ORIGINAL ARTICLE

Prefrontal Cortical Deficits in Type 1 Diabetes Mellitus

Brain Correlates of Comorbid Depression

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Context: Neural substrates that may be responsible for the high prevalence of depression in type 1 diabetes mellitus (T1DM) have not yet been elucidated.

Objective: To investigate neuroanatomic correlates of depression in T1DM.

Design: Case-control study using high-resolution brain magnetic resonance images.

Settings: Joslin Diabetes Center and McLean Hospital, Massachusetts, and Seoul National University Hospital, South Korea.

Participants: A total of 125 patients with T1DM (44 subjects with ≥1 previous depressive episodes [T1DM-depression group] and 81 subjects who had never experienced depressive episodes [T1DM-only group]), 23 subjects without T1DM but with 1 or more previous depressive episodes (depression group), and 38 healthy subjects (control group).

Main Outcome Measures: Spatial distributions of cortical thickness for each diagnostic group were compared with the control group using a surface-based approach. Among patients with T1DM, associations between metabolic control measures and cortical thickness deficits were examined.

Results: Thickness reduction in the bilateral superior prefrontal cortical regions was observed in the T1DM-depression, T1DM-only, and depression groups relative to the control group at corrected $P<.01$. Conjunction analyses demonstrated that thickness reductions related to the influence of T1DM and those related to past depressive episode influence were observed primarily in the superior prefrontal cortical region. Long-term glycemic control levels were associated with superior prefrontal cortical deficits in patients with T1DM ($\beta=-0.19$, $P=.02$).

Conclusions: This study provides evidence that thickness reduction of prefrontal cortical regions in patients with T1DM, as modified by long-term glycemic control, could contribute to the increased risk for comorbid depression.

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In 1684, Thomas Willis first suggested that diabetes mellitus and depression might be related to one another.[1] Recent epidemiologic and clinical evidence has demonstrated a higher than expected prevalence of depression among patients with type 1 diabetes mellitus (T1DM).[2-8]

The high comorbidity of depression in diabetes has commonly been attributed to increased psychosocial demands of having a chronic medical illness rather than to neurobiological deficits derived from diabetes.[9-11] However, emerging evidence for a bidirectional association between depression and type 2 diabetes mellitus suggests the presence of potential common neurobiological mechanisms of diabetes and depression.[12,13]

A growing body of neuroanatomic data has found structural abnormalities in both gray and white matter in patients with T1DM.[14-18] Patients with T1DM have recently been reported to have functional and structural deficits, more specifically in prefrontal regions.[15,19-24] Interestingly, the prefrontal region may subserve an explicit role in regulating emotion; therefore, these regional alterations have long been implicated in the pathophysiology of depression.[25-30] Considering that the age at depression onset is often later than the age at diabetes diagnosis in patients with T1DM,[31,32] T1DM-related neuroanatomic deficits in brain regions that have

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been implicated in mood regulation may increase susceptibility toward later depression.

In addition to the neurobiological path from T1DM to depression, accumulating evidence suggests that the clinical course of T1DM could be more serious when depression is also present. Patients with T1DM and depression have more frequent and severe hyperglycemia[6,33-35] and diabetic complications.[5,6,8,36] This has been partly explained by depression-related changes in lifestyle factors including physical inactivity, noncompliance with dietary or weight loss recommendations,[37-39] and associated obesity.[40,41] Considering that poor glycemic control may be a moderator for T1DM-related brain abnormalities,[19,20] comorbid depression could also play a major role in exacerbating T1DM-related brain structural deficits by altering metabolic factors such as glycemic control levels in patients with T1DM.

In this study, we used a surface-based approach to measure cortical thickness from high-resolution brain magnetic resonance images (MRIs) comparing patients with T1DM having 1 or more previous depressive episodes, those without a history of depressive episodes, non-T1DM subjects with 1 or more previous depressive episodes, and healthy control subjects without depression history. We hypothesized that a similar pattern of prefrontal thickness reduction would be observed in both T1DM and depression groups in view of accumulating evidence for common regional brain abnormalities implicated in the pathophysiology of both disease entities.[14] We further expected that patients with T1DM with past depressive episodes would show greater structural deficits than patients with T1DM without depressive episodes, with a similar regional pattern. Because diabetes mellitus and depression could independently[42-48] as well as additively[49] yield cognitive deficits, those brain abnormalities could lead to a risk for more severe cognitive deficits in patients with T1DM with depression in comparison with those without depression. We also studied the relationship of these changes in the brain structure among subjects with T1DM to the degree of persistent hyperglycemia, as indicated by time-weighted hemoglobin A_{1C} (HbA_{1C}) levels for illness duration, as well as a history of severe and recurrent hypoglycemia leading to unconsciousness and/or seizure.

To our knowledge, little research has focused on neuroanatomic correlates that might underlie the relationship between T1DM and depression; thus, examining the neurobiological mechanisms underlying the comorbidity of both diseases could provide key information for developing mechanism-based strategies for their treatment or prevention.

