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Brain changes in overweight/obese and normal-weight adults with type 2 diabetes mellitus

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Abstract

Aims/hypothesis Overweight and obesity may significantly worsen glycaemic and metabolic control in type 2 diabetes. However, little is known about the effects of overweight and obesity on the brains of people with type 2 diabetes. Here, we investigate whether the presence of overweight or obesity influences the brain and cognitive functions during early stage type 2 diabetes.

Methods This study attempted to uncouple the effects of overweight/obesity from those of type 2 diabetes on brain structures and cognition. Overweight/obese participants with type 2 diabetes had more severe and progressive abnormalities in their brain structures and cognition during early stage type 2 diabetes compared with participants with normal weight. Relationships between each of these measures and disease duration were also examined.

Results Global mean cortical thickness was lower in the overweight/obese type 2 diabetes group than in the normal-weight type 2 diabetes group ($z = -2.96$, p for group effect = 0.003). A negative correlation was observed between disease duration and global mean white matter integrity ($z = 2.42$, p for interaction = 0.02) in the overweight/obese type 2 diabetes group, but not in the normal-weight type 2 diabetes group. Overweight/obese individuals with type 2 diabetes showed a decrease in psychomotor speed performance related to disease duration ($z = -2.12$, p for interaction = 0.03), while normal-weight participants did not.

Conclusions/interpretation The current study attempted to uncouple the effects of overweight/obesity from those of type 2 diabetes on brain structures and cognition. Overweight/obese participants with type 2 diabetes had more severe and progressive abnormalities in brain structures and cognition during early stage type 2 diabetes compared with normal-weight participants.

Sujung Yoon and Hanbyul Cho contributed equally to this study.

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Abbreviations

FA	Fractional anisotropy
Hs-CRP	High-sensitivity C-reactive protein
ICV	Intracranial volume
ROI	Region of interest

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Introduction

Chronic type 2 diabetes increases the risk of various complications in multiple organs, including the brain [1]. Complications in the brain due to type 2 diabetes may accelerate cognitive dysfunction and may even increase the risk of dementia [2–5]. Type 2 diabetes-related cerebral atrophy and white matter lesions have been considered brain correlates linking type 2 diabetes and cognitive dysfunction [6]. Although the exact mechanism underlying type 2 diabetes-related brain alterations is not fully understood, several metabolic dysfunctions including insulin resistance, poor glycaemic control and inflammation have been suggested to be involved [5, 6].

In general, obesity may precede the onset of type 2 diabetes and is associated with an increased risk of developing type 2 diabetes [7, 8]. Furthermore, obesity has been linked to metabolic dysfunction and may further exacerbate type 2 diabetes-related metabolic abnormalities [9, 10]. Obesity-related metabolic dysfunction is also independently associated with brain alterations [11–13] and may impair cognitive function, which further increases the risk of dementia [14]. However, little is known about how the concurrent presence of overweight/obesity and type 2 diabetes may affect the brain. As the type 2 diabetes phenotype was recently suggested to differ between normal-weight and obese people [15, 16], it is important to study type 2 diabetic individuals according to their weight status.

As the increasing prevalence of overweight/obesity may contribute to the global epidemic of type 2 diabetes [17], it is important to understand the potential combined effects of overweight/obesity and type 2 diabetes on brain structure and cognitive function.

The primary aim of this study was to examine whether the presence of overweight/obesity may influence type 2 diabetes-related brain structural changes and cognitive dysfunction. Since brain structural changes may begin a long time before the clinical manifestation of cognitive impairment [18, 19], our study participants consisted of participants who had been diagnosed with type 2 diabetes within the past 5 years and had no chronic diabetic complications. Thus, they were considered to be in the early stages of type 2 diabetes.

Methods

Participants

Participants included 50 overweight/obese individuals with physician-diagnosed type 2 diabetes and aged between 30 and 60 years (disease duration <5 years). Standard BMI cut-offs were used to define overweight (25–29.9 kg/m^2) and obesity ($\geq$30 kg/m^2) [20, 21]. Fifty normal-weight (BMI <25 kg/m^2) individuals with type 2 diabetes matched for age, sex and disease duration and 50 normal-weight control individuals (without type 2 diabetes) matched for age and sex were also included in the study. The latter were defined as having a fasting plasma glucose level of <5.55 mmol/l and a 2 h postprandial plasma glucose level of <7.77 mmol/l [22]. HbA$_{1c}$ levels of all normal-weight control individuals were <5.7% (39 mmol/mol) [23].

Individuals with type 2 diabetes who had chronic diabetic complications including clinical diabetic nephropathy, proliferative diabetic retinopathy, painful or symptomatic diabetic neuropathy, or major cerebrovascular or cardiovascular events were excluded. Individuals with major medical, neurological or psychiatric disorders and those with contraindications to MRI were also excluded from the study.

All type 2 diabetic patients were undergoing lifestyle modification therapy and/or taking oral glucose-lowering agents to achieve adequate glycaemic control. None had received stable insulin therapy or experienced prior hypoglycaemic episodes requiring medical assistance [24].

