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What magnetic resonance imaging reveals – A systematic review of the relationship between type II diabetes and associated brain distortions of structure and cognitive functioning

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ABSTRACT

Due to its increasing prevalence, Type 2 diabetes mellitus (T2DM) represents a major health challenge for modern society. Despite it being of fundamental interest, only a few MRI studies have conducted statistical analyses to draw scientifically valid conclusions about the complex interplay of T2DM and its associated clinical, structural, functional, metabolite, as well as cognitive distortions. Therefore, a systematic review of 68 manuscripts, following the PRISMA guidelines, was conducted. Notably, although the associations between imaging, clinical, and cognitive variables are not fully homogeneous, findings show a clear trend towards a link between altered brain structure and a decline in cognitive processing ability. The results of the review highlight the heterogeneity of the methods used across manuscripts in terms of assessed clinical variables, imaging, and data analysis methods. This is particularly significant as, if the subjects' criteria are not carefully considered, results are easily prone to confounding factors.

1. Introduction

Metabolic diseases, and particularly diabetes mellitus, represent the biggest health challenge for modern society. While high blood glucose level (i.e., hyperglycaemia) is a hallmark of diabetes mellitus, the underlying causes may be deficits in insulin secretion (formerly called insulin-dependent diabetes and defined as type 1 diabetes), or insufficient sensitivity to insulin, or both (formerly called non-insulin dependent diabetes and commonly known as type 2 diabetes mellitus (T2DM)). About 95% of diabetic patients suffer from T2DM, where up to half of these people are unaware of their condition ("IDF diabetes atlas - 2017 Atlas," 2017). Without scientific breakthroughs, this pandemic will become economically unsustainable and will negatively impact life expectancy. In recent years, due to improvements in the therapeutic care of diabetes, organ damage involving the eyes (e.g., retinopathy), kidneys (e.g., nephropathy), peripheral nerves (e.g., gangrene), and heart (e.g., myocardial infarction) has become more widely acknowledged. These symptoms have been reasonably managed to the extent that fewer T2DM patients are suffering from them. Nevertheless, as people are living longer with the disease, it has been observed that T2DM can alter the function and the structure of tissues not directly associated with the above-mentioned symptoms and may, in particular, affect the brain (Seaquist, 2010).

The brain plays a prominent role in glucose homeostasis, because it responds to the input of adiposity and nutrient-related signals by producing adaptive changes in energy intake, energy use, and hepatic glucose production (Schwartz et al., 2013; Schwartz and Porte, 2005). Due to reduced neuronal insulin and/or leptin action in the brain, the energy balance becomes disturbed, leading to obesity and insulin resistance (IR) (Schwartz et al., 2013; Schwartz and Porte, 2005). In addition, patients with T2DM show an accelerated decline in cognitive functioning, which exceeds the rate of aging-related cognitive decrements (Geijselaers, 2015; King et al., 1998; Luchsinger, 2012; McCrimmon et al., 2012; Reijmer et al., 2011; Ruis et al., 2009; Strachan et al., 1997). Longitudinal studies have linked T2DM to an increased risk of developing vascular dementia or Alzheimer's disease (Biessels et al., 2006; De Felice et al., 2014; Luchsinger, 2012).

In this context, Magnetic Resonance Imaging (MRI) provides the

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cornerstone of the non-invasive diagnosis and monitoring of T2DM. High-resolution MRI images of the underlying brain characteristics of T2DM patients can be used to track the earliest effects of IR and glucose distortions on the brain. Furthermore, these techniques can be used to investigate the relationship between structural brain anatomy, functioning, and cognitive impairments. Thus, a comprehensive evaluation of the relationship between T2DM and distortions in brain structure and cognitive function is of fundamental interest. Some studies have conducted statistical analyses to draw scientifically valid conclusions about the complex interplay between these different factors. Therefore, the purpose of this systematic review is to assess the statistical significant relevance of what imaging can reveal about the relationship between T2DM and its associated clinical, structural, functional, metabolite, as well as cognitive distortions, in the brains of these patients.

2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009), using an advanced document protocol (S1). The checklist associated with the protocol for reporting systematic reviews is provided in (S2). For the sake of clarity, the main MRI parameters, clinical and physiological measures, as well as physiological tests commonly used in T2DM studies, are briefly introduced in Fig. 1.

2.1. Search strategy

Electronic searches were performed using PubMed and Web of Knowledge for literature published prior to December 15, 2017. No start date was used. The following search terms were used: “diabetes type 2” OR “type 2 diabetes” OR “type 2 diabetes mellitus” AND “MRI” OR “Magnetic Resonance Imaging” AND “human”. Results were refined by human AND brain AND English. References with titles including the search terms above were selected for the next step of data processing.

2.2. Inclusion and exclusion criteria

Following the removal of duplicates, the search strategy yielded a total number of 469 manuscripts. The manuscripts were considered by three independent reviewers, and any disagreements were resolved through discussion. Studies were included based on the following criteria: the investigation of subjects of any gender, studies investigating T2DM patients and healthy controls (HC), the existence of a statistical correlation between a variable characterising clinical parameters or cognitive functioning in T2DM patients and a variable featuring an MRI parameter. Studies were excluded based on the following criteria: case studies, review manuscripts, book chapters, investigations with non-human subjects, conference proceedings, no imaging technique used, no T2DM patients, no HC, sample size < 10 subjects, subjects’ age < 19. In addition, manuscripts were excluded if no statistical analysis of a variable characterising physiological or cognitive functioning in T2DM, associated with a variable featuring an MRI parameter, was performed.

2.3. Data extraction

Data were extracted from all included manuscripts using a data extraction template (S3). Initially, a draft template was created at the start of the process and was used on a random sample of 5 of the included manuscripts. After extracting data from these five manuscripts, the independent reviewers compared findings, and the data extraction template was modified to accommodate the necessary changes. This resulted in 68 manuscripts being included in the data synthesis.

3. Results

3.1. Overview

Following the removal of duplicates based on the selection criteria described in the methods section, the search strategy yielded a total of 469 manuscripts. Three used non-human subjects, one was not written in English, 17 did not use MR techniques or image the brain, 33 were review manuscripts, 98 were case studies, 109 did not investigate T2DM patients, 29 only existed as abstracts or conference proceedings, one was a technical manuscript, 19 investigated other diabetes types, 46 had no HC group, six had a sample size < 10, and one included volunteers with an age < 19. This resulted in 106 full-text records being assessed for eligibility. 32 of these manuscripts were excluded because they did not investigate relationships between a variable characterising physiological or cognitive functioning in T2DM patients and a variable featuring an MRI parameter. Six manuscripts missed clinical variables. This resulted in 68 manuscripts being included in the data synthesis. Fig. 2 visualises the study selection process. Extracted data are tabulated in Table 1.

3.2. Investigating relationships between imaging and clinical or cognitive parameters in T2DM patients

Thus, the present systematic review focuses on (1) manuscripts that provided clinical parameters, e.g. glucose levels or blood pressure, and associated them statistically with values from imaging parameters, e.g. fractional anisotropy (FA) or blood oxygen level dependent (BOLD), and on (2) manuscripts that reported results from cognitive tasks, e.g. reaction times or data of neuropsychological test batteries, and associated them statistically with values from imaging parameters. The most common way to investigate the relationships was to use a statistical software package to perform statistical correlations (e.g. Pearson correlation) or regression analyses between the measurements (see Table 1).

3.2.1. Relationships between imaging and clinical parameters in T2DM patients

Four of the included studies (Ajilore et al., 2010; Brundel et al., 2010; Z. Chen et al., 2015; Yau et al., 2014) investigated associations between cortical thickness and clinical parameters. Yau et al. (2014) did not observe any significant changes in cortical thickness between patients and HC. One study (Z. Chen et al., 2015) showed a positive correlation between cortical thickness and clinical parameters, and two studies showed both negative as well as no significant correlations (Ajilore et al., 2010; Brundel et al., 2010). Z. Chen et al. (2015) reported a positive correlation between cortical thickening in the middle temporal gyrus (MTG), the entorhinal cortex, and the left inferior temporal gyrus regions bilaterally and noted the presence of recovery effects after one-year of insulin therapy. Cortical thickness correlated negatively with small vessel diseases (Brundel et al., 2010), as well as the risk of cerebrovascular stroke (Ajilore et al., 2010). Brundel et al. (2010) focussed on the cortical thickness of the MTG and reported no correlation with vascular or metabolic determinants. Ajilore et al. (2010) did not restrict their analysis to particular regions of interest and did not observe any significant correlation between cortical thickness and disease duration, the glycated haemoglobin (HbA1c) level, the Cumulative Illness Rating Scale for Geriatrics (CIRS), or the Hamilton Rating Scale for Depression (HAM-D) scores.