METHODS

SUBJECTS

We studied 125 patients with T1DM. These included 44 patients who had 1 or more previous depressive episodes but were not currently depressed (herein defined as the T1DM-depression group) and 81 who had never experienced a depressive episode (herein defined as the T1DM-only group). Of the 61 nondiabetic subjects, 23 had 1 or more previous depressive episodes but were not currently depressed (herein defined as the depression group) and 38 healthy control subjects had neither T1DM nor any past or current depressive episodes (herein defined as the control group).

Subjects with a current depressive episode were excluded to minimize potential confounding influences that are related to current depressive symptoms.[50-52] For the T1DM-depression group, only patients whose onset of T1DM was earlier than that of depression were included (elapsed time between T1DM and depression: mean [SD], 13.8 [5.2] years; range, 4-25 years). Past and current depressive symptoms were assessed by using the Structured Clinical Interview for *DSM-IV*[53] and the Hamilton Depression Rating Scale (HDRS).[54]

All subjects were between 25 and 40 years of age, and the disease duration of subjects with T1DM was between 15 and 25 years. Patients with T1DM who had serious diabetic complications including end-stage renal disease, painful or symptomatic neuropathy, or gastroparesis were excluded. Subjects with major medical and neurologic disorders and contraindications to MRI were excluded. Exclusion criteria also included a history of psychosis; schizophrenia; bipolar disorder; attention-deficit hyperactivity disorder; or cocaine, heroin, or alcohol dependence, as assessed using the Structured Clinical Interview for *DSM-IV*.

Subjects were recruited at the Joslin Diabetes Center, Boston, Massachusetts, and MRI and cortical thickness analyses were performed at the Brain Imaging Center of McLean Hospital, Belmont, Massachusetts, and the Brain Imaging Center of the Seoul National University Hospital, Seoul, South Korea, respectively. The study was approved by the institutional committees on human subjects of each institution, and written informed consent was obtained from all subjects prior to their participation.

CLINICAL ASSESSMENTS

Diabetic and metabolic characteristics were obtained from medical records and laboratory tests. Glycemic control levels were measured by the average value of HbA_{1C}, grouped and time weighted every 4 years for the duration of illness.[19,20] A severe hypoglycemic episode was defined as an event that led to a coma, seizure, or unconsciousness, according to the Diabetes Control and Complications Trial Research Group Criteria.[19,20,55] Retinopathy status was assessed by ophthalmologists of the Joslin Diabetes Center Beetham Eye Institute. The date of diagnosis was acquired from the medical records or patient self-report.

Body mass index (BMI, calculated as weight in kilograms divided by height in meters squared); blood pressure; and serum lipid levels of total, triglyceride, high-density lipoprotein, and low-density lipoprotein cholesterol were also measured.

Cognitive performance on executive and memory function, both of which are primary domains that are subserved by the prefrontal cortex and the medial temporal lobe,[56,57] were measured using a battery of neuropsychologic tests.[20,58-60] Adjusted z scores for age, sex, and education level for each neuropsychologic test were calculated using group means and standard deviations of control subjects. If necessary, test scores were reversed to indicate better performance with positive z scores. Detailed descriptions of cognitive domains and reliability measures for neuropsychologic tests are presented in eAppendix 1 (http://www.archgenpsychiatry.com).

Hand preference was examined using the Edinburgh Handedness Inventory.[61] Subjects who were categorized as either right-handed or ambidextrous-handed were included. Self-reported anxiety levels were evaluated using the Symptom Checklist-90-Revised.[62]

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MRI ACQUISITION AND CORTICAL THICKNESS ANALYSIS

Brain MRIs were obtained using a 1.5-T GE whole body imaging system (Horizon LX; GE Medical Systems) at the McLean Brain Imaging Center. We used a custom-made linear birdcage coil that has improved signal to noise ratio by approximately 40% and homogeneity vs a standard quadrature head coil.[63] A 3-dimensional spoiled gradient echo pulse sequence was used to produce 124 1.5-mm-thick contiguous coronal images (echo time = 5 milliseconds; repetition time = 35 milliseconds; matrix = 256 × 192; field of view = 24 cm; flip angle = 45°; number of excitations = 1). Axial T2-weighted images (echo time = 80 milliseconds; repetition time = 3000 milliseconds; matrix = 256 × 192; field of view = 20 cm, flip angle = 90°; number of excitations = 0.5; slice thickness/gap = 3/0 mm) and fluid-attenuated inversion recovery axial images (echo time = 133 milliseconds; repetition time = 9000 milliseconds; inversion time = 2200 milliseconds; matrix = 256 × 192; field of view = 20 cm; flip angle = 90°; number of excitations = 1; slice thickness/gap = 5/2 mm) were acquired to screen for gross brain structural abnormalities.

Brain surface extraction and measurement of cortical thickness were conducted using FreeSurfer Tools (http://surfer.nmr.mgh.harvard.edu/). The detailed method for reconstructing representation of the gray and white matter boundary and the cortical surface[64-68] and then measuring cortical thickness have been described in previous articles[27,69] as well as in eAppendix 2. Individual subject data were smoothed using a Gaussian Kernel across the surface with a full-width at half maximum of 20 mm. This measurement for the thickness of the cerebral cortex has been validated using histologic[70] and manual[70,71] estimations with submillimeter precision. Reliability for estimation of cortical thickness using this method has also been established across variations in field strength, scanner upgrade, and manufacturer.[72]

To ensure the image quality for processing and the absence of any structural abnormalities including malformations, all MRIs were examined by a board-certified neuroradiologist.