Fifty overweight/obese type 2 diabetic participants (BMI range, 25.2–34.1 kg/m^2; hereafter referred to as the overweight/obese type 2 diabetes group), 50 normal-weight type 2 diabetic participants (BMI range, 17.9–24.9 kg/m^2; hereafter referred to as the normal-weight type 2 diabetes group) and 50 normal-weight control participants (BMI range, 19.0–24.9 kg/m^2; hereafter referred to as the normal-weight control group) completed assessments that included metabolic, brain and cognitive measures. Of these 150 individuals, 23 in the overweight/obese type 2 diabetes group, 28 in the normal-weight type 2 diabetes group and 39 in the normal-weight control group underwent another assessment 1 year after the initial visit (Table 1). A total of 240 sets of brain images and cognitive performance data were included in the final analyses. Electronic supplementary material (ESM) Fig. 1 shows BMI changes in the overweight/obese and normal-weight type 2 diabetes groups plotted against disease duration.

The study protocol was approved by the institutional review board of the College of Medicine, Catholic University of Korea. All individuals provided written informed consent prior to participation.

Clinical and metabolic assessments

The characteristics, medical history and medication status of all participants were assessed at the initial visit and 1 year follow-up. BP, glycaemic control, renal function and lipid profiles were also evaluated. HbA$_{1c}$,

Table 1 Baseline characteristics of study participants

Characteristic	Control (n = 50)	Type 2 diabetes (n = 100)	p value	Type 2 diabetes		p value
				Normal-weight (n = 50)	Overweight/obese (n = 50)	
Availability of 1 year follow-up data, n	39	51	–	28	23	–
Demographic characteristic						
Age, mean (SD), years	49.0 (7.8)	49.2 (7.7)	0.93	49.3 (8.1)	49.0 (7.4)	0.85
Women, n (%)	25 (50.0)	50 (50.0)	1.00	25 (50.0)	25 (50.0)	1.00
Right handedness, n (%)	48 (96.0)	95 (95.0)	–	49 (98.0)	46 (92.0)	–
Smoking history, n (%)						
Never	30 (60.0)	49 (49.0)	0.44	22 (44.0)	27 (54.0)	0.08
Former	7 (14.0)	19 (19.0)	–	7 (14.0)	12 (24.0)	–
Current	13 (26.0)	32 (32.0)	–	21 (42.0)	11 (22.0)	–
Lower education level[a], n (%)	31 (62.0)	77 (77.0)	0.05	39 (78.0)	38 (76.0)	0.81
Diabetes-related clinical characteristics						
Time since diagnosis of T2DM, mean (SD), months	–	22.0 (18.4)	–	21.4 (18.7)	22.6 (18.4)	0.74
HbA$_{1c}$, mean (SD), mmol/mol	34.3 (2.0)	54.3 (15.7)	<0.001	52.5 (15.7)	56.0 (15.6)	0.26
HbA$_{1c}$, mean (SD),%	5.29 (0.15)	7.12 (1.43)	–	6.95 (1.43)	7.28 (1.43)	–
Fasting plasma glucose, mean (SD), mmol/l	5.24 (0.21)	7.67 (2.24)	<0.001	7.41 (2.40)	7.94 (2.06)	0.24
Fasting insulin, mean (SD), pmol/l	–	48.4 (58.2)	–	42.5 (56.8)	54.3 (59.6)	0.31
Fasting C-peptide, mean (SD), nmol/l	–	0.66 (0.36)	–	0.58 (0.27)	0.73 (0.43)	0.04
HOMA-IR, mean (SD) [b]	–	2.34 (2.83)	–	1.96 (2.43)	2.73 (3.16)	0.17
HOMA-beta cell function[b], mean (SD),%	–	43.5 (59.7)	–	44.1 (70.8)	42.9 (46.7)	0.92
Hs-CRP, mean (SD), nmol/l	–	18.5 (17.0)	–	17.8 (17.6)	19.2 (16.6)	0.66
Glucose-lowering agents[c], n (%)			–			
None	–	10 (10.0)	–	7 (14.0)	3 (6.0)	0.23
One class	–	55 (55.0)	–	29 (58.0)	26 (52.0)	–
Two or more classes	–	35 (35.0)	–	14 (28.0)	21 (42.0)	–
Anthropometric characteristics						
BMI, mean (SD), kg/m^2	22.7 (1.8)	25.5 (3.4)	<0.001	22.8 (2.0)	28.1 (2.2)	<0.001
Weight, mean (SD), kg	61.9 (9.0)	66.9 (11.1)	0.006	60.9 (9.1)	73.0 (9.5)	<0.001
BP						
Systolic, mean (SD), mmHg	120.5 (9.9)	126.1 (11.6)	0.004	124.4 (10.5)	127.7 (12.6)	0.15
Diastolic, mean (SD), mmHg	75.1 (8.5)	76.5 (8.7)	0.35	75.0 (8.5)	78.1 (8.6)	0.07
Antihypertensive medications, n (%)	0 (0.0)	28 (28.0)	–	14 (28.0)	14 (28.0)	1.00
Lipid profiles						
Total cholesterol, mean (SD), mmol/l	4.87 (0.93)	4.77 (0.97)	0.54	4.89 (0.97)	4.65 (0.96)	0.21
LDL-cholesterol, mean (SD), mmol/l	2.92 (0.88)	2.77 (0.73)	0.27	2.86 (0.74)	2.69 (0.72)	0.24
HDL-cholesterol, mean (SD), mmol/l	1.48 (0.41)	1.26 (0.31)	<0.001	1.30 (0.37)	1.22 (0.23)	0.22
Triacylglycerol, mean (SD), mmol/l	1.27 (0.74)	1.88 (1.05)	<0.001	1.85 (1.09)	1.91 (1.01)	0.78
Lipid-lowering medication, n (%)	0 (0.0)	37 (37.0)	–	19 (38.0)	18 (36.0)	0.84

[a] High-school graduate or lower

[b] HOMA-IR and HOMA-beta cell function were calculated using the formula previously reported [42]

[c] The number of patients with T2DM who used at least two of the six distinct classes of oral glucose-lowering agents (sulfonylureas, biguanide, thiazolidinedione, α-glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors and glinides) [43]; detailed information on oral glucose-lowering agent use is presented in ESM Table 4

T2DM, type 2 diabetes mellitus

HOMA-IR and high-sensitivity C-reactive protein (hs-CRP) were evaluated as metabolic markers for glycaemic control, insulin resistance and subclinical systemic inflammation, respectively.

