Altered Hippocampal White Matter Connectivity in Type 2 Diabetes Mellitus and Memory Decrements

Citation for published version (APA):

Document status and date:
Published: 01/03/2016

DOI:
10.1111/jne.12366

Document Version:
Publisher's PDF, also known as Version of record

Document license:
Taverne

Please check the document version of this publication:
• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:
www.umlib.nl/taverne-license

Take down policy
If you believe that this document breaches copyright please contact us at:
repository@maastrichtuniversity.nl
providing details and we will investigate your claim.

Download date: 17 Sep. 2023
Altered Hippocampal White Matter Connectivity in Type 2 Diabetes Mellitus and Memory Decrements


*Department of Radiology & Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands.
†School for Mental Health and Neuroscience (MHeNS), Maastricht University Medical Center, Maastricht, The Netherlands.
‡Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands.
§Department of Psychiatry and Neuropsychology, Maastricht University Medical Center, Maastricht, The Netherlands.
¶Department of Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands.

Type 2 diabetes mellitus is associated with cognitive decrements. Specifically affected cognitive domains are learning and memory, for which the hippocampus plays an essential role. The pathophysiological mechanism remains to be revealed. The present study examined whether local hippocampal microstructure and white matter connectivity are related to type 2 diabetes and memory performance. Forty participants with type 2 diabetes and 38 participants without type 2 diabetes underwent detailed cognitive assessment and 3-Tesla diffusion magnetic resonance imaging (MRI). Diffusion MRI was performed to assess microstructure (fractional anisotropy and mean diffusivity) and white matter connectivity (tract volume) of the hippocampus, which were compared between participants with and without type 2 diabetes. No differences in hippocampal microstructure were observed. Participants with type 2 diabetes had fewer white matter connections between the hippocampus and frontal lobe ($P = 0.017$). Participants who scored lower on memory function, regardless of type 2 diabetes, had fewer white matter connections between the hippocampus and temporal lobe ($P = 0.017$). Taken together, type 2 diabetes and memory decrements appear to be associated with altered hippocampal white matter connectivity.

Key words: cognition, memory, diffusion, white matter connectivity, hippocampus

doi: 10.1111/jne.12366
and might therefore influence the connectivity. However, because the two concepts describe different aspects of microstructure, it is relevant to report on both.

Previous dMRI studies on type 2 diabetes demonstrated reduced FA and increased MD in different brain regions (14–16) or in white matter tracts connecting frontal, parietal and temporal regions (17). Other type 2 diabetes studies have related increased MD in the parahippocampal gyrus to lower memory performance (18) and reduced FA in the cingulum bundle to higher memory performance (19). To identify microstructural correlates of cognitive decrements, it is important to focus on white matter connectivity because cognitive function depends on the transfer of information between different brain regions via white matter fibre bundles. Besides the commonly used local diffusion measures of specific white matter fibre bundles, it is important to investigate whether white matter connectivity (i.e., total tract volume of white matter fibres) differs and correlates with cognitive performance in type 2 diabetes.

To the best of our knowledge, there are no type 2 diabetes studies that focus specifically on the hippocampus and memory performance using (hippocampal) white matter connections. Therefore, the present study aimed to examine whether hippocampal microstructural abnormalities and white matter connections are related to type 2 diabetes and memory performance.

Materials and methods

Study population

Forty-seven participants with type 2 diabetes and 41 participants without type 2 diabetes were recruited from the first 866 participants of The Maastricht Study for additional brain MRI measurements. The Maastricht Study is an ongoing observational prospective population-based cohort study that focuses on the aetiology, pathophysiology, complications and comorbidities of type 2 diabetes. Participants are aged between 40–75 years and live in the southern part of The Netherlands (20). Participants are considered to have diabetes according to the WHO 2006 criteria if they use diabetes medication, or if they have a fasting blood glucose ≥ 7.0 mmol/l and/or an impaired fasting blood glucose ≥ 11.1 mmol/l after an oral glucose tolerance test. Participants without type 2 diabetes are characterised by fasting blood glucose < 6.1 mmol/l and a 2-h blood glucose < 7.8 mmol/l. At baseline inclusion, participants underwent an extensive battery of measurements, including cognitive performance tasks, blood pressure measurements and blood sampling. A detailed overview of all procedures is provided in Schram et al. (20).

After the baseline measurements of The Maastricht Study, participants were invited to participate in the present MRI study.

