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Task-Induced Brain Activity Patterns in Type 2 Diabetes: A Potential Biomarker for Cognitive Decline

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Patients with type 2 diabetes demonstrate reduced functional connectivity within the resting state default mode network (DMN), which may signal heightened risk for cognitive decline. In other populations at risk for cognitive decline, additional magnetic resonance imaging abnormalities are evident during task performance, including impaired deactivation of the DMN and reduced activation of task-relevant regions. We investigated whether middle-aged type 2 diabetic patients show these brain activity patterns during encoding and recognition tasks. Compared with control participants, we observed both reduced 1) activation of the dorsolateral prefrontal cortex during encoding and 2) deactivation of the DMN during recognition in type 2 diabetic patients, despite normal cognition. During recognition, activation in several task-relevant regions, including the dorsolateral prefrontal cortex and DMN regions, was positively correlated with HbA_{1c} and insulin resistance, suggesting that these important markers of glucose metabolism impact the brain's response to a cognitive challenge. Plasma glucose ≥ 11 mmol/L was associated with impaired deactivation of the DMN, suggesting that acute hyperglycemia contributes to brain abnormalities. Since elderly type 2 diabetic patients often demonstrate cognitive impairments, it is possible that

these task-induced brain activity patterns observed in middle age may signal impending cognitive decline.

Patients with type 2 diabetes are at increased risk for dementia and cognitive decline (1,2). Neuroimaging is useful for determining structural and functional biomarkers that may predict future cognitive impairment, thereby elucidating the mechanisms involved in cognitive decline and informing strategies to target vulnerable brain regions (3,4).

Recent research has focused on the default mode network (DMN), a set of medial prefrontal and temporoparietal regions that are most active at rest and deactivated during cognitive tasks. The DMN exhibits both reduced functional connectivity (5) and impaired task-induced deactivation (6) in Alzheimer disease (AD) and mild cognitive impairment (MCI). These changes have been observed before atrophy and cognitive decline and are concurrent with other signals that are known predictors of cognitive decline (6). The DMN also has high metabolic activity, making it susceptible to the effects of type 2 diabetes and hypo- or hyperglycemia (7). Patients with type 2 diabetes show impaired functional connectivity (8) and abnormal glucose metabolism (9) in the DMN, but no study has investigated

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whether they show reduced ability to suppress DMN activity during a cognitive task.

This study investigates brain activity patterns during encoding and recognition tasks using functional magnetic resonance imaging (fMRI) in middle-aged type 2 diabetic patients, focusing on the DMN. These regions, in particular the prefrontal cortex, are involved in both encoding (10) and recognition (11). Since elderly patients with type 2 diabetes often demonstrate cognitive impairments (12), it is important to identify task-related functional alterations that may precede cognitive decline so that preventative therapies can be introduced in middle age.

RESEARCH DESIGN AND METHODS

Subjects

We studied 22 patients with type 2 diabetes and 29 nondiabetic healthy control subjects between the ages of 45 and 65 years (Table 1). Patients were group matched on education, IQ, sex, and BMI, and we accounted for a group age difference in our analyses.

We gathered medical history and current medications from medical records and questionnaires. Since insulin resistance was of interest, we excluded patients treated with the insulin-sensitizing medications metformin or thiazolidinediones. Eligible patients were on stable therapy with diet, insulin, or oral medications. After approval from the institutional review boards of the Joslin Diabetes Center and Beth Israel Deaconess Medical Center (where the MRI was performed), subjects provided informed consent and information about psychiatric history, handedness, medical history, current medications, height, and weight. Exclusionary criteria were as follows: 1) stroke or myocardial infarction; 2) unstable or current episode of a DSM-IV Axis I disorder; 3) sleep, eating, or learning disorder; 4) sensorimotor handicap, central nervous system disorder, or illness affecting neurological function; 5) history of substance abuse (including alcohol and excluding nicotine); 6) left-handedness (13); 7) contraindications to magnetic resonance imaging (MRI); and 8) BMI $>40 \text{ kg/m}^2$.

