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Hyperactivation of working memory related brain circuits in newly-diagnosed middle-aged type 2 diabetics

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Abstract

Type 2 diabetes mellitus (T2DM) is well known for its adverse impacts on brain and cognition, which lead to multidimensional cognitive deficits and widely-spread cerebral structure abnormalities. However, existing literatures are mainly focused on patients with advanced age or extended T2DM duration. Therefore, it remains unclear whether and how brain function would be affected at the initial onset stage of T2DM in relatively younger population. In current study, twelve newly-diagnosed middle-aged T2DM patients with no previous diabetic treatment history and twelve matched controls were recruited. Brain activations during a working memory task, the digit n-back paradigm (0-, 1- and 2-back), were obtained with functional magnetic resonance imaging (fMRI) and tested by repeated measures ANOVA. Whereas patients performed the n-back task comparably well as controls, significant load-by-group interactions of brain activation were found in the right dorsolateral prefrontal cortex (DLPFC), left middle/inferior frontal gyrus, and left parietal cortex, where patients exhibited hyperactivation in the 2-back but not the 0-back

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Statement of Human and Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent: Informed consent was obtained from all participants for being included in the study.

or 1-back condition compared to controls. Furthermore, the severity of chronic hyperglycemia, estimated by glycosylated hemoglobin (HbA_{1c}) level, was entered into partial correlational analyses with task-related brain activations, while controlling for the real-time influence of glucose, estimated by instant plasma glucose level measured before scanning. Significant positive correlations were found between HbA_{1c} and brain activations in the anterior cingulate cortex and bilateral DLPFC only in patients. Taken together, these findings suggest there might be a compensatory mechanism due to brain inefficiency related to chronic hyperglycemia at the initial onset stage of T2DM.

Keywords

type 2 Diabetes; chronic hyperglycemia; working memory; functional magnetic resonance imaging (fMRI)

Introduction

Type 2 diabetes mellitus (T2DM) is a common metabolic disease characterized by hyperglycemia due to reduced insulin sensitivity and relative insulin deficiency [1], which is also well known for its adverse impacts on the brain [1, 2]. For example, insulin resistance is associated with reduced insulin transportation across the blood-brain barrier in humans, leading to alterations in body weight, food intake, and glucose homeostasis [3]. So far, T2DM is found to be associated with impairments of cerebral signal conduction, neurotransmission, synaptic plasticity, cerebral structure and finally cognitive function, which are in all referred to as “diabetic encephalopathies” [4, 5] and now accepted as complications of diabetes [5]. A large and growing body of epidemiological literatures has provided evidence for T2DM related dysfunction in multiple cognitive domains, such as psychomotor speed [6-10], executive function [9, 11], and memory [8-17]. In line with these cognitive impairments, cerebral atrophy [10, 11, 18], white matter lesions [10, 19], and altered resting-state functional connectivity [19-21] are frequently reported in T2DM patients as well. However, it should be noted that most of these studies included patients with advanced age which could be influencing both behavioral performances and imaging assessments. Even in studies with middle-aged patients [6, 12, 16, 19], the results could also be confounded with recurrent hypoglycemic attacks during years of medical treatment [1], not to mention impacts from duration [9] and medication [22] themselves. Therefore, whether T2DM mainly by itself can influence the brain at the initial onset stage remains unclear.

Accordingly in current study, a blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) experiment was conducted to explore the brain function in newly-diagnosed middle-aged T2DM patients during a working memory task, the digit n-back task, which requires participants to monitor a series of digits and to respond to the one presented N trials back [23, 24]. The focus on working memory related brain circuits was inspired by previous structure imaging studies, whereas T2DM related grey matter loss is mainly found in an extended brain network including the prefrontal [10, 25], medial frontal [10], precentral [18], and parietal [26] regions, which is also consistent with the brain

network involved in working memory process [23, 27, 28]. Especially, prefrontal atrophy, shown as enlarged lateral ventricles, was found in a group of recent onset middle-aged T2DM patients who were diagnosed and treated within a year [25]. However despite the widely-spread structure abnormalities within the working memory related brain circuits, neuropsychological results regarding to working memory dysfunction in T2DM patients were divergent. Some studies reported preserved working memory function in T2DM patients [14, 15, 17], while significant working memory dysfunction was observed in T2DM patients during acute hyperglycemia [8, 13]. Considering fMRI is sensitive to modest functional reorganization even in patients who can achieve comparable behavioral performance [29-31], we hypothesized that at least altered brain activation would be found in these patients, whether with or without declined working memory task performance.