Brain imaging

Brain MRI data were acquired using a 1.5 Tesla whole-body imaging system (Signa HDx, GE Healthcare, Milwaukee, WI, USA) at the initial visit and 1 year follow-up.

Mean thickness across the entire cortex (global mean thickness) was the primary outcome measure of type 2 diabetes-related grey matter alterations. In addition, vertex-wise analyses were performed to examine group differences in global mean thickness between the total type 2 diabetes group (comprising the overweight/obese and normal-weight type 2 diabetes groups) and the normal-weight control group.

The mean fractional anisotropy (FA) value across the whole brain white matter skeleton (global mean FA) was the primary outcome measure for type 2 diabetes-related white matter alterations. In addition, voxel-wise analyses were performed to examine differences in FA values between the total type 2 diabetes group and the normal-weight control group.

Detailed information on acquisition variables and imaging preprocessing is presented in the following ESM Methods sections: MRI acquisition and preprocessing, Cortical thickness measurement and FA measurement.

Cognitive assessments

Memory, psychomotor speed and executive function were assessed using a series of neuropsychological tests because these cognitive functions are known to be affected in people with type 2 diabetes [6, 25, 26].

The Rey–Osterrieth complex figure test and California Verbal Learning Test were used to assess memory function. Psychomotor speed was measured using the digit symbol substitution test, the Stroop test – C form and the grooved pegboard test. Executive function was examined using trail making test B, the Stroop test – interference and the Wisconsin card sorting test.

Composite scores in the memory, psychomotor speed and executive function tests were chosen as the outcome measures to examine between-group differences in cognitive changes during early stage type 2 diabetes. Neuropsychological tests are described in ESM Table 1.

Statistical analysis Group differences in brain and cognitive measures between the total type 2 diabetes group and the normal-weight control group were examined using a linear mixed-effects model with group (type 2 diabetes vs control group) as a fixed-effect term and within-individual dependence as a random-effect term. Age and sex were included as covariates. Intracranial volume (ICV) and educational level were included as additional covariates for estimating group differences in global mean thickness and cognitive measures, respectively.

A linear mixed-effects model was used to estimate whether disease duration has different effects on metabolic, brain and cognitive measures between the two subgroups of type 2 diabetic participants. This model included weight status (overweight/obese vs normal-weight) as a linear term for disease duration (time since diagnosis of type 2 diabetes) and their interactions as fixed effects and as within-individual random effects. Models including disease duration and interaction as additional higher-order terms were also tested and then a likelihood ratio test was performed to compare models for selecting the best-fitting model. Age and sex were included in the models as covariates. ICV and education level were included as additional covariates for estimating global mean thickness and cognitive measures, respectively. Terms included in each final best-fitting model are shown in ESM Table 2.

We also investigated region-specific interaction effects between disease duration and weight status on brain measures using a linear mixed-effects model. Mean cortical thickness and FA values for regions of interest (ROIs; defined as significant grey and white matter clusters for the total type 2 diabetes group effects; Tables 2 and 3, ESM Table 3), were also estimated.

Raw values for global mean thickness, global mean FA values and composite scores for cognitive functions were standardised into z scores using the means and SDs for the normal-weight control group.

The sample size of 50 control and 100 type 2 diabetic participants was large enough to detect an effect size of 0.6 for differences in each measurement (SD = 15%) between groups, with a power of 0.90 and an α level of 0.05.

An α level of 0.05 in two-tailed tests was considered as statistically significant. Data were analysed using Stata version 11 (Stata Corp, College Station, TX, USA).

Results

Study participants Baseline demographic and clinical characteristics of study participants are presented in Table 1. At the initial assessment, the overweight/obese and normal-weight type 2 diabetes groups had similar demographic characteristics, metabolic data and medication use, except for fasting C-peptide levels (t = −2.07, p = 0.04).

Disease duration-related alterations in metabolic measures in the overweight/obese and normal-weight type 2 diabetes groups Metabolic measures including HbA_{1c}, HOMA-IR and hs-CRP for the two type 2 diabetes subgroups are presented in Fig. 1.