Participants with the highest and lowest cognitive scores were selected from the first 866 participants to increase the probability of finding MRI differences associated with cognitive decrements (Table 1). A detailed selection procedure is provided in van Bussel et al. (21). In brief, the division of participants in a low and high cognition group was based on a cumulative score of three neuropsychological tests covering the domains of verbal memory, attention and flexibility, and executive functioning (Table 1). Scores were adjusted for age, sex and education level using linear regression. Exclusion criteria for participants were: (i) a known history of stroke or neurological disease; (ii) a time span between enrollment in The Maastricht Study and MRI > 15 years; (iii) incomplete cognitive assessments; (iv) type 1 diabetes mellitus; (v) an impaired fasting blood glucose level, in participants without type 2 diabetes; (vi) mild cognitive impairment or dementia; (vii) the metabolic syndrome; (viii) colour blindness; and (ix) unknown diabetes status. The prior to MRI, these participants underwent a general cognitive function test [Mini-Mental State Examination, MMSE (22)] to assess clinically significant differences in cognitive performance compared to the baseline cognitive tests at enrollment in The Maastricht Study. Structural and dMRI brain scans were obtained from all participants. The study was approved by the Medical Ethics Committee of the Maastricht University Medical Center (MUMC+), The Netherlands, and all participants provided their written informed consent. The study is registered at: http://www.clinicaltrials.gov (with identifier NCT01705210).

MRI

MRI data were acquired on a 3T scanner (Achieva TX; Philips Healthcare, Best, The Netherlands) using a 32-element head coil for parallel imaging. The MRI protocol consisted of structural scans for neuroradiological evaluation (including T1-, T2-, T2*-weighted and fluid attenuated inversion recovery (FLAIR) sequences) and high angular resolution diffusion imaging (HARDI). A three-dimensional T1-weighted (T1) fast field echo sequence (TR/TE 8.1/3.7 ms, 1.00 mm isotropic voxel size, 170 continuous slices, matrix size of 240 × 240; 7 min 56 s acquisition time) and FLAIR (TR/TE/TI 4800/1650 ms, 1.12 mm isotropic voxel size, matrix size of 224 × 224; 4 min 53 s acquisition time) were acquired. HARDI data were obtained using an echo-planar imaging (EPI) sequence (TR/TE 6890/84 ms, 2.4 mm isotropic voxel size, 128 diffusion sensitising gradient directions, a b-value of 1500 s/mm²; 15 min 56 s acquisition time). In addition, a single minimally diffusion-weighted image (b0-scan) was acquired (23).

Data analysis

The T1 images were automatically segmented to obtain both hippocampal volumes, intracranial volume, subcortical grey matter and the cortical areas using FREESurfer (Martinos Center for Biomedical Imaging, Boston, MA, USA) (24) and the segmentations were inspected visually. dMRI data analysis

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the Two Cognition Groups.*</th>
<th>Lower cognition (n = 40)</th>
<th>Higher cognition (n = 38)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes (%; n)</td>
<td>55.0 (n = 22)</td>
<td>47.4 (n = 18)</td>
<td>0.500b</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.1 ± 9.5</td>
<td>62.7 ± 6.7</td>
<td>0.367a</td>
</tr>
<tr>
<td>Sex (male, %; n)</td>
<td>57.5 (n = 23)</td>
<td>52.6 (n = 20)</td>
<td>0.666b</td>
</tr>
<tr>
<td>Education</td>
<td>0.769b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (%; n)</td>
<td>15.0 (n = 6)</td>
<td>21.1 (n = 8)</td>
<td></td>
</tr>
<tr>
<td>Middle (%; n)</td>
<td>47.5 (n = 19)</td>
<td>42.1 (n = 16)</td>
<td></td>
</tr>
<tr>
<td>High (%; n)</td>
<td>37.5 (n = 15)</td>
<td>36.8 (n = 14)</td>
<td></td>
</tr>
<tr>
<td>WLT total score</td>
<td>37.1 ± 10.0</td>
<td>50.1 ± 9.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stroop (s)</td>
<td>63.3 ± 35.2</td>
<td>34.9 ± 13.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>20.3 ± 4.9</td>
<td>27.3 ± 5.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cumulative cognition score</td>
<td>−2.30 ± 2.18</td>
<td>2.10 ± 1.25</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

WLT, (verbal memory) Word Learning Test. *Only participants who were included in the final analysis; independent samples t-test. bPearson’s chi-squared test.
(preprocessing, tractography, connectivity analyses) was performed with the diffusion MR toolbox EXPLOREDTI, version 4.8.2 (25). In brief, the preprocessing steps included: (i) visual image quality assessment; (ii) correction of dMRI images for eddy current induced geometric distortions and head motion; (iii) correction of dMRI images for EPI distortions and transformation to T1 space; and, finally, (iv) estimation of the diffusion tensor for calculating the FA and MD maps.