Surface-based comparisons on vertex by vertex contrasts of cortical thickness were performed for control vs T1DM-only groups, control vs depression groups, and control vs T1DM-depression groups using general linear models adjusting for age and sex. Mean cerebral cortical thickness and intracranial volume were initially considered as potential covariates but not included in the main analysis because models with or without these covariates produced similar results (eFigure 1).

Conjunction analyses were also performed to identify the shared influence of past depression (T1DM-depression and depression groups vs control group) and that of T1DM (T1DM-only and T1DM-depression groups vs control group).[73]

To correct for multiple comparisons in imaging data, cluster size limits were generated with a Monte Carlo simulation[74-76] of 10 000 iterations for an initial vertexwise threshold of $P < .01$ for the analyses (2-tailed). We reported results when additional clusterwise probability was met ($P < .05$; 2-tailed). This determined the probability that a cluster of certain size would have been found by chance for a given threshold under the null hypothesis.

STATISTICAL ANALYSIS

Continuous and categorical demographic and clinical variables were compared between each group using independent t tests and χ^2 tests, respectively. Performance on each cognitive domain was compared among the control, T1DM-only, and T1DM-depression groups using an analysis of covariance with a test for linear trends.[77]

Mean thicknesses of regions, defined using the significant clusters from the conjunction analyses, were compared among the control, T1DM-only, and T1DM-depression groups using an analysis of covariance with a test for linear trends.[77]

Potential effects of diabetes-related metabolic control measures (lifetime glycemic control and hypoglycemic episodes) on the thickness of significant clusters from the conjunction analyses for the influence of T1DM were examined using a multiple linear regression model. Age and sex were included as potential covariates. The number of hypoglycemic episodes was log transformed because it was not normally distributed.

Statistical significance, 2-tailed, was defined at an alpha level of $P < .05$. All statistical analyses were performed using Stata version 11.0 (StataCorp).

RESULTS

The **Table** summarizes other demographic characteristics and their between-group comparisons. Groups did not differ in age or sex. Depression characteristics including HDRS scores ($t = 1.31$, $P = .20$), age at the onset of the first depressive episode ($t = 0.51$, $P = .61$), and the number of previous depressive episodes ($t = -1.21$, $P = .23$) did not differ between the T1DM-depression and depression groups. The group differences in HDRS scores are presented in the Table. The HDRS scores were higher in the T1DM-depression (mean score = 6.75; $t = 6.67$; $P < .001$), T1DM (mean score = 2.93; $t = 2.02$; $P = .04$), and depression (mean score = 5.39; $t = 4.78$; $P < .001$) groups relative to the control group (mean score = 1.82). There was a significant difference between the T1DM-depression and T1DM groups ($t = 5.86$, $P < .001$). Although the mean t scores for anxiety subscale of the Symptom Checklist-90-Revised were less than a cutoff score for screening anxiety in each group,[62] the scores were higher in the T1DM-depression (mean score = 59.8; $t = 7.13$; $P < .001$), T1DM (mean score = 50.7; $t = 3.34$; $P < .001$), and depression (mean score = 57.5; $t = 5.38$; $P < .001$) groups relative to the control group (mean score = 44.8).

Mean BMI values of the T1DM-depression group were greater than those of both the T1DM-only and control groups ($t = 2.16$, $P = .03$ and $t = 2.83$, $P = .006$, respectively). Mean BMI values of the depression group were also greater than those of the control group ($t = 2.83$, $P = .006$). Thus, participants were more likely to be overweight when they had previous depressive episodes. Although all lipid profiles were within normal range for each group, high-density lipoprotein cholesterol and triglyceride levels differed between the T1DM-depression and control groups ($t = 2.73$, $P = .008$ and $t = -2.11$, $P = .04$, respectively), indicating more favorable lipid profiles in the T1DM-depression group. This may be partly because more subjects in the T1DM-depression group took lipid-lowering medication than control subjects ($\chi^2 = 6.94$, $P = .008$).

Diabetes-specific characteristics including the duration of illness, age at onset, long-term average HbA_{1C}, and the number of hypoglycemic episodes were not different between the T1DM-depression and T1DM-only groups (Table).

