), and regional homogeneity (ReHo) [19]. ALFF is the most commonly employed indicator of spontaneous activity at the level of a single voxel, which has high sensitivity and specificity [20]. The fractional amplitude of low-frequency fluctuation (fALFF) is an improved measure of ALFF that allows better control of physiological noise [21]. The ReHo assesses the correlation between the time series of

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BOLD signals of a given voxel and those of its nearest neighbors at a larger cluster level, thereby providing valuable insights into the regional activity synchronization in the brain [22]. ALFF and fALFF reflect the spontaneous brain activities of a single voxel, and ReHo detects the synchronization in the cluster [4]. These metrics have commonalities and differences, providing complementary information to promote the understanding of regional spontaneous brain activities. Thus, the combination of these three methods may provide more information about the pathophysiological framework of the human brain [23], leading to a better exploration of the structural brain abnormalities in T2DM. Li et al. [4] has already identified concordant regional brain activity abnormalities in patients with T2DM through the meta-analysis combined ALFF, fALFF, and ReHo study.

Rs-fMRI indirectly reflects neural activity by observing changes in blood oxygen levels in the brain [24]. However, abnormal brain function is often closely associated with structural damage [25]. Therefore, it is not sufficient to examine only abnormal brain activity in patients with T2DM. In structural neuroimaging, voxel-based morphometry (VBM) is a fully automated processing method that has been applied to examine abnormal grey matter volume (GMV). The importance of the VBM approach is that it is not biased toward one particular structure and gives an even-handed and comprehensive assessment of anatomical differences throughout the brain [26]. VBM employs statistical techniques to identify differences in brain anatomy between groups of subjects, which in turn can be used to infer the presence of atrophy or tissue expansion in individuals with disease [27]. Many studies have examined GMV alterations in patients with T2DM using VBM [28–30]. Meta-analysis of VBM studies in diabetic patients by Moulton et al. [31] and Wu et al. [30] not only confirmed the presence of abnormal GMVs in patients with T2DM in a wide range of brain regions distributed throughout the brain but also associated with the risk of cognitive impairment and even dementia. The integration of local metrics and VBM can provide a comprehensive analysis to examine the spontaneous neural activity and grey matter structural abnormalities of brain regions in patients with T2DM from both functional and structural perspectives.

Previous researchers have conducted some studies on the local neural activity, FC within the DMN, and GMV in patients with T2DM. However, limited by small sample size, clinical heterogeneity, and methodological differences, previous studies have yielded a large number of inconsistent results. Specifically, small sample size can undermine the reliability of neuroscience research [32], which can increase the number of false-positive and false-negative results [33, 34], overestimate or underestimate effect sizes, and even reverse the direction of the effect, ultimately leading to misleading conclusions [35–37]. As for clinical heterogeneity, research has pointed out that disease duration (e.g., < 5 years vs. > 10 years), the presence of comorbid hypertension or dyslipidemia, and treatment regimens can all influence the neural mechanisms of patients with T2DM [17, 38]. Finally, the seed of FC, and whether whole-brain analysis or ROI analysis is used can also affect the final results [39, 40]. Therefore, an increasing number of researchers are adopting meta-analysis, hoping to combine empirical studies with the same or similar methods for large-sample analyses to detect more common and more reproducible brain functional and structural abnormalities in patients with T2DM. Seven previous meta-analyses have examined the local neural activity and FC in patients with T2DM, and found common abnormal neural activity in the lingual gyrus, superior temporal gyrus, superior frontal gyrus, and cerebellum [41–47]. In addition, ten meta-analyses have examined the gray matter structural changes in patients with T2DM and found common gray matter structural abnormalities in the middle temporal gyrus, insula, precuneus, cerebellum, and basal ganglia [29–31, 41, 43, 44, 48–51]. However, reviewing previous meta-analysis studies, we can find that most studies only focus on

research using a certain method or a certain modality of MRI, and thus cannot comprehensively reflect the neural mechanism abnormalities of patients with T2DM. To our knowledge, at present, only four studies have included data from multiple modalities for analysis [41, 43, 44, 51], and one of these studies examined changes in gray and white matter structure [51], while another study focused on T2DM-related cognitive dysfunction [43]. Therefore, it is necessary to conduct a meta-analysis of patients with T2DM to comprehensively examine their local neural activity, FC, and gray matter structural changes.

Given the current status quo of inconsistent results of functional and structural alterations in individual studies, in this study, we conducted a coordinate-based meta-analysis (CBMA) of existing studies in local metrics, DMN, and VBM using anisotropic effect-size-based seeded mapping (AES-SDM) to explore consistent results of functional and structural alterations in brain regions of patients with T2DM. In addition to this, we used the activation likelihood estimation (ALE) and multilevel kernel density analysis (MKDA) as validation analyses for additional validation of the AES-SDM results.

METHODS
Search strategy and literature screening
The protocol for this neuroimaging meta-analysis was registered on PROSPERO International Prospective Register of Systematic Reviews with the registration number "CRD4202454977" (https://www.crd.york.ac.uk/PROSPERO/export_details_pdf.php). We searched comprehensively in PubMed, Web of Science, and Embase datasets for literature up to July 2023, using the combined keywords: ("T2DM" OR "type 2 diabetes mellitus") AND ("ALFF" OR "amplitude of low-frequency" OR "fALFF" OR "fractional amplitude of low-frequency" OR "ReHo" OR "regional homogeneity" OR "DMN" OR "default mode network" OR "VBM" OR "voxel-based morphometry").

For literature selection, we used the following inclusion criteria: (1) employed MRI analysis; (2) compared patients with T2DM and HCs and reported three-dimensional Talairach or Montreal Neurologic Institute (MNI) coordinates of the brain regions; (3) written in English; (4) a sample size of more than 10 in a single group [52, 53]; (5) utilized local metrics, seed-based or ICA methods to analyze DMN, grey matter volume/density for VBM; (6) different studies had partially or wholly overlapped samples, only the study with the largest sample size was included. In addition, studies were excluded if: (1) written in non-English; (2) animals research; (3) articles were review, case report, or meeting abstract; (4) non-MRI studies (5) non-T2DM patients; (6) studies were non-whole-brain analysis; (7) studies not reported Talairach or MNI coordinates; (8) non T2DM vs HCs comparison; (9) Methods not used in the current study; (10) only ANOVA results without post-hoc tests results.