The volume of the hippocampus was associated with clinical parameters in eleven studies (Ajilore et al., 2015; Bruehl et al., 2009b, 2009a; Brundel et al., 2010; X. Cui et al., 2014; Gold et al., 2007; Hayashi et al., 2011; Musen et al., 2012; Wisse et al., 2014; H. Zhang et al., 2015; Y.-W. Zhang et al., 2015). Four of them could not reveal any significant differences in hippocampal volume between T2DM patients and HC (Ajilore et al., 2015; Musen et al., 2012; Wisse et al.,

Cerebral blood flow/brain perfusion (CBF) is considered as a fundamental biological function, through the vital delivery of oxygen and nutrients to the tissue via blood flow. CBF is determined by a number of factors (e.g., viscosity, vessel dilatation). Due to its non-invasive nature (i.e., no exogenous tracers) and ability to measure tissue perfusion (i.e., blood flow) quantitatively, arterial spin labelling (ASL) is usually preferred for clinical studies. The basic principle of this technique is to employ the blood water protons itself as an endogenous tracer to measure perfusion. The subtraction of the labelled and control acquisitions suppresses the signal from the static tissue and provides a perfusion-weighted image.
C-peptide blood serum level is found in amounts equal to insulin reflecting how much insulin is being released by the pancreas. It is mainly used to differentiate between diabetes types and to track the cause of hypoglycemia.
Diffusion tensor imaging (DTI) is sensitive to subtle white matter (WM) microstructure changes such as demyelination and axonal loss. The main DTI parameters are mean diffusivity (MD) and fractional anisotropy (FA). MD reflects the magnitude of water diffusion, which makes it suitable to assess grey matter (GM) tissue density. FA measures the degree of directionality of water diffusion and ranges from 0, i.e., isotropic diffusion, to 1, i.e., anisotropic diffusion. Lower values indicate microstructural alterations and loss of integrity.
Dyslipidemia and hypertension are established risk factors of importance in diabetes disease. Most adults with diabetes have elevated blood pressure (i.e., >140 for systolic and >80 mmHg for diastolic blood pressure), and patients with hypertension alone often show evidence of insulin resistance, more likely because diabetes damages arteries (i.e., atherosclerosis).
Functional Magnetic Resonance Imaging (fMRI) represents a technique for investigating the neurophysiological mechanisms underlying cerebral abnormalities and affecting, for instance, functional connectivity. During resting-state fMRI (rs-fMRI), the blood oxygen level dependent (BOLD) signal is measured at rest. Task-based fMRI (task-fMRI) detects the changes in the BOLD signal during a task (e.g., reaction time task) to determine the involved brain regions.
Insulin Resistance (IR) Insulin regulates glucose metabolism and helps cells through the body to absorb glucose and use it for energy. Distortions in the insulin response by cells or in its secretion by the pancreas, excess glucose builds up in the bloodstream, leading to hyperglycaemia state. Due to the simplicity of its determination, homeostatic model assessment to quantify IR (HOMA-IR) has been the most frequently employed technique. It describes glucose-insulin homeostasis by means of mathematically derived equations from the use of the insulin-glucose product divided by a constant.
Magnetic transfer (MT) reflects the biophysical integrity of macromolecular protein pools and their microenvironment. It exploits magnetization exchange between protons bound to macro-molecules and free protons. Bound protons are selectively saturated by applying an off-resonance prepulse. Magnetization is then transferred from bound protons to free protons, leading to a decreased signal from free protons. The contrast between MT images with and without the saturation is defined as the MT ratio (MTR). Lower MTR in WM is associated with axonal loss and myelin compromise, while in the GM, MTR reflects heterogeneous etiology such as membrane damages, reduction in dendritic density, neuronal size, and Wallerian degeneration.
Neuropsychological tests of cognitive performance is usually assessed by neuropsychological test batteries. Hereby tests of working memory (e.g. letter-number sequences), language (e.g., word associations or verbal fluency), attention processing (e.g., digit symbol substitution), procedural learning (e.g., Wisconsin card sorting test), executive function (e.g., Stroop, trail making), visuospatial conceptualization (e.g., block designs) and declarative learning and recall (e.g., California verbal learning test) are applied.
Plasma glucose (glucose tolerance) test is a determinant variable measuring the level of blood sugar. Diabetes can be assessed using several methods, mainly: glycated hemoglobin (HbA1c) tests which measure average blood glucose for the past 3 months (>6.5%), fasting blood glucose (FPG) levels (>126 mg/dl) after 8 hours fasting, oral glucose tolerance (OGTT) test which reflects body's ability to use and process glucose (>200 mg/dl) 2 hours after oral glucose administration. When blood glucose level is consistently high, impaired fasting glucose (IFG, 100-125 mg/dl) or impaired glucose tolerance (IGT, 140-199 mg/dl), a pre-diabetic state is defined.
Small vessel disease (SVD) is located mainly in the brain parenchyma in the deep white matter, including white matter hyperintensity (WMH) of presumed vascular origin, white matter lesions (WML), lacunar infarcts, large haemorrhages, and micro bleeds. Lesions imaging of SVD is usually detected by manual or automatic segmentation on T_2-weighted images but some studies focus mainly on hypo-intensities of T_1-weighted and FLAIR sequences.
Voxel based morphometry (VBM) is an automatic quantitative volumetric technique mainly used in the detection of subtle brain structural changes, including, GM and WM volume, hippocampal volume, cortical thickness, at the early stage of the disease.

Fig. 1. Glossary of MRI techniques and biomarkers in T2DM used in the included manuscripts.

2014; H. Zhang et al., 2015). One study by Bruehl et al. (2009a) reported a positive correlation between hippocampal volume and clinical parameters, seven studies (Bruehl et al., 2009b, 2009a; Brundel et al., 2010; X. Cui et al., 2014; Gold et al., 2007; Hayashi et al., 2011; Y.-W. Zhang et al., 2015) observed negative correlations, and three studies reported, in addition to their findings about negative correlations, that some of their statistical comparisons could not reach significance (Brundel et al., 2010; Gold et al., 2007; Hayashi et al., 2011). Bruehl et al. (2009a) identified a positive correlation between lower hippocampal volumes and a lower cortisol awakening response (CAR). In a follow-up study, they reported that lower hippocampal volume correlated negatively with higher body mass index (BMI) (Bruehl et al., 2009b, 2009a). This correlation, however, became non-significant after controlling for the glycaemic level. Additionally, negative correlations were identified when lower hippocampal volume was associated with an increased duration of the disease, higher HbA1c values, (Bruehl et al., 2009a) and obesity (Bruehl et al., 2009b). Brundel et al.(2010) associated hippocampal volume reduction to the presence of small vessel disease. X. Cui et al. (2014) showed that glycaemic variability cycles (GVC_{1-3}), at multiple time scales with frequencies 1–3, is a strong predictor of hippocampal atrophy. This result was confirmed by Gold et al. (2007), who further reported a negative correlation between hippocampal volume and glycaemic control and also found a negative correlation between hippocampal volume and HbA1c levels. This additional finding was supported by Y.-W. Zhang et al. (2015). Hayashi et al. (2011) reported a significant negative correlation between