Screening Visit

Participants provided a blood sample after an 8-h fast to assess creatinine, HbA_{1c}, lipids, serum insulin, plasma glucose (PG), and apolipoprotein E (APOE) allele status, as the $\epsilon 4$ isoform confers risk for AD. Medication administration occurred after baseline blood draws. Nondiabetic participants drank 75 g flavored dextrose, and blood samples were taken intravenously at 30, 60, and 120 min postingestion to measure PG and serum insulin to calculate insulin resistance using the homeostasis model assessment of insulin resistance (HOMA-IR). HOMA-IR was not assessed for insulin-treated type 2 diabetic patients because it would not reflect their natural insulin sensitivity. Participants also answered demographic and socioeconomic questionnaires, completed a fitness assessment, and underwent cognitive testing.

Cognitive Assessment

We measured executive function (Delis-Kaplan Executive Function System), memory (Rey Auditory Verbal Learning Test; Wechsler Memory Scale-III), intelligence (Wechsler Abbreviated Scale of Intelligence), and psychomotor speed (Grooved Pegboard Test) as described previously (8) (Table 1).

MRI Acquisition

PG measures were taken prior to magnetic resonance scanning for diabetic participants. Treatment was provided for PG $<4.4 \text{ mmol/L}$ or $>16.6 \text{ mmol/L}$ ($N = 2$). Images were collected on a GE Healthcare Signa HDxt 3.0T system (Milwaukee, WI). Participants underwent screening for metal objects, pacemakers, pregnancy, and claustrophobia. Of the 57 eligible participants, 6 were excluded owing to head movement during scanning. Exclusion criteria included translations or rotations of $>3 \text{ mm}$ in x , y , or z directions.

Functional Images

Functional images were collected in the axial plane using a gradient echo planar imaging sequence sensitive to blood oxygen level dependent (BOLD) contrast (repetition time/echo time = 2,000/25 ms; flip angle = 90° ; slice thickness = 4 mm; two-dimensional in-plane: field of view = $24 \times 24 \text{ cm}^2$, matrix size = 64×64 ; voxel size = $3.75 \times 3.75 \times 4 \text{ mm}^3$).

fMRI Cognitive Task

fMRI scans were collected during both the encoding and recognition tasks (5 min each). Stimuli were presented using Presentation software (Neurobehavioral Systems, Albany, CA), projected on a screen visible via mirror attached to head coil. Trials were synchronized with the acquisition sequence. Responses were collected using a four-button Lumina fiberoptic response pad (<http://www.cedrus.com/lumina>), connected to a personal computer via optical cable interface.

During encoding, subjects saw green and red images and concentrated on the pairing of the object and its color (14). During recognition, subjects indicated via button press the original color of the same images now presented in black and white. Control and rest blocks were used during both tasks. Block order was randomized, and images were presented for 3,000 ms followed by a fixation cross for 1,000 ms.

Image Processing

fMRI image analyses and processing were completed using the Functional MRI of the Brain Software Library (FSL) software package version 5.0.4. Images were registered to the standard MNI152 brain (Montreal Neurological Institute). The first two volumes were deleted for T1 equilibration. Motion and slice time correction, brain extraction, spatial smoothing with Gaussian filter of 6 mm full width at half maximum, linear trend removal, and a temporal high-pass filter with cutoff of 120 s were performed. All image analysts were blind to group status.