Mean thickness maps for each group and statistical maps for demonstrating regions of significant between-

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Table. Demographic and Clinical Characteristics of Patients With T1DM and Control Subjects[a]

Characteristics	Mean (SD)				
	Patients With T1DM				
	T1DM-Depression Group (n = 44)	T1DM-Only Group (n = 81)	All Patients (N = 125)	Depression Group (n = 23)	Control Group (n = 38)
Demographics					
Age, y	32.4 (4.2)	32.5 (4.6)	32.4 (4.4)	30.8 (5.8)	30.8 (5.1)
Female, No. (%)	28 (63.6)	41 (50.6)	69 (55.2)	17 (73.9)	19 (50.0)
Educational level, y	16.0 (2.5)[b]	16.3 (2.2)[b]	16.2 (2.3)[b]	16.3 (2.1)	17.3 (1.9)
Race, No. (%)					
White	40 (90.9)	78 (96.3)	118 (94.4)	20 (87.0)	29 (76.3)
Nonwhite	4 (9.1)	3 (3.7)	7 (5.6)	3 (13.0)	9 (23.7)
HDRS score, mean (SD)	6.75 (4.15)[b,c]	2.93 (3.07)[b]	4.27 (3.93)[b]	5.39 (3.82)[b]	1.82 (2.02)
Age at onset of depressive episodes, y[d]	25.2 (5.7)	NA	NA	24.4 (4.9)	NA
Previous depressive episodes[e]	1.87 (1.14)	NA	NA	2.78 (4.39)	NA
Received antidepressants, No. (%)					
SSRI	11 (25.0)	NA	NA	8 (34.8)	NA
Other classes	11 (25.0)	NA	NA	7 (30.4)	NA
Metabolism-related clinical characteristics					
BMI	27.6 (5.4)[b,c]	25.8 (3.9)	26.5 (4.5)[b]	28.1 (5.4)[b]	24.6 (4.3)
Blood pressure, mm Hg[f]					
Systolic	118.5 (12.5)	120.6 (14.6)[b]	119.9 (13.9)[b]	114.3 (12.9)	114.5 (11.9)
Diastolic	76.8 (9.9)	75.0 (8.3)	75.6 (8.9)	74.3 (8.9)	74.2 (8.1)
Received antihypertensive medications, No. (%)[f]	9 (21.4)[b]	20 (24.7)[b]	29 (23.6)[b]	2 (8.7)	0 (0.0)
Lipids, mg/dL					
HDL cholesterol	59.7 (15.4)[b]	56.8 (16.9)	57.8 (16.4)[b]	53.3 (13.9)	50.7 (14.3)
LDL cholesterol	111.1 (25.3)	111.7 (36.1)	111.5 (32.6)	114.4 (27.2)	107.0 (32.5)
Total cholesterol	184.0 (30.2)	186.0 (45.2)	185.3 (40.5)	190.6 (25.0)	178.2 (32.3)
Triglycerides	73.9 (49.4)[b,g]	89.4 (72.2)	84.0 (65.3)	139.0 (112.7)	98.6 (56.6)
Received lipid-lowering medications, No. (%)[f]	7 (16.7)[b]	14 (17.3)[b]	21 (17.0)[b]	1 (4.4)	0 (0.0)
Diabetes-specific clinical characteristics					
Duration of illness, y	20.2 (3.6)	19.8 (3.5)	20.0 (3.5)	NA	NA
Age at onset, y	12.2 (5.4)	12.8 (5.1)	12.6 (5.2)	NA	NA
Lifetime average HbA_{1C}, %	8.25 (1.08)	7.99 (1.19)	8.08 (1.16)	NA	NA
Hypoglycemic episodes	2.52 (4.67)	6.41 (14.7)	5.04 (12.3)	NA	NA
Current HbA_{1C}, %	7.92 (1.17)[b,g]	7.73 (1.43)[b]	7.80 (1.34)[b]	5.16 (0.30)	5.08 (0.33)
Retinopathy level, No. (%)[h]					
None	21 (52.5)	48 (63.2)	69 (59.5)	NA	NA
Mild nonproliferative	17 (42.5)	22 (28.9)	39 (33.6)	NA	NA
Moderate nonproliferative	2 (5.0)	2 (2.6)	4 (3.5)	NA	NA
Proliferative	0 (0.0)	4 (5.3)	4 (3.5)	NA	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HbA_{1C}, hemoglobin A_{1C}; HDL, high-density lipoprotein; HDRS, Hamilton Depression Rating Scale; LDL, low-density lipoprotein; NA, not available or not applicable; SCID, Structured Clinical Interview for *DSM-IV*; SSRI, selective serotonin reuptake inhibitor; T1DM, type 1 diabetes mellitus.

[a] Group differences were tested by independent *t* test for continuous variables and by χ^2 tests for categorical variables. If present, significant differences between groups are presented with footnotes below.

[b] Significant difference at $P < .05$ compared with the control group.

[c] Significant difference at $P < .05$ compared with T1DM-only group.

[d] Data for 8 and 5 subjects from the T1DM-depression and depression groups, respectively, were not specified in the SCID.

[e] Data for 6 and 5 subjects from the T1DM-depression and depression groups, respectively, were not specified in the SCID.

[f] Data for 2 subjects from the T1DM-depression group were unavailable.

[g] Significant difference at $P < .05$ compared with depression group.

