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Functional Brain Networks Are Altered in Type 2 Diabetes and Prediabetes: Signs for Compensation of Cognitive Decrements? The Maastricht Study

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Type 2 diabetes is associated with cognitive decrements, accelerated cognitive decline, and increased risk for dementia. Patients with the metabolic syndrome, a major risk factor for diabetes, may display comparable cognitive decrements as seen in type 2 diabetes. Currently, the impact of diabetes and prediabetes on cognition and the underlying organization of functional brain networks still remain to be elucidated. This study investigated whether functional brain networks are affected in type 2 diabetes and prediabetes. Forty-seven participants with diabetes, 47 participants with prediabetes, and 45 control participants underwent detailed cognitive testing and 3-Tesla resting state functional MRI. Graph theoretical network analysis was performed to investigate alterations in functional cerebral networks. Participants with diabetes displayed altered network measures, characterized by a higher normalized cluster coefficient and higher local efficiency, compared with control participants. The network measures of the participants with prediabetes fell between those with diabetes and control participants. Lower processing speed was associated with shorter path length and higher global efficiency. Participants with type 2 diabetes have altered functional brain networks. This alteration is already apparent in the prediabetic stage to a somewhat lower level, hinting at functional reorganization of the cerebral networks as a compensatory mechanism for cognitive decrements.

The worldwide prevalence of diabetes is increasing rapidly, with the majority of patients having type 2 diabetes (1). Along with cardiovascular risk factors, type 2 diabetes is associated with cognitive decrements, accelerated cognitive decline, and an increased risk for dementia and Alzheimer disease (2,3). A broad range of cognitive domains are affected in type 2 diabetes, and one of the most commonly affected is processing speed (4,5). However, the underlying pathological mechanism is not yet clear.

The progression of normal glucose metabolism to type 2 diabetes is a gradual process in which insulin resistance plays a crucial role. Before the clinical presentation of type 2 diabetes, insulin resistance often is accompanied by other metabolic and vascular abnormalities. The cluster of these cardiovascular risk factors is referred to as the metabolic syndrome and is considered a major risk factor for diabetes (6). Patients with the metabolic syndrome have a high likelihood for diabetes and may display comparable cognitive decrements as seen in patients with type 2 diabetes (5). Furthermore, the cardiovascular risk factors are associated with an increased risk of late-life dementia (7).

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PATHOPHYSIOLOGY

Previous studies on cognitive decrements in diabetes using functional MRI (fMRI) have focused on changes in activation patterns, functional connectivity, and signal fluctuations. These studies have revealed associations among impaired cognition, altered activation, and decreased functional connectivity (8–14). Although functional connectivity was measured by correlating signal time series of various and a priori–selected cerebral regions, aberrant connections outside these predefined regions remain undiscovered. Moreover, the broad range of affected cognitive domains in type 2 diabetes suggests more widespread, global network disturbances rather than perturbations of merely localized processes or specific functional networks. Because several domains are affected in type 2 diabetes, the decreased cognitive performance in individuals with type 2 diabetes might be the result of a reduced efficiency or effectiveness of various processing resources (15). In this context, novel brain connectivity analyses that examine the integrity of networks in the entire brain are appropriate.

Disturbances in local and global network organization (or efficiency) can be assessed by graph theoretical analysis (16–18). In general, the brain can be thought of as a graph, which is a collection of nodes (i.e., regions) and edges (i.e., functional connections between two regions). The organization of this graph can be characterized in terms of various so-called graph measures, including the cluster coefficient, local efficiency, characteristic path length, and global efficiency (Table 1). The cluster coefficient is a measure of local network connectivity and quantifies the extent that neighboring brain regions are also connected. A network with a high cluster coefficient contains densely connected local clusters. A measure that is closely related to the cluster coefficient is the local efficiency, which reflects the average efficiency of local clusters. The characteristic path length is a measure of global network connectivity and represents the shortest average number of connections between any two brain regions. A network is considered highly efficient if the path length is relatively short, and this is reflected in the graph measure global efficiency. It has been shown that the brain network organization typically behaves like a small-world network (18) and that this organization is disrupted in Alzheimer disease (19). Small-world networks are characterized by a high cluster coefficient and a low characteristic path length (16) and are more efficient in synchronizing neural activity between brain regions (20).