The second goal of this study was to explore the role of chronic hyperglycemia in the disruption of brain functioning at the initial onset stage of T2DM. Glycosylated hemoglobin (HbA_{1c}) was used to reflect the severity of chronic hyperglycemia in these patients, since its concentration is positively associated with the mean blood sugar concentration over previous weeks to months [32]. Then the potential association between HbA_{1c} and brain function was tested with correlational analysis. Besides, in order to minimize the confounding influences of aging, recurrent hypoglycemic attacks, diabetic duration, and medication, all patients were middle-aged, and had been diagnosed with diabetes for the first time, hence were not previously treated with any kind of diabetic treatment. We also excluded patients with hyperlipidemia or hypertension to avoid confounding factors from other diabetes-associated comorbidities.

Material and Methods

Participants

Twelve right-handed middle-aged T2DM patients and twelve demographically matched right-handed euglycemic controls (see respective demographic information in Table 1) participated in the present study. All patients were outpatients of the First Affiliated Hospital of Anhui Medical University with recent onset of diabetes related symptoms, who were diagnosed with T2DM according to the World Health Organization 1999 criteria [33] for the first time and had no previous diabetic treatment history. Both patients and controls in this study had normal or correct-to-normal vision and normal liver and renal functions. Magnetic resonance images were visually inspected by an experienced radiologist blind to the diabetic diagnosis, who ruled out the presence of moderate atrophy or other structural changes in each participant. Furthermore, we verified the visual inspection by implementing a supplementary voxel-based morphometry (VBM) [34] analysis on the anatomical imaging data of participants, which revealed no significant global or regional difference of grey matter volume between patients and controls (procedure described in Supplementary Document 1). Participants were excluded if they had a history of cerebral hemorrhage or infarction, neurological or psychiatric disorders, or had systolic blood pressure ≥ 140 mmHg and (or) diastolic blood pressure ≥ 90 mmHg, plasma triglycerides ≥ 1.7 mmol/L, or plasma total cholesterol ≥ 5.2 mmol /L. No presence of ketoacidosis was recorded in any participant during the entire experiment.

All patients underwent the fMRI scanning the day immediately after their diagnosis^{*}. To avoid the influence of medication, they were asked to withhold their medical treatment until the scanning was over. The total withholding time (from diagnosis to the end of the scanning) was less than 24 hours in every patient. Written informed consent was obtained from all participants in this study. The experiments were performed with the approval of Anhui Medical University Human Subjects Review Committee, and were conducted according to the principles expressed in the Declaration of Helsinki.

Glucose and insulin levels

Plasma glucose (PG) and insulin levels were measured during Oral Glucose Tolerance Test (OGTT). The HbA_{1c} was assayed as an estimate for chronic hyperglycemia. In order to control for the real-time influence of glucose on brain activation, instant PG level, which was measured immediately before scanning as an estimate for the averaged real-time PG level during the whole fMRI experiment, was used as a controlled variable in the following correlational analyses.

Homeostasis model assessment version 2 (HOMA2) was used to assess pancreatic β -cell function (HOMA2-% β) from fasting PG and fasting insulin levels, which was completed by using the HOMA Calculator version 2.2, available from the Diabetes Trials Unit website (<http://www.dtu.ox.ac.uk>) [35, 36].

Paradigm of fMRI experiment

A blocked digit n-back design [24] was used in the present study with three gradually increased task-loads (0-, 1-, and 2-back). Each task block started with a 2-s instruction (0-back: “report the current digit”; 1-back: “report the first digit prior to the current one”; 2-back: “report the second digit prior to the current one”. Displayed in Chinese). After a 1-s delay, 10 digits were presented serially with 2-s duration and followed by a 1-s fixation. During this 3-s period, the participants gestured the recalled digit with right hand, which was recorded by one author standing beside the scanner. Another 2-s instruction (“rest” in Chinese) followed by 31-s fixation was used as a baseline control block, during which the participants were asked to rest with their eyes open. The fixation, instruction and digits extended about $0.8^\circ \times 0.8^\circ$, $8^\circ \times 2^\circ$, and $2^\circ \times 1^\circ$, respectively in visual angle.