Table 1—Demographics, clinical variables, and cognitive scores

	Type 2 diabetic patients (N = 22)		Control subjects (N = 29)		P
	Mean	SD	Mean	SD	
Age, years	56.0	5.5	52.7	5.5	0.03
Education, years	14.9	2.5	16.0	2.5	0.14
Current HbA _{1c} , %	7.8	2.4	5.6	0.3	<0.01
Current HbA _{1c} , mmol/mol	62	26	38	3	<0.01
Lifetime average HbA _{1c} , %	7.7	2.1			
Lifetime average HbA _{1c} , mmol/mol	61	23			
Fasting plasma glucose, mmol/L	8.5	5.6	4.5	0.4	<0.01
Fasting serum insulin, pmol/L	84.7	66.6	54.2	48.6	0.03
Prescan PG, mmol/L	10.2	4.4			
HOMA-IR	5.4*	5.8	1.6	1.4	<0.01
Diabetes duration, years	9.0	6.3			
BMI, kg/m ²	30.1	4.8	28.6	4.8	0.20
Systolic blood pressure, mmHg	127.9	13.5	118.7	13.6	0.02
Diastolic blood pressure, mmHg	72.4	10.1	72.8	10.3	0.94
Serum creatinine, mmol/L	0.04	0.01	0.04	0.01	0.19
Total cholesterol, mmol/L	11.1	2.5	10.4	1.7	0.39
Triglycerides, mmol/L	8.4	9.3	5.6	3.8	0.03
HDL cholesterol, mmol/L	3.2	1.1	2.9	0.9	0.40
LDL cholesterol, mmol/L	6.2	1.5	6.1	1.5	0.96
Hamilton Depression Rating Score	4.9	4.5	3.4	3.8	0.18
WASI full-scale IQ	108.1	14.2	112.7	12.3	0.21
WASI vocabulary score	55.4	8.8	57.5	9.4	0.41
DKEFS verbal fluency, scaled score	11.3	4.4	12.5	3.3	0.39
DKEFS trail-making number-letter switching, scaled score	9.4	3.8	10.3	3.3	0.35
RAVLT immediate-recall T score	49.8	11.8	50.2	13.9	0.95
RAVLT delayed-recall T score	49.9	8.4	48.4	12.2	0.82
WMS letter-number sequencing score	11.3	3.5	12.5	2.3	0.17
Grooved Pegboard, dominant hand, time in seconds	88.6	20.3	81.9	10.8	0.51
Recognition fMRI task performance percentage correct	73.6	17.0	68.7	15.0	0.25
	N	%	N	%	P
Female/male (% female)	11/11	50	10/19	34	0.27
Race/ethnicity					0.27
African American	2	9	6	21	
Asian	2	9	1	3	
Caucasian	14	64	21	72	
Hispanic	2	9	0	0	
More than one	2	9	1	3	
APOE4 allele	3	14	6	21	0.71
Blood pressure-lowering medications	7	32	4	14	0.17
Cholesterol-lowering medications	5	23	1	3	0.07
History of smoking	9	41	13	45	0.78
Retinopathy	1	5			
Neuropathy	2	9			
Nephropathy	0	0			

DKEFS, Delis-Kaplan Executive Function System; RAVLT, Rey Auditory Verbal Learning Test; WASI, Wechsler Abbreviated Scale of Intelligence; WMS, Wechsler Memory Scale-III. *Noninsulin users only, N = 12.

Data Analysis

Demographic, clinical, and cognitive data were compared between groups using Mann-Whitney U tests for all continuous variables and Fisher exact tests for all categorical variables except sex, for which a Pearson χ^2 test was used.

For examination of regional brain activation in response to the encoding and recognition tasks, a general linear model was used to compute statistical parametric maps by random-effects multiple regression analysis for each task. Model predictors for BOLD signal time courses were constructed using the boxcar time courses for the task stimulus paradigm convolved with a γ function to account for hemodynamic response. The model for the baseline rest condition predictor was a constant function. Cerebral BOLD activations and deactivations were determined by applying relevant contrast F tests to β -weights

for each voxel position (Fig. 1). Activations were computed by contrasting the encoding and recognition blocks to their respective control blocks, and deactivations were compared with their respective rest periods.

To verify hippocampal activation, we created binary masks of the left and right hippocampus using the Harvard-Oxford Subcortical Structural Atlas thresholded at the 50% probability level. We extracted average- and maximal-activation z scores from the hippocampal regions of interest (ROI) using FSL's `fsldata` tool.