A U-shaped relationship was observed between disease duration and HbA_{1c} levels in type 2 diabetic individuals. HbA_{1c} levels were lower in the first 2 years after type 2 diabetes diagnosis. After the 2 year mark since diagnosis, HbA_{1c} levels were elevated in both the overweight/obese and normal-weight type 2 diabetes

Table 2 Detailed information on clusters of significant group differences (total type 2 diabetes group vs normal-weight control group) in cortical thickness measures[a]

No.	Region(s)	Corresponding brain lobar regions	Cluster size (mm^2)	Vertices in the cluster (n)	Talairach coordinate			Clusterwise p value
					x	y	z	
Right								
1	Fusiform	Temporal region	1628.6	2595	42.1	−59.7	−5.7	< 0.001
	Inferior temporal cortex							
2	Superior temporal cortex	Temporal region	9945.1	21,091	51.2	−35.6	8.3	< 0.001
	Banks of the superior temporal sulcus	Parietal region						
	Supramarginal cortex	Frontal region						
	Superior frontal cortex							
	Middle frontal cortex							
	Inferior frontal cortex							
	Insula							
3	Lingual cortex	Occipital region	1425.8	2245	14.3	−60.5	5.1	< 0.001
	Pericalcarine cortex							
	Cuneus							
4	Premotor/supplementary motor cortex	Frontal region	671.7	1550	10.3	3.9	45.6	0.02
Left								
1	Fusiform	Temporal region	789.4	1310	−40.8	−50.2	−10.0	0.006
2	Superior temporal cortex	Temporal region	2393.1	5380	−55.7	−48.3	28.4	< 0.001
	Banks of the superior temporal sulcus	Parietal region						
	Supramarginal cortex							
3	Superior frontal cortex	Frontal region	838.5	1434	−7.5	26.0	35.4	0.004
4	Lingual	Occipital region	865.5	1700	−10.8	−62.9	5.1	0.004
5	Orbitofrontal cortex	Frontal region	1915.0	4346	−54.8	−7.1	9.6	< 0.001
	Inferior frontal cortex	Parietal region						
	Precentral cortex							
	Postcentral cortex							

[a] There were no regions of thinner cortex in the normal-weight control group relative to the total type 2 diabetes group

groups, although they were higher in the former. However, there was no interaction effect of disease duration and weight status on HbA$_{1c}$ levels ($z = 0.65$, p for interaction = 0.51; Fig. 1b).

HOMA-IR, which reflects insulin resistance, correlated negatively with disease duration in both type 2 diabetes groups, and there was no between-group difference in the relationship between HOMA-IR and disease duration ($z = -0.61$, p for interaction = 0.54; Fig. 1d).

A positive relationship between hs-CRP level and disease duration was observed in the overweight/obese type 2 diabetes group, while a negative relationship was observed in the normal-weight type 2 diabetes group ($z = 2.57$, p for interaction = 0.01; Fig. 1f).

Differences in brain measures between the type 2 diabetes and control groups There were differences in the global mean thickness ($z = -2.72$, p for group effect = 0.006) and the global mean FA ($z = -3.73$, p for group effect <0.001) between the total type 2 diabetes group and the normal-weight control group. Vertex-wise cortical thickness analysis showed that grey matter was significantly thinner in clusters in the temporal, prefrontoparietal, motor and occipital cortices in the total type 2 diabetes group than in the normal-weight

control group (at a corrected p value of <0.05; Table 2 and ESM Fig. 2a). Voxel-wise FA analysis showed that FA values were significantly lower in clusters in the temporal, prefrontoparietal, motor and occipital regions in the total type 2 diabetes group than in the normal-weight control group (at a corrected p value of <0.05; Table 3, ESM Fig. 2b). In addition, tract-specific alterations were examined using the Johns Hopkins University diffusion tensor imaging-based white matter atlas [27]. FA values from the major fibre tracts were extracted and compared between groups (ESM Fig. 3).

Disease duration-related alterations in brain measures in the overweight/obese and normal-weight type 2 diabetes groups Brain measures including global mean thickness and global mean FA of the two type 2 diabetes subgroups are presented in Fig. 2. Global mean thickness was significantly lower in the overweight/obese type 2 diabetes group than in the normal-weight type 2 diabetes group ($z = -2.96$, p for group effect = 0.003; Fig. 2a), and there was no between-group difference in the relationship between disease duration and global mean thickness ($z = 0.65$, p for interaction = 0.52; Fig. 2b). There was a significant interaction between disease duration and weight status on global mean FA ($z = 2.42$, p for

Table 3 Detailed information on clusters of significant group differences (total type 2 diabetes group vs normal-weight control group) in FA measures

No.	Region(s)	Corresponding regions of tract-based anatomical map	Voxels in the cluster (n)	Maximum t value	MNI atlas coordinates[a]		
					x	y	z
1	Fornix Sagittal stratum IFOF UF Corticospinal tract	Left temporal region	1171	6.11	−39	−8	−18
2	Corpus callosum	Bilateral frontal regions Left parietal	1166	6.07	−5	27	1
3	Corticospinal tract	Right temporal region	315	5.79	13	−22	−17
4	Anterior thalamic radiation Fornix	Bilateral temporal regions	309	5.93	−6	−9	10
5	Corpus callosum Superior corona radiata	Right frontal region	264	4.37	18	12	35
6	Cerebellar white matter	Left cerebellum	227	5.28	−23	−70	−32
7	Cerebellar white matter	Right cerebellum	211	5.76	22	−71	−32
8	Forceps minor	Right frontal region	196	4.92	21	44	17
9	Optic radiation	Right occipital region	187	6.36	24	−78	23
10	Anterior corona radiata	Right frontal region	179	4.76	29	13	7
11	External capsule	Right temporal region	171	4.79	36	−11	−12
12	Anterior corona radiate Forceps minor	Left frontal region	167	4.25	−20	35	8
13	Corticospinal tract	Right frontal region	153	4.72	21	−34	51
14	Cerebellar white matter	Left cerebellum	151	5.75	−34	−55	−44
15	Cerebellar white matter	Right cerebellum	134	5.45	31	−60	−42
16	Optic radiation	Right occipital region	123	6.36	22	−86	4
17	Corpus callosum	Right parietal region	111	5.17	19	−39	30
18	Optic radiation	Left occipital region	107	5.48	−24	−75	13
19	Optic radiation	Right occipital region	105	5.06	37	−76	1
20	External capsule	Left temporal region	94	3.69	−30	10	1
21	Parietal white matter	Right parietal region	90	5.59	23	−46	48
22	Temporal white matter	Right temporal region	89	5.23	57	−17	−15