Quality assessment and data extraction
To ensure high data quality, we used a 20-point checklist to assess the quality of the included studies [54, 55]. The checklist mainly includes the assessment of subject quality (e.g., demographic and clinical characteristics) and the study methodology (e.g., image acquisition, method description), the details of the checklist are presented in Supplementary Table S1. All the above process were conducted by two authors (D.H. and M.Q.Z) independently. If there was a disagreement, it would be solved through discussion with a third author (X.J.Z) until a consensus is reached. After quality assessment, important information was extracted and collated from each included study, mainly including the first author, T2DM type, and statistical threshold.

Voxel-wise meta-analysis by AES-SDM
An anisotropic effect size seed-based *d* mapping (AES-SDM) software package version 5.15 for Windows was used for the

quantitative coordinate-based meta-analysis (https://www.sdmproject.com/software/). First, the corresponding text was generated for each study. The content of the texts includes peak coordinates and the corresponding effect size. The Talairach coordinates can be automatically converted to MNI coordinates using the Lancaster transform by the SDM online converter, and if the study does not specify an effect size, we represent the effect size of the peak coordinates as 'p' for increased and 'n' for decreased [56–58]. In the current study, there were 5 studies required coordinate conversion [59–62], 3 studies reported results using effect sizes [63–65], and 3 studies reported no significant findings [66–68]. Second, the effect size map of each study was reconstructed using an anisotropic Gaussian kernel [69]. Third, based on the effect size map of each study, the mean effect size map of all studies was calculated using a random effects model that accounts for the sample size, intra-dataset variability, and between-dataset heterogeneity [70]. We used the recommended threshold (peak height $Z > 1$, uncorrected voxel $p < 0.005$, and cluster extent > 10 voxels), which is approximate equivalent to a corrected p-value < 0.05. This recommended threshold can achieve an optimal balance between and specificity of false positives [57].

Analyses of sensitivity, heterogeneity, and publication bias
To verify the robustness and reliability of the meta-analysis results, we conducted a systematic jackknife sensitivity analysis. Jackknife sensitivity analyses were performed using the Leave-One-Out Cross-Validation (LOOCV) method to verify the reproducibility of results [57, 71]. The main analyses were repeated n times (n = the total number of studies) and a different study was discarded each time. The results were considered stable and reproducible if significant brain regions obtained after each LOOCV analysis were present in all or most of the previously significant brain regions [72]. In the current analysis, we removed one study each time to test whether the results regions remained significant. Additionally, we carried out a heterogeneity analysis using a random-effects model with Q statistics to explore between-study variability in the results (peak height $Z > 1$, voxel $p < 0.005$, and cluster extent > 10 voxels). Furthermore, we performed Egger's test to quantify publication biases [73]. Publication bias refers to the tendency of a study with statistically significant results to be published more often than results with no significant results [74]. A p-value less than 0.05 was considered statistically significant, which could indicate that the result is only published if they find statistically significant results [75].

Confirmatory analyses
To further test and validate our results, we conducted two analyses to validate the meta-analysis results: one is ALE analysis using GingerALE 3.0.2 software (https://www.brainmap.org/) with an activation likelihood estimation algorithm. The other is MKDA analysis using a multilevel kernel density analysis toolbox [76] in MATLAB2017b.

In the ALE analysis, Foci reported in the Talairach space were converted into MNI space using the GingerALE software [77]. According to the ALE manual, the required information, such as the MNI coordinates, the name of the study, and the sample size of each study, was compiled into a text file. Subsequently, the file was input into GingerALE software, enabling a fully automated analysis. A statistical threshold (uncorrected $p < 0.005$) was used [78, 79].

In the MKDA analysis, before conducting the analyses, relevant information (e.g., coordinates in MNI or Talairach, the name of the study, contrasts, the total sample size of each study, and coordinate system) was extracted from all the studies to create a text file. The Talairach coordinates reported in the included studies were transformed into the MNI space using Lancaster transformation [56]. To generate comparison indicator maps, the peak coordinates from each relevant contrast map were independently convolved with a 10-mm spherical kernel. According to previous meta-analytic studies, this default kernel size is appropriate [80, 81]. Additionally, the number of Monte Carlo simulations was set to 10,000 iterations. Family-wise error rate correction (FWE) was utilized, and a p-value of less than 0.05 was considered statistically significant [82].

RESULTS
Included studies and sample characteristics
Following strict inclusion and exclusion criteria, we found 52 studies with 58 datasets that met our requirements and consisted of 2160 patients with T2DM and 2124 HCs. Overall, there were 22 local metrics datasets composed of 570 patients with T2DM and 601 HCs [18, 24, 62, 63, 66, 83–98], 18 DMN-FC datasets included 678 patients with T2DM and 705 HCs [10, 11, 17, 28, 61, 64, 68, 86, 87, 90, 99–106], and 18 VBM datasets included 912 patients with T2DM and 818 HCs [7, 28, 59, 60, 65, 67, 93, 107–117]. Noticeably, there were 5 studies both including local metrics and DMN [66, 86, 90, 106, 118], 1 study both including local metrics and VBM [93], and 1 study both including DMN and VBM [28]. Among the 52 studies, 5 required coordinate conversion from Talairach to MNI space [17, 59–62], which was performed using the SDM online converter with the Lancaster transform [119]. Three studies did not report effect sizes [63–65]; for these, we followed the SDM manual recommendations and applied standardized symbolic notation (using "p" to denote increased activity and "n" to indicate decreased activity). Additionally, 3 studies reported null findings [66–68], and 1 study did not report the mean age or standard deviations (SD) of subjects [93]. Figure S1 shows the flowchart for the identification and exclusion of studies. Table S2–S4 provides detailed information on the studies included.

The results of the voxel-wise meta-analysis
The results of the local metrics meta-analysis. Compared to HCs, patients with T2DM showed increased regional brain activity in the bilateral inferior cerebellum, left superior cerebellum, left paraHippocampal gyrus (paraHip), and decreased regional activity in the left precentral gyrus, left lingual gyrus (LG), left inferior frontal gyrus (IFG), left superior temporal gyrus (STG), right Heschl's gyrus, and left superior frontal gyrus (SFG). The results are presented in Fig. 1 and Table 1.