Table 1—Description of graph theoretical network measures (normalized to random networks)

Graph measure	Symbol	Description
Cluster coefficient	γ	Quantifies the number of connections between the nearest neighbors of a region as a proportion of the maximum number of possible connections
Characteristic path length	λ	The minimum number of connections that must be traversed to go from one region to another
Global efficiency	E_{global}	The average inverse shortest path length, which is inversely related to the characteristic path length
Local efficiency	E_{local}	Mean of the global efficiency of subgraphs computed on the immediate neighbors of a region, which is related to the cluster coefficient

How cognitive decrements in diabetes reflect alterations in functional brain organization needs to be resolved. In particular, to what extent diabetes and prediabetes (i.e., the metabolic syndrome with impaired glucose tolerance) share the same alterations in functional brain networks or whether prediabetic alterations exist is unknown. Therefore, the current study investigated whether and to what extent global functional brain networks are affected in patients with type 2 diabetes and prediabetes.

RESEARCH DESIGN AND METHODS

Study Population and Design

We used data from The Maastricht Study, an ongoing observational, prospective, population-based cohort study. The rationale and methodology have been described previously (21). In brief, the study focuses on the etiology, pathophysiology, complications, and comorbidities of type 2 diabetes and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged 40–75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from municipal registries and the regional Diabetes Patient Registry through mailings. Recruitment was stratified according to known type 2 diabetes status for reasons of efficiency. The present report is derived from cross-sectional data from the first 3,451 participants who completed the baseline survey between November 2010 and September 2013. The baseline surveys for each participant were performed within a 3-month time window. MRI was performed ~12.7 ± 3.7 months later. The study was approved by the institutional medical ethical committee (NL31329.068.10) and the Netherlands Health Council under the Dutch Law for Population Studies (Permit 131088-105234-PG). All participants gave written informed consent.

Of the 3,451 participants, MRI measurements were available in 1,109 (MRI assessments started in December 2013 and are ongoing). From this group, we selected all participants with both the metabolic syndrome and impaired glucose tolerance (which was chosen to represent

prediabetes). Forty-seven (out of 1,109) participants met both criteria; hence, we matched them one to one according to age, sex, and education level to the same number of participants with type 2 diabetes and participants without type 2 diabetes, the metabolic syndrome, or prediabetes. When this was not possible, we matched participants within the smallest age range (with a maximum of ±3 years) and/or within an education range of one level. This resulted in 47 participants with prediabetes with both the metabolic syndrome and impaired glucose tolerance, 47 participants with type 2 diabetes, and 47 participants without type 2 diabetes or the metabolic syndrome. No incidental findings at radiological examination were reported in the selected participants.

Glucose Metabolism Status

All participants (except those who used insulin) underwent a standardized oral glucose tolerance test. Participants were considered to have diabetes according to the World Health Organization 2006 criteria if they use diabetes medication or if they had a fasting blood glucose ≥7.0 mmol/L or a 2-h blood glucose ≥11.1 mmol/L. Participants were considered to have both an impaired glucose tolerance and the metabolic syndrome if they had a fasting blood glucose <7.0 mmol/L and a 2-h blood glucose ≥7.8 and <11.1 mmol/L, if they did not use any diabetes medication or did not have type 2 diabetes, and if they met two or more of the following criteria according to the adapted Adult Treatment Panel III criteria (22): waist circumference ≥88 cm for women and ≥102 cm for men, triglycerides ≥1.7 mmol/L, HDL cholesterol <1.3 mmol/L for women and <1.03 mmol/L for men, and blood pressure ≥130/85 mmHg or antihypertensive medication use. Participants without type 2 diabetes or prediabetes were defined by fasting blood glucose <6.1 mmol/L and a 2-h blood glucose <7.8 mmol/L and no use of diabetes medication.

MRI

For each participant, MRI data were acquired on a 3-T clinical magnetic resonance scanner (Magnetom Prisma Fit; Siemens Healthcare, Erlangen, Germany) by using a 64-element head/neck coil for parallel imaging with an acceleration factor of 2. The MRI protocol comprised structural scans for radiological evaluation (including T1-weighted, T2-weighted, and fluid attenuated inversion recovery sequences) and resting state fMRI scans. Resting state fMRI data were acquired using echoplanar imaging pulse sequence sensitive to blood oxygen level–dependent contrast (repetition time 2,000 ms, echo time 29 ms, flip angle of 90°, pixel size 2 × 2 mm, slice thickness 4 mm) and 195 volumes per acquisition. For anatomic references, a T1-weighted three-dimensional magnetization-prepared rapid acquisition gradient echo (repetition time 2,300 ms, echo time 2.98 ms, isotropic voxel size 1.00 mm, 176 continuous slices, matrix size 256 × 240, field of view 256 mm, inversion time 900 ms) was acquired.