There were no regions of smaller FA values in the normal-weight control group relative to the total type 2 diabetes group

[a] Location of maximum t value

FA, fractional anisotropy; IFOF, inferior fronto-occipital fasciculus; UF, uncinate fasciculus

interaction = 0.02), where a gradual decrease in global mean FA was found in the overweight/obese but not in the normal-weight type 2 diabetes groups (Fig. 2d).

To ensure that the results were robust, repeated analyses were performed using baseline data while excluding 1 year follow-up data. The general linear model was applied to estimate the interaction effects between disease duration and weight status on brain measures. The same covariates as those used in the original linear mixed-effects model, except for within-individual random effects, were included in the model. Similar results were obtained for these repeated analyses (ESM Results).

Brain region-specific interaction between disease duration and weight status The overweight/obese type 2 diabetes group had a thinner cortex in the temporal and motor ROIs

compared with the normal-weight type 2 diabetes group ($z = -4.36$, p for group effect <0.001 and $z = -2.91$, p for group effect = 0.004, respectively; Fig. 3a, c). Mean FA values in the prefrontoparietal ROI were lower in the overweight/obese type 2 diabetes group than in the normal-weight type 2 diabetes group ($z = -2.06$, p for group effect = 0.04; Fig. 3b). The relationships between disease duration and mean FA for the temporal and occipital ROIs in the overweight/obese type 2 diabetes group differed from those in the normal-weight type 2 diabetes group ($z = 2.22$, p for interaction effect = 0.03 and $z = -2.07$, p for interaction effect = 0.04, respectively; Fig. 3a, d).

Differences in cognitive measures between the type 2 diabetes and control groups There were differences in memory
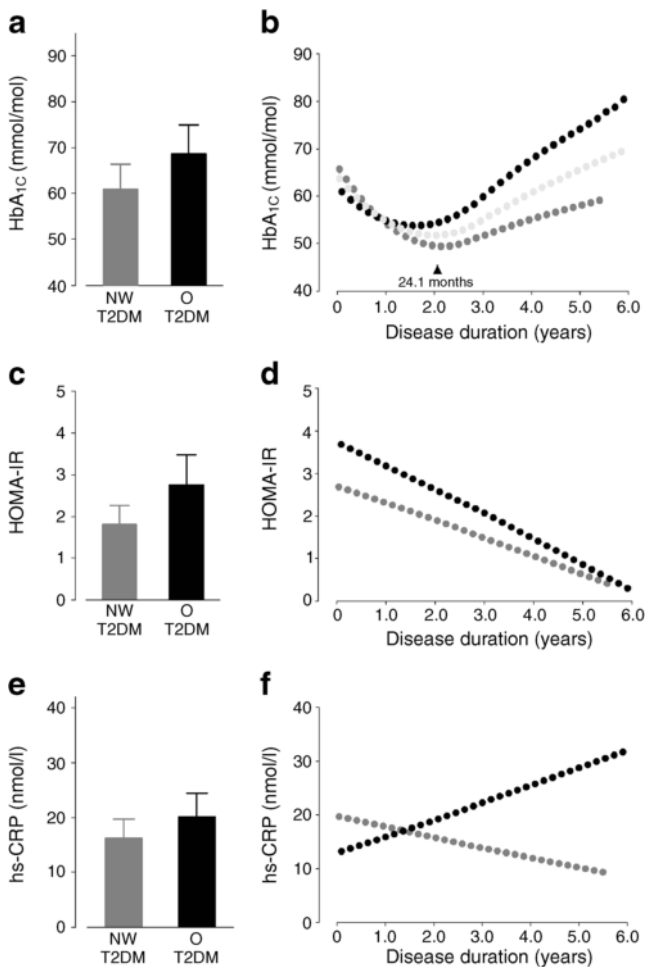
Fig. 1 Metabolic measures in the early stage of type 2 diabetes (**a**, **c**, **e**). Relationship between disease duration and HbA$_{1c}$ (**b**), HOMA-IR (**d**) and hs-CRP (**f**). Time point for the nadir HbA$_{1c}$ level corresponds to 24.1 months (black triangle). Estimated values were smoothed using locally weighted scatterplot smoothing (LOESS), a locally polynomial regression method [44]. Error bars represent 95% CIs. To convert values for HbA$_{1c}$ in mmol/mol into %, multiply 0.0915 and add 2.15. Grey bars and dots, normal-weight NW type 2 diabetes; black bars and dots, overweight/obese O type 2 diabetes. T2DM, type 2 diabetes mellitus

and psychomotor speed between the total type 2 diabetes group and the normal-weight control group ($z = -3.11$, p for group effect = 0.002 and $z = -5.58$, p for group effect <0.001, respectively). Differences in executive function between the total type 2 diabetes group and the normal-weight control group were not statistically significant ($z = -1.78$, p for group effect = 0.08).