### The results of the DMN meta-analysis
Compared to HCs, patients with T2DM showed increased DMN-FC in the right SFG, left middle occipital gyrus (MOG), left superior parietal gyrus (SPG), left precuneus (PCUN), left SFG, left middle cingulate cortex (MCC) and decreased DMN-FC in the right PCUN, bilateral STG, bilateral angular gyrus (AG), and left anterior cingulate cortex (ACC). The results are presented in Fig. 2 and Table 2.

The results of the VBM meta-analysis
Compared to HCs, patients with T2DM showed increased GMV in the right insula, left superior cerebellum, right superior occipital gyrus (SOG), right postcentral gyrus, right inferior temporal gyrus (ITG), and decreased GMV in the left PCUN, left ITG, left putamen, right IFG, left middle temporal gyrus (MTG). The results are presented in Fig. 3 and Table 3.

Analyses of Jackknife sensitivity, heterogeneity, and publication bias
As shown in Tables S5–S7, the Jackknife sensitivity analysis demonstrated high reproducibility in most regions, with all results ensuring a sensitivity of over 77%. In addition, the majority of the results for local metrics showed no heterogeneity, and almost all results for both local metrics and DMN-FC exhibited no publication bias.
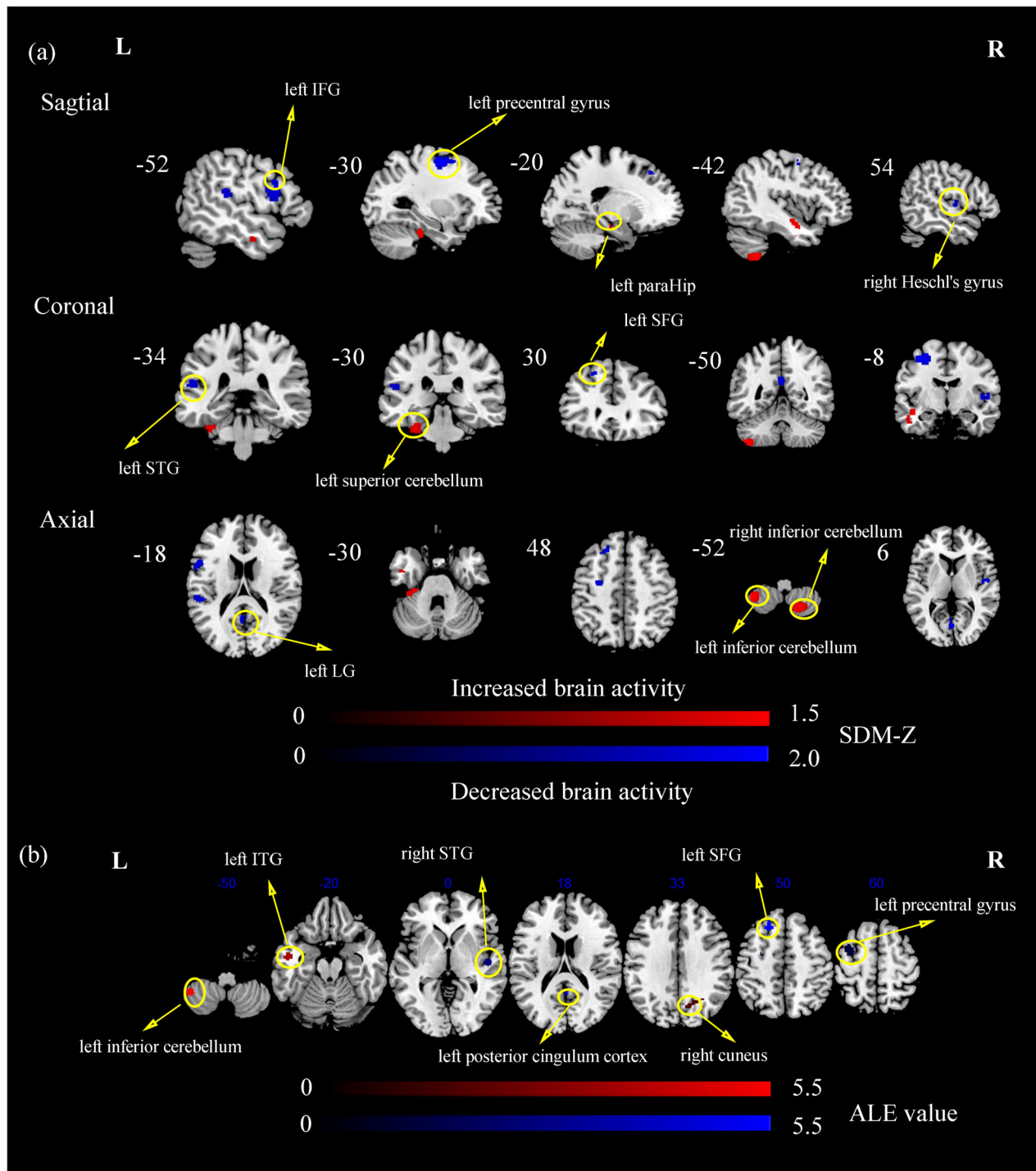
Fig. 1 The significant differences in local metrics between patients with T2DM and HCs. a The AES-SDM analysis was threshold with an uncorrected p < 0.005. The color bar indicates the maximum and minimum SDM-Z values. Compared with HCs, the increased brain activity in patients with T2DM were marked in red, while the decreased brain activity in patients with T2DM were marked in blue; **b** The ALE analysis was threshold with an uncorrected p-value < 0.005. The color bar indicates the probability of significant ALE values. Compared with HCs, the increased brain activity in patients with T2DM were marked in red, while the decreased brain activity in patients with T2DM were marked in blue. IFG inferior frontal gyrus, paraHip paraHippocampal gyrus, STG superior temporal gyrus, SFG superior frontal gyrus, LG lingual gyrus, ITG inferior temporal gyrus.

