Disruption of the cerebral white matter network is related to slowing of information processing speed in patients with type 2 diabetes

Yael D. Reijmer¹, Alexander Leemans², Manon Brundel¹, L. Jaap Kappelle¹, Geert Jan Biessels¹, on behalf of the Utrecht Vascular Cognitive Impairment (VCI) Study Group

¹ Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, the Netherlands
² Image Sciences Institute, University Medical Center Utrecht, the Netherlands

Corresponding author:
Yael Reijmer, University Medical Center Utrecht, Department of Neurology G03.228, PO Box 85500, 3508 GA Utrecht, The Netherlands. Phone: +31 88 75 59488; Fax: +31 30 2542100; E-mail: y.d.reijmer@umcutrecht.nl

Short running title:

Brief report

Word count main text: 1982
References: 24
Tables: 3 / Figures: 1
Abstract

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 present study reconstructed the white matter network of 55 non-demented individuals with type 2 diabetes (mean age 71±4y) and 50 age-, sex- and education-matched controls using diffusion MRI 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 to 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 MRI and graph theory can provide new insights into how abnormalities in the white matter affect cognitive function in patients with diabetes.
Introduction

Slowing of information processing is one of the most prominent cognitive features in non-demented patients with type 2 diabetes (1). This may be due to disturbances in the cerebral white matter, secondary to cerebrovascular lesions such as lacunar infarcts, white matter hyperintensities, and microstructural lesions (2;3). The white matter consists of 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 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 white matter hyperintensities have been related to impairments in structural network efficiency in non-diabetic individuals (8). The impact of diabetes on the white matter network, however, is still unclear.

We therefore examined 1) whether white matter brain networks are affected in patients with diabetes; 2) whether vascular lesions were related to network disturbances and 3) 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 one year and were receiving diabetes medication or had a fasting blood glucose ≥7.0 mmol/l. Exclusion criteria for both groups were TIA or non-invalidating stroke in the past 2 years or any invalidating stroke, neurological diseases (unrelated to diabetes) likely to affect cognition, known history of psychiatric disorders requiring hospitalization, indication of (early) dementia based on a MMSE score ≤ 26, or alcohol abuse. Participants were excluded after the work-up because of low MMSE score (n=6), missing or low quality scan data (n=10), and control subjects with high fasting glucose (n=3), 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 before (2). IQ 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 WAIS-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-scores 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 3D T1 (192 continuous slices, reconstructed voxel size: 1.00x1.00x1.00 mm$^3$), a fluid attenuated inversion recovery (FLAIR) scan (48 continuous slices, reconstructed voxel size: 0.96x0.95x3 mm$^3$), and diffusion-weightedMRI 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 1200 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, WM tracts of the brain network were reconstructed using constraint spherical deconvolution (CSD) based tractography and allows 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 (AAL). Using this procedure, we obtained 90 cortical and subcortical regions (with the cerebellum excluded). Each ROI of the AAL template represented a node of the network (Figure 1). Two AAL 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 x 90 connectivity matrix was obtained for each subject using the above procedure. To account for any abnormal microstructure of the white matter connection, each connection was weighted by the mean diffusivity (MD), since this measure has previously 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 relative high local clustering ($\gamma > 1$) and approximate equivalent characteristic path length ($\lambda \sim 1$) compared with random networks.

**MRI markers of small vessel disease**

White matter hyperintensity load (WMH), lacunar and cortical infarcts were assessed on FLAIR images, with the T1 as reference, by two raters (M.B., Y.R.) who were blinded for clinical data. Total WMH load was assessed with the Age Related White Matter Changes
(ARWMC) scale (17) and quantified as the sum score of all brain regions (range 0-30). Infarcts were identified and scored as present/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 IQ 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.

**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 ($\lambda$ ~ 1, mean:1.08±0.02), compared to random networks. This is consistent with previous reports in 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 to controls ($p<0.05$), while 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 (WMH 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: \( r=0.362; p=0.007 \); global efficiency: \( r=0.304; p=0.024 \); and path length: \( r=-0.292; p=0.031 \) (Table 3, see supporting data 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: \( 0.288, p=0.036 \); global efficiency: \( 0.226, p=0.104 \); path length: \( -0.193, p=0.165 \)).

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 non-demented patients compared to 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 WMH 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’s disease for example, white matter network impairments are indeed related to worse memory performance (21;22). Whether the network abnormalities observed in non-demented 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 has also 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 regime 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 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 non-demented patients with type 2 diabetes.
Author contributions

YDR acquired data, wrote the manuscript and performed the analysis; MB acquired data and made critical revision of the manuscript; AL, LJK and GJB made substantial contributions to conception and design of the study, and critically revised the manuscript for important intellectual content. All authors gave final approval of the version to be published and agreed to be listed as authors.