Disease duration-related alterations in cognitive measures in the overweight/obese and normal-weight type 2 diabetes groups Cognitive measures, including memory, psychomotor speed and executive function, for the two type 2 diabetes subgroups are presented in Fig. 4. There was a significant interaction effect of disease duration and weight status on
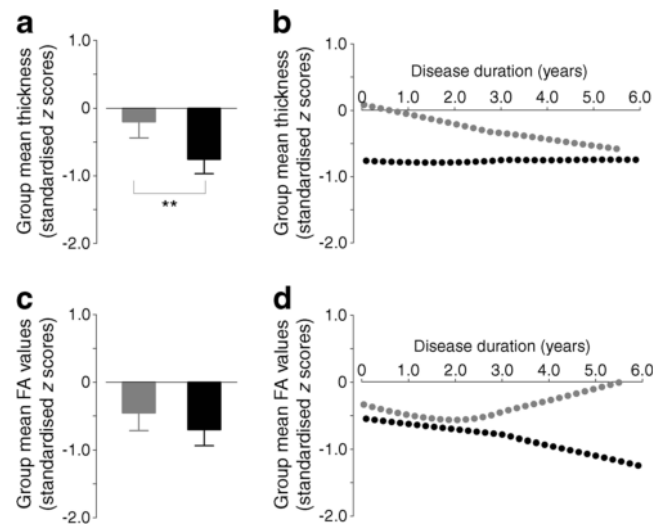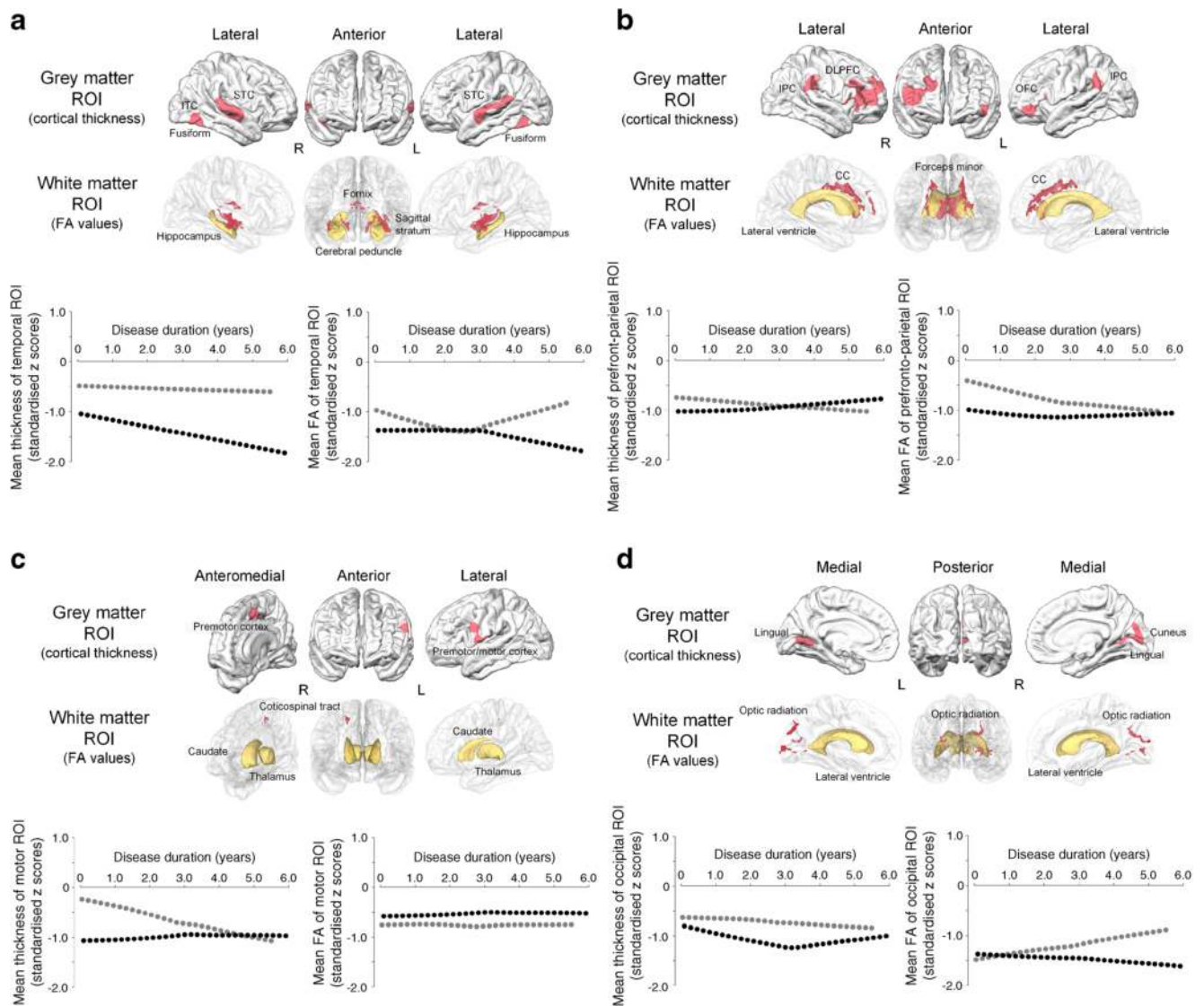