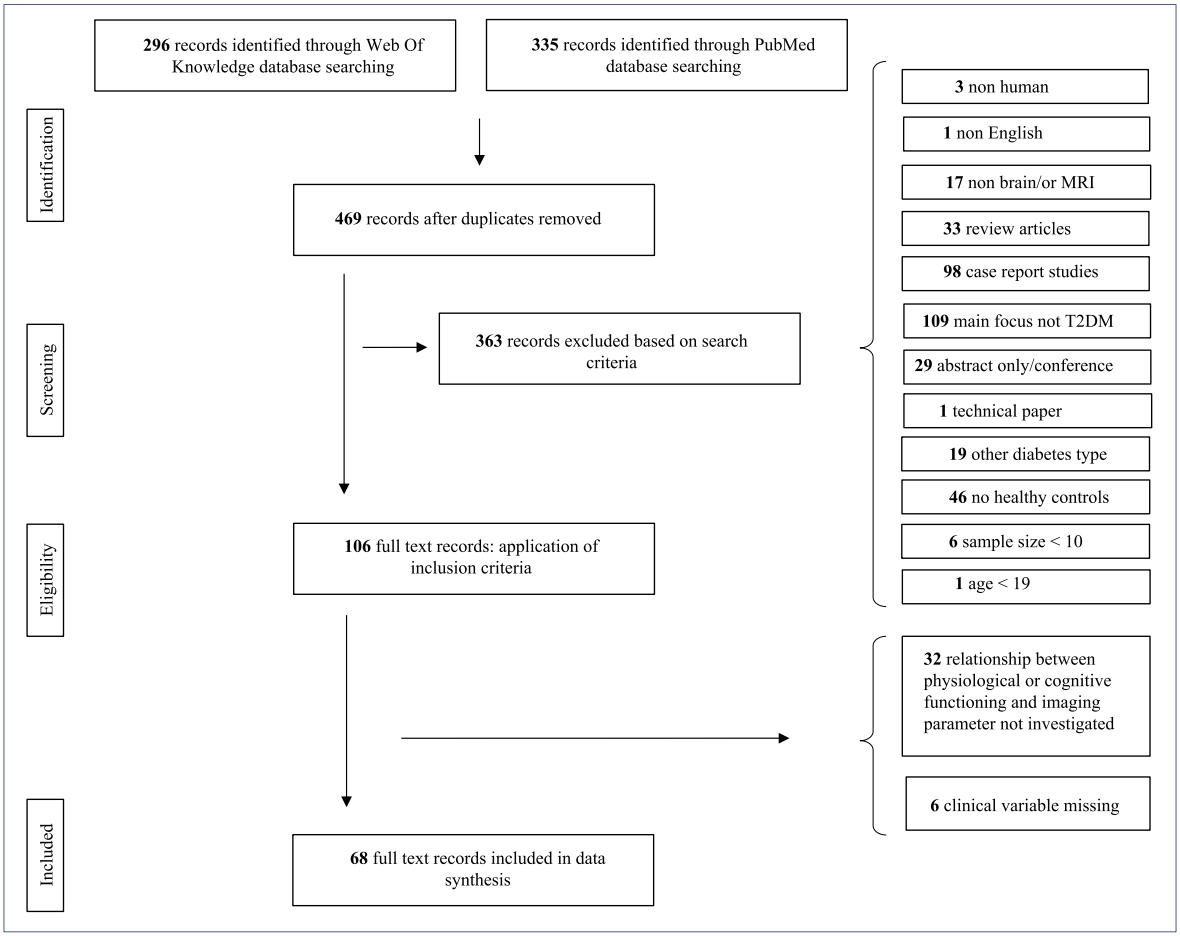

Fig. 2. Screening and selection process for the included studies.

hippocampal atrophy and BMI and weight. However, they were unable to observe any other significant correlations (e.g., between age, years of education, height, systolic and diastolic blood pressure, duration of diabetes, fasting plasma glucose (FPG), fasting serum human C-peptide immunoreactivity (CPR), HbA1c, smoking, insulin therapy, neuropathy, retinopathy, nephropathy and cardiovascular disease). Gold et al. (2007) found no association between a lower hippocampal volume and BMI, hypertension or dyslipidaemia. No significant association with metabolic determinants was reported by Brundel et al. (2010).

All of the six included studies (Jongen et al., 2007; R. Kumar et al., 2008; Last et al., 2007; Lee et al., 2013; Novak et al., 2011; Samaras et al., 2014), which investigated the associations of cerebrospinal fluid (CSF) volume with clinical variables, showed significant differences when comparing HC to T2DM volunteers. Five studies (Jongen et al., 2007; R. Kumar et al., 2008; Last et al., 2007; Novak et al., 2011; Samaras et al., 2014) demonstrated positive correlations. One study (Novak et al., 2011) revealed a negative correlation. Another study (Lee et al., 2013) identified no correlation between CSF and any clinical variable. Jongen et al. (2007) showed a positive correlation which associated a history of macrovascular diseases with a larger total CSF volume. R. Kumar et al. (2008) linked high CSF volume to enhanced BMI in T2DM patients. Last et al. (2007) observed that a higher HbA1c level and the presence of retinopathy are correlated with increased CSF within the temporal region. More recently, a longitudinal study by Samaras et al. (2014) revealed a significant increase in CSF volume at a baseline measurement, with a trend in the decline of total brain volume over 2 years in T2DM patients, compared to participants without diabetes. In another work, Novak et al. (2011) focussed on the analysis of serum soluble vascular cell and intercellular adhesion molecules (sVCAM and sICAM, respectively) that serve as endothelial integrity markers. They reported a significant positive correlation between the circulating adhesion molecules sVCAM and greater CSF, as well as a negative correlation between sICAM and smaller CSF volume for their control group. Moreover, Lee et al. (2013) reported no significant correlation between CSF and disease duration, or with HbA1c levels.

GM and white matter (WM) volume were of interest in twenty-one studies (Chen et al., 2012; Z. Chen et al., 2014; Climie et al., 2014; X. Cui et al., 2014; Y. Cui et al., 2014; Falvey et al., 2013; Franke et al., 2013; García-Casares et al., 2014b, 2014a; He et al., 2015; Jongen et al., 2007; A. Kumar et al., 2008; Last et al., 2007; Manor et al., 2012; Mehta et al., 2014; Moran et al., 2013; Novak et al., 2011; Raji et al., 2010; Xia et al., 2015a, 2015c; Zhang et al., 2014; Y.-W. Zhang et al., 2015) of which seven did not find any significant structural changes between HC and T2DM patients (Y.-W. Zhang et al., 2015; Franke et al., 2013; Manor et al., 2012; Xia et al., 2015a, 2015c; He et al., 2015; Chen et al., 2012).

From the remaining manuscripts, positive correlations were identified in four (Z. Chen et al., 2014; García-Casares et al., 2014b; Jongen et al., 2007; Last et al., 2007), negative correlations in eight (Climie et al., 2014; X. Cui et al., 2014; García-Casares et al., 2014a; A. Kumar et al., 2008; Mehta et al., 2014; Moran et al., 2013; Novak et al., 2011; Raji et al., 2010), and no significant correlations in four studies (Z. Chen et al., 2014; X. Cui et al., 2014; Falvey et al., 2013; Zhang et al., 2014). Z. Chen et al. (2014) reported both GM and WM expansion following the administration of insulin for over one year, while García-Casares et al. (2014b) noticed that less GM density correlates with reduced glucose metabolism. Jongen et al. (2007) found a significant positive association between higher HbA1c levels and a higher volume

Table 1
Extracted data of the included studies.

	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
1.	Ajilore et al. (2010)	26	20	Structural: cortical grey matter thickness	1.5 T Signa GE; **SPGRE T_1: c**oronar; no gap; TR/TE = 20/6 ms; FLIP ANGLE = 45°; FOV = 22 cm; NEX = 1.5; matrix size = 256 × 192 mm; inplane resolution = 0.86 × 192 × 1.4 mm^3	Partial correlations	All subjects with diabetes demonstrated decreased cortical grey matter thickness in the left anterior cingulate region. Additionally, depressed diabetic subjects showed significant cortical grey matter decreases in bilateral prefrontal areas compared with HC. Correlations between clinical variables and cortical grey matter thickness revealed a significant negative relationship with cerebrovascular risk factors across all three groups, most consistently in the left dorsomedial prefrontal cortex. A significant positive relationship between performance on attention and executive function tasks and cortical grey matter thickness predominately in left hemisphere regions was also seen across all subjects.
2.	Ajilore et al. (2015)	24	32	Structural: hippocampal volume	1.5 T Signa GE; **SPGRE T_1:** TR/TE = 20/6 ms; FLIP ANGLE = 45°; no gap; FOV = 22 cm; NEX = 1.5; matrix = 256 × 192 mm; inplane resolution = 0.86 × 0.86 × 1.4 mm^3	ANCOVA: differences group performance Stepwise linear regression: for cognition impairment predictors assessment	Higher stroke risk profiles. No significant difference in hippocampal volume between 3 groups. Worse performance on CVLT: Cohen's d for differences between HC and T2DM subjects was 0.71 and 0.81 for differences between HC and depressed diabetes group. Hippocampal volume and age were significant predictors in T2DM on CVLT (larger hippocampal volumes associated with better verbal list recall). In depressed T2DM group, only age was a significant predictor of performance (younger age associated with better verbal list recall).
3.	Bruehl et al. (2009a)	18	12	Structural: hippocampal volume	1.5TAvanto SIEMENS; **MPRAGE:** TR/TE = 1300/4.38 ms; 192 slices; slice thickness = 1.2 mm; no gap; FOV = 250 × 250 mm; matrix = 256x128; flip angle = 15°. **Fast FLAIR** used for white matter ratings: TR/TE = 9000/97 ms; matrix size = 154 × 256; FOV = 210 × 210; slice thickness = 3 mm; 50 slices; no gap	Pearson's correlations	T2DM had smaller hippocampal volumes and exhibited a blunting of the CAR relative to HC, while diurnal cortisol was not affected. Across all subjects, fasting insulin and hippocampal volume were associated with the CAR, independent of diagnosis.
4.	Bruehl et al. (2009b)	41	47	Structural: WMHs	1.5 T Vision GE; 1.5 T Avanto SIEMENS; **MPRAGE:** TR/TE = 1300/4.38 ms; 192 slices; slice thickness = 1.2 mm; no gap; FOV = 250 × 250 mm; matrix = 256 × 128; FA = 15°. **Fast FLAIR** used for white matter ratings: TR/TE = 9000/97 ms; matrix size = 154 × 256; FOV = 210 × 210;	Linear regression analysis	T2DM had specific verbal declarative memory deficits, reduced hippocampal and prefrontal volumes, and impaired HPA a × is feedback control. Diminished cortisol suppression after dexamethasone and dyslipidaemia were associated with decreased cognitive performance, whereas obesity was negatively related to hippocampal volume. Moreover, prefrontal