The reproducible meta-analysis results of ALE and MKDA

To test and verify the present results, we conducted two additional meta-analyses (ALE analysis and MKDA analysis). In the results of the local metrics meta-analysis by ALE, we found that patients with T2DM had increased neural activity in the right cuneus, left ITG, left inferior cerebellum, and decreased activity in left precentral gyrus, right STG, left posterior cingulate cortex, and left SFG. In the results of the DMN-FC meta-analysis by ALE, patients with T2DM had decreased FC in right PCUN. In the results of the VBM meta-analysis by ALE, patients with T2DM had

Table 1. Brain regions of consistent abnormal activity in patients with T2DM relative to HCs by AES-SDM, ALE, and MKDA analyses for local metrics.

Brain regions	BA	MNI coordinates			Voxels	*p*-value	Value
		x	y	z			
AES-SDM							
Right inferior cerebellum	NA	20	−68	−50	409	<0.005	1.368
Left inferior cerebellum	NA	−42	−50	−52	174	<0.005	1.413
Left superior cerebellum	20	−30	−30	−30	118	<0.005	1.353
Left parahippocampal gyrus	35	−18	−18	−18	13	<0.005	1.213
Left precentral gyrus	6	−30	−6	56	479	<0.005	−1.918
Left lingual gyrus	NA	0	−76	4	287	<0.005	−1.657
Left inferior frontal gyrus	NA	−52	12	28	187	<0.005	−1.642
Left superior temporal gyrus	42	−52	−34	18	70	<0.005	−1.593
Right Heschl's gyrus	48	54	−8	6	57	<0.005	−1.504
Left superior frontal gyrus	9	−20	30	48	25	<0.005	−1.561
ALE							
Right cuneus	7	12	−68	36	148	<0.005	5.065
Left inferior temporal gyrus	20	−50	−8	−24	98	<0.005	5.480
Left inferior cerebellum	NA	−44	−52	−52	89	<0.005	5.171
Left precentral gyrus	6	−34	−2	58	148	<0.005	−5.379
Right superior temporal gyrus	48	48	−16	2	101	<0.005	−4.710
Left posterior cingulum cortex	NA	0	−52	24	91	<0.005	−4.660
Left superior frontal gyrus	NA	−18	28	48	83	<0.005	−4.769
MKDA							
None							

The AES-SDM analysis was thresholded with Voxel threshold *p*-value < 0.005; The ALE analysis was thresholded with an uncorrected *p*-value < 0.005.
BA Brodmann, *L* left, *R* right, *MNI* montreal neurological institute.

increased GMV in right IFG, and decreased GMV in left caudate. The MKDA analysis had no significant result in three analyses. Detailed information about the results of the ALE analysis was provided in Tables 1–3, Figs. 1–3.

DISCUSSION
In the current study, we used the quantitative AES-SDM meta-analysis to reveal abnormal functional activity and structure in patients with T2DM. Results exhibit altered neural activity and GMV in sensorimotor, cognition and attention related brain regions. In particular, brain regions involved in visual processing, including visual input, visual memory, and visual cognition, showed abnormalities in whatever local neural activity, FC of the DMN, and GMV. To validate the results, other two meta-analyses methods (ALE and MKDA) were employed to corroborate the findings of AES-SDM, and the results of ALE and MKDA were found to be largely consistent with those of AES-SDM.

Results of local metrics
The current study demonstrated decreased spontaneous neural activity in sensorimotor-related brain regions such as left LG, right Heschl's gyrus, left STG, and left precentral gyrus in patients with T2DM. Among them, LG is closely related to visual processing, previous study has shown that abnormal brain activity in occipital lobe of patients with T2DM is associated with impaired visual processing speed and spatial memory, potentially affecting global cognitive performance [120]. A study by Peng et al., [121] found that the ReHo value of LG was associated with the Trail-Making Test, which assesses attention, psychomotor speed, and executive function. Previous meta-analysis also found decreased activity in LG [42, 43, 45]. Clinically, patients with T2DM are often associated