We investigated the effects of the AD risk allele APOE4 (15,16), current and lifetime average HbA_{1c} (calculated by averaging 4-year means), and HOMA-IR on BOLD activation and deactivation within each group by performing separate mixed-effects general linear model group analyses in FSL. We also compared BOLD activation and

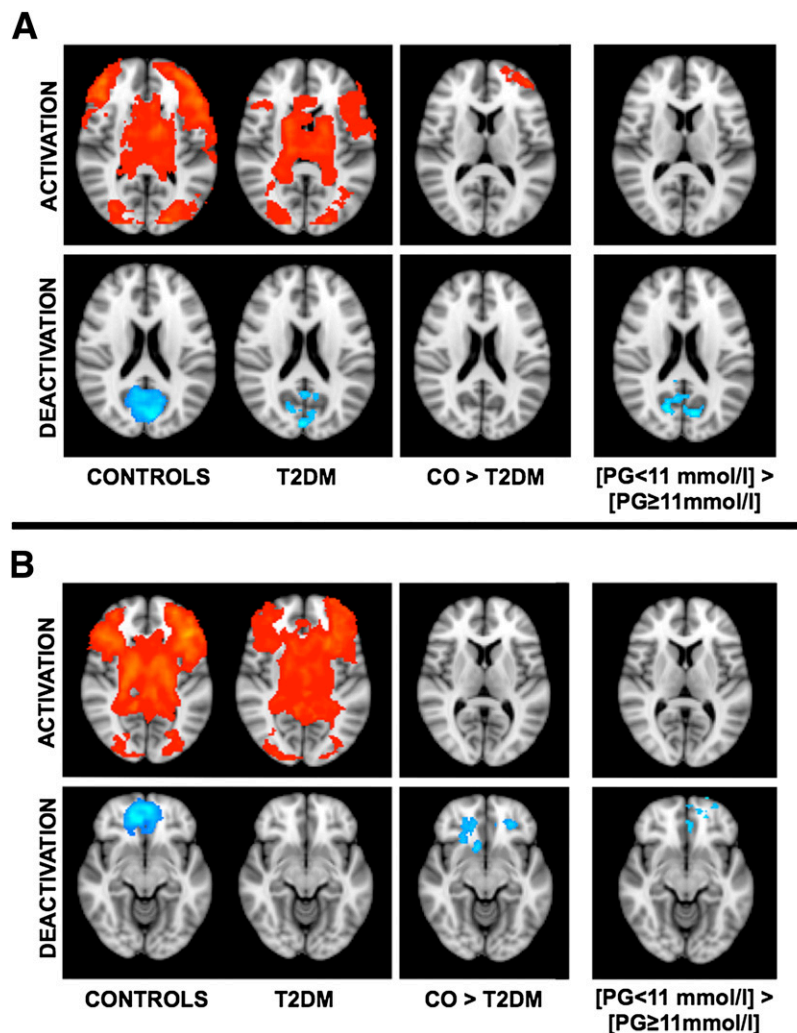


Figure 1—Regions activated (red) and deactivated (blue) during the encoding (A) and recognition (B) tasks in control subjects (CO) and type 2 diabetic patients (T2DM). Group differences between control subjects and diabetic patients and between diabetic patients with PG ≥ 11 mmol/L and < 11 mmol/L. Age was controlled for in these analyses. See Table 2 for region lists. Statistical parametric brain activation maps within and between groups were computed using one-sample t tests for within-group and unpaired two-sample t tests for between-group analyses with a significance threshold of $P < 0.05$ (corrected). A z statistic threshold value of 2.3 was applied using the standard cluster-based thresholding Gaussian Random Field theory for inference provided by FSL (25).