All participants underwent 2 fMRI runs with 4 epochs in each run. Each epoch consisted of a 0-back, a 1-back and a 2-back task block, and followed by a baseline control block. The sequence of the task blocks was 0-, 1-, 2-back in one run, and 2-, 1-, 0-back in the other. The two task sequences were counterbalanced across all the participants in each group.

MRI data acquisition

Imaging data were collected on a 1.5 Tesla Philips Infinion MR System (Royal Philips Electronics, Netherlands). During each functional scan, 179 volumes consisting of 16 axial slices were obtained with a T2*-weighted echo-planar imaging (EPI) sequence (TR = 3 s,

^{*}In order to better understand how the brain is affected by daily hyperglycemic events, we intentionally scanned our patients about one hour after their regular lunches, to mimic the “worst scenario” of their circadian glycemic fluctuations. All controls were also scanned with the same arrangement.

TE = 40 ms, FOV = 24 cm × 24 cm, matrix = 64 × 64, flip angle = 90°, slice thickness = 4 mm, gap between two adjacent slices = 1.2 mm). Corresponding high-resolution T1-weighted imaging data were also obtained with a spin echo (SE) sequence (2D anatomical data) and a spoiled gradient recalled echo (SPGR) sequence (3D anatomical data).

Analysis of fMRI data

MRI data were analyzed using AFNI (Analysis of Functional NeuroImages, <http://afni.nimh.nih.gov/afni/>) [37]. The first three volumes of each scan were excluded from the analysis in order to account for the approach to steady state of the longitudinal magnetization. Then data was processed to remove any linear drift and to correct motion and subsequently smoothed with a Gaussian filter (FWHM = 6 mm) and normalized. Any scan in which the head motion was larger than 2 mm was excluded from further analysis.

The preprocessed data were analyzed in two ways: group and individual analysis [24]. In the group analysis, all the participants' functional data sets of each group were averaged after being stereotactically transformed into Talairach space with 4 mm resolution. Correlation analyses based on the direct contrast between the task (including the 0-, 1- and 2-back block) and baseline were then carried out to generate the activation map for each group ($P < 10^{-10}$, cluster size = 4 voxels), which were related to the n-back task irrespective of the task-load (0-, 1-, and 2-back). For individual analysis, a mixed regression analysis with General Linear Model was employed, comprising three task-related square-wave block regressors, each for 0-, 1-, and 2-back condition, respectively, and 6 regressors corresponding to the head motion covariates [38]. As a result, three activation maps ($P < 0.05$, cluster size = 4 voxels) were generated, and a combined activation map was obtained by the logical 'OR' of these maps. The regions of interests (ROIs) for individual participants were then identified on this combined map. For each ROI, mean parameter estimates at the three n-back task-loads were calculated for each participant.

Statistical analysis

Group level comparisons of demographic and clinical characteristics were conducted with independent two-sample t-test except for gender, which was analyzed by a Chi-square test. In addition, Pearson and Spearman correlation analyses were carried out between HbA_{1c} and instant PG level to verify whether they were associated with each other.

The performance accuracies and BOLD responses in the n-back task were evaluated with a 2 (patients, controls) × 3 (0-, 1-, 2-back) repeated measures ANOVA. In order to explore the relationship between chronic hyperglycemia and brain activation while controlling for the real-time influence of glucose, partial correlational analyses were conducted between HbA_{1c} and task-related BOLD responses (averaged across all task-loads for better signal-to-noise ratio), with instant PG level as the controlled variable. All statistical analyses were performed using SPSS for windows (version 17, SPSS Inc, Chicago, IL, USA), with the level of significance set to 0.05 (two-tailed).

Results

Clinical data

During the OGTT, the patients showed significantly higher PG levels ($P < 0.001$, all time points) and lower plasma insulin levels ($P < 0.01$, within 60 minutes) than controls (See plotting in Supplementary Fig. 1). Besides, the patients also exhibited significantly elevated HbA_{1c} and instant PG level but lower HOMA2- β index, in contrast with controls ($P < 0.001$, Table 1). There were no significant differences in the plasma level of triglyceride, cholesterol, and systolic/diastolic pressures between groups ($P > 0.05$, Table 1).

It is noteworthy that neither Pearson nor Spearman correlation analysis could reveal a significant correlation between HbA_{1c} and instant PG level ($P > 0.05$), which meant patients with severer chronic hyperglycemia did not correspondingly exhibit higher averaged real-time PG level during the experiment.