Fig. 2 Brain measures in early stage type 2 diabetes. Negative standardised z scores represent values below the means of the normal-weight control group in SD units. Standardised z scores and relationships between disease duration and brain measures of global mean thickness (**a**, **b**) and global mean FA values (**c**, **d**). Estimated values were smoothed using locally weighted scatterplot smoothing (LOESS) [44]. Error bars represent 95% CIs. Grey bars and dots, normal-weight type 2 diabetes; black bars and dots, overweight/obese type 2 diabetes. **$p < 0.01$

psychomotor speed performance ($z = -2.12$, p for interaction = 0.03; Fig. 4d). A progressive decline in psychomotor speed performance was found in the overweight/obese type 2 diabetes group. There was no significant interaction effect on memory ($z = -1.53$, p for interaction = 0.13; Fig. 4b) or executive function ($z = -0.25$, p for interaction = 0.80; Fig. 4f).

Relationships between insulin resistance and brain measures As HbA$_{1c}$ levels fluctuated in a U-shaped pattern, first decreasing in the first 2 years after diagnosis and then gradually increasing, HOMA-IR may be a more accurate marker than HbA$_{1c}$ levels for estimating brain and cognitive alterations that occur in early stages of the disease. Therefore, partial correlation analysis adjusting for age and sex was performed for insulin resistance and brain measures in type 2 diabetic patients whose disease duration was <2 years (90 data points). During the first 2 years after diagnosis, insulin resistance (as measured by HOMA-IR) was negatively associated with global mean thickness ($r_p = -0.24$, $p = 0.02$) but not with global mean FA ($r_p = 0.06$, $p = 0.58$).

Discussion

In the current study, we report for the first time that cortical thinning and disrupted white matter integrity are more pronounced in early stage type 2 diabetes. Furthermore, we found that disease duration-related alterations in cortical thickness and white matter integrity were more prominent in

Fig. 3 Region-specific brain measures of ROIs in early stage type 2 diabetes. Pink regions on the standard cortical surface (upper) and the glass brain (lower), a render with transparent cortical structures, indicate ROIs of the study (ESM Table 3). Grey dots, normal-weight type 2 diabetes; black dots, overweight/obese type 2 diabetes. For relationships between disease duration and brain measures, estimates were smoothed using locally weighted scatterplot smoothing (LOESS) [44]. CC, corpus callosum; DLPFC, dorsolateral prefrontal cortex; IPC, inferior parietal cortex; ITC, inferior temporal cortex; L, left; OFC, orbitofrontal cortex; R, right; STC, superior temporal cortex

overweight/obese type 2 diabetic individuals than in those with normal weight. A similar trend was also found in psychomotor speed performance. These findings suggest that weight status may play additive roles in type 2 diabetes-related brain and cognitive alterations.

We selected grey and white matter ROIs in the temporal, prefrontoparietal, motor and occipital regions that showed type 2 diabetes-related alterations in cortical thickness or white matter integrity. We explored whether the concomitant presence of overweight or obesity influences grey and white matter of the brain in a region-specific manner. Interestingly, region-specific interaction effects were primarily observed in the temporal region, indicating that the temporal lobe is vulnerable to the

combined effects of overweight/obesity and type 2 diabetes. An exploratory analysis also suggested that the reduction in FA values in white matter tracts including the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and cingulum, which are mainly located in or pass through the temporal regions, were more pronounced in overweight/obese compared with normal-weight type 2 diabetic individuals.

Overweight/obesity and type 2 diabetes independently increase the risk of dementia [2, 28–30], and previous studies have shown that temporal lobe atrophy is one of the earliest neuroanatomical changes in Alzheimer's dementia [18, 31]. Therefore, the temporal deficits specifically observed in the overweight/obese type 2 diabetes group may represent
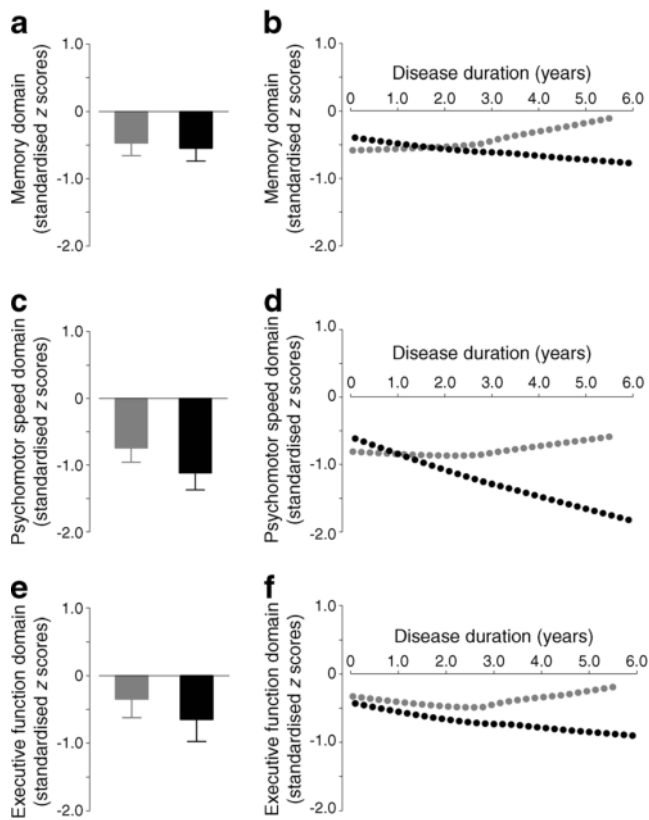
Fig. 4 Cognitive measures in early stage type 2 diabetes. Negative standardised *z* scores represent values below the means of the normal-weight control group in SD units. Standardised *z* scores and relationships between disease duration and cognitive measures of memory (**a**, **b**), psychomotor speed (**c**, **d**) and executive function (**e**, **f**). Estimated values were smoothed using locally weighted scatterplot smoothing (LOESS) [44]. Error bars represent 95% CIs. Grey bars and dots, normal-weight type 2 diabetes; black bars and dots, overweight/obese type 2 diabetes