[h] Data for 4 and 5 subjects from the T1DM-depression and T1DM-only groups, respectively, were unavailable.

group differences at clusterwise probability of less than .05 (corrected for multiple comparisons with an initial cluster-forming threshold of $P < .01$[78-80]) are shown in **Figure 1**. Significant thickness reductions of the superior prefrontal cortical (sPFC) regions were observed in the T1DM-only, depression, and T1DM-depression groups compared with the control group (Figure 1 and eFigure 2). Although the size of the regions differed in between-group comparisons (eTable 1), their locations largely overlapped with each other (Figure 1 and eFigure 2). Details for cluster size, Talairach coordinates, cortical thickness, and cluster-level *P* values are summarized in eTable 1. In the comparison of the T1DM-depression and control groups, there was also a significant cluster of group difference in the right occipital area (Figure 1). The group differences in thickness at a less conservative statistical level with an initial cluster-forming threshold of $P < .05$ are also presented in Figure 1 and eTable 1. *T* statistic maps are also demonstrated in eFigure 2. Repeated analyses, including the HDRS scores or the anxiety subscale scores of the Symptom Checklist-90-Revised as additional covariates, showed that

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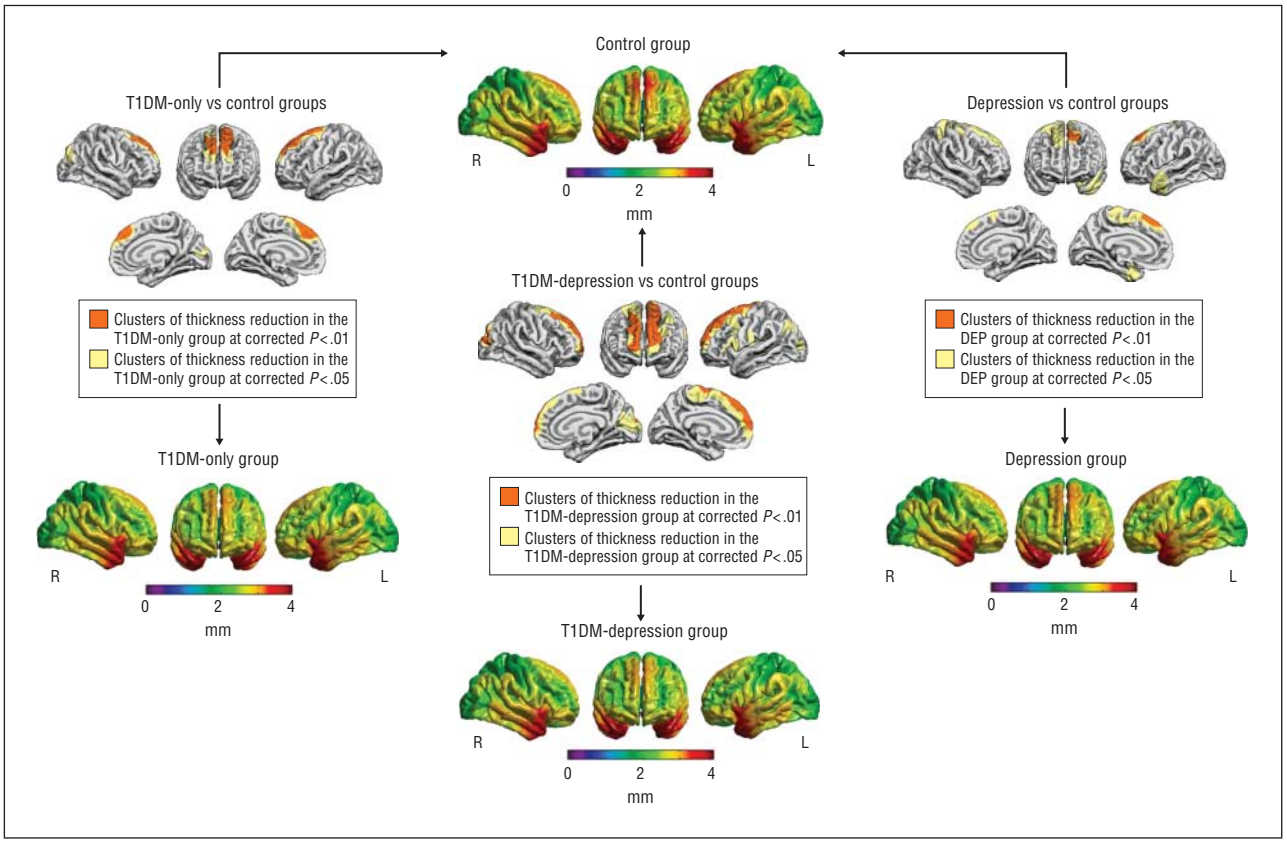

Figure 1. Mean cortical thickness maps for the type 1 diabetes mellitus (T1DM)–only (n = 81), depression (n = 23), T1DM-depression (n = 44), and control (n = 38) groups and statistical maps showing differences in cortical thickness between groups. Patients with T1DM who have never experienced depressive episodes are defined as the T1DM-only group. Subjects who had 1 or more previous depressive episodes but were not currently depressed are defined as the depression group. Patients with T1DM who had 1 or more previous depressive episodes but were not currently depressed are defined as the T1DM-depression group. Healthy individuals who have not had either T1DM or past depressive episodes are defined as the control group. Brain regions in orange and light yellow of the brain template indicate clusters of significant group differences, thinner than control subjects, adjusting for age and sex at initial cluster-forming thresholds of $P < .01$ and $P < .05$, respectively, corrected for multiple comparisons. There were no regions of increased cortical thickness in the T1DM-only, T1DM-depression, or depression groups relative to the control group. L indicates left; R, right.

sPFC region was where between-group effects for each contrast were detected (eFigure 1).