Table 2—Local maxima of activation and deactivation during encoding and recognition tasks in control subjects and diabetic patients; group differences in activation and deactivation between control subjects and diabetic patients and between diabetic patients with prescan plasma glucose ≥ 11 mmol/L and < 11 mmol/L

	Hemisphere	Region	MNI coordinates			Peak z score*
			x	y	z	
Encoding						
Activation						
Control						
Cerebellum	L+R	Cerebellum	-26	-59	-17	8.77
Frontal	L	Precentral gyrus	-39	3	27	6.25
	L+R	Inferior frontal gyrus	-39	15	-7	6.23
Limbic	L+R	Middle frontal gyrus	44	37	20	6.13
	L	Superior frontal gyrus	-28	-9	68	4.33
	L+R	Hippocampus†	57	47	31	5.71
Parietal	L	Anterior cingulate	-9	21	19	4.44
	L	Precuneus	-28	-76	40	5.94
Sublobar	L	Inferior parietal lobule	-52	-41	44	5.26
	R	Supramarginal gyrus	42	-45	35	4.34
	L+R	Insula	-37	19	-1	6.14
	L	Caudate	-5	21	12	4.42
Diabetic patients						
Cerebellum	L+R	Cerebellum	-39	-44	-29	7.84
Frontal	L	Medial frontal gyrus	-5	1	58	5.28
	L	Precentral gyrus	-39	1	28	4.73
Limbic	L+R	Parahippocampal gyrus	-26	-29	-10	5.27
	L+R	Hippocampus†	58	48	30	4.94
Sublobar	R	Caudate	14	8	9	5.01
	L	Lentiform nucleus	-24	-5	1	4.89
	L+R	Thalamus	-26	-31	-1	4.39
Control > diabetic patients						
Frontal	L	Middle frontal gyrus	-31	47	24	4.34
	L	Inferior frontal gyrus	-46	39	2	3.09
Deactivation						
Control						
Limbic	L+R	Posterior cingulate cortex	-13	-66	10	5.18
Occipital	L	Cuneus	-7	-76	16	4.63
	L	Precuneus	1	-59	19	4.16
Diabetic patients						
Limbic	L	Cingulate gyrus	-11	-56	29	3.59
Occipital	L+R	Cuneus	0	-82	20	3.77
Parietal	L+R	Precuneus	-11	-57	23	3.27
Diabetic patients (PG <11 mmol/L) > (PG ≥ 11 mmol/L)						
Limbic	L+R	Posterior cingulate	16	-66	18	3.94
Occipital	L+R	Cuneus	-10	-72	18	3.70
Recognition						
Activation						
Control						
Cerebellum	R	Cerebellum	35	-62	-28	7.82
Frontal	L	Medial frontal gyrus	-1	12	44	8.07
	L	Inferior frontal gyrus	-39	17	-5	7.75
Limbic	L+R	Hippocampus†	31	50	30	6.04
Parietal	L+R	Precuneus	-32	-69	29	7.09
	L+R	Inferior parietal lobule	-39	-62	41	6.24
	R	Angular gyrus	37	-58	32	5.76
Sublobar	L	Postcentral gyrus	-24	-35	57	4.74
	R	Lentiform nucleus	16	-7	3	8.06
	L	Insula	-31	22	-1	7.82
Temporal	R	Middle temporal gyrus	33	-66	28	5.23
	R	Superior temporal gyrus	37	-48	26	4.66
Diabetic patients						
Cerebellum	L+R	Cerebellum	-22	-85	-26	7.12
Frontal	L	Medial frontal gyrus	1	12	44	6.80
	L+R	Middle frontal gyrus	37	24	29	4.99
Limbic	L	Superior frontal gyrus	-37	54	14	4.87
Limbic	L+R	Hippocampus†	31	48	33	5.29