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Table 1 (*continued*)

	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
					slice thickness = 3 mm; 50 slices; no gap		volume was influenced by worse glycaemic control.
5.	Brundel et al. (2010)	56	30	Structural: cerebral cortical Thickness	1.5 T PHILIPS; **T_1:** axial; TR/TE = 234/2 ms; **IR**: TR/TE = 2919/22 ms; TI = 410 ms; **FLAIR:** TR/TE = 6000/100 ms; TI = 2000 ms; 38 contiguous slices; voxel size: 0.9 × 0.9 × 4.0 mm^3 **3D T_1**: sagittal; TR/TE = 7.0/3.2 ms; 170 slices; voxel size: 0.94 × 0.9 × 1.00 mm^3	Linear regression analysis	Total cortical surface, total cortical volume and mean cortical thickness for both hemispheres were consistently lower in the T2DMgroup (between group differences: 0.5–4%), but the effects were only significant in the right hemisphere (pb0.05). Posthoc regional analyses revealed significant differences in the hippocampal region (between group differences cortical thickness and volume: 5–20.5%) and the middle temporal gyrus (between group differences cortical surface and volume ~8%).Within the T2DMgroup, smaller cortical thickness of the hippocampal region was associated with cerebral small vessel disease, but no associations between vascular or metabolic determinants and cortical atrophy were found.
6.	Brundel et al. (2014)	48	49	Structural: VBM, WMH, microbleeds, microinfarcts	7 T PHILIPS; **Dual echo gradient:** TR = 20 ms; TE1 = 6.9 ms; TE2 = 15.8 ms; voxel size = 0.39 × 0.39 × 0.35 mm^3 **3D T_1:** TR/TE = 4.8/2.2 ms; TI = 1240 ms; voxel size = 0.66 × 0.66 × 0.50 mm^3; **3D FLAIR:** TR = 8000 ms; TI = 2325 ms; TE = 300 ms; voxel size = 0.49 × 0.49 × 0.40 mm^3 3 T PHILIPS data used for detection of brain infarcts and determination of brain volumes and WMH; **FLAIR:** TR/TE 11,000/125 ms; TI = 2800 ms; voxel size = 0.96 × 0.95 × 3 mm^3 **3D T_1:** TR/TE = 7.9/4.5 ms; TI = 955 ms; voxel size = 1 × 1 × 1 mm^3 **Dual echo T_2:** TR = 3198 ms; TE1 = 19 ms; TE2 = 140 ms; reconstructed voxel size 0.96 × 0.95 × 3 mm^3	linear regression analyses: relationship between microvascular lesions and cognition examined with, adjusted for age, sex, estimated IQ, and group. Because the numbers of microbleeds and microinfarcts showed a skewed distribution, 3 groups with 0, 1, or > 1 more lesions were distinguished.	Slightly worse performance on all cognitive domains: information processing speed 0.24 [95% CI 0.58–0.11]); attention & executive functioning 0.21 [0.50–0.09]; memory 0.14 [0.44–0.17]; all P > 0.05) → Statistically not significance. Micro infarcts found in 23 T2DM patients (48%) compared to 19 HC (38%). Micro bleeds present in 16 T2DM patients (33%) compared to 20 HC (41%). Smaller cerebral grey matter and larger lateral ventricle volumes in T2DM. No difference in WMH, WM volumes and infarcts occurrence. Cognitive performance not related to microvascular lesion load.
7.	Chechlacz et al. (2009)	11	12	fMRI	1.5 T SIEMENS; **BOLD:** axial; 39 slices; slice thickness = 4 mm; 1 mm gap; matrix size = 64 × 64; resolution 3 × 3 × 5 mm^3; flip angle = 90°; TR/TE = 2000/40 ms; **T_1:** structural image 1 × 1 × 1 mm^3 resolution	Not given	Increased activation with food within the insula and OFC positively correlated with external eating, dietary self-efficacy, and dietary self-care. In contrast T2DM increased responses to pictured foods in the insula, orbitofrontal cortex (OFC) and basal ganglia and, within these regions, the effect of the fat content of the foods was larger in participants, responses within subcortical structures (amygdala and basal ganglia) were positively correlated with emotional

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Table 1 (*continued*)

	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
							eating and rated appetite for the food stimuli and negatively correlated with dietary self-care.
8.	Y. Chen et al. (2014)	30	37	task fMRI	3 T Tim Trio SIEMENS; **EPI:** axial; 33slices; TR/TE = 2000/30 ms; slice thickness = 3.5 mm; flip angle = 90°; FOV = 200 × 200 mm^2; matrix = 64 × 64	Independent twosample t-tests: to assess the betweengroup differences in age and education. χ^2 test to compare sex ratios of the groups ANCOVA: used to test betweengroup differences (age, sex, and education included as covariates) for neuropsychological assessment and lipid levels	Significantly worse performance on working memory tasks (backward digit span, P = 0.027; digit span, P = 0.05) and executive function task (SCWTCB time, P = 0.045). Less brain activation in frontal areas :SFG, bilateral MFG, and IFG. Higher SFG activity associated with better performances on MMSE (r = 0.57, P = 0.002), ROCFdelay recall (r = 0.50, P = 0.009), digit span (r = 0.48, P = 0.011), CVFT (r = 0.43, P = 0.025), ROCFcopy (r = 0.57, P = 0.002), and SCWTB time (r = 0.42, P = 0.031) after controlling for age, sex, and education.
9.	Y. Chen et al. (2015)	37	40	Structural: WMH RS-FMRI: DMN	3 T Tim Trio SIEMENS; **EPI:** TR/TE = 2000/25 ms; 36 slices; slice thickness = 4 mm; no gap; FOV = 240 × 240 mm^2; matrix = 64 × 64; flip angle = 90° **T_1 3D SPGRE**: TR = 1900/2.48 ms; 176 slices; slice thickness = 1 mm; no gap; flip angle = 90°; matrix size = 256 × 256; FOV = 250 × 250 mm^2; **FLAIR:** TR/94 = 8500/94 ms; 20 slices; thickness = 5 mm; voxel size 1.3 × 0.9 × 5 mm^3	Twosample t-tests between group differences in age and years of education. χ^2 test to compare gender ratios of the groups. ANCOVA for neuropsychological assessment and biochemical indicator, for between group differences (age, gender, and education included as covariates). Pearson correlation analyses to explore relationship between FPG level and the connectivity of the clusters with significant intergroup differences after controlling for the influences of age, gender, and education	All participants had not WML. No differences in lacunar infarcts occurrence (P = 0.71). Groups did not differ significantly in age, gender, or years of education, vascular brain lesions, smoking habits, or medical history of hypertension. Significantly poorer score on working memory (Backward digit span, p = 0.02 and digit span, p = 0.04), visuospatial processing (ROCFCopy, p = 0.01), and executive function (SCWT CB Time, p < 0.001). Significantly higher HbA1c, FPG, and BMI, (TG), and low-density lipoprotein (LDL). Higher connectivity in DMN and LFPN, relative to HC. Significantly increased connectivity located in right MTG (MTG·R) within DMN and left middle occipital gyrus (MOG·L), left middle frontal gyrus (MFG·L), and right angular gyrus (ANG·R) within LFPN (FDR corrected, q < 0.05).
10.	Y.-C. Chen et al. (2014)	30	31	RS-FMRI	3 T GE; **3D T_1FSPGR:** axial; 118 contiguous slices; TR/TE = 6.3/2.8 ms; flip angle = 15°; FOV = 24 × 24 cm; matrix size = 256 × 256; inplane resolution = 0.9375 × 0.9375 mm; NEX = 1. For voxel based analysis. **T_2:** TR = 5000 ms; TE = 113.4 ms; FOV = 24x24 cm; matrix size = 384 × 384; **T_1 FLAIR:** TR/TE = 2040/6.9 ms; FOV = 24 × 24 cm; matrix size = 384 × 192	Between group *t*-test for means and χ^2 test for proportions Pearson correlation	Poorer scores on CFT/CFT delay, TMTA/ TMTB, CDT, and VFT (P < 0.05). Significantly decreased functional connectivity between PCC and right MTG, left lingual gyrus, left middle occipital gyrus, and left precentral gyrus. Increased functional connectivity of PCC in left cerebellum posterior lobe, right superior frontal gyrus, and right middle frontal gyrus. Significant negative correlation between PCCright MTG connectivity and HOMA-IR (P = 0.014; r = 0.446) and positively with VFT performance (r = 0.495; P = 0.005). Functional

