Disruption of the Cerebral White Matter Network Is Related to Slowing of Information Processing Speed in Patients With Type 2 Diabetes

Yael D. Reijmer,[1] Alexander Leemans,[2] Manon Brundel,[1] L. Jaap Kappelle,[1] and Geert Jan Biessels,[1] on behalf of the Utrecht Vascular Cognitive Impairment (VCI) Study Group*

Patients with type 2 diabetes often show slowing of information processing. Disruptions in the brain white matter network, possibly secondary to vascular damage, may underlie these cognitive disturbances. The current study reconstructed the white matter network of 55 nondemented individuals with type 2 diabetes (mean age, 71 ± 4 years) and 50 age-, sex-, and education-matched controls using diffusion magnetic resonance imaging–based fiber tractography. Graph theoretical analysis was then applied to quantify the efficiency of these networks. Patients with type 2 diabetes showed alterations in local and global network properties compared with controls ($P < 0.05$). These structural network abnormalities were related to slowing of information processing speed in patients. This relation was partly independent of cerebrovascular lesion load. This study shows that the approach of characterizing the brain as a network using diffusion magnetic resonance imaging and graph theory can provide new insights into how abnormalities in the white matter affect cognitive function in patients with diabetes. ***Diabetes*** **62:2112–2115, 2013**

Slowing of information processing is one of the most prominent cognitive features in nondemented patients with type 2 diabetes (1). This may be attributable to disturbances in the cerebral white matter, secondary to cerebrovascular lesions such as lacunar infarcts, white matter hyperintensities (WMHs), and microstructural lesions (2,3). The white matter consists of a complex network of fiber connections. The extent to which the brain can efficiently transfer information between regions depends on the integrity and the organization of these white matter connections. Recently, in vivo human white matter networks have been reconstructed using diffusion magnetic resonance imaging (MRI) (4,5). The efficiency and robustness of these white matter networks can be characterized quantitatively using graph theoretical analysis (6).

With this approach, previous studies have demonstrated that brain network properties are related to slowing of information processing speed in healthy older individuals (7). In addition, vascular WMHs have been related to impairments in structural network efficiency in nondiabetic individuals (8). The impact of diabetes on the white matter network, however, is still unclear.

We therefore examined whether white matter brain networks are affected in patients with diabetes, whether vascular lesions were related to network disturbances, and whether disruption of the white matter network is related to slowing of information processing.

RESEARCH DESIGN AND METHODS

Participants. Sixty-three participants with type 2 diabetes and 61 age-, sex-, and education-matched controls were recruited through their general practitioners as part of the second Utrecht Diabetic Encephalopathy Study (UDES2). Details of the study are described elsewhere (2). For inclusion, participants had to be between 65 and 80 years of age, functionally independent, and Dutch-speaking. Participants were considered to have diabetes if they were known with diabetes for at least 1 year and were receiving diabetes medication or had a fasting blood glucose ≥7.0 mmol/L. Exclusion criteria for both groups were transient ischemic attack or noninvalidating stroke in the past 2 years or any invalidating stroke, neurologic diseases (unrelated to diabetes) likely to affect cognition, known history of psychiatric disorders requiring hospitalization, indication of (early) dementia based on a Mini-Mental State Examination score ≤26, or alcohol abuse. Participants were excluded after the work-up because of low Mini-Mental State Examination score ($n = 6$) or missing or low-quality scan data ($n = 10$), and control subjects with high fasting glucose ($n = 3$) were excluded, leaving 55 patients and 50 control participants for the current analysis. The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht, the Netherlands. Written informed consent was obtained from all participants.

Cognitive testing. All participants underwent a detailed standardized cognitive assessment as described previously (2). Intelligence quotient was estimated with the Dutch version of the National Adult Reading Test, which is generally accepted to reflect the premorbid level of intellectual functioning. Information processing speed was assessed by the Trail-Making Test, the Stroop Color–Word Test, and the subtest Digit Symbol of the Wechsler Adult Intelligence Scale III. In addition, measures of verbal memory and executive functioning were obtained. Verbal memory was assessed by the immediate and delayed task of the Rey Auditory Verbal Learning Test. Executive functioning was assessed by the Trail-Making Test–Part B, the Stroop Color–Word Test, and a Verbal Fluency Test. For each domain, the raw test scores were standardized into z-scores and averaged to obtain one composite z-score per cognitive domain.