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Table 2—Continued

	Hemisphere	Region	MNI coordinates			Peak
			x	y	z	z score*
Parietal	L	Precuneus	−30	−77	36	4.95
	L	Angular gyrus	−39	−62	37	4.35
Sublobar	R	Clastrum	31	18	1	6.14
Temporal	L	Middle temporal gyrus	−32	−63	28	5.37
Deactivation						
Control						
Frontal	L+R	Medial frontal gyrus	−5	50	3	4.88
Limbic	L+R	Anterior cingulate	5	39	−3	5.21
Temporal	L	Middle temporal gyrus	−45	−78	23	5.48
	L	Angular gyrus	−53	−67	31	4.86
	L	Superior temporal gyrus	−62	−61	22	3.42
Control > diabetic patients						
Limbic	L+R	Anterior cingulate	5	34	18	4.29
Sublobar	R	Caudate	8	13	−1	4.18
Diabetic patients (PG <11 mmol/L) > (PG ≥11 mmol/L)						
Limbic	L	Anterior cingulate	−4	38	−14	3.46
Frontal	L	Superior frontal gyrus	−20	68	−12	3.28
Frontal	L	Medial frontal gyrus	−18	50	−12	3.10
Frontal	L	Middle frontal gyrus	−20	38	−20	2.69

L, left; R, right. *z score for the voxel with the highest level of activation/deactivation or greatest group difference for each region, bilaterally. The threshold for activations and deactivations was $P < 0.05$ after correction for multiple comparisons using the cluster-based threshold method. †Results of a hippocampal ROI analysis. Coordinates represent local maxima for the bilateral region of interest.

deactivation between diabetic patients with prescan PG ≥ 11 mmol/L and < 11 mmol/L to determine the effects of acute hyperglycemia (Fig. 1). We then performed anatomical ROI analyses using the Harvard-Oxford atlas and FSL's Featquery tool to examine Spearman correlations between prescan PG and deactivation in DMN regions.

All data are presented as mean \pm SD, and statistical tests were conducted using a two-sided α -level of 0.05 with SPSS Statistical Software, version 19.

RESULTS

Demographics and Clinical Variables

Table 1 shows demographic and clinical data for diabetic patients and healthy control subjects.

Cognitive Performance

There were no significant differences between groups on any cognitive tests, including vocabulary (a measure of premorbid IQ [17]) and the fMRI task (Table 1).

Functional Imaging

For both tasks, Fig. 1 shows activated and deactivated regions and Table 2 lists local maxima. Table 3 lists the effects of covariates. APOE4 was evaluated in each group separately, HOMA-IR only in control subjects, and current and lifetime average HbA_{1c} only in diabetic patients.

During both encoding and recognition, we observed bilateral activation of the hippocampus in diabetic patients (mean z score \pm SD, encoding, left 3.89 ± 0.62 , right 3.06 ± 1.13 ; recognition, left 3.48 ± 0.48 , right 3.82 ± 0.93) and control subjects (encoding, left

4.44 ± 0.85 , right 4.09 ± 1.16 ; recognition, left 4.42 ± 0.60 , right 4.11 ± 0.68), with no group differences. Local maxima for the hippocampus are listed in Table 2.

We observed negative correlations between PG and deactivation in anatomically defined ROIs, including the cuneus ($\rho = -0.49$, $P = 0.04$) and precuneus ($\rho = -0.49$, $P = 0.04$) during encoding and the medial frontal gyrus ($\rho = -0.52$, $P = 0.03$) during recognition.

DISCUSSION

This study demonstrates impaired task-induced deactivation in the DMN and aberrant activation in task-relevant regions during a memory task in type 2 diabetic patients. During encoding, we observed reduced activation of task-relevant regions and less extensive deactivation of the DMN in type 2 diabetic patients relative to control subjects. During recognition, we observed impaired deactivation of the DMN in type 2 diabetic patients.