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Table 1 (*continued*)

	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
							connectivity of PCC to left lingual gyrus and left middle occipital gyrus were positively associated with CFTdelay scores, respectively (r = 0.446, P = 0.014; r = 0.480, P = 0.007).
11.	Chen et al. (2012)	16	16	Structural: VBM, GM/WM Volume	3 T GE; **3D T_1FSPGR:** axial; 118 contiguous slices; TR/TE = 6.3/2.8 ms; flip angle = 15°; FOV = 24x24 cm; matrix size = 256 × 256; inplane resolution = 0.9375 × 0.9375 mm^2; NEX = 1; For voxel based analysis. **T_2:** TR/TE = 5000/113.4 ms; FOV = 24 cm × 24 cm; matrix size = 384 × 384 **T_1:** TR/TE = 2040/6.9 ms; FOV = 24 × 24 cm; matrix size = 384 × 192	ANCOVA	No correlation found between VBM results and clinical measures and cognitive test (MMSE). Partial correlation analysis for grey and white matter volume of the right temporal lobe with clinical variables (FPG, HbA1c, disease duration, and BMI) showed no significant correlation (P > 0.05).
12.	Z. Chen et al. (2014)	11	11	Structural: VBM Perfusion: rCBF	3 T Signa Excite GE; FSE (T2); FLAIR (T_1); FLAIR (T_2); DWI for general assessment and for excluding cerebral infarction; inflammatory disease; malacia **3D T_1FSPGR:** axial ; 118 contiguous slices; TR/TE = 6.3/2.8 ms; flip angle = 15°; FOV = 24 × 24 cm; matrix size = 256 × 256; inplane resolution = 0.9375 × 0.9375 mm^2; NEX = 1; **FAIR/ASL:** TR/TE = 800/17.6 ms; flip angle = 90°; FOV = 24 × 24 cm; matrix size = 128 × 128; slice thickness = 6.0 mm	test (clinical/demographic param) ANCOVA (cov. Age and BMI)	Follow-up after insulin therapy: GMV smaller (P = 0.003) in patients. WMV no difference between patients and HC Follow-up. GMV & WMV no significant difference between patients & HC (P = 0.2, P = 0.25). GM expansion regions mainly located in bilateral frontal, parietal, left occipital lobe. GMV and WMV significantly increased (P = 0.01, P = 0.01) after 1 year. Bilateral frontal cortex, left occipital cortex, and right temporal cortex had higher rCBF in T2DM. rCBF showed no significant difference in the bilateral parietal cortex, right occipital cortex, left temporal cortex, and the expanded WM. BMI, MMSE, FPG, HbA1c, total cholesterol, UP, and Ccr showed no significant difference between the two time points of baseline and follow-up.
13.	Z. Chen et al. (2015)	11	11	Structural: VBM	3 T Signa GE; **T_1 3D SPGRE:** 118 axial contiguous slices; TR/TE = 6.3/2.8 ms; flip angle = 15°; FOV = 24 × 24 cm; matrix = 256 × 256; inplane resolution = 0.9375 × 0.9375 mm^2; NEX = 1; **FLAIR:**TR/TE = 8802/124.3 ms; TI = 2200 ms; slice thickness = 4 mm; 1 mm gap; matrix size = 256 × 256; FOV = 24 × 24 cm; NEX = 1	Paired *t*-test: compare age, BMI, MMSE, disease duration, FPG, HbA1c, total cholesterol, triglyceride, UP, Ccr and mean cortical thickness between baseline and follow-up. Independent sample *t*-test to compare age and BMI between patients and HC	Thinner cortex in T2DM compared with HC. Regions with cortical thickening after insulin therapy located in middle temporal gyrus, entorhinal cortex and left inferior temporal gyrus bilaterally. Age, BMI, MMSE, FPG, HbA1c, total cholesterol, UP, and Ccr showed no significant differences between the two time points.
14.	Climie et al. (2014)	37	37	Structural: WML, VBM	3 T Signa GE; **T_1 SPGRE:** TR/TE = 35/7 ms; flip angle = 35°; FOV = 24 cm; resolution = 1 × 1 × 1 mm^3; 120 contiguous slices; **T_2 FSE:** TR/TE = 4300/120 ms; NEX = 1; turbo factor = 48;	Independent t-tests and Chi square tests: compare groups Independent *t*-tests were used to compare unadjusted brain volumes between	Resting aPWV inversely associated with GMV (standardized r = −0.45, p = 0.005) and remained associated after adjusting for age, sex, antihypertensive medication, BMI, albumin, and cholesterol. Significantly greater values in most aortic reservoir characteristics and other hemodynamic

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Table 1 (*continued*)

	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
					resolution = 0.90 × 0.90 × 3mm^3 **FLAIR:** TR/TE = 8802/130 ms; TI = 2200 ms; resolution = 0.50 × 0.50 × 3 mm^3	groups, ANCOVA	variables at rest and exercise. Aortic reservoir characteristics were not related to WML volume in either group (p > 0.05 for all). Exercise hemodynamic variables were not stronger correlates of brain structural abnormalities than resting variables.
15.	X. Cui et al. (2014)	43	26	Structural: WML, Brain volume	3 T GHX GE; **MPRAGE** **FLAIR** Parameters not defined	Oneway ANOVA and nonparametric tests For the relationship between MultiScale GV and brain volumes, only models with adjusted $r^{2=}$0.25, and < ,0.05 from models adjusted for age, sex, group were selected. Least square model	T2DM had lower global GM (P = 0.02) and WM (P = 0.01) volumes. Subjects exhibited reduced GM. Within the hippocampus, insular cortex, superior parietal gyri and supramarginal gyri (P < 0.05). Greater variability in GVC_2 was correlated with lower GM volumes within the cingulate gyrus (r^2 = 0.40, P = 0.02) and insular cortex (r^2 = 0.33, P = 0.032). HbA1c, fasting glucose, SD, and MAGE were not independently associated with brain volumes and functional outcomes after controlling for GVC variability measures. Greater glycaemic variability $GVC_{2,3}$ was associated with worse learning and memory function (learning and memory T score, r^2 = 0.28–0.37, P < 0.03), greater variability in GVC_2 was also associated with worse overall cognitive performance (Composite T score, r^2 = 0.44, P = 0.02) and greater variability in GVC_5 was associated with more depression (GDS, r^2 = 0.18, P = 0.014). Combined effects of greater variability in GVC2, lower GM in the cingulate gyrus and longer DM duration were highly associated with more depression (r^2 = 0.69, P < 0.02).
16.	Y. Cui et al. (2014))	29	27	Structural: VBM, WML, Infarcts RS-FMRI: ALFF, ReHo	3 T SIEMENS; **GRE:** 36 slices; TR/TE = 2000/25 ms; slice thickness = 4 mm; flip angle = 90°; FOV = 240 × 240; T1: 3D SPGRE; 176 slices; TR/TE = 1900/2.48; thickness = 1 mm; flip angle = 9°; TI = 900 ms; FOV = 250 × 250 mm; inplane resolution = 1.3 × 0.9 × 5 mm^3	One sample *t*-tests on individual ALFF and ReHo maps for each group. RESTanalysis	T2DM had significantly decreased ALFF and ReHo Values in the occipital lobe and postcentral gyrus compared to HC. T2DM performed worse on several cognitive tests. No difference in brain volume between groups.
17.	Cui et al. (2015)	42	42	RS-FMRI: DMN		Between group differences, two sample *t*-tests were performed on the spatial maps of DMN Relationship between DMN connectivity and clinical variables, performed using Pearson correlation analyses Mean z values of each ROI were correlated against the	No significant differences in total cholesterol, WMH and lacunar infarcts, and BMI. Worse performance on TMTB and CFT delayed recall tests involving executive function, processing speed, and spatial episodic memory. Disease duration and HOMA-IR, instead of hyperglycaemic indices themselves (FPG, HbA1c), were the main contributors to this paired performance. Increased FC in anterior DMN (P < 0.05) specifically in bilateral superior