Data Analysis

Image Preprocessing

The T1 images were automatically segmented to obtain cortical and subcortical gray and white matter areas and cerebrospinal fluid (CSF) by using the FreeSurfer software package (Martinos Center for Biomedical Imaging, Boston, MA) (23), and the segmentations were visually inspected. Data from two control participants were excluded due to image artifacts preventing reliable FreeSurfer segmentation; thus, data from 47 participants with type 2 diabetes, 47 participants with prediabetes, and 45 control participants were suitable for the final analysis.

Image preprocessing of the time series of the fMRI data were performed in Statistical Parametric Mapping 8 software (The Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, London, U.K.). fMRI images were corrected for slice timing and realigned to the mean image to correct for head movement. These images were then transformed to T1 space and spatially smoothed by using a 4-mm full-width half-maximum Gaussian kernel. Next, the individual anatomical T1 segmentations were registered to the fMRI images (24) to calculate the average time series for the cortical and subcortical gray and white matter areas and CSF. To reduce the effect of physiological noise (respiratory and cardiac artifacts), the fMRI data were filtered by using a band pass filter (0.01–0.1 Hz) and linear regression with the averaged time series of white matter, CSF, and movement parameters acquired in the previous realignment step as nuisance regressors (25,26). Finally, the averaged time series of the cortical and subcortical segmented areas (27,28) (a total of 82 areas, 41 for each hemisphere) was used to form a correlation matrix by calculating the Pearson correlation coefficients between all pairs of the segmented brain areas. Negative values were set to 0 (29). The correlation matrix stands for a brain graph in which each brain area represents a node and each connection between brain areas i and j represents an edge. For each participant, the brain graph was thresholded by a sparsity value (i.e., which percentage of the connections with the highest correlation coefficient were included while removing all other connections) based on the mean correlation matrix of the control participants. In addition, for a given sparsity value, the network (and, thus, the number of edges) was the same for each participant. Because no criteria are available for which sparsity value is the most biologically meaningful, a sparsity range of 0.1–0.9 with a step size of 0.01 was chosen, corresponding to 664–5,978 connections. A high sparsity value represents a relatively low number of connections with the highest correlation coefficients.

Network Parameters

For the global organization of large-scale networks, graph theoretical network measures (16–18) were calculated from the brain graphs by using the Brain Connectivity Toolbox (30) in MATLAB (The MathWorks, Natick, MA).

The following graph theoretical measures were calculated (Table 1): *1*) the cluster coefficient, which is a measure of local network connectivity (i.e., a network with a high cluster coefficient is characterized by densely connected local clusters); *2*) the characteristic path length, a measure of the average step length between two nodes (i.e., a network with low path length is characterized by short distances between two nodes); *3*) global efficiency, a measure of the average inverse shortest path length and is inversely related to the path length; and *4*) local efficiency, a measure of the mean global efficiency of subgraphs computed on the immediate neighbors of a node and related to the cluster coefficient. Furthermore, for each participant, the graph measures were normalized to comparable values from randomly generated networks (N = 100) (16,17) to evaluated whether the network had small-world properties. Small-world networks are characterized by a high normalized cluster coefficient >1 and a low normalized characteristic path length of ~1.

Covariates

Educational level was assessed by interview and classified into eight levels commonly used in the Netherlands: *1*) no education, *2*) primary education, *3*) lower vocational education, *4*) intermediate general secondary education, *5*) intermediate vocational education, *6*) higher general secondary education, *7*) higher vocational education, and *8*) university degree. For this study, educational level was divided into three groups: low (levels 1–3), middle (levels 4–6), and high (levels 7 and 8). Office blood pressure was assessed three times on the right arm after a 10-min rest by using a noninvasive blood pressure monitor (Omron 705IT; Omron, Kyoto, Japan). A fourth measurement was performed when the difference between measurements two and three exceeded >10 mmHg. Here, we used the averaged blood pressure values over all the available measurements (21).

Cognition

Information processing speed was derived (z score over the 3,451 participants) from the Stroop Color Word Test (parts I and II) (31), Concept Shifting Test (parts A and B) (32), and the Letter-Digit Substitution Test (33) in which participants were instructed to match digits to letters as quickly as possible within 90 s. Global cognitive function was measured by the Mini-Mental State Examination (score range 0–30) (34). Memory function was derived from the immediate and delayed recall Verbal Word Learning Test (35) in which 15 words are presented in five subsequent trials followed by a recall phase immediately after each trial (score range 0–75) and a delayed recall phase after 20 min (score range 0–15). Executive functioning and attention was derived from the Stroop Color Word Test (part III) (31) and Concept Shifting Test (part C) (32).