Conjunction analyses also demonstrated that thickness reductions related to the influence of T1DM as well as those related to past depressive episode influence were observed in the sPFC regions (**Figure 2** and eTable 2).

There were no regions where the T1DM, depression, and T1DM-depression groups showed increased thickness relative to the control group at corrected $P < .01$.

Additional comparisons between the T1DM-only vs depression groups as well as between the T1DM-depression vs depression groups were conducted. A general linear model including age and sex as covariates was applied to determine the cortical thickness difference on each vertex between groups. There were no significant regions of group difference between the T1DM-only and depression groups as well as between the T1DM-depression and depression groups at corrected $P < .01$. eFigure 3 shows the *t* statistic maps of cortical thickness differences for each contrast.

There were stepwise thickness reductions in the bilateral sPFC regions at corrected $P < .01$ from the control through the T1DM-only, and finally to the T1DM-depression groups (eFigure 4A). Stepwise thickness reductions in the sPFC clusters, which were defined from the conjunction analyses for the influence of T1DM (right sPFC region: $z = -3.46$, $P = .001$; left sPFC region: $z = -4.73$, $P < .001$; Figure 2A and eFigure 4B) and for the influence of prior depression (left sPFC region: $z = -4.43$, $P < .001$; Figure 2B and eFigure 4B), were observed from the control through the T1DM-only and finally to the T1DM-depression groups (control>T1DM-only>T1DM-depression). Results from a parcellated region of the superior frontal gyri based on the Desikan-Killiany Atlas[81] showed the similar linear trend (right sPFC region: $z = -2.98$, $P = .003$; left sPFC region: $z = -4.30$, $P < .001$; eFigure 4B).

Because sPFC regions may play an important role in both executive and memory function,[56,57] comparisons of performance on these 2 cognitive domains were conducted. The T1DM-depression group showed the lowest performance on tests of both executive and memory functions, followed by the T1DM-only group and the control group (executive function: $z = -3.56$, $P < .001$ for trend; memory function: $z = -3.02$, $P = 0.003$ for trend) (eFigure 5).

We also determined whether and how metabolic disturbances including persistent hyperglycemia or frequent severe hypoglycemic episodes would affect T1DM-related sPFC deficits. Among all patients with T1DM

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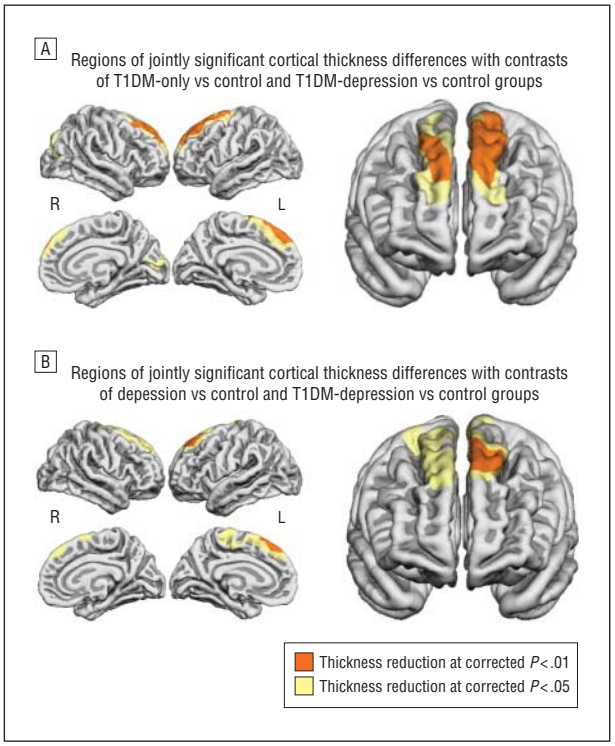

Figure 2. Conjunction analyses for the brain regions of jointly significant cortical thickness differences between the type 1 diabetes mellitus (T1DM)–only and T1DM-depression vs control groups (A) and between the depression and T1DM-depression vs control groups (B). There were no regions of significantly greater cortical thickness in the T1DM-only, T1DM-depression, and depression groups relative to the control group. L indicates left; R, right.