MRI data acquisition and network reconstruction. MRI data were acquired on a Philips 3.0-Tesla scanner using a standardized protocol and consisted of a three-dimensional T1 (192 continuous slices, reconstructed voxel size 1.00 × 1.00 × 1.00 mm^3), a fluid-attenuated inversion recovery scan (48 continuous slices, reconstructed voxel size 0.96 × 0.95 × 3 mm^3), and diffusion-weighted MRI data using a single-shot spin-echo EPI sequence (48 contiguous slices, acquired isotropic voxel size 2.50 mm, 45 isotropically distributed diffusion-sensitizing gradients with a b-value of 1,200 s/mm^2, and one b = 0 s/mm^2).

The diffusion MRI data were corrected for subject motion and eddy current distortions (9) and analyzed in *ExploreDTI* (www.exploredti.com) (10) as described previously (11). For each dataset, white matter tracts of the brain network were reconstructed using constraint spherical deconvolution-based tractography and allowed fiber tracking to proceed through crossing fiber regions (12). The whole-brain fiber tract reconstructions of the previous step were parcellated using the automated anatomical labeling atlas. Using this procedure, we obtained 90 cortical and subcortical regions (with the

From the [1]Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Utrecht, the Netherlands; and the [2]Image Sciences Institute, University Medical Center Utrecht, Utrecht, the Netherlands.
Corresponding author: Yael D. Reijmer, y.d.reijmer@umcutrecht.nl.
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*A complete list of the members of the Utrecht Vascular Cognitive Impairment Study Group can be found at http://diabetes.diabetesjournals.org/lookup/suppl/doi:10.2337/db12-1644/-/DC1.

cerebellum excluded). Each region of interest of the automated anatomical labeling template represented a node of the network (Fig. 1). Two automated anatomical labeling nodes were considered to be connected if a fiber bundle was present with two end points located in these regions. False-positive connections were controlled for by taking into consideration only those connections that were present in at least 50% of all subjects. A binary 90 × 90 connectivity matrix was obtained for each subject using this procedure. To account for any abnormal microstructure of the white matter connection, each connection was weighted by the mean diffusivity because this measure previously has shown to be a sensitive marker of structural white matter abnormalities in patients with type 2 diabetes (13). These steps resulted in a weighted connectivity matrix for each individual (5,14).

Network measures. We investigated the properties of the structural network using the Brain Connectivity Toolbox (15). For each network measure of local interconnectivity (i.e., clustering coefficient and local efficiency) and global connectivity (i.e., characteristic shortest path length and global efficiency) were obtained (15).

The clustering coefficient quantifies the extent to which neighboring brain regions are connected with each other. The local efficiency reflects the average efficiency of local clusters, an indicator of fault tolerance of the network. The characteristic shortest path length quantifies the average number of connections between regions along the shortest paths. The shorter the path length, the higher the efficiency of the network. This is reflected in global efficiency, a measure of parallel information processing ability.

In addition, we evaluated the small-world architecture of the network by dividing the clustering coefficient and path length by the values obtained from 100 matched random networks (16). Small-world networks are defined as networks that have a relatively high local clustering ($\gamma > 1$) and approximately equivalent characteristic path length ($\lambda \sim 1$) compared with random networks.

MRI markers of small vessel disease. WMH load and lacunar and cortical infarcts were assessed on fluid-attenuated inversion recovery images, with the T1 as reference, by two raters (M.B., Y.R.) who were blinded to clinical data. Total WMH load was assessed with the Age-Related White Matter Changes scale (17) and quantified as the sum score of all brain regions (range, 0–30). Infarcts were identified and scored as present or not present.

Statistical analysis. Between-group differences in brain white matter networks were analyzed with an independent samples *t* test. Cognitive outcome measures were transformed into *z*-scores using the pooled mean of the whole study sample and adjusted for age, sex, and estimated intelligence quotient for each individual patient, based on the residuals from linear regression analyses. Pearson correlations were calculated to evaluate the relation between affected network parameters, WMH load, lacunar infarcts, and cognitive performance.

TABLE 1
Group characteristics

	Controls (n = 50)	Type 2 diabetes (n = 55)	P
Age (years)	70.9 ± 4.5	70.9 ± 4.4	0.967
Sex (% male)	64%	60%	0.673
Estimated IQ*	105 ± 15	101 ± 13	0.194
Mini-Mental State Examination	29 (26–30)	29 (27–30)	0.782
Systolic blood pressure (mmHg)	146 ± 21	148 ± 16	0.614
Antihypertensive medication	52%	78%	0.005
BMI (kg/m^2)	26 ± 3	29 ± 5	<0.001
Total cholesterol (mmol/L)	5.5 ± 1.1	4.7 ± 0.9	<0.001
Cholesterol-lowering drugs	44%	78%	<0.001
Fasting glucose (mmol/L)	5.5 ± 0.6	7.8 ± 1.7	<0.001
HbA_{1c} (%)	5.7 ± 0.4	6.7 ± 0.7	<0.001
Diabetes duration (years)		8 (1–51)	
WMH load†	3 (0–12)	3.5 (0–12)	0.342
Lacunar infarcts	32%	33%	0.937
Cortical infarcts	2%	6%	0.346