Statistical Analysis

Descriptive participant characteristics are reported as mean ± SD. Group characteristics were tested using one-way ANOVA for continuous variables and Pearson χ^2 test for categorical variables. Post hoc two-sided independent-samples t and Pearson χ^2 tests were used for significant group differences. Linear regression analyses were performed to assess the association of the graph theoretical network measures with the type 2 diabetes, prediabetes, and control conditions (model 1). In addition, to evaluate whether the associations were robust, model 1 was extended with potential confounders (i.e., age, sex, education level, systolic blood pressure) (model 2). Finally, to assess whether the graph measures were associated with cognition, model 2 was further extended with information processing speed (model 3). Processing speed was chosen for this analysis because it is mediated by multiple brain regions globally distributed throughout the entire brain. Furthermore, model 2 was extended with the addition of alcohol consumption to assess the effect of alcohol on the graph measures (model 4). Additionally, linear regression analyses with continuous measures for fasting blood glucose levels, HbA_{1c} levels, and insulin levels instead of the dichotomous prediabetes and diabetes status in model 1 were performed.

RESULTS

Table 2 shows the general characteristics of the participants. The groups were matched on age, sex, and education. As expected, the groups had different fasting blood glucose levels, HbA_{1c} levels, BMI, waist circumference, systolic blood pressure, and cholesterol levels. Cognition scores were not significantly different; however, post hoc analysis showed that participants with type 2 diabetes had significantly lower scores on information processing speed than control participants.

Figure 1 displays the graph theoretical network measures over a wide range of sparsity values for the three groups. The networks of the three groups all exhibited a topology in the small-world regimen, with cluster coefficient >1 and characteristic path length close to 1 (Fig. 1A and *B*). Participants with type 2 diabetes displayed generally higher values for cluster coefficient and global and local efficiency over almost the entire sparsity range compared with control participants, and participants with prediabetes were between these two groups. Moreover, in participants with type 2 diabetes, these cluster coefficient and local efficiency values were significantly higher by sparsity values (0.77–0.88 and 0.90, and 0.62–0.90, respectively) compared with that in control participants. For participants with prediabetes, local efficiency was also significantly higher over a wide range of sparsity values (0.73–0.90) compared with control participants. For characteristic path length, the control group displayed higher values than the other two groups, which were significantly higher for a narrow range of sparsity values (0.83–0.86) compared with the prediabetes group. No significant differences in graph measures were found between participants with type 2 diabetes and prediabetes. Table 3 shows the results of the linear regression analysis performed for the graph measures

Table 2—Clinical characteristics of the type 2 diabetes, prediabetes, and control groups

	Participants with type 2 diabetes (n = 47)	Participants with prediabetes (n = 47)	Control participants (n = 45)	P value
Demographic factors				
Age (years)	61.0 ± 6.7	61.0 ± 6.7	60.7 ± 6.5	0.962
Male sex (%)	51.1	51.1	51.1	1.000[a]
Education (%)				0.983[a]
Low	46.8	46.8	44.4	
Middle	25.5	21.3	24.4	
High	27.7	31.9	31.1	
Alcohol consumption (%)†§				0.023[a]
None	31.9	25.5	8.9	
Low	44.7	57.4	51.1	
High	23.4	17.0	40.0†§	
Smoking status (%)				0.238[a]
Never	29.8	21.3	33.3	
Former	48.9	59.6	60.0	
Current	21.3	19.1	6.7	
Cardiovascular disease (%)	10.6	6.4	11.1	0.689[a]
Type 2 diabetes–related characteristics				
Duration of diabetes (years)	8.7 ± 6.3*	—	—	
Newly diagnosed diabetes (%)¶	21.3	—	—	
Fasting blood glucose (mmol/L)	8.0 ± 2.2	6.0 ± 0.5‡	5.2 ± 0.3†§	<0.001
HbA_{1c} (%)	6.8 ± 1.1	5.7 ± 0.4‡	5.4 ± 0.4†§	<0.001
HbA_{1c} (mmol/mol)	51.2 ± 11.7	38.6 ± 4.7‡	35.8 ± 4.2†§	<0.001
Fasting blood insulin (pmol/L)	95.8 ± 64.8	106.0 ± 50.5	52.3 ± 23.5†§	<0.001
Type 2 diabetes medication, yes (%)		—	—	
Oral medication	70.2	—	—	
Insulin medication	14.9	—	—	
Insulin and oral medication	12.8	—	—	
Blood pressure medication, yes (%)	63.8	51.1	24.4†§	0.001[a]
Lipid medication, yes (%)	70.2	27.7‡	22.2†	<0.001[a]
Clinical variables				
BMI (kg/m^2)	29.4 ± 5.2	29.8 ± 4.0	25.4 ± 3.0†§	<0.001
Waist circumference (cm)	104.0 ± 15.0	102.5 ± 10.3	90.4 ± 8.9†§	<0.001
SBP (mmHg)	136 ± 14	141 ± 17	132 ± 17§	0.046
DBP (mmHg)	77 ± 8	79 ± 11	76 ± 8	0.131
Total cholesterol (mmol/L)	4.4 ± 1.0	5.5 ± 1.3‡	5.4 ± 1.1†	<0.001
HDL cholesterol (mmol/L)	1.4 ± 0.4	1.4 ± 0.4	1.8 ± 0.5†§	<0.001
LDL cholesterol (mmol/L)	2.3 ± 0.9	3.2 ± 1.0‡	3.2 ± 0.9†	<0.001
Triglycerides (mmol/L)	1.8 ± 1.2	1.9 ± 1.0	1.1 ± 0.5†§	<0.001
Cognitive score				
MMSE total score	28.9 ± 1.2	29.0 ± 1.3	29.1 ± 1.2	0.794
Memory function	−0.23 ± 1.00	−0.24 ± 1.08	0.03 ± 0.93	0.351
Information processing speed	−0.17 ± 0.80	−0.005 ± 0.86	0.19 ± 0.77†	0.109
Executive functioning and attention	−0.13 ± 0.86	−0.12 ± 0.86	−0.02 ± 0.77	0.782