with retinopathy, which suggests that impaired spontaneous neural activity in the occipital lobe may be associated with retinopathy in patients with T2DM and be present before the onset of symptoms [105]. Although the ALE results did not detect abnormal activity in the LG, but abnormal neural activity was found in an important visual-related brain region (cuneus). This indirectly confirms that there is abnormal activity in the visual-related brain regions of patients with T2DM. The right Heschl's gyrus includes the primary auditory cortex and lies on the upper surface of the STG [122]. Current studies have shown that the activity of the STG and Heschl's gyrus is reduced in patients with T2DM. Two meta-analyses of T2DM supported the current results, they both found decreased activity in STG [41, 42]. Another meta-analysis found patients with T2DM had decreased GMV in STG [51]. Other empirical study has also indicated the abnormal degree centrality and FC of the STG and Heschl's gyrus in early-onset patients with T2DM [28], and another study demonstrated that the metabolic interaction between the IFG and Heschl's gyrus was a risk factor for T2DM [123]. In addition, previous study have shown that STG is critical for speech perception [124]. Defects in the STG, which is one of the cortical components that serve language processing, may be associated with impaired language processing due to chronic abnormalities in glucose metabolism [125]. As for precentral gyrus, it not only serves as a core sensorimotor brain area but is also closely related to cognitive functions such as executive and attentional functions [126, 127]. A 5-year long-itudinal follow-up study, consistent with the current study found that regional neurovascular coupling (NVC) was reduced in precentral gyrus of patients with T2DM, and suggested that reduced NVC in precentral gyrus may be associated with diabetic peripheral neuropathy such as numbness, pain, and other paresthesia [104]. In addition, ALE analysis also identified
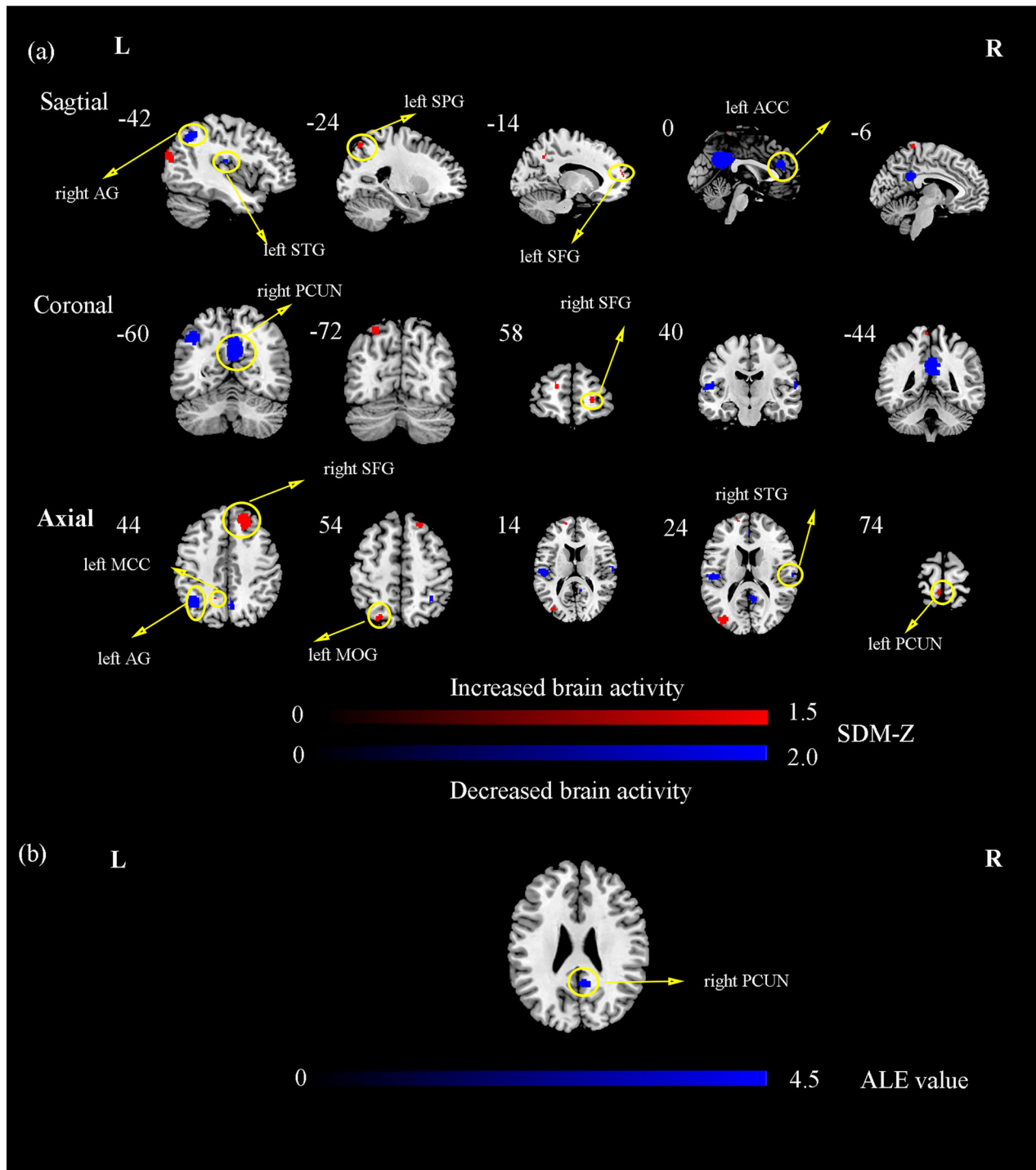
Fig. 2 The significant differences in DMN between patients with T2DM and HCs. a The AES-SDM analysis was threshold with an uncorrected p-value < 0.005. The color bar indicates the maximum and minimum SDM-Z values. Compared with HCs, the increased FC in patients with T2DM were marked in red, while the decreased FC in Patients with T2DM were marked in blue; **b** The ALE analysis was threshold with an uncorrected p-value < 0.001. The color bar indicates the probability of significant ALE values. Compared with HCs, the decreased FC in patients with T2DM were marked in blue. AG angular gyrus, SPG superior parietal gyrus, ACC anterior cingulate cortex, PCUN precuneus, SFG superior frontal gyrus, MCC middle cingulate cortex, MOG middle occipital gyrus, STG superior temporal gyrus.

decreased brain activity in precentral gyrus and STG, which further confirmed the important role of precentral gyrus and STG in T2DM.

The frontal lobe plays a central role in cognition and is associated with emotion, social behavior, motivation, perception, and other processes. Moreover, cognitive functions such as attention, working memory, and decision-making are also commonly attributed to the prefrontal cortex [128]. Current studies have shown that there is decreased activity in the left IFG and the left SFG in patients with T2DM. The decreased activity in SFG was also found in ALE. This is consistent with previous studies, a previous meta-analysis also found decreased activity in

Table 2. Brain regions of abnormal DMN-FC in patients with T2DM relative to HCs by AES-SDM, ALE, and MKDA analyses for DMN.

Brain regions	BA	MNI coordinates			Voxels	*p*-value	Value
		x	y	z			
AES-SDM							
Right superior frontal gyrus	9	20	36	46	422	<0.005	1.847
Left middle occipital gyrus	19	−34	−78	20	334	<0.005	1.402
Right superior frontal gyrus	11	22	56	2	31	<0.005	1.120
Left superior parietal gyrus	7	−24	−72	54	30	<0.005	1.120
Left precuneus	5	−6	−44	74	24	<0.005	1.070
Left superior frontal gyrus	10	−14	58	14	19	<0.005	1.149
Left middle cingulate cortex	NA	−16	−54	40	12	<0.005	1.205
Right precuneus	23	8	−54	22	1412	<0.005	−2.646
Left superior temporal gyrus	48	−54	−20	14	258	<0.005	−1.756
Left angular gyrus	39	−42	−60	44	218	<0.005	−1.936
Left anterior cingulate cortex	NA	0	40	24	157	<0.005	−1.621
Right angular gyrus	40	36	−54	50	73	<0.005	−1.739
Right superior temporal gyrus	22	62	−14	12	34	<0.005	−1.562
ALE							
Right precuneus	31	8	−52	26	76	<0.005	−4.221
MKDA							
None							

The AES-SDM analysis was thresholded with Voxel threshold p-value < 0.005; The ALE analysis was thresholded with an uncorrected *p*-value < 0.005.
*BA* Brodmann, *L* left, *R* right, *MNI* montreal neurological institute.

the SFG, other 2 meta-analyses of GMV changes in patients with T2DM also found patients with T2DM and T2DM-related cognitive dysfunction (T2DM-CD) both had decreased GMV in the SFG [42, 51]. Other empirical studies have also found functional and structural impairments in the inferior and superior frontal gyrus in patients with T2DM, which are related to cognitive impairments in patients with T2DM [129–131]. The paraHip is an important component of the limbic system and is also associated with emotions, behavior, motivation, and long-term memory [132]. A previous meta-analysis found decreased GMV of the paraHip in patients with T2DM [29]. Another study also indicated that the changes in gray matter density and glucose metabolism in the paraHip of patients with T2DM were related to poorer executive function and memory [133]. In the current study, we found increased activity in the left paraHip of patients with T2DM. However, previous study has shown decreased ALFF in the paraHip of patients with T2DM [96], which may be related to the fact that the patients with T2DM had mild cognitive impairment comorbidity in this study. In addition, consistent with the results of previous meta-analyses [41, 42, 44, 46], AES-SDM and ALE both demonstrated increased neural activity in the cerebellum. The cerebellum is a multifunctional brain region, and previous studies have shown that it is not only closely related to sensorimotor functions [89], but is also extensively involved in processing such as attention, working memory, and social cognition [134].