Data are presented as mean ± SD, percentages, or median (range). IQ, intelligence quotient. *Estimated by the Dutch version of the National Adult Reading Test. †WMHs were assessed in both hemispheres with the Wahlund Age-Related White Matter Changes scale.

RESULTS

Between-group differences in white matter networks. Group characteristics are shown in Table 1. The structural brain networks of all subjects studied had a small-world architecture, i.e., exhibited a much higher level of local clustering ($\gamma > 1$; mean, 2.00 ± 0.29) and an equivalent characteristic shortest path length between any pair of nodes ($\lambda \sim 1$; mean, 1.08 ± 0.02) compared with random networks. This is consistent with previous reports of healthy subjects (5,18), suggesting that the white matter networks were constructed reliably.

Patients with type 2 diabetes showed significant differences in local and global network connectivity relative to controls (Table 2). The mean clustering coefficient and the global efficiency of the network was decreased and the shortest path length was increased compared with controls ($P < 0.05$), whereas the total number of connections in the network did not differ between the patient and control group ($P = 0.637$). These between-group differences were independent of vascular lesion load (WMHs and infarcts; $P < 0.05$).

Relation network parameters with information processing speed and with vascular lesions. In patients with type 2 diabetes, network parameters were associated with slowing of information processing (clustering coefficient: $r = 0.362$ and $P = 0.007$; global efficiency: $r = 0.304$

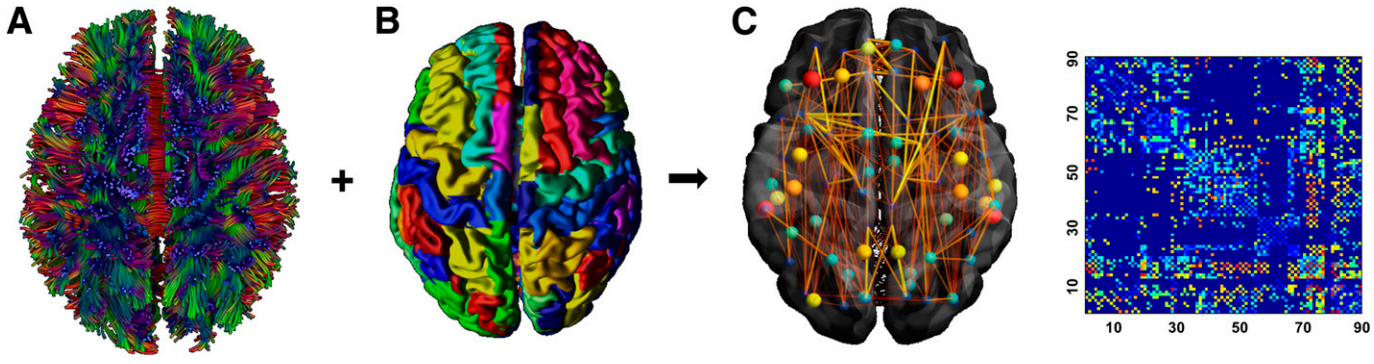

FIG. 1. Flow chart of constructing a diffusion weighted imaging-based network. For each diffusion MRI dataset, whole-brain deterministic tractography was performed (*A*). The whole-brain fiber tract reconstructions were parcellated using the automated anatomical labeling (AAL) atlas consisting of 90 cortical and subcortical brain regions, excluding the cerebellum (*B*). Two brain regions were considered to be connected if a fiber bundle was present with two end points located in these regions. Each connection was weighted by the microstructural integrity of that connection. Using this procedure a weighted brain network was obtained, which can be represented by a 90 × 90 connectivity matrix (*C*).

TABLE 2
Group differences in whole-brain white matter network parameters

	Controls	Type 2 diabetes	*P*
Clustering coefficient	0.31 ± 0.13	−0.28 ± 0.14	0.002
Local efficiency	−0.11 ± 0.12	0.10 ± 0.15	0.288
Shortest path length	−0.21 ± 0.12	0.19 ± 0.15	0.035
Global efficiency	0.25 ± 0.11	−0.23 ± 0.15	0.013

Data are presented as mean standardized *z*-scores ± SE. Decreased network measures indicate less network efficiency, except for path length.

and $P = 0.024$; and path length: $r = -0.292$ and $P = 0.031$; Table 3, see Supplementary Fig. 1 for correlation plots). The total strength of the network was not related to information processing speed ($r = 0.196$; $P = 0.152$). No relation was observed between network measures and memory or executive functioning. Also, no relation was found between network measures and cognitive performance within the control group.