Among diabetic patients, prescan PG levels ≥ 11 mmol/L were associated with reduced deactivation of DMN regions during both encoding and recognition. There was some overlap between these regions and the regions that differed between diabetic patients and control subjects (e.g., anterior cingulate). We also observed that current HbA_{1c}, lifetime average HbA_{1c}, and HOMA-IR influence brain activity in the DMN. These observations suggest that several aspects of diabetes, including acute hyperglycemia, short- and long-term glycemic control, and insulin sensitivity, influence DMN activity. Additionally, diabetic patients differed significantly from control subjects on triglycerides

Table 3—Effect of covariates on activation and deactivation during encoding and recognition tasks

	Activation or deactivation	Group	Lobe	Hemisphere	Region	MNI coordinates			Peak z score*
						x	y	z	
Encoding									
APOE4	Deactivation	CON	Posterior Temporal	Right Right	Cerebellum Fusiform gyrus	25 52	-66 -55	-19 -18	3.74 4.27
Lifetime average HbA _{1c}	Activation	DM	Frontal Temporal Sublobar Parietal	Right Right Right Right	Precentral gyrus Superior temporal gyrus Insula Postcentral gyrus	38 54 50 58	-4 2 10 -4	26 -4 0 16	3.25 2.97 2.89 2.79
Recognition									
Current HbA _{1c}	Activation	DM	Frontal Limbic Parietal	Right Right Right	Precentral gyrus Cingulate gyrus Postcentral gyrus	50 12 39	-16 -30 -24	30 39 33	3.24 3.09 4.22
HOMA-IR	Activation	CON	Frontal	Right Right Right	Middle frontal gyrus Precentral gyrus Inferior frontal gyrus	33 33 46	-9 -14 15	41 59 12	4.79 3.82 3.72

Note: only covariates with significant effects are listed. CON, control subjects; DM, type 2 diabetic patients. *z score for the voxel with the highest level of correlation with the covariate for each region. The threshold for correlation was $P < 0.05$ after correction for multiple comparisons using the cluster-based threshold method.

and blood pressure. These variables, often comorbid with diabetes, may also contribute to brain differences. Thus, it is possible that the observed abnormalities are related to both metabolic and vascular dysfunction, which are often associated with type 2 diabetes.

The observed brain activity patterns are similar to those found in patients with AD (6) prior to evident cognitive problems. Recent research has focused on the putative relationship between type 2 diabetes and AD, which may stem from the crucial role that insulin plays in both disorders (16,18). Glucose metabolism may also be involved (19); however, the results are not clear (20). We observed that control subjects who carry the AD risk allele APOE4 showed reduced deactivation in the cerebellum and fusiform gyrus during encoding. Others have found that these regions are recruited during episodic memory tasks (21), and the cerebellum has previously been shown to be less active in E4 carriers as they age (22). Differences between our finding and those of others who have observed effects of APOE4 in the medial temporal lobe (23) may stem from particulars about the memory task and ages of the participants.

This study is cross-sectional; thus, we cannot assert that the observed pattern of functional abnormalities confers increased risk for AD or MCI, although similar abnormalities are seen in populations at risk for AD and in patients with current AD or MCI (6). There was no evidence of cognitive impairment in this sample; however, significant impairment has often been shown in elderly type 2 diabetic patients (12), suggesting that the observed fMRI abnormalities may precede cognitive decline. Future studies should use longitudinal designs and evaluate the impact of previous hypoglycemia, exogenous insulin administration, white matter hyperintensities, vascular reactivity, and task vigilance. Exogenous insulin, in particular,

has been shown to reduce the BOLD response in a visual task (24). By incorporating these variables into the design of future studies, we can begin to isolate the etiology of DMN abnormalities in diabetes.

In summary, this study demonstrates that type 2 diabetic patients show hypoactivation of task-relevant regions during encoding and impaired deactivation in the DMN during recognition despite normal cognitive performance, suggesting a reduced ability to modulate task-related brain activity. Acute hyperglycemia, short- and long-term glycemic control, and insulin resistance likely contribute to this abnormality. Through a better understanding of the functional brain abnormalities observed in type 2 diabetes, diagnostic tests and therapies can be developed to detect abnormalities and ameliorate function in vulnerable brain regions, networks, and pathways. Beginning therapies in middle age can help prevent development of clinically significant cognitive impairment.

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study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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