Data are mean ± SD. Memory function, information processing speed, and executive functioning and attention are presented as mean standardized z scores ± SD. DBP, diastolic blood pressure; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure. *n = 22 based on only the participants with diabetes, excluding those with newly diagnosed diabetes. One-way ANOVA: [a]Pearson χ^2 test. Post hoc t tests and Pearson χ^2 tests were used to calculate significant group differences: †$P < 0.05$ comparing the type 2 diabetes group with the control group. ‡$P < 0.05$ comparing the type 2 diabetes group with the prediabetes group. §$P < 0.05$ comparing the prediabetes group with the control group. ¶As newly revealed by the oral glucose tolerance test.

corresponding to a sparsity value of 0.8. Supplementary Fig. 1 shows the relative (to the control participants) differences in graph measures for the type 2 diabetes and prediabetes groups. All results were intact after adjusting for age, sex, education level, and systolic blood pressure (model 2) (Supplementary Table 1).

Additional analyses incorporating information processing speed (model 3) revealed that increased characteristic path length was associated with improved processing speed, whereas an increased global efficiency was associated with lower processing speed (Supplementary Fig. 2). In addition, alcohol consumption was not significantly associated with any graph measures (model 4). Analyses with fasting blood glucose levels and HbA_{1c} levels showed similar results for the local efficiency: High fasting blood glucose and high HbA_{1c} levels were significantly associated with a high local efficiency. Both measures showed a trend for the cluster coefficient: High fasting blood