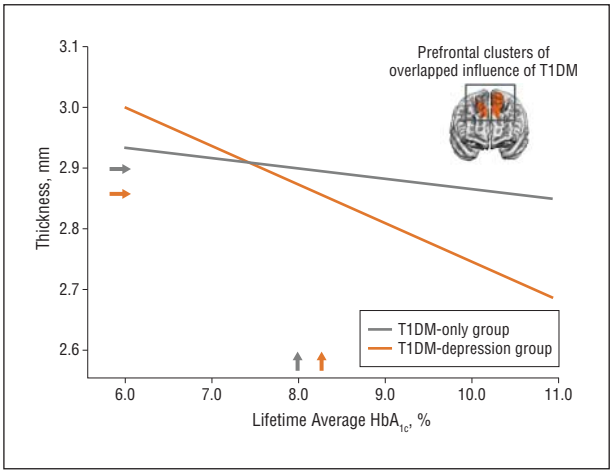

Figure 3. Regression slopes for lifetime glycemic control levels and prefrontal cortical deficits in the type 1 diabetes mellitus (T1DM)–only and T1DM–depression groups. The superior prefrontal cortical (sPFC) cluster is defined from the conjunction analysis for T1DM influence shown in Figure 2A. The gray and orange lines correspond to the regression lines (lines of best fit) of associations between lifetime average hemoglobin A_{1C} (HbA_{1C}) and thickness of the sPFC cluster for the T1DM-only ($\beta = -0.13$, $P = .23$) and the T1DM-depression ($\beta = -0.29$, $P = .03$) groups, respectively. Age and sex were included into the regression model as covariates. Gray and orange arrows on the y-axis represent the mean age-adjusted and sex-adjusted thickness of the sPFC cluster of the T1DM-only and the T1DM-depression groups, respectively, and there was a significant difference in the mean thickness of the sPFC region of interest between groups ($t = 2.11$, $P = .03$). Gray and orange arrows on the x-axis represent the mean values of lifetime average HbA_{1C} of the T1DM-only and the T1DM-depression groups, respectively. Although the T1DM-depression group shows numerically higher lifetime average HbA_{1C} levels than the T1DM-only group, there is no significant difference in lifetime average HbA_{1C} levels between groups ($t = 1.23$, $P = .22$).

(T1DM-depression and T1DM-only groups combined), the thickness of sPFC clusters where significant T1DM-related thickness reductions were found in the conjunction analysis had a significant relationship with lifetime glycemic control levels ($\beta = -0.19$, $P = .02$), indicating more sPFC deficits in patients with T1DM with poor glycemic control. When this relationship was separately tested according to a history of depressive episodes, the effect (β) of the lifetime glycemic control levels on PFC deficits was significant in the T1DM-depression group ($\beta = -0.29$, $P = .03$) but not in the T1DM-only group ($\beta = -0.13$, $P = .23$) (**Figure 3**). Repeated analyses using the prefrontal clusters where significant depression-related thickness reductions were found in the conjunction analysis as well as a parcellated region of the superior frontal gyri based on the Desikan-Killiany Atlas produced similar results (eFigure 6).

In contrast, there were no significant relationships between the log-transformed number of hypoglycemic episodes and sPFC thickness in all patients with T1DM ($\beta = 0.02$, $P = .83$) or patients in the T1DM-depression ($\beta = -0.07$, $P = .63$) or T1DM-only ($\beta = 0.02$, $P = .88$) groups.

COMMENT

The relationship between diabetes and depression has been a long-standing research topic because of the increasing global health burden and debilitating effects of both diseases.[82-84] We have previously reported T1DM-related structural[19] and neurochemical[20] changes in the prefrontotemporal regions. To our knowledge, we have here provided the first neuroanatomic evidence of prefrontal cortical deficits as brain correlates of comorbid depression in T1DM.

We found that patients with T1DM, relative to healthy control subjects, had thinner cortical thickness in the sPFC region. This brain region was similar to the sPFC region where individuals with prior depressive episodes had thinner cortex relative to healthy control subjects. Subjects with T1DM with previous depressive episodes also showed thinner cortex than those without previous depressive episodes. Findings from conjunction analyses also suggest that similar regional involvements in the prefrontal regions may be related to both T1DM and depression. Neurocognitive performance abnormalities on executive and memory function, as a surrogate for prefrontal cortical dysfunction,[57,85] were also consistent with the pattern of sPFC cortical deficits. Our study also documents that T1DM-related prefrontal regional deficits can occur at a relatively young age (mean, 32.4 years) and even in the absence of clinically evident peripheral and autonomic neuropathy.

We also noted that poor long-term glycemic control was associated with greater sPFC deficits in patients with T1DM and that this effect seems to be more prominent in patients with T1DM with prior depressive episodes (eFigure 7). However, we did not find a significant re-

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lationship between severe hypoglycemic episodes and sPFC cortical deficits. Although there is no debate that profound hypoglycemia involving prolonged coma as well as respiratory failure can cause permanent brain damage,[86] the effects on the brain of moderately severe hypoglycemic episodes remain to be clarified.[86,87] The effects of hypoglycemic episodes on neurocognitive deficits were not observed in long-term cohort studies of subjects with T1DM[88-90] or in a meta-analysis.[42] In the present study, cohort characteristics of less frequent hypoglycemic episodes (mean, 5.04; median, 1.00) of subjects with T1DM may have contributed to the absence of associations between hypoglycemic episodes and cortical thickness.