neuroanatomical substrates underlying the links among overweight/obesity, type 2 diabetes and the risk of dementia.

As pronounced deficits in the brain and in cognitive functions of people with type 2 diabetes may be potentiated by obesity, these patients can be divided into distinct prognostic subtypes according to their weight status [15, 16]. Our findings also highlight the need for early intervention aimed to reduce risk factors for overweight or obesity in type 2 diabetic individuals to preserve their brain structure and cognitive function. Furthermore, the contributory factors are unknown, our findings suggest that insulin resistance without obesity has distinct effects on the brain compared with conventional type 2 diabetes.

However, it is noteworthy that the current study did not recruit overweight/obese individuals without type 2 diabetes. Therefore, we could not determine the potential effects of overweight/obesity that are completely independent of type 2 diabetes on metabolic, brain and cognitive measures. Further studies using a more elaborate framework are recommended to better describe the independent and combined

(additive, synergistic or interactive) effects of type 2 diabetes and obesity/overweight on the brain. To achieve this, we suggest using a balanced cohort comprising the following groups: normal-weight control individuals, obese individuals without type 2 diabetes, normal-weight type 2 diabetic patients and obese type 2 diabetic patients.

Interestingly, HbA_{1c} levels (reflecting symptom severity) seem to decrease shortly after the diagnosis of type 2 diabetes. Furthermore, preliminary correlation analyses revealed that insulin resistance may be a significant determinant of cortical atrophy in early stage type 2 diabetes. Although the underlying mechanisms have not yet been clearly identified, impaired insulin signalling and consequent effects on synaptic plasticity may link insulin resistance and cortical atrophy [32]. Insulin receptors are widely distributed in the brain and are highly abundant in the hippocampus and specific cortical areas [33, 34]. Given that the current consensus recommendation for treating type 2 diabetes aims to maintain near-normal blood glucose and HbA_{1c} levels, these findings suggest that it may be more important to manage insulin resistance (the underlying cause of the disease) during early stage type 2 diabetes than previously thought.

Although the final model included 1 year follow-up data, the current results may represent a cross-sectional estimation of trajectories in relation to the disease duration, rather than individual longitudinal changes. We used a linear mixed-effect model that accounted for within-individual random effects by assuming that changes occurring during the disease course are comparable among individuals [19]. This estimation was corroborated by a repeated analysis including only baseline data, which produced similar findings. Future longitudinal studies are necessary to estimate the longitudinal trajectory of brain measures in early stage type 2 diabetes.

The actual onset of type 2 diabetes often begins several years before its clinical diagnosis [35]. Thus, longitudinal follow-up of individuals with impaired glucose tolerance may be necessary to confirm the effects of overweight/obesity on the brain in individuals with type 2 diabetes. In this study, type 2 diabetic participants had not experienced previous hypoglycaemic episodes, so the potential effects of hypoglycaemia could not be determined [36].

Given that a series of studies suggest that glucose-lowering medications may have effects on the brain [37], the current findings should be interpreted with caution regarding the use of glucose-lowering medications. Specifically, glucagon-like peptide-1 receptor agonist, dipeptidyl peptidase 4 inhibitors, metformin and thiazolidinedione are known to have favourable effects on the brain [37]. Further longitudinal studies using larger cohorts are needed to discriminate and trace the potential interaction between glucose-lowering medication use and weight status on the brain in type 2 diabetic patients.

Our results suggest that a relationship exists between disease duration and metabolic measures in each diabetic group

(classified according to BMI). However, as there was no information on fasting insulin and C-peptide levels in the normal-weight control group, differences in metabolic measures between the type 2 diabetic and control groups could not be determined in the present study.

The current WHO BMI cut-offs between overweight and obesity do not differ according to ethnic origin [17]. In Koreans, the overall risk of death was reported to be lowest for individuals with a BMI of 23.0–24.9 kg/m^2 [38]. However, it is noteworthy that people of Asian ethnicity tend to be more vulnerable to slight increases in BMI even within the overweight range and are at a higher risk of type 2 diabetes than those of other ethnicities [39, 40]. Pre-existing functional deficits in beta cells, along with a tendency toward insulin resistance even in lean individuals, may contribute to the specific vulnerability of Asian people [17, 41]. Potential ethnic differences in brain vulnerability to type 2 diabetes and/or overweight/obesity may therefore need to be considered when interpreting the results of these studies.

This study showed that the concurrent presence of overweight/obesity was associated with cortical atrophy, disrupted white matter integrity and cognitive dysfunction in early stage type 2 diabetes. An increased awareness of overweight/obesity-related risk is necessary to prevent and manage type 2 diabetes-related brain atrophy and cognitive dysfunction from early stage type 2 diabetes onward.

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