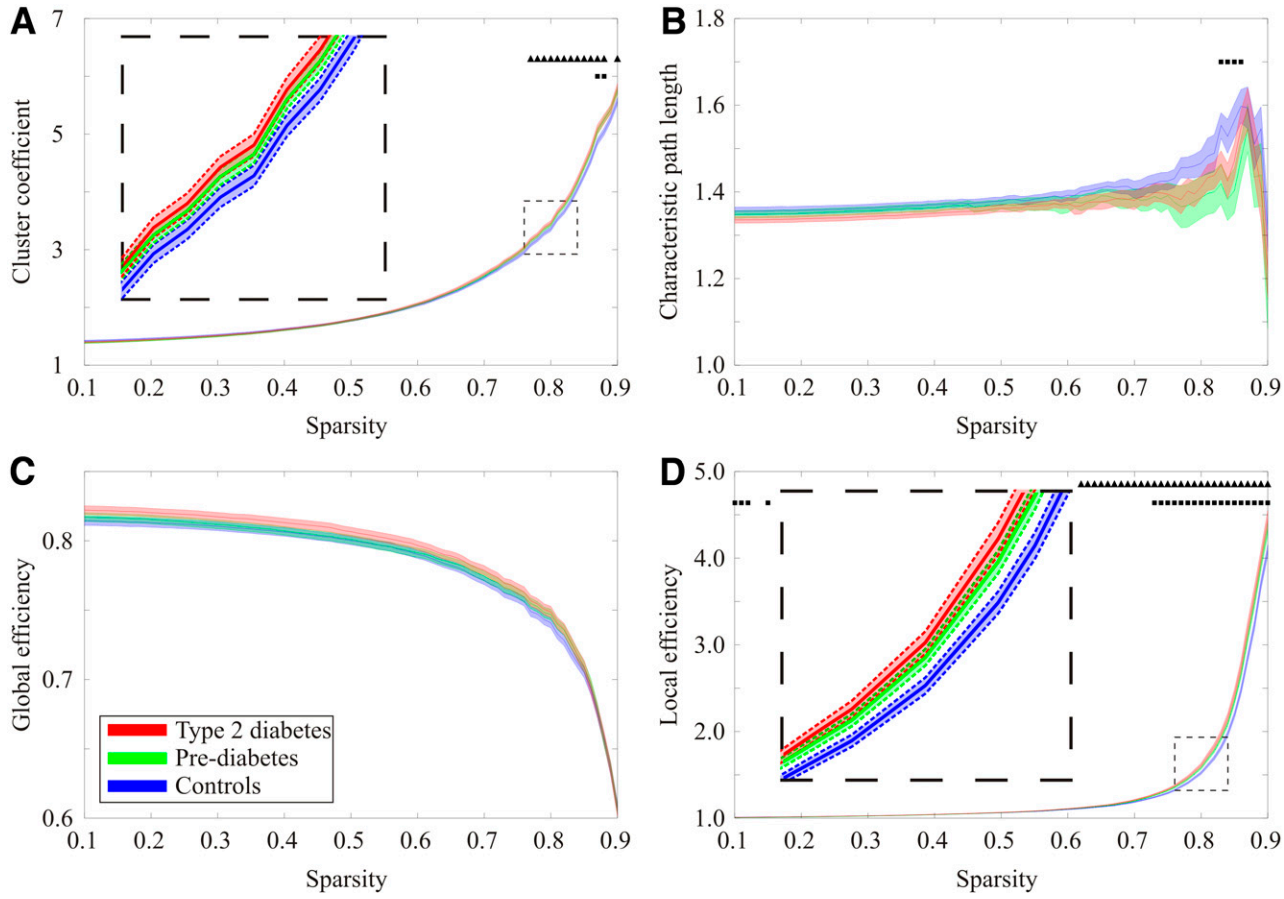

Figure 1—Network measures of the global organization of the entire cerebrum over a wide range of sparsity values for participants with type 2 diabetes, participants with prediabetes, and control participants. Continuous lines indicate the mean values of the groups, and dashed lines and the corresponding filled, transparent areas represent the SEM. ▲, which sparsity values participants with type 2 diabetes differ significantly from those of control participants. ■, which sparsity values participants with prediabetes differ from those of control participants. The normalized (to random matrices) graph theoretical network measures are cluster coefficient (*A*), characteristic path length (*B*), global efficiency (*C*), and local efficiency (*D*). All results remained significant after adjustment for potential confounders (model 2) (Supplementary Table 1).

glucose and high HbA_{1c} levels were associated with a higher cluster coefficient. The other graph measures did not show a significant association. With respect to insulin levels, no consistent results were obtained because only a few scattered sparsity values displayed significant associations with characteristic path length and global efficiency.

DISCUSSION

This cross-sectional study is the first to evaluate global functional brain networks by exploring various graph measures in participants with type 2 diabetes, participants with prediabetes, and matched control participants in one study. Graph theoretical network measures were

Table 3—Relationship of fMRI graph theoretical network measures in participants with type 2 diabetes and prediabetes relative to control participants at a sparsity value of 0.8

	Type 2 diabetes vs. control			Prediabetes vs. control		
Normalized graph measure	β	95% CI	*P* value	β	95% CI	*P* value
Cluster coefficient	0.106	0.007 to 0.204	**0.036**	0.074	−0.025 to 0.173	0.140
Characteristic path length	−0.054	−0.156 to 0.047	0.290	−0.079	−0.181 to 0.022	0.125
Global efficiency	0.008	−0.003 to 0.019	0.159	0.006	−0.005 to 0.017	0.285
Local efficiency	0.090	0.035 to 0.145	**0.001**	0.059	0.005 to 0.114	**0.034**

Boldface *P* values are statistically significant ($P < 0.05$). Unstandardized β (95% CI) indicates increments/decrements of the graph measures with participants with type 2 diabetes or prediabetes. The model is not adjusted for potential confounders (model 1). Supplementary Table 1 presents the results of the model adjusted for potential confounders.

compared among these groups, and the relation with processing speed was investigated. First, participants with type 2 diabetes displayed altered network parameters, including a higher normalized cluster coefficient and a higher local efficiency than control participants. In addition, participants with prediabetes displayed higher normalized local efficiency than control participants, although these values were qualitatively lower than in participants with type 2 diabetes. Furthermore, no significant differences in network parameters were observed between prediabetes and type 2 diabetes, and all groups exhibited small-world organization of their networks indicative of an efficient cerebral topology. Cognitive performance was similar for the three groups, and lower information processing speed was associated with a lower normalized characteristic path length and a higher global efficiency.