Acknowledgements

The authors express their special thanks to the primary care practices Ametisthof, Glennhof, De Poort, ’t Steyn, and De Weegbree of Huisartsenzorg IJsselstein, IJsselstein, the Netherlands (mentor Ph.L. Salomé), and G. Visser, Nieuwegein, the Netherlands, for their supportive role in the recruitment process; We thank C. Buvens and A.W. Kingma, Utrecht University, the Netherlands, for assisting with the data collection.

Y.D. Reijmer and G.J. Biessels are the guarantors of this study and take full responsibility for the contents of the article.

Funding

The research of GJB is supported by VIDI grant 91711384 from ZonMw, The Netherlands Organisation for Health Research and Development, grant 2010T073 from the Netherlands Heart Foundation. YR is supported by a Hersenstichting Nederland grant 2011(1)-87. The research of AL is supported by the project Care4Me (Cooperative Advanced REsearch for Medical Efficiency) in the framework of the EU research programme ITEA (Information Technology for European Advancement).

The authors have no relevant conflict of interest.
References


### Table 1. Group characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=50)</th>
<th>Type 2 diabetes (n=55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>70.9±4.5</td>
<td>70.9±4.4</td>
<td>0.967</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>64%</td>
<td>60%</td>
<td>0.673</td>
</tr>
<tr>
<td>Estimated IQ&lt;sup&gt;a&lt;/sup&gt;</td>
<td>105±15</td>
<td>101±13</td>
<td>0.194</td>
</tr>
<tr>
<td>MMSE</td>
<td>29 (26-30)</td>
<td>29 (27-30)</td>
<td>0.782</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>146±21</td>
<td>148±16</td>
<td>0.614</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>52%</td>
<td>78%</td>
<td>0.005</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>26±3</td>
<td>29±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.5±1.1</td>
<td>4.7±0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol lowering drugs</td>
<td>44%</td>
<td>78%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.5±0.6</td>
<td>7.8±1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.7±0.4</td>
<td>6.7±0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>-</td>
<td>8 (1-51)</td>
<td></td>
</tr>
<tr>
<td>WMH load&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (0-12)</td>
<td>3.5 (0-12)</td>
<td>0.342</td>
</tr>
<tr>
<td>Lacunar infarcts</td>
<td>32%</td>
<td>33%</td>
<td>0.937</td>
</tr>
<tr>
<td>Cortical infarcts</td>
<td>2%</td>
<td>6%</td>
<td>0.346</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, percentages, or median (range)

<sup>a</sup> Estimated by the Dutch version of the National Adult Reading Test

<sup>b</sup> White matter hyperintensities (WMH) were assessed in both hemispheres with the Wahlund ARWMC scale.
Table 2. Group differences in whole-brain WM network parameters

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Type 2 diabetes</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clustering coeff.</td>
<td>0.31±0.13</td>
<td>-0.28±0.14</td>
<td>0.002</td>
</tr>
<tr>
<td>Local efficiency</td>
<td>-0.11±0.12</td>
<td>0.10±0.15</td>
<td>0.288</td>
</tr>
<tr>
<td>Shortest Path len.</td>
<td>-0.21±0.12</td>
<td>0.19±0.15</td>
<td>0.035</td>
</tr>
<tr>
<td>Global efficiency</td>
<td>0.25±0.11</td>
<td>-0.23±0.15</td>
<td>0.013</td>
</tr>
</tbody>
</table>

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

Table 3. Relation between vascular brain lesions and whole-brain WM connectivity in patients with type 2 diabetes

<table>
<thead>
<tr>
<th>Information processing speed</th>
<th>WMH load</th>
<th>Lacunar infarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p-value</td>
</tr>
<tr>
<td>Clustering coefficient</td>
<td>0.362</td>
<td>0.007</td>
</tr>
<tr>
<td>Shortest Path length</td>
<td>0.304</td>
<td>0.024</td>
</tr>
<tr>
<td>Global efficiency</td>
<td>-0.292</td>
<td>0.031</td>
</tr>
</tbody>
</table>

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

WMH: white matter hyperintensity
Figure 1. Flow chart of constructing a DTI-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 x 90 connectivity matrix (C).
**Figure 1. Flow chart of constructing a DTI-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 x 90 connectivity matrix (C).
Figure 2. Correlation between network measures and cognitive performance in patients with type 2 diabetes. Cognitive z-scores are adjusted for age, sex, and estimated IQ.