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	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
						cognitive performance and T2DMrelated variables in each patient	frontal gyrus. Decreased FC in posterior DMN ($P < 0.05$) specifically in PCC and precuneus. FC strength in pDMN positively correlated with CFTdelay and TMTB performance, and negatively correlated with insulin resistance level (HOMA-IR). Hypoconnectivity in PCC is related to higher insulin resistance level ($r = -0.404$, $p = 0.024$) Mean z value in the precuneus had positive correlations with CFTdelay score ($r = 0.395$, $p = 0.020$) and negative correlations with time spent on TMTB ($r = -0.346$, $p = 0.025$). No correlations between glycaemic control and functional changes.
18.	Elderkin-Thompson et al. (2009)	31	28	Structural: Cortical Thickness	1.5 T Signa GE;	Correlations (no details given)	MT ratios of the caudate correlated with cognitive performance, and the correlations were stronger among diabetic patients than healthy control subjects. Comorbid depression increased the strength of the correlation compared with diabetes alone. Comparison regions showed no evidence of a diabetes effect on cognition.
19.	Falvey et al. (2013)	85	223	Structural: Brain volume Diffusion: MD, FA	3 T Tim Trio SIEMENS; **3D MPRAGE**: TR/TE = 2300/3.43 ms; TI = 900 ms; flip angle = 9°; FOV = 256 × 224 mm; resolution: 1 × 1 mm^2; matrix = 256 × 22; 176 slices; thickness = 1 mm; **FLAIR**: axial; TR/TE = 9160/89 ms; TI = 2500 ms; flip angle = 150°; FOV = 256 × 212 mm; matrix size = 256 × 240; 48 slices; thickness = 3 mm; resolution = 1 × 1 mm^2; **Single shot SE:** TR = 5300 ms; TE = 88 ms; TI = 2500 ms; flip angle = 90°; FOV = 256 × 256 mm; b = 0 & 1 s/mm^2; 12 diffusion directions; 4 repeats; 40 slices; thickness = 3 mm; matrix size = 128 × 128; resolution = 2 × 2 mm; GRAPPA = 2	Linear regression models to test for associations between diabetes status and volumetric measures and DTI indices for the total brain and ROIs in each hemisphere. Models were adjusted for age race sex stroke hypertension myocardial infarction, apoE e4 depression 3MS score	Lower: TBV ($P = 0.04$), total GMV ($P = 0.0006$) and GMV in putamen ($P = 0.02$) and greater cerebral atrophy ($P = 0.02$). Lower WM FA ($P = 0.006$), greater MD in hyppocampus ($P = 0.006$ left, $P = 0.01$ right) dorsolateral prefrontal cortex ($P = 0.0007$ left, $P = 0.002$ right), left posterior cingulate ($P = 0.02$), and right putamen ($P = 0.02$). Adj. For age sex and race, stroke hypertension produce similar results. No association with WMH ($P = 0.93$) and MD of GM ($P = 0.49$), 3MS (0.1).
20.	Franke et al. (2013)	98	87	Structural: Brain aging, VBM	3 T HDx GE; **3D MPRAGE:** TR/TE/TI = 7.8/3.1/600 ms; slice thickness = 3.0 mm; 52 slices; BW = 122 Hz/pi; flip angle = 10°; FOV = 24 cm × 24 cm; matrix size = 256 × 192 **FLAIR:** TR/TE/TI = 11000/161/2250 ms; slice thickness = 5 mm; 30 slices;	Student's t-test:withingroup differences Effect of DM on BrainAGE was determined with ANOVA Univariate correlation analyses Pearson's pairwise correlation	**Within DM group** Brain age of DM subjects was 4.6 ± 7.2 years greater than their chronological age ($p = 0.0001$). BrainAGE scores of DM increased by 0.2 years per follow-up year ($p = 0.034$). Higher BrainAGE scores were associated with longer diabetes duration ($r = 0.31$, $p = 0.019$) and increased FPG levels

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	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
					BW = 122 Hz/pi; flip angle = 90°; FOV = 24 cm × 24 cm; matrix size = 256 × 160	Bonferroni–Holm correction ANCOVA multivariate linear regression	(r = 0.34, p = 0.025), smoking (F = 5.13, p0.05), alcohol (F = 7.63, p < 0.01), increased TNFα (F = 6.24, p < 0.05), decreased verbal fluency (F = 4.07, p < 0.05), increased GDS scores (F = 7.17, p0.01). GM, WM total brain volumes did not differ between groups. Brain age increased with disease duration, higher fasting blood glucose levels, suggesting a potential link between worse glycemic control and pathologic brain atrophy.
21.	García-Casares et al. (2014a)	25	25	Structural: VBM PET: FFDG	3 T Intera PHILIPS; **MPRAGE:** TR = 9.9 ms; TE = 4.6 ms; flip angle = 8°; matrix size = 256 × 256; FOV = 240 mm; slice thickness = 1 mm; 190 slices; voxel size = 0.9 × 0.9 × 1 mm^3	2 sample *t*-tests: for intergroup comparisons of population characteristics for continuous variables, and the Wilcoxon Rank Sum test if assumptions for test were violated, and the chi squared test for dichotomous variables.	Lower GM densities in the premotor cortex, anterior cingulate cortex, rostral pole of the superior temporal gyrus, part of BA36 of the left hemisphere. Reduced cerebral glucose metabolism in left prefrontal and premotor areas, and bilateral middle and inferior temporal gyri (even after adj. for all clinical and physiological covariates). There was a negative correlation between HbA1c levels and GM density in right medial prefrontal cortex and left angular gyrus. HbA1c did not correlate with findings other studies. Disease duration correlated negatively with GM density in left orbital prefrontal gyrus, right premotor, and right prefrontal areas, left rostral pole of the superior temporal gyrus, left inferior temporal gyrus, right superior temporal gyrus. Disease duration correlated negatively with reduced cerebral glucose metabolism in the medial prefrontal cortex, right orbital prefrontal cortex, right angular gyrus, and left anterior cingulate. HOMA-IR correlated negatively with cerebral glucose metabolism in left middle temporal gyrus and left insula.
22.	García-Casares et al. (2014b)	25	25	Structural: VBM PET: FFDG	3 T Intera PHILIPS; **MPRAGE:** TR = 9.9/4.6 ms; flip angle = 8°; matrix size = 256 × 256; FOV = 240 mm; slice thickness = 1 mm; 190 slices; voxel size = 0.9 × 0.9 × 1 mm^3	2 sample t-tests; Wilcoxon Rank Sum test if assumptions for test were violated, and the chi squared test for dichotomous variables. αlevel was p < 0.05 twotailed statistical comparisons. Linear regression	Lower scores in Trailmaking Test B (p < 0.004), ColorWord Stroop test (p < 0.005), Semantic Fluency (p < 0.006), DigitSymbol modalities test (p < 0.02), Text Recall from the Wechsler Memory Scale (p < 0.0001), Rey-Osterrieth Complex Figure-copy (p < 0.004), and delayed reproduction (p < 0.03). Worse executive functions and memory functioning correlated predominantly with less GM density and reduced glucose metabolism in the orbital and prefrontal cortex, temporal (middle gyrus, parahippocampus, and uncus), and cerebellum regions (p < 0.001).
23.	Gold et al. (2007)	23	23	Structural: Hippocampal volume	Scanner not defined; **T_1:** TR = /TE = 2/30 ms; 124 slices; slice	Multivariate regression analysis	The inverse relationship between glycaemic control and hippocampal volume; in

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	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
					thickness = 1.5 mm; no gap; FOV = 250 × 250 mm; matrix = 256 × 128; flip angle = 60°		multivariate regression analysis, HbA1c was the only significant predictor of hippocampal volume, accounting for 33% of the observed variance. Other variables commonly associated with type 2 diabetes, such as elevated BMI, hypertension or dyslipidaemia, did not independently contribute to the variance in hippocampal volume.
24.	Hayashi et al. (2011)	61	53	Structural: VBM	1.5 T Magneton SIEMENS; **T_1** TR/TE = 4.4/11.4; flip angle = 158; acquisition matrix 256 × 256; NEX = 1; FOV = 22 cm; slice thickness = 1.5 mm)	Linear Regression analysis	Type 2 diabetes showed significant increases in hippocampal and whole brain atrophies. The MMSE and HDSR scores in type 2 diabetic patients showed significant negative correlations with age and significant positive correlations with years of education. These scores were also significantly negatively correlated with hippocampal atrophy, but not whole brain atrophy. Hippocampal atrophy in diabetic patients did not, however, correlate with age, years of education, or diabetes-related parameters.
25.	He et al. (2015)	12	12	TaskfMRIBOLD Structural: VBM	1.5 T Infinion PHILIPS; **EPI T_2*w:** 16 axial slices: TR/TE = 3000/40 ms; FOV = 24 cm × 24 cm; matrix = 64 × 64; flip angle = 90°; slice thickness = 4 mm; 1.2 mm gap. **T_1** obtained using 2D **SE** and 3D **SPGR**	Independent two sample *t*-test to compare demographic and clinical characteristics except for gender, which was analyzed by χ^2 test Pearson and Spearman correlation analyses ANOVA: for performance accuracies and BOLD responses in nback task Partial correlational analyses comparing HbA1c and taskrelated BOLD responses	No group difference of grey matter volume was found at neither global nor regional level. Significant load by group interaction was found in right dorsolateral prefrontal cortex (DLPFC), left middle/inferior frontal gyrus (M/IFG), and left PA ($F(2, 44) > 3.8$, $P < 0.05$). Patients showed elevated BOLD responses than controls during the 2back ($P < 0.05$) but not 0back or 1back condition. Positive correlations between HbA1c and the BOLD responses in the ACC ($r = 0.71$, $P = 0.015$) and bilateral DLPFC (Left: $r = 0.61$, $P = 0.046$; Right: $r = 0.65$, $P = 0.032$).
26.	Hoogenboom et al. (2014)	18	19	FMRI: Diffusion: MD, FA, AD, RD	3 T Signa GE; **DTI:** 56 slices parallel to the anterior posteriorcommissure line covering the whole brain: resolution = 0.9375 × 0.9375 × 2.6 mm^3; 30 gradient directions at b = 1000 s/mm^2; 5 baseline scans at b = 0 s/mm^2; TR/TE = 16000/84 ms; FOV = 24 cm; 256 × 256 matrix. TA = 9min20s **EPI:** T = 3000 ms; TE = 30 ms; flip angle = 90°; wholebrain volumes with 26 contiguous 5 mm thick transverse slices; no interslice gap; 3.125 × 3.125 mm^2 inplane resolution.	Student *t*-tests or MannWhitney *U* tests to analyse group differences Differences in medication use, smoking history, gender, and race distributions were analysed using Fisher exact-tests or χ^2test. Multivariate ANCOVA Spearman's correlation	Lower than the HC group on fullscale IQ ($t = 2.19$, $df = 35$, $P = 0.04$, Cohen's $d = 0.74$), verbal fluency ($t = 2.41$, $df = 35$, $P = 0.02$, Cohen's $d = 0.82$), and Rey Auditory Verbal Learning Test immediate recall ($t = 2.06$, $df = 35$, $P = 0.047$, Cohen's $d = 0.63$). Diabetes duration and HbA1C were not significantly correlated with performance on any cognitive test. Stronger connectivity in HC within DMN compared to T2DM in several regions, including left fusiform gyrus ($P < 0.02$) and left medial frontal gyrus ($P = 0.08$). Connections between the PCC and both left superior parietal lobule and left middle temporal gyrus approached