In normal brain networks, the combination of a high cluster coefficient and a high local efficiency reflects a high local specialization of the brain in processing information. We observed this combination in participants with type 2 diabetes, suggesting that the brain is better organized than the cerebral networks of the control participants. In view of the known effect of diabetes on cognition, such as cognitive decrements and higher risk of dementia or Alzheimer disease, these results may seem contradictory because one could expect that the cerebral networks are less, rather than better, organized in diabetes. The diabetes population in this study is relatively healthy in terms of their mildly affected cognitive performance (in the range of normal performance) and in terms of good treatment control according to glucose levels. A better-organized cerebral network in diabetes can be attributed to an earlier stage of structural brain damage, where compensatory mechanisms, such as functional reorganization of networks, might play a role (36). In addition, all four network measures investigated in the current study showed the same direction, thus supporting an underlying compensatory mechanism. To further support the compensatory interpretation, additional analysis showed no effect of age (data not shown), which is known to have an impact on the network parameters (37,38). Of note, increased functional connectivity was previously observed in patients with type 1 diabetes without retinopathy compared with healthy control subjects (39). In addition, graph theoretical network analysis of diffusion data have already shown disrupted white matter networks in type 2 diabetes (40), and it will be interesting to investigate the relationship with the current findings.

The findings with respect to the participants with prediabetes, who showed intermediate topological values of the functional networks, also strengthen the explanation of an underlying compensatory mechanism. Therefore, a higher local efficiency might be an early marker for cognitive decrements that may eventually lead to brain degeneration. It was previously shown that patients with Alzheimer disease showed a decline of the small-world network organization characterized by a decreased normalized cluster coefficient and a decreased local efficiency, indicative of disrupted local network connectivity (19). Taken together, a hypothetical overview over time (Fig. 2) illustrates that before the onset of clinically manifested cognitive decrements, functional reorganization of the cerebral networks may already have started as a compensatory mechanism to counteract the slight decrements in cognitive performance in participants with prediabetes and type 2 diabetes. Then, when the functional reorganization fails, functional networks become disrupted, and the first signs of cognitive decrements will be recognizable in the participants with diabetes. Finally, this might possibly explain the increased risk to develop mild cognitive impairment and Alzheimer disease in a later stage. It remains to be explored how the graph theoretical network measures behave in patients with diabetes with more severe cognitive decrements or mild cognitive impairment (3) (Fig. 2, gray area) because those results could support the presumed underlying compensatory mechanism.

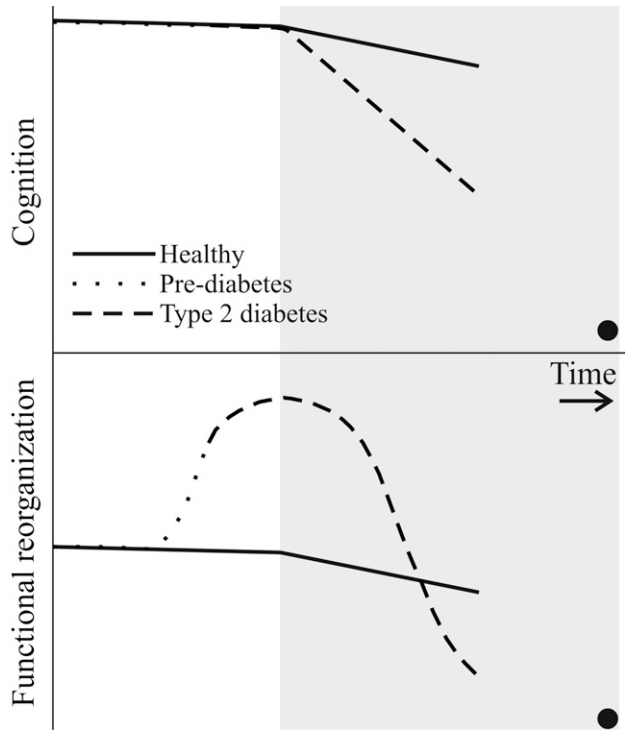

Figure 2—Hypothetical overview of cognitive performance and functional reorganization over time. Before the onset of recognizable cognitive decrements, functional reorganization of the cerebral networks already has started as a compensatory mechanism for the (slight) decrements in cognitive performance in participants with prediabetes (dotted line) and type 2 diabetes (dashed line). When the functional reorganization fails, the functional networks will become disrupted, and the first signs of cognitive decrements will manifest. This might possibly explain the increased risk for dementia in a later stage. The white area indicates the study findings in control participants, participants with prediabetes, and participants with type 2 diabetes, whereas the gray area still requires exploration for which longitudinal studies can be beneficial. ●, previously reported findings in patients with Alzheimer disease (19). Of note, diabetes will not develop in all patients with prediabetes and Alzheimer disease will not develop in all patients with diabetes.