Performance accuracy of the n-back task

The overall accuracies of all 3 task-loads of the n-back task were very high in both groups (Patients: 0-back, $100.0 \pm 0\%$; 1-back, $98.5 \pm 3.1\%$; 2-back, $92.6 \pm 5.3\%$; Controls: 0-back, $99.7 \pm 0.6\%$; 1-back, $98.5 \pm 2.2\%$; 2-back, $95.8 \pm 5.4\%$). The accuracies were significantly decreased with difficulty level across the three n-back task-loads in either groups ($F(2, 22) > 4.1$, $P < 0.05$). No group difference ($F(1, 22) = 2.8$, $P = 0.11$) or load-by-group interaction ($F(2, 44) = 2.0$, $P = 0.14$) was found.

Functional MRI data

Regions of interest—During the n-back task, a common brain network, including bilateral dorsolateral prefrontal cortices (DLPFC), bilateral middle/inferior frontal gyri (M/IFG), bilateral premotor areas (PM), the anterior cingulate cortex (ACC), and bilateral parietal cortices (PA) (Fig. 1), was activated in both groups, which is consistent with previous reports [23, 24]. These regions were then identified from the combined activation map described above as ROIs. The bilateral visual cortices were used as the control ROIs to rule out the potential global effect of T2DM since the perceptual load of visual stimuli is sustained in all task conditions.

BOLD responses as a function of n-back load—Consistent with early studies [23], the load effect of BOLD response, which referred to the increase of BOLD response corresponding to the increase of task difficulty (load), appeared in the DLPFC, M/IFG, PM, ACC, and PA of both hemispheres in both groups ($F(2, 22) > 5$, $P < 0.01$). No load effect was found in visual cortices for either groups ($F(2, 22) < 3.2$, $P > 0.05$) except in the left visual cortex of controls ($F(2, 22) = 4$, $P = 0.03$), which was also identified in a previous study [39] and may result from top-down modulation.

Notably, significant load-by-group interaction was found in right DLPFC, left M/IFG, and left PA ($F(2, 44) > 3.8$, $P < 0.05$). In these regions, patients showed elevated BOLD responses than controls during the 2-back ($P < 0.05$) but not 0-back or 1-back condition

(Fig. 2). No significant group difference or load-by-group interaction was detected in the bilateral visual cortices, the control ROIs.

To further validate our observation, ANCOVA analyses were also used to retest above load-by-group interactions. Potential confounding factors, such as age, cholesterol, and blood pressure, were included one at a time as the covariate, to rule out the possible residual effects. Consistent with above results, significant load-by-group interaction still could be found in right DLPFC, left M/IFG, and left PA ($F(2, 42) > 3.4$, $P < 0.05$).

Correlational analysis—After controlling for the instant PG level, positive correlations between HbA_{1c} and the BOLD responses in the ACC ($r = 0.71$, $P = 0.015$) and bilateral DLPFC (Left: $r = 0.61$, $P = 0.046$; Right: $r = 0.65$, $P = 0.032$) were revealed in patients (see residual plotting in Supplementary Fig. 2). However, no significant correlation between HbA_{1c} and BOLD responses was found in any of the ROIs in the control group ($P > 0.05$, Table 2).

Discussion

Our present study provided neurobiological evidence that newly-diagnosed middle-aged T2DM patients exhibited abnormal brain activation during a working memory task. Specifically, compared to controls, greater BOLD responses during the 2-back condition were found in multiple brain regions of patients, including the right DLPFC, left M/IFG, and left PA. Furthermore, T2DM patients but not controls with higher HbA_{1c} level tended to have larger BOLD responses in the ACC and bilateral DLPFC, after controlling for the instant PG level. Since other factors which might also affect brain function, such as aging, diabetic duration, recurrent hypoglycemia attacks, medication, or other diabetic comorbidities were mainly controlled in this study, the above findings may suggest a major role of chronic hyperglycemia in the alteration of brain function at the initial onset stage of T2DM.

A notable fact is that our patients showed abnormally elevated BOLD responses within the right DLPFC, left M/IFG, and left PA only during the 2-back but not the 0-back and 1-back conditions, whereas their task performances were comparably high as controls'. Such “extra” recruitment of brain activation or so called hyperactivation has been suggested as a compensational strategy of the brain during the early stage of progressive inefficiency, which was more commonly reported in Alzheimer's Disease (AD) related studies [40, 41]. In these studies, compensating hyperactivation is considered as an important imaging maker for the prognosis of AD since greater hippocampal hyperactivation is associated with severer hippocampus atrophy [42, 43] and predicts more subsequent cognitive decline [44, 45]. In analogy to these findings, for recent onset middle-aged T2DM patients, the present results showed hyperactivation in their prefrontal brain regions, whereas previous study revealed their prefrontal atrophy represented by enlarged lateral ventricles [25]. In line with recently accumulating literatures, these evidence may further support the idea that T2DM and AD may share a similar pathophysiological pathway [46].