After preprocessing, the local diffusion measures (FA and MD) were extracted from both hippocampi as derived from FRESURFER. Subsequently, fibre orientation distributions (FOD) were estimated using constrained spherical deconvolution with a maximum harmonic degree of 8 (26), which allows fibre tracking through regions with crossing fibres. The FOD represents the local fibre orientation. Whole brain probabilistic tractography was performed using FOD sampling (27) with a seed point resolution of 1 mm³, a step size of 1 mm, and an FOD and maximum deflection angle threshold of 0.1 and 30°, respectively, yielding approximately 4.3 million streamlines for each dataset. Next, connectivity analysis was performed to obtain white matter tracts (tract volumes) from the individually segmented hippocampi, used as seed region (i.e. include tracts that only go through the hippocampus) to the segmented grey matter. The segmented grey matter was subdivided into five regions: frontal lobe, parietal lobe, temporal lobe, occipital lobe and subcortical grey matter (28,29). Examples of white matter tracts between both hippocampi and the frontal lobe are provided in Fig. 1. Subsequently, the tract volumes seeded from both hippocampi to each region were normalised to the intracranial volume to reduce inter-individual variation (30). A previous study from our group showed that white matter tracts (tract volumes) are reproducible (31). The local diffusion measures (FA and MD) were averaged and tract volumes were added up over the left and right hippocampus, respectively. Tract volumes are interpreted as a measure for connectivity (32).

After careful analyses, data from forty type 2 diabetes participants and 38 participants without type 2 diabetes remained suitable for final analysis. Data from nine participants were excluded as a result of incomplete data (n = 1), claustrophobia (n = 2), nondiabetes participants with impaired fasting blood glucose levels (n = 2), Parkinsonism (n = 1), brain injury because of an accident (n = 1), an incidental finding (i.e. tumour, n = 1) and susceptibility artefacts (n = 2).

Cognition
As described in Schram et al. (20), participants completed an extensive cognitive battery at enrollment in The Maastricht Study. Global cognitive functioning was measured using the MMSE. Verbal memory was assessed by the 15-Word Learning Test (WLT) total score, in which 15 words are presented in five subsequent trials. Immediately after each trial, participants recall as many words as they are able. The maximum score that could be reached, was 75.

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 the present study, educational level was subdivided into three groups: low (level 1–3), middle (level 4–6) and high (level 7–8). Office blood pressure was assessed three times on the right arm after a 10-min rest, using a non-invasive blood pressure monitor (Omron 705IT; Omron, Kyoto, Japan). A

![Fig. 1. White matter fibre bundles seeded from both hippocampi (yellow regions of interest) to the frontal lobe of representative participants with (A) and without (B) type 2 diabetes (a1 and a1, coronal view; a2 en a2, sagittal view), projected on a semitransparent T1-weighted image. The colours of the tracts represent the left–right (red), anterior–posterior (green) and bottom–top (blue) directions. Depicted coronal and sagittal levels are purely for illustrative purposes; quantitative analyses was performed independent of the visual presentation selected.](image-url)
The present study investigated whether hippocampal microstructural abnormalities are related to type 2 diabetes and verbal memory. To our knowledge, this is the first study to investigate white matter connections from the hippocampus to different brain lobes in type 2 diabetes. The results of the present study demonstrate fewer white matter connections to the frontal lobe in participants with type 2 diabetes compared to nondiabetic participants. For the frontal lobe in type 2 diabetes participants (P = 0.017, which remains significant after correction for multiple testing). For participants (regardless of type 2 diabetes) who scored lower on memory performance, multivariable linear regression (Table 3) revealed a decreased relative tract volume to the temporal lobe (P = 0.017, which remains significant after correction for multiple testing).

Additional multivariable linear regression including the interaction term (type 2 diabetes times WLT total score) showed no significant interaction (P > 0.15). Analyses with fasting blood glucose levels and HbA1c both showed a trend: high fasting blood glucose levels and high HbA1c levels are associated with a decreased relative tract volume from the hippocampi to the frontal lobe (P = 0.069 and P = 0.081, respectively).

Discussion

The present study investigated whether hippocampal microstructural abnormalities are related to type 2 diabetes and verbal memory. To our knowledge, this is the first study to investigate white matter connections from the hippocampus to different brain lobes in type 2 diabetes. The results of the present study demonstrate fewer white matter connections to the frontal lobe in participants with type 2 diabetes compared to nondiabetic participants. For...
participants who scored relatively low on memory performance, we observed fewer white matter connections to the temporal lobe.