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	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
							significance (P < 0.10). No interhemispheric or intra-tract differences in FA found. FA is 6% lower in cingulum bundle CB and 4.7% lower in uncinate fasciculi (UF). Differences were maintained after adjusting for age, IQ, gender, verbal fluency and memory for CB (F = 4.76; df = 1, 30; P = 0.037; adjusted model R^2 = 0.20) and UF (F = 4.76; df = 1, 26; P = 0.038; adjusted model R^2 = 0.23). AD is 2.3% lower in cingulum bundle (axonal damage). Shorter fiber tract (CB: t = 2, df = 35, P = 0.053; UF: t = 1.83, df = 31, P = 0.077; and SLF: t = 1.81, df = 34, P = 0.079). No significant differences observed for RD. Age, education, diabetes duration, and HOMA-IR were not correlated with FA (CB and UF) (P > 0.05). Positive correlation between HbA1c and UF FA (ρ = 0.569, P = 0.034). Lower UF FA associated with higher creatinine level (ρ = 0.644, P = 0.013) and slowing of information processing speed (ρ = 0.587, P = 0.027). Lower CB FA associated with higher BMI (ρ = 0.482, P = 0.043) and higher delayed memory (ρ = 0.498, P = 0.035). No correlation between CB or UF FA and lifetime HbA1c (P > 0.246).
27.	Hsu et al. (2012)	40	97	Structural: WMH	1.5 T SIEMENS; Transaxial **T_2:** TR/TE = 4860/98 ms; NEX = 2; voxel size 0.43 × 0.43 × 5 mm^3 **FLAIR:** TR/TE = 9790/106 ms; TI = 2500 ms; NEX = 2; voxel size 0.45 × 0.455 mm^3 **T_1:** TR/TE = 8.8/4.7 ms; NEX = 1; voxel size 1.0 × 1.0 × 1.0 mm^3 singleshot spinecho echoplanar wholebrain **DTI** scans were acquired axially with a fat suppression sequence: TR/TE = 7600/82 ms; 3 mm slice thickness without gap; slice acquisition matrix = 128 × 128 with FOV = 256 × 256 mm^2; 6/8 partial Fourier; NEX = 2; 55 slices; 12 gradient directions with bvalue = 1000 s/mm^2; and one b = 0 s/mm^2 image	Pearson's correlations	No significant differences in age, gender, and WM hyper intensity scores derived from the conventional MRI scans between HC and T2DMpatients. For the T2DM patients, however, the MD of the brain parenchyma was significantly increased compared to HC and was positively correlated with disease duration. The voxel-based analyses revealed (i) a significantly decreased FA in the bilateral frontal WM compared to HC which was mainly caused by an increased TD and not a decreased AD within these regions; (ii) a significant association between disease duration and microstructural properties in several brain regions including bilateral cerebellum, temporal lobe WM, right caudate, bilateral cingulate gyrus, pons, and parahippocampal gyrus.
28.	Jongen et al. (2007)	99	46	Structural: White matter volume, Grey matter volume, WML volumes, cerebrospinal fluid, lateral ventricles	1.5 T PHILIPS Medical System; slice thickness = 4 mm; 38 contiguous slices; FOV = 230 × 230 mm; matrix size = 256 × 256 **T_2**: **PD** and **FLAIR** scans were made: **T_1**: TR/TE = 234/2 ms; **IR**:	Regression analysis	Type 2 diabetes was associated with a smaller volume of grey matter (−21.8 ml; 95% CI −34.2, −9.4) and with larger lateral ventricle volume (7.1 ml; 95% CI 2.3, 12.0) and with larger white matter lesion volume (56.5%; 95% CI 4.0, 135.8),

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	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
					TR/TI/TE = 2919/410/22 ms; **T_2:** TR/TE = 2200/100 ms; **PD**: TR/TE = 2200/11 ms; **FLAIR:** TR/TI/TE = 6000/2000/100 ms.		whereas white matter volume was not affected. In separate analyses for men and women, the effects of diabetes were only significant in women.
29.	A. Kumar et al. (2008)	52	25	Structural: Grey matter volume	No details given	Correlations coefficients (no details given)	Patients with diabetes, both with and without depression, had smaller total brain grey matter volumes when compared with the HC subjects after controlling for age, intracranial volume, and years of education. This group also had smaller grey matter volumes in the anterior cingulate and orbitofrontal regions when compared with the HC after additionally controlling for total grey matter volume. The depressed and non-depressed diabetic groups did not differ on any neuroimaging measure. Cerebrovascular risk factors correlated negatively with grey matter volumes.
30.	R. Kumar et al. (2008)	39	428	Structural: Grey matter volume, White matter volume, White matter hyperintensities	1.5 T PHILIPS; **T_1:** TR/TE = 28.05/2.64; flip angle = 30°; matrix size = 256 × 256; FOV = 260 × 260 mm; slice thickness = 2.0 mm; interslice distance = 1.0 mm; yielding over contiguous coronal slices and an inplane spatial resolution of 1.016 × 1.016 mm/pixel **FLAIR:** TR/TE/TI = 11000/140/2600 ms; matrix size = 256 × 256; FOV = 230 × 230 mm; slice thickness = 4.0 mm; no gap; inplane spatial resolution = 0.898 × 0.898 mm/pixel	Multiple regression analysis	Subjects with diabetes were more likely to have poor physical health, a higher body mass index, and higher scores of depression and anxiety compared with comparison subjects without diabetes. In multiple regression analyses, diabetes was associated with greater total brain atrophy and larger CSF volume but did not differ in the WM, GM, and WMH volumes. Diabetes patients performed less well on a task of fine motor dexterity.
31.	Last et al. (2007)	26	25	Structural: Grey matter volume, White matter volume, Cerebrospinal fluid	3 T VHI GE VHI; **T_1 IRFGE**: TI/TE/TR = 600/3.3/8.1 ms; FOV = 24 × 19; matrix size = 256 × 192; slice thickness = 3 mm **FLAIR:** TI/TE/TR = 2250/161/11,000 ms; FOV = 24 × 24; matrix size = 256 × 160	Multiple regression analysis	Hypoperfusion in the frontal region was associated with grey matter atrophy ($P < 0.0001$). Higher A1C was associated with lower CBF ($P < 0.0001$) and greater CSF ($P = 0.002$) within the temporal region. Type 2 diabetes is associated with cortical and subcortical atrophy involving several brain regions and with diminished regional cerebral perfusion and vasoreactivity.
32.	Laugesen et al. (2013)	89	89	Structural: WML	1.5 T Achieva PHILIPS; **T_2FLAIR:** slice thickness = 5 mm; TE/TR = 130/6000 ms; TI = 2200 ms; ETL = 19; flip angle = 90°; 2 averages	Paired t-tests and t-tests The estimated volumes of WMLs were not normally distributed even if log transformed nptrendtest with signed rank test.	PWV in diabetic group was significantly higher 0.3 ± 2.0 vs. 8.0 ± 1.6 m/s; $P < 0.0001$ PWV increased with Breteler score ($P < 0.001$ for trend) and remained significant after adjustment Association remained significant even after inclusion of HbA1c, duration of diabetes, or treatment modality in the model ($P < 0.05$ for all)