The T2DM related hyperactivation observed in this study may not be interpreted as a global effect. Firstly, it is task-load specific since the group level difference was only found in the 2-back condition. Secondly, it is also regional specific since no group level difference was found in the bilateral visual cortices during either task condition. The preservation of visual cortical activation in these T2DM patients who were scanned during instant hyperglycemic state is also in line with a previous study, which showed the lack of effect of acute hyperglycemia on visual cortical activation [47]. Therefore our findings may not reflect the consequence of a global elevation of glucose metabolism or oxygen consumption due to the progress of T2DM.

As the second goal of this study, the association between chronic hyperglycemia and brain activation was also explored. After controlling for the instant PG level, we found that T2DM patients with higher HbA_{1c} level had larger task-related BOLD responses in the ACC and bilateral DLPFC. Previous epidemiological studies showed that higher HbA_{1c} was associated with lower cognitive function [48, 49] in T2DM patients. Particularly in middle-aged T2DM patients, HbA_{1c} was negatively correlated with psychomotor efficiency [6] and inhibitory control ability [50], which are dominantly related to the function of DLPFC and ACC [51, 52]. Other than decline in behavioral performance, elevated HbA_{1c} was also associated with severer prefrontal atrophy in middle-aged [16] and adolescent [53] T2DM patients. In line with above evidence, our results indicated that T2DM patients with severer chronic hyperglycemia tend to have more compensating activation in the anterior part of the working memory related brain network even at the initial onset stage of the disease, which may provide a novel insight of T2DM related regional vulnerability.

The partial correlation analysis was used to rule out the confounding from the real-time influence of glucose on brain function, since patients with higher HbA_{1c} could also happen to exhibit higher real-time PG level during the experiment, especially given the fact that our patients were treatment-free and HbA_{1c} did reflect the daily accumulation of instant PG levels. Therefore we firstly tested the association between HbA_{1c} and instant PG level, and found non-significant correlation both with parametric and non-parametric methods. Then by implementing the instant PG level as a controlled variable, the ACC and bilateral DLPFC survived in the correlation between HbA_{1c} level and brain activation, leaving the right PM marginal significant. Taking all these evidence into consideration, it seemed that the association between HbA_{1c} level and brain function in our results might not be confounded by the real-time influence of glucose but represent an impact from chronic hyperglycemia.

The mechanisms underlying changes in the brain activation during hyperglycemia are not clear [54]. One possible explanation is the metabolic changes caused by hyperglycemia, such as suppressed blood-brain glucose transfer [55], decreased regional cerebral blood flow [56] and reduced regional glucose metabolism [57]. Another possibility is the “toxic” effect of hyperglycemia which can lead to progressive structural and functional abnormalities in the brain [58]. Such glucose toxicity is mediated by increased flux of glucose through the polyol and hexosamine pathway [59], increased productions of oxidative stress [60], and accumulations of advanced glycation end-products [61]. Nevertheless, the present study may provide some clues for the role that hyperglycemia could have played in the pathogenesis of cerebral dysfunction at the early stage of T2DM.

Note that the T2DM related brain hyperactivation may also be associated with underlying brain atrophy [10] or cerebrovascular lesions that are frequently reported in former T2DM studies, such as white matter hyperintensities [9, 10], cerebral infarcts [9, 10], or microbleeds [10] (for reviews, see [62, 63]). In the present study, moderate to severe atrophy or structural changes were ruled out by visual inspection in the first instance since they could also be caused by other etiologies and confound with our results. Then a supplementary VBM analysis was implemented (see Supplementary Document 1 for details) but no group difference of grey matter volume was found at neither global nor regional level. Therefore the functional change we observed in these T2DM patients may not be attributed to potential gray matter atrophy in their brain. However, still it should be admitted that cerebrovascular lesions like white matter hyperintensities, cerebral infarcts, or microbleeds are better assessed with more specific MRI sequences [64] which hence are beyond the scope of current study. Accordingly, the potential existence of such cerebrovascular lesions at the initial onset stage of T2DM remains to be explored in the future.