Results of DMN
Retinopathy, one of the common complications of diabetes, can lead to visual impairment. Most studies on patients with T2DM with optic nerve-related complications have reported negative changes in the MOG, including reduced dynamic brain activity [1], reduced centrality [135], and reduced FC [86, 125, 136]. Two meta-analyses also reported decreased activity and cerebral blood flow in the MOG of patients with T2DM [46, 137]. However, we found that the increased FC in the left MOG (BA 19) in the current study. The differences from previous studies may be related to different

functional subregions of MOG. Previous studies have shown that BA 19 is the visual association cortex responsible for high-level processing and interpretation of visual input [138], and a part of MOG also belongs to BA 17, which is a primary visual cortex and located around the talonavicular fissure in the occipital lobe. It is a typical Koniocortex Cortex that receives inputs from the thalamus lateral geniculate body related to visual information input from the lateral geniculate body of the thalamus [139]. Thus, the different FC of MOG.L in patients with T2DM between the current results and previous studies may reflect subregions where MOG is responsible for different visual functions.

SPG is involved in attention and visuospatial orienting, including information manipulation in working memory [29]. Previous studies have shown that decreased FC of SPG in patients with T2DM is associated with impaired visual conceptual and visuo-motor tracking [140]. Another study also indicated that both short-range and long-range FC strength of the SPG were reduced in patients with T2DM [141]. The abnormal FC of the SPG implied that the neural circuits related to attention and spatial orientation may be impaired in patients with T2DM, which was manifested as inattention and the need for more time to complete spatial orientation function. The ACC is another brain region that is closely related to executive and attention functions. Studies have shown that the ACC plays an important role in the top-down control network, monitoring and resolving conflicts by enhancing the salience of attentional targets and inhibiting distracting stimuli [142, 143]. Previous meta-analysis and empirical studies have indicated that patients with T2DM exhibit increased activity in the ACC, and this hyperactivity is thought to be a compensatory mechanism for cognitive impairment and the maintenance of normal cognition [15, 43, 87, 144]. The current study showed that patients with T2DM had decreased FC in the left ACC, which may reflect that despite compensation in local activity, the overall coordination of the attention network is still impaired, thereby affecting the attention regulation function in patients with T2DM. Previous meta-analysis also found that patients with T2DM had
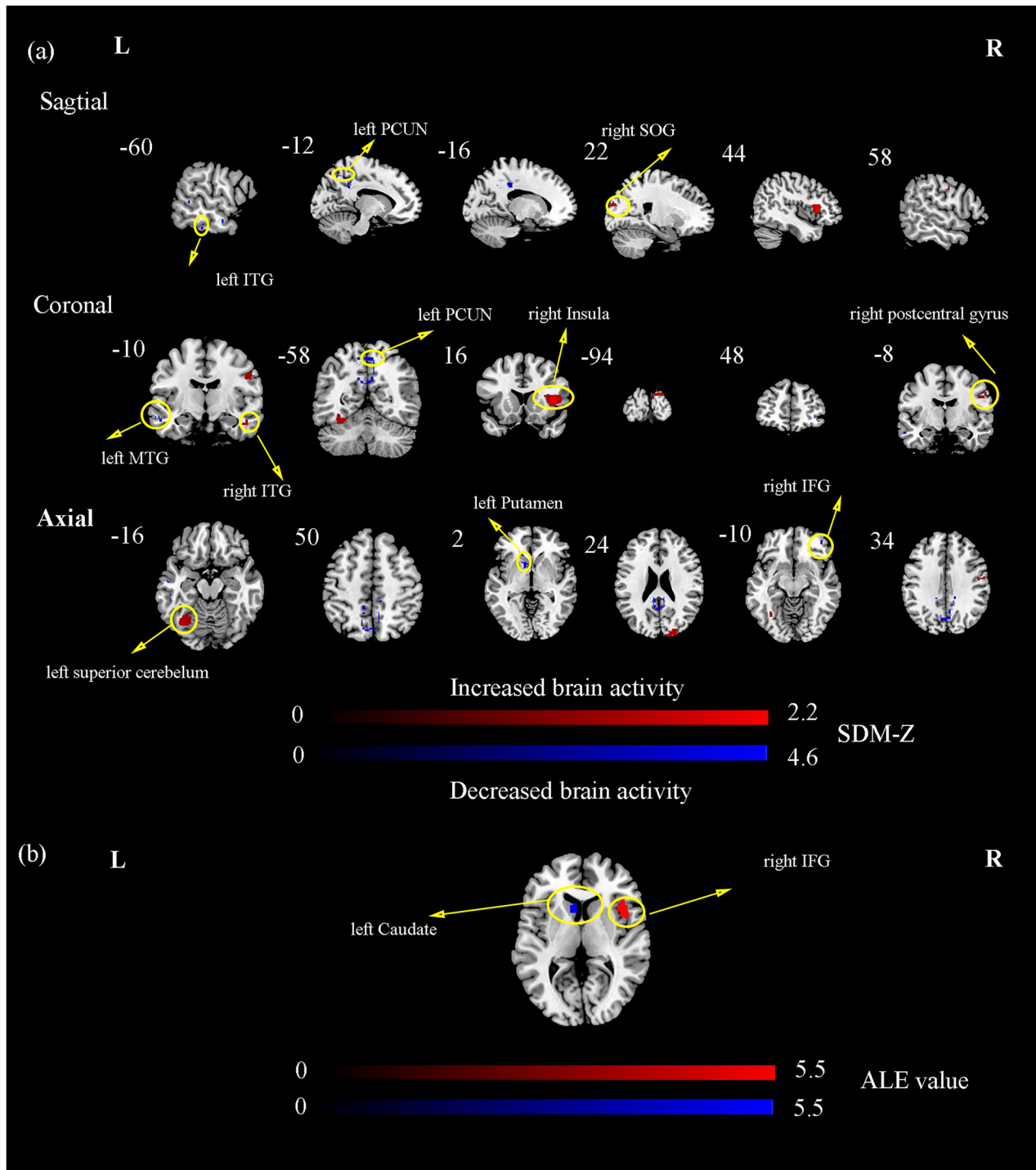
Fig. 3 **The significant differences in VBM between patients with T2DM and HCs. a** The AES-SDM analysis was threshold with an uncorrected *p*-value < 0.005. The color bar indicates the maximum and minimum SDM-*Z* values. Compared with HCs, the increased GMV in patients with T2DM were marked in red, while the decreased GMV in patients with T2DM were marked in blue; **b** The ALE analysis was threshold with an uncorrected *p*-value < 0.005. The color bar indicates the probability of significant ALE values. Compared with HCs, the increased GMV in patients with T2DM were marked in red, while the decreased GMV in patients with T2DM were marked in blue. ITG inferior temporal gyrus, PCUN precuneus, SOG superior occipital gyrus, MTG middle temporal gyrus, IFG inferior frontal gyrus.