Among metabolic control measures, history of glycemic control, rather than the number of severe hypoglycemic episodes, was a strong modifier of the prefrontal thickness reduction in patients with T1DM. This correlation is consistent with results from a longitudinal study of patients with T1DM having a similar disease duration (approximately 24 years) to our sample (20 years) that indicated persistent hyperglycemia-induced cognitive impairments in the prefrontal functional domains including psychomotor efficiency and motor speed.[88] In our prior smaller sample size studies of subjects with T1DM, prolonged hyperglycemia was also associated with reduced gray matter density[19] as well as cerebral neurochemical changes.[20]

Structural and functional deficits in the prefrontal cortex have consistently been linked to the development of depression.[26,27] In a study of American veterans of the war in Vietnam, damage to the prefrontal cortex including the superior and middle frontal gyri was strongly associated with later development of depression.[26] Similarly, mild traumatic brain injury–related sPFC thickness reduction was related to later depression.[27] On the functional side, altered activation in lateral prefrontal cortical regions has been reported in depressed patients.[91-94] Consistent with findings in this study, our previous work also suggested that higher glutamate levels, indicating potential excitotoxic neuronal damage induced by glutamate in the prefrontal region of patients with T1DM, are associated with depression and altered cognitive functioning in the domains of memory and psychomotor efficiency.[20] Taken together, our findings of greater sPFC deficits in the T1DM-depression group relative to the T1DM-only group suggest the potential role of sPFC in the development of depression in subjects with T1DM. Regarding the time sequence for the diagnosis of T1DM and depression, diagnosis of T1DM preceded depression by about 12 years, which is in general accord with prior studies of T1DM and comorbid depression.[31,32]

Psychosocial demands imposed by diabetes, including disease severity and an increasing number of complications, have long been implicated as important contributing factors for comorbid depression.[9-11] Patients with T1DM who had previous depressive episodes showed a greater deficit in sPFC regions compared with patients with T1DM without any previous depressive episodes, despite a similar pattern of diabetes-related clinical characteristics including disease duration, long-term glycemic control levels, or the number of hypoglycemic episodes. Considering the restricted age range of our T1DM sample (25-40 years) and limited inclusion of patients with serious diabetic complications, confounding from increased psychosocial demands related to long-term diabetes and the development of complications may contribute less to the development of secondary depression in this sample.

In our sample, BMI levels were greater in the T1DM-depression group relative to the T1DM-only group in accord with results from recent large-scale epidemiologic studies of diabetes.[12] Exploratory correlational analyses showed associations between higher BMI levels and hyperglycemia in the T1DM-depression group, but not in the T1DM-only group (eAppendix 3 and eFigure 8). Based on these findings, it could cautiously be speculated that depression-related, increased BMI levels may contribute to PFC deficits in patients with T1DM with depression through modulating the effects of hyperglycemia.

Although the current data cannot prove nor sufficiently test whether prefrontal cortical deficits subserve a shared pathophysiological role for the comorbidity of T1DM and depression, it is possible that these deficits may help mediate a self-perpetuating cycle from T1DM, depression, and hyperglycemia. Progressive T1DM-induced neurotoxic changes in brain regions that are linked to mood regulation may thus contribute to secondary depression in patients with T1DM. In turn, comorbid depression may also contribute to the exacerbation of sPFC deficits by further undermining metabolic stability via increased hypothalamic-pituitary-adrenal axis activity.[95-97]

Relative to the control group, we also found thickness reductions of the right visual cortex in the T1DM-only group at corrected $P < .05$ and in the T1DM-depression group at corrected $P < .01$, but not in the depression group. Conjunction analysis for the brain regions of T1DM influence also demonstrated involvement of this region. These may largely be consistent with previous results from several neuroimaging studies that reported reduced gray matter density in the right occipital regions of patients with T1DM[22] and reduced fractional anisotropy in the optic radiation.[98,99] Concurrent white and gray matter deficits have also been demonstrated in the visual cortex of patients with T1DM.[99]

Several limitations of the study should be considered in interpreting the current findings. First, the sPFC, where deficits are reported in the current study, is only 1 component of a network of brain regions that have been reported to be involved with the pathophysiology of depression. Furthermore, T1DM-related functional or structural deficits in other brain regions or structures may also play important roles in comorbid depression. Second, a history of depression in subjects with T1DM was selected as a marker for comorbid depression in T1DM to decrease the potential confounding effect of current depression on cortical thickness measurement. In this regard, it is also possible that there may be another pathophysiological mechanism for depressive symptoms in a cohort of T1DM with current depressive symptoms. Third, sPFC was the only region that correlated with the diagnosis of T1DM with or without depression in the current cortical thickness analysis study, while in prior brain

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imaging studies of T1DM that used region of interest or voxel-based morphometry, there were noted deficits in other brain regions than the sPFC.[19,24] These methodologic differences along with those in clinical characteristics of T1DM and comorbid depression may have contributed to variations in findings.

In summary, the current study strongly suggests that T1DM-related thickness reduction in the superior frontal cortex may mediate the development of comorbid depression. The current findings also highlight the potential importance of prevention or early intervention for reducing the comorbidity of diabetes and depression. Future longitudinal studies will be needed to confirm this brain-based and potentially self-perpetuating cycle between T1DM and depression.

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