In summary, our study showed that newly-diagnosed middle-aged T2DM patients exhibited brain hyperactivation within the right DLPFC, left M/IFG, and left PA during a high working memory load task condition (2-back). Furthermore, patients with severer chronic hyperglycemia, represented by higher HbA_{1c}, tended to have greater brain activation in the ACC and bilateral DLPFC. These findings provided exploratory evidence for the impact of chronic hyperglycemia on patients' brain network and suggested a compensational mechanism at the initial onset stage of T2DM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Brain areas involved in the digit n-back task were presented. The activation map for the controls was depicted ($P < 10^{-10}$) upside while the activation map for the type 2 diabetic patients was depicted ($P < 10^{-10}$) downside. The patients presented a similar but more wildly distributed activation pattern comparing to controls. Abbreviations: T2DM: Type 2 diabetes mellitus. DLPFC: dorsolateral prefrontal cortex. M/IFG: middle/inferior frontal gyrus. ACC: anterior cingulate cortex. PA: parietal cortex. PM: premotor area. R: right. L: Left

Fig. 2.

Graphs representing brain activation in selected regions of interest at each task load of the N-back task. The right DLPFC, left M/IFG, and left parietal cortex showed significant load-by-group interaction, where type 2 diabetic patients elicited higher BOLD responses in the 2-back task relative to controls. No significant group difference or load-by-group interaction was found in the bilateral visual cortices (left visual cortex was shown as an example).

Abbreviations: DLPFC: dorsolateral prefrontal cortex. M/IFG: middle/inferior frontal gyrus. Hollow diamond, type 2 diabetic patients ($n = 12$); hollow square, normal controls ($n = 12$). Error bar is 1 SE. * $P < 0.05$, two tailed

Table 1
Comparison of type 2 diabetic (n = 12) and control (n = 12) participants on demographic and clinical characteristics

	Type 2 Diabetics	Healthy controls	P
Age (years)	41.1 ± 6.1 (33-52)	40.5 ± 6.2 (31-53)	0.8
Gender (M/F)	11/1	8/4	0.1
Education (years)	9.8 ± 4.4 (1-15)	9.3 ± 3.7 (2-15)	0.8
Triglyceride	1.22 ± 0.25 (0.72-1.50)	1.22 ± 0.22 (0.82-1.51)	0.9
Cholesterol	3.72 ± 0.57 (2.59-4.70)	3.86 ± 0.64 (2.95-4.81)	0.6
Blood pressure (mm Hg):			
Systolic	115.3 ± 7.0 (105-126)	118.3 ± 7.0 (109-129)	0.3
Diastolic	77.3 ± 4.2 (72-83)	78.2 ± 3.5 (72-83)	0.6
HOMA2-%β	12.1 ± 4.8 (5.3-19.3)	105.8 ± 21.1 (74.9-141.9)	<0.001
Instant plasma glucose (mmol/L)	23.5 ± 3.1 (17.7-27.7)	6.8 ± 1.0 (5.4-8.7)	<0.001
HbA _{1c} (%)	10.0 ± 1.8 (8.1-13.2)	5.1 ± 0.5 (4.8-6.0)	<0.001

Notes: Abbreviations: HOMA2-%β: homeostasis model assessment for b-cell function. HbA_{1c}: glycosylated hemoglobin. Data are means ± S.D. (range)

Table 2
Partial correlations (controlled for plasma glucose level before scanning) between averaged BOLD responses and glycosylated hemoglobin (HbA_{1c}) concentration

ROI	Type 2 diabetics (n = 12)		Controls (n = 12)	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
DLPFC	Left	.611 *	.046	-.012 .973
	Right	.646 *	.032	-.352 .289
M/IFG	Left	.179	.598	-.179 .598
	Right	.005	.989	-.161 .636
ACC		.707 *	.015	-.189 .578
Premotor	Left	.370	.263	.099 .773
	Right	.559	.074	.074 .828
PA	Left	.376	.254	.025 .941
	Right	.383	.245	-.240 .477
VC	Left	.300	.371	-.257 .446
	Right	.169	.620	-.428 .189

Notes: Abbreviations: ROI: regions of interests. DLPFC: dorsolateral prefrontal cortex. M/IFG: middle/inferior frontal gyri. ACC: anterior cingulate cortex. Premotor: premotor area. PA: parietal cortex. VC: visual cortex.

* $P < 0.05$, two tailed