WMH load and lacunar infarcts were associated with reduced clustering, reduced global efficiency, and increased path length in patients (Table 3). Exclusion of individuals with cortical infarcts ($n = 3$) did not change these results. The correlation between network parameters and information processing speed remained significant after adjusting for WMH load ($P < 0.05$). Lacunar infarcts partly attenuated this relationship (clustering: 0.288 and $P = 0.036$; global efficiency: 0.226 and $P = 0.104$; path length: −0.193 and $P = 0.165$).

DISCUSSION

This is the first study that examined whole-brain white matter connectivity in patients with type 2 diabetes using a network-based approach. Our results showed disruptions in the white matter network in nondemented patients compared with controls. In the patients, these network abnormalities were related to slowing of information processing speed and increased cerebrovascular lesion load.

The approach of characterizing the brain as a network using fiber tractography and graph theoretical analysis can provide new insights into how white matter abnormalities can affect cognitive function in patients with diabetes. In this study, vascular lesions, such as WMHs and infarcts, only partly explain the relation between network disturbances and cognitive functioning. In addition to these classical markers of cerebrovascular disease, microstructural white matter pathology has shown to contribute to cognitive deficits in type 2 diabetes (2). Furthermore, the impact of these structural alterations on information processing also depends on the integration of the affected connections within the network. In contrast to MRI markers of small vessel disease, diffusion-based network measures take into account the microstructural properties of the white matter fiber connections as well as the organization of those connections within the brain (14). As such, network measures can be regarded as a powerful integrated marker of different structural changes contributing to the functional deficits in patients with diabetes.

Functional MRI studies in patients with type 1 and type 2 diabetes demonstrated impaired neuronal synchronization between cortical regions during rest (19,20). In line with these findings, our study indicates that altered connectivity in the white matter network contribute to these early functional deficits.

Subtle disturbances in the brain network will most prominently affect information processing speed. However, as the white matter pathology becomes more severe, other cognitive functions are expected to be affected as well. In patients with Alzheimer disease, for example, white matter network impairments are related to worse memory performance (21,22). Whether the network abnormalities observed in nondemented patients with type 2 diabetes contribute to more severe diabetes-associated cognitive impairment and dementia (23) is not yet known.

Strengths of our study include the comprehensive scan protocol, including high-quality clinical diffusion MRI data, and the assessment of multiple cognitive domains in a large well-defined population-based cohort. Our study also has some limitations. First, selection bias may have led to a relatively healthy patient sample and thus an underestimation of the effect. The more intensive cardiovascular treatment regimen in the diabetes group relative to the controls reflects the current clinical practice guidelines (24). This does make our results generalizable to the population of well-controlled patients, but the results are likely to underestimate the effect in less controlled patient populations. Finally, we examined the relation between brain structure and behavioral outcome in diabetes. The incorporation of functional MRI data would have allowed us to examine whether the anatomical changes underlying cognitive impairment in diabetes are associated with functional network alterations. Further studies that integrate different imaging modalities will be helpful to clarify this issue. This study shows that network-based analysis provides a novel way to reveal the structural correlates of cognitive dysfunction observed in nondemented patients with type 2 diabetes.

TABLE 3
Relation between vascular brain lesions and whole-brain white matter connectivity in patients with type 2 diabetes

	Information processing speed		WMH load		Lacunar infarcts	
	r	*P*	*r*	*P*	Mean difference	*P*
Clustering coefficient	0.362	0.007	−0.324	0.016	−0.523	0.047
Shortest path length	0.304	0.024	0.341	0.011	0.634	0.019
Global efficiency	−0.292	0.031	−0.329	0.014	−0.530	0.075

Decreased network measures indicate less network efficiency, except for path length.

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Y.D.R. acquired data, wrote the manuscript, and performed the analysis. A.L., L.J.K., and G.J.B. made substantial contributions to conception and design of the study and critically revised the manuscript for important intellectual content. M.B. acquired data and made critical revision to the manuscript. All authors gave final approval of the version to be published and agreed to be listed as authors. Y.D.R. and G.J.B. are the guarantors of this work and, as such, had full access to all of 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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