decreased FC between DMN and ACC [47]. The MCC is connected to the ACC and is sometimes referred to as the dorsal ACC, which can integrate different types of information over time to achieve diversity in behavioral associations through the integration of information from various input types [145]. Previous study on the MCC in T2DM has been relatively limited, with only two studies

showing increased FC [146] and decreased cortical thickness [147] of the MCC in patients with T2DM, respectively. Moreover, the decreased in MCC cortical thickness was found to be associated with the duration of T2DM. The current study also found increased FC of the MCC in patients with T2DM, which suggests that the MCC may be of great significance in understanding the pathologic

Table 3. Brain regions of gray matter structural abnormalities in patients with T2DM relative to HCs by AES-SDM and ALE analyses for VBM.

Brain regions	BA	MNI coordinates			Voxels	*p*-value	Value
		x	y	z			
AES-SDM							
Right insula	45	42	20	4	392	<0.005	2.142
Left superior cerebelum	19	−34	−64	−18	158	<0.005	1.506
Right superior occipital gyrus	18	22	−94	24	143	<0.005	1.622
Right postcentral gyrus	3	58	−8	34	50	<0.005	1.382
Right inferior temporal gyrus	20	48	−10	−24	13	<0.005	1.378
Left precuneus	7	−2	−70	46	525	<0.005	−4.524
Left inferior temporal gyrus	20	−56	−26	−24	29	<0.005	−3.690
Left putamen	11	−16	16	−2	21	<0.005	−3.978
Right inferior frontal gyrus	47	44	48	−10	14	<0.005	−3.551
Left precuneus	NA	−12	−58	50	11	<0.005	−3.558
Left middle temporal gyrus	21	−60	−10	−16	10	<0.005	−3.711
Left middle temporal gyrus	22	−58	−42	4	10	<0.005	−3.516
ALE							
Right inferior fontal gyrus	48	42	14	6	115	<0.005	5.295
Left caudate	25	−8	16	10	87	<0.005	−5.414
MKDA							
None							

The AES-SDM analysis was thresholded with Voxel threshold *p*-value < 0.005; The ALE analysis was thresholded with an uncorrected *p*-value < 0.005.
BA Brodmann, *L* left, *R* right, *VBM* voxel-based morphometry, *MNI* montreal neurological institute.

mechanisms of T2DM. However, further research is needed to clarify its specific role in T2DM.

The current study showed that there was abnormal FC in the bilateral PCUN and bilateral AG. The current ALE results and previous meta-analysis also found abnormal FC in the right PCUN [47]. The PCUN and AG are core regions of the DMN, which is widely involved in cognitive processing, including self-reference, social cognition, episodic memory, language and semantic memory, and mind wandering [148]. Numerous previous studies have shown that the abnormal FC of the AG and PCUN in patients with T2DM is associated with impairments in executive function and memory performance [140, 149–151]. The current study found that the FC of the left PCUN increased, while that of the right PCUN decreased, which may be associated with hemispheric lateralization. Future studies could further examine the PCUN in terms of hemispheric dominance. In addition, the current study found decreased FC in the STG and increased FC in SFG. Combined the results that we found decreased activity in STG and increased activity in SFG at meta-analysis of local metrics, we speculated that the abnormal FC of STG and SFG were affected by the activity of STG and SFG.

Results of VBM
In the current findings, significant changes in GMV of sensorimotor-related brain regions, such as postcentral gyrus, PUT.R, and SOG.R, were observed in patients with T2DM. Among them, the postcentral gyrus is a higher-level sensory receptive area, primarily receiving sensory afferents from thalamocortical projections and being responsible for somatosensory processing [152]. Previous meta-analysis and empirical studies have demonstrated that there are abnormalities in the resting-state activity [24, 45], FC [153], effective connectivity [154], topological structure [155], cortical thickness [147, 156], neurovascular coupling of the postcentral gyrus [157], as well as the neural fibers connecting the motor and somatosensory areas in patients with T2DM [158]. Moreover, some studies have pointed out that the abnormalities

in the postcentral gyrus of patients with T2DM may be associated with the decreased pain and temperature sensations in diabetic limbs [121]. In addition, previous research has shown that approximately 60% of patients with T2DM will exhibit peripheral neuropathy to varying degrees [159], which may also be related to the damage to the sensorimotor brain regions in patients with T2DM. As an important region of the basal ganglia, putamen is related to motor control, and previous meta-analysis [44] and empirical studies have shown that GMV abnormalities in putamen in patients with T2DM may be associated with impaired motor control [4, 160]. ALE also observed reduced GMV in caudate, which is another important region of basal ganglia. SOG is a core brain region for visual function [161], the current study found that the local spontaneous neural activity, FC of DMN, and grey matter structure showed abnormalities in visual-related regions. This suggested that abnormal visual function may be a core symptom of patients with T2DM.