In the present study, participants with type 2 diabetes revealed decreased white matter connections between the hippocampi and the frontal lobe. As a result of decreased white matter connectivity, the white matter appears to be less well organised to transfer and integrate information in participants with type 2 diabetes. Therefore, the affected white matter connectivity, rather than the intrinsic microstructure of the tracts in participants with type 2 diabetes, might underlie the memory decrements. The fact that the frontotemporal connection was affected is in close agreement with the type of cognitive decrements (i.e. memory, executive functioning, processing speed) in type 2 diabetes (8), as well as previous studies reporting frontal and/or temporal structural alterations (11,35).

Only two other studies (17,19) have previously investigated white matter connectivity (tract volumes) in participants with type 2 diabetes and focused, not on the hippocampal, but other white matter tracts (including the superior longitudinal fasciculus and the uncinate fasciculus), for which they did not observe any differences in volume. Hoogenboom et al. (19) related cognitive decline to reduced FA of the uncinate fasciculus bundle. Reijmer et al. (17) showed microstructural abnormalities in specific white matter bundles. Another study by Reijmer et al. (36) observed disruptions of the more global white matter network in patients with type 2 diabetes, which was related to cognitive decline. The decreases in hippocampal white matter connections in type 2 diabetes observed in the present study likely contribute to those global network disruptions.

For participants who scored relatively low on memory performance, we observed fewer hippocampal white matter connections to the temporal lobe. The temporal lobe plays an important role in memory and our results potentially indicate that there is less optimal transfer and integration of information between the hippocampus and the temporal lobe, which could play a role in the underlying memory decrements. The involvement of the temporal lobe in memory performance that we observed is in line with studies by Yau et al. (18,37), who showed that white matter abnormalities in the temporal stem (decreased FA) and parahippocampal gyrus (increased MD) explained the lower memory performance in type 2 diabetes. It was concluded that type 2 diabetes has a deleterious effect on the vulnerability of the temporal lobe memory networks (37), especially the hippocampus and parahippocampal gyrus (18).

The intrinsic microstructure measures (FA and MD) were not different between participants with and without type 2 diabetes or were not associated with memory performance after controlling for the study characteristics. Falvey et al. (15) observed increased MD for type 2 diabetes in both hippocampi after controlling for age, sex and race. When using the same statistical model as Falvey et al.
A number of issues limit the conclusions. First, the study had a cross-sectional design. Therefore, the results should be interpreted cautiously. Nevertheless, the initial results are promising and open directions for future (longitudinal) studies. Second, the time span between enrollment for The Maastricht Study (i.e. baseline, in which cognitive tests were performed) and the subsequent MRI assessment was 16.4 ± 3.1 months, which might have limited the validity of the subject characteristics and the long-term validity of the WLT score at the time of the MRI evaluation. Nevertheless, the baseline and repeated MMSE did not differ, which is indicative of no clinically significant cognitive differences within this time frame. Third, tract volume was used as a measure for white matter connection (32). In theory, alterations in axon diameters or myelination can also lead to differences in tract volume at the same time as maintaining the number of actual connections, although this explanation is less likely. Finally, the present study does not consider specific tracts, such as the cingulum bundle or the uncinate fasciculus (17,19), and therefore cannot provide details of specific effects on these tracts. However, the applied approach, which considers all connections from the hippocampus to other cerebral regions, facilitates a more global assessment of hippocampal connectivity, which might be more sensitive to effects of type 2 diabetes and cognition.

In conclusion, dMRI tractography revealed reduced white matter connectivity between the hippocampus and the frontal lobe in type 2 diabetes. For participants who scored lower on memory performance, tractography revealed reduced white matter connectivity between the hippocampus and the temporal lobe. Memory decrements in participants with type 2 diabetes appear to be associated with altered hippocampal white matter connectivity. The findings of the present study contribute to a better understanding of diabetes-associated memory performance, although the exact mechanism remains to be revealed in future studies.

Acknowledgements

All of the authors approved the final manuscript submitted for publication. The authors declare that they have no potential conflicts of interest. JFAJ was funded by VENI Research Grant 916.11.059 from The Netherlands Organization for Scientific Research (NWO) and The Netherlands Organization for Health Research and Development (ZonMw). Additionally, this work was supported by 'Stichting de Weijerhorst' foundation. We would like to acknowledge Marc Geerlings and Jos Slenter (Department of Radiology & Nuclear Medicine, Maastricht University Medical Center, Maastricht, the Netherlands) for continuous hardware and software support. We also would like to acknowledge Alfons Kessels (Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center, Maastricht, the Netherlands) for statistical support.
Hippocampal connectivity in diabetes

References