In normal brain networks, the combination of a shorter characteristic path length and a higher global efficiency reflects the great ability of the brain to globally integrate information. We observed that this combination was associated with less processing speed and that participants with type 2 diabetes scored lower on processing speed than control participants (Table 2). These results also fully complement the hypothetical underlying compensatory mechanism (Fig. 2).

Supplementary Fig. 3 plots local efficiency as a function of fasting blood glucose level. It can be seen that local efficiency increases with blood glucose level. As the results indicate, the effect of a high blood glucose level on local efficiency is already apparent in the prediabetic stage. Moreover, additional analysis with continuous fasting blood glucose and HbA_{1c} levels instead of the dichotomous diabetes and prediabetes status showed that higher local efficiency was significantly associated with higher fasting blood glucose and HbA_{1c} levels. Similar analyses with insulin did not yield comparable results because participants with diabetes had excellent control and displayed even lower insulin levels than participants with prediabetes (Table 2). This is consistent with other studies suggesting that hyperinsulinemia alone may not be a strong determinant of cardiovascular disease (41), which might possibly also hold for cerebral alterations. Because improved glycemic control in type 2 diabetes is associated with improved cognition (42), good blood glucose management in the prediabetes stage seems essential to reduce its impact on the brain. In this way, the onset of cognitive decrements may be postponed or, hopefully, halted. We should not neglect, however, the additional role of the other metabolic syndrome factors on local efficiency. A post hoc analysis revealed that participants with type 2 diabetes who also meet the criteria for the metabolic syndrome displayed even higher local efficiency values (data not shown). Moreover, the effect of the medication on the graph theoretical network measures in diabetes should be investigated in future studies.

The blood oxygen level–dependent signal is likely affected in type 2 diabetes because of an impaired vascular reactivity as a consequence of an altered hemodynamic response and changes in neurovascular coupling (43). How exactly changes in the hemodynamic response translate to changes in functional connectivity and network efficiency remains to be elucidated.

This study has several strengths. First, to our knowledge, the study is the first to investigate graph theoretical network measures in participants with diabetes and prediabetes compared with matched control participants. Second, the participants were extensively characterized. Because correction for age, sex, and blood pressure did not change the significant results, we are confident that these factors do not underlie the observed differences among groups.

The study also has some limitations. First, it had a cross-sectional design; therefore, the results should be interpreted cautiously in terms of causality. In addition, the time span between the biochemical measurements and MRI acquisition of an average 12.7 months might limit the validity of the participant characteristics, although it is expected that the number of substantial biochemical alterations would be low (44). Nevertheless, the first results provide new insights and prompt new questions for future studies to investigate the behavior of network measures over time. Second, because of the inclusion of a relatively healthy study population, we were not able to investigate the full range of the hypothetical curve because participants with severe diabetes complications did not participate in the study. Therefore, an investigation of the functional network properties of participants with diabetes and severe complications would be interesting. Third, numerous other factors of potential influence that deserve attention could not be investigated, for instance, the effects of sleep, fasting, estrogen/hormone medication, therapy compliance, and disease duration (45–48). Finally, the effect of diabetes medication within the diabetes group (treated vs. untreated) should be investigated in future studies.

To conclude, this study reveals altered functional brain networks in patients with type 2 diabetes as well as in patients with prediabetes, indicating a more-efficient cerebral organization. This was observed in patients with mild cognitive decrements, which are still in the range of normal cognitive functioning. The functional network measures of the prediabetes group were intermediate between the type 2 diabetes and control groups, hinting at compensation for cognitive decrements in terms of functional reorganization of the cerebral networks. Furthermore, the study shows that functional graph theoretical network measures provide new insights and may serve as an early MRI biomarker for subtle cerebral alterations in relation to cognitive decline.

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of the manuscript. T.M.v.V., P.A.M.H., M.P.J.v.B., M.T.S., S.J.S.S., P.C.D., N.S., C.D.A.S., and J.E.W. contributed to the discussion and critical review and editing and final approval of the manuscript. F.C.G.v.B. and J.F.A.J. are the guarantors of this work, and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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