In the current findings, patients with T2DM also showed significant changes in GMV in bilateral ITG and MTG.L. In previous meta-analysis studies, they only found patients with T2DM had decreased GMV in MTG [29, 30], but there were some studies demonstrated that ITG and MTG had abnormal neural activity and FC [41, 45, 46, 136, 162]. The ITG is involved in cognitive processes such as semantic processing and concept retrieval [163], and contributes to social cognition [164], self-referential processing [165], and emotional stimulus processing [166]. Regarding the temporal lobe in diabetic patients, there is a finding that shows that microscopic abnormalities based on the temporal lobe reveal lower emotional memory performance in diabetic patients [167]. Previous study has linked structural features of the ITG to clinical symptoms, and their results suggested that the GMV content of the ITG may contribute to larger network-level abnormalities associated with negative emotions and rumination [168]. Previous VBM studies have also found that MTG in patients with T2DM exhibit significant alterations in GMV, which have been correlated with poor neurocognitive performance, and the severity of persistent hyperglycemia [45, 110].

INS serves as important components of the limbic system, supporting a variety of functions such as emotion, behavior, motivation, and long-term memory [132, 169]. Cui et al. [24] found that blood glucose variability at different time scales affected grey matter content within the limbic system, with subjects with greater blood glucose variability exhibiting less grey matter and poorer cognitive performance. Previous studies have shown changes in GMV in the bilateral INS [29, 170]. Hirabayashi et al. [171] found that patients with diabetic had significantly lower mean GMV values in the INS than non-diabetic patients. Previous meta-analysis also demonstrated that patients with T2DM had decreased GMV in left insula [29]. However, inconsistent with previous study, the current study demonstrated increased GMV in right insula. On the one hand, this may be influenced by hemispheric lateralization. On the other hand, compared with the previous meta-analysis (7 studies, 8 datasets), the current study included a larger number of studies (16 studies, 18 datasets). Therefore, the results of the two meta-analyses were inconsistent. Future research needs to control for more extraneous variables and include more high-quality studies to further verify the GMV changes in the insula of patients with T2DM. In addition, the current study demonstrated that patients with T2DM had decreased GMV in IFG and PCUN, and had increased GMV in cerebellum. The abnormal GMV in IFG was also examined by ALE, but it found increased GMV in IFG. This may be because the abnormal IFG detected by AES-SDM was located in the orbital part, while it detected by ALE was located in the opercular part. In the previous meta-analysis sections on local metrics and DMN-FC, we similarly found abnormalities in local activity or FC in these brain regions, which suggested that patients with T2DM have both functional and structural alterations in these areas. Consistent with the current study, previous meta-analyses also found abnormalities in the FC and GMV of the PCUN in patients with T2DM [29, 47]. Future studies can further investigate the temporal sequence of the emergence of functional and structural abnormalities in these brain regions.

This study comprehensively explored the changes of local spontaneous neural activity, DMN-FC, and GMV in patients with T2DM. Through integrating three common meta-analysis methods to examine more reliable and reproducible neural markers, thereby deepening the understanding of the neural mechanisms of T2DM. On the one hand, the research results indicated that these neural changes revealed unique patterns of brain function and structure in patients with T2DM, providing potential targets for future clinical interventions, especially in the application of neuromodulation techniques such as transcranial magnetic stimulation (TMS) [172, 173]. Previous studies have shown that TMS treatment targeting specific brain regions identified through meta-analysis can significantly improve cognitive function [174, 175], suggesting that these neural markers have the potential to become new strategies for the intervention of diabetes-related cognitive impairment. On the other hand, from the perspective of the integration of machine learning and MRI, this study provides an important reference for future interdisciplinary exploration. In recent years, with the increasing integration of machine learning and neuroimaging techniques, more and more studies have begun to focus on identifying potential neural markers of T2DM to play a greater role in clinical diagnosis and treatment outcome prediction [176]. The abnormal brain regions were identified through meta-analysis could be used as regions of interest (ROIs) in future machine learning research. Based on these findings, future machine learning research can avoid extensive analysis across the whole brain and instead focus on these highly relevant and influential specific regions, thereby effectively reducing computational burden and enhancing research efficiency. Moreover, focusing on these key regions can also enhance the precision and specificity of the research, providing more reliable and effective input data for machine learning models, which is conducive to improving the accuracy of disease prediction and clinical intervention [177]. In summary, this study not only delves deeply into the neural mechanisms of T2DM at the theoretical level, revealing new perspectives on the disease's underlying pathology, but also has significant clinical application value. The research results provide important insights for the clinical diagnosis, treatment intervention, and design of personalized medical plans for diabetes. At the same time, based on the ROIs determined in this study, it lays the foundation for future innovative research combining machine learning, which is conducive to promoting the precision and individualization of diabetes treatment and further improving the effectiveness of clinical intervention.

Limitations

The study in question advances the field's comprehension of the neural mechanisms associated with T2DM, however, some limitations that should be considered. On the one hand, this study utilized a coordinate-based meta-analysis to delineate the most consistent regions of abnormal spontaneous brain activity in patients with T2DM. This approach is valuable in shedding light on the neural mechanisms underlying T2DM. However, coordinate-based meta-analyses may result in a greater loss of information compared to image-based meta-analyses. Therefore, in this study, we supplemented the results by combining multiple coordinate-based meta-analysis methods as much as possible. Considering that image-based meta-analysis can utilize more whole-brain statistical information, we encourage researchers to share the original statistical parametric maps whenever possible. Further studies should use image-based meta-analyses to validate the current results. On the other hand, because it is difficult to collect fMRI data from patients, to include more studies, we set a sample size of at least 10 as one of the inclusion criteria for this meta-analysis. We hope that future studies will conduct a meta-analysis of T2DM based on a larger sample size to validate the results of this study.

CONCLUSION

In the current study, we utilized coordinate-based meta-analysis to conduct the changes of local metrics, DMN, and VBM in patients with T2DM. The results of our comprehensive meta-analysis showed that patients with T2DM have abnormal brain activity and structure, mainly affecting areas related to visual, cognition and attention. These findings provide valuable insights into the pathophysiological mechanisms of T2DM.

DATA AVAILABILITY

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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