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Table 1 (*continued*)

	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
							Interaction between PWV and diabetic/ control group was not significant (P = 0.67) No significant difference between the diabetic group and the control group with regard to Breteler score (48/31/10 vs. 50/ 26/13; P = 0.64) WMLs was not significantly different between the diabetic and the control groups (mean difference −0.3 cm^3 [95% CI −1.2 to 0.7 cm^3]; P = 0.55) Subjects with cerebral infarctions had significantly higher PWV than subjects without (9.9 ± 1.7 vs. 8.5 ± 1.9 m/s; P = 0.002).
33.	Lee et al. (2013)	23	23	Structural: Ventricles volume	1.5 T GE; **3D SPGR; sagittal T_1:** TE/TR = 5/24 ms; matrix = 256 × 192; FOV = 24 cm; flip angle = 45°; NEX = 2; slice thickness = 1.2 mm. **Axial T_2:** TE/TR = 126/2817 ms; matrix = 256 × 192; FOV = 22 cm; flip angle = 90°; NEX = 1; slice thickness = 5 mm **FLAIR** axial; TR/TE = 8802/88 ms;TI = 2200 ms; matrix = 256 × 192; FOV = 22 cm; flip angle = 90°; NEX = 1; slice thickness = 5 mm	Group comparisons with t-tests or chisquare tests ANCOVA Partial correlation analyses Multivariate analysis of covariance	Enlarged lateral and 3rd ventricles in T2DM ($F_{1,41}$ = 7.96, P = 0.007; $F_{1,41}$ = 11.16, P = 0.002, respectively). No difference in ICV between groups ($F_{1,41}$ = 0.05, P = 0.82) z scorization for the lateral and the third ventricles were 0.97 and 1.41, respectively. Volumes of the fourth ventricle were not different between groups ($F_{1,41}$ = 0.23, P = 0.63). No significant association of lateral ventricle enlargement and disease duration (r = 0.40, P = 0.079). No relationship between lateral ventricular volume and HbA1c levels (r = 20.27, P = 0.25). Volume of the third ventricle was correlated neither with disease duration (r = 0.26, P = 0.26) nor with HbA1c levels (r = 20.36, P = 0.12). Localized expansion of the frontal horns of the bilateral lateral ventricles to the surrounding brain regions including the medial frontal lobe (P < 0.05).
34.	Manor et al. (2012)	68	89	Structural: VBM, GM volume	3 T HDx GE; **3D MPRAGE:** TR/TE /T I = 6.5/2.8/1100 ms; 3.0 mm slice thickness; 52 slices; BW = 122 Hz/pixel; flip angle = 158°; FOV = 24 × 24 cm; matrix size = 256 × 192	One way ANOVA (clinical/ demographic param) ANCOVA (volume changes between groups) Boferroni adj. For significance P < 0.005 Turkey's post hoc group difference within significant models	No association with clinical param, clinical neuropathy score found and walking outcome. Smaller cerebellum volume associated with T2DM P < 0.001. Smaller cerebellum volume is associated with slower walking speed greeter stride duration variability and longer double support.
35.	Manschot et al. (2006)	113	51	Structural: Grey matter volume, White matter volume, WML	1.5 T; PHILIPS; **T_1: axial T_2** and **T_2 FLAIR**: TR/TE/TI = 6000/100/2000 ms; FOV = 230 mm; matrix size = 180 × 256; slice thickness = 4.0 mm; contiguous slices; 38 slices	Linear regression analysis	Type 2 diabetes was associated with deep WMLs (P _ 0.02), cortical (P < 0.001) and subcortical (P < 0.05) atrophy, (silent) infarcts (P _ 0.06), and impaired cognitive performance (attention and executive function, information processing speed, and memory, all P < 0.05). Adjustment for hypertension did not affect the results. There was a modest association with HbA1c

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	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
							and diabetes duration. This association was strongest for age.
36.	Manschot et al. (2007)	122	56	Structural: Grey matter volume, White matter volume, WML	1.5 T; PHILIPS; **T_1; axial T_2** and **T_2 FLAIR**: TR/TE/TI = 6000/100/2000 ms; FOV = 230 mm; matrix size = 180 × 256; slice thickness = 4.0 mm; contiguous slices; 38 slices	Multivariate regression analysis	Patients with type 2 diabetes had more cortical ($p < 0.001$) and subcortical ($p < 0.01$) atrophy and deep WML ($p = 0.02$) than the HC group and their cognitive performance was worse. In multivariate regression analyses within the type 2 diabetes group, hypertension ($p < 0.05$) and a history of vascular events ($p < 0.01$) were associated with worse cognitive performance, while statin use was associated ($p < 0.05$) with better performance. Retinopathy and brain infarcts on MRI were associated with more severe cortical atrophy (both $p < 0.01$) and statin use with less atrophy ($p < 0.05$). Insulin level and brain infarcts were associated with more severe WML and statin use with less severe WML (all $p < 0.05$).
37.	Manschot et al. (2008)	122	56	Structural: Grey matter volume, White matter volume, WML	1.5 T; PHILIPS; **T_1; axial T_2** and **T_2 FLAIR**: TR/TE/TI = 6000/100/2000 ms; FOV = 230 mm; matrix size = 180 × 256; slice thickness = 4.0 mm; contiguous slices; 38 slices	Linear regression analysis	Overall 38% of the patients with DM2 and 12% of the HC were classified as having any neuropathy (pb0.001). Patients with DM2 had a lower performance on the neuropsychological tests, more white matter lesions (pb0.01) and more atrophy (pb0.01) than HC. Within the DM2 group none of the measures of peripheral neuropathy was related to MRI abnormalities or cognitive dysfunction.
38.	Marder et al. (2014)	22	29	Rs and taskfMRI: DMN	3 T Signa HDxt GE; **EPI:** TR = 2;000/25 ms; flip angle = 90°; slice thickness = 4 mm; FOV = 24 × 24 cm^2; matrix size = 64 × 64; voxel size = 3.75 × 3.75 × 4 mm^3	Group differences with MannWhitney U tests Pearson $\chi 2$ test tasks	No significant differences between groups on any cognitive tests including vocabulary and fMRI task. Bilateral activation of the hippocampus (z score ± SD, encoding, left 3.89 ± 0.62, right 3.06 ± 1.13; recognition, left 3.48 ± 0.48, right 3.82 ± 0.93). Negative correlations between PG and deactivation in cuneus ($\rho = -0.49$, $P = 0.04$), precuneus ($\rho = -0.49$, $P = 0.04$) during encoding and medial frontal gyrus ($\rho = -0.52$, $P = 0.03$) during recognition. PG levels ≥ 11 mmol/L were associated with reduced deactivation of DMN regions during both encoding and recognition.
39.	Mehta et al. (2014)	85	40	Structural: VBM, GM	3 T GHx GE; **FLAIR:** parameter not defined **MPRAGE:** parameter not defined	Descriptive analyses were used for demographic characteristics and oneway ANOVA and Wilcoxon tests for group comparisons Linear regression and least square (LS) models were used to find relationships	Increased UACR associated with lower GM volume in frontal lobe ($r^2_{adj} = 0.2$–0.4, $P = 0.01$–0.05) and related to global GM atrophy ($r^2_{adj} = 0.1$, $P = 0.04$). Results are independent of DM duration, HbA1c, and hypertension. Lower global GM volume was related to worse executive function ($P = 0.04$).

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	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
40.	Moran et al. (2013)	350	363	Structural: VBM, Lesion load, Microbleeds, Infarcts, WMH	1.5 T GE; **T_1:** TR/TE = 7/35 ms; flip angle = 35°; FOV = 24 cm; 120 contiguous slices; isotropic voxel size 1 mm^3 **T_2:** TR/TE = 4300/120 ms; NEX 1; **FLAIR:** TR/TE = 8802/130 ms; IT 2:200 ms; voxel size 0.50 × 0.50 × 3 mm^3 turbo factor 48; voxel size 0.90 × 0.90 × 3 mm **GRE:**TR/TE = 0.8/0.015 ms; flip angle = 30°; voxel size 0.9 × 0.9 × 7 mm^3	Multivariable regression Linear regression and logistic regression.	T2DM associated with cerebral infarcts, lower total GM, WM, and hippocampal volume. No association with microbleeds and WMH. GM loss distributed in medial temporal, anterior cingulate, medial frontal lobes, and WM loss distributed in frontal and temporal regions. T2DM associated with poorer visuospatial construction, planning, visual memory, and speed (P 0.05) independent of age, sex, education, and vascular risk factors. The strength of these associations was attenuated by almost one-half when adjusted for hippocampal and GM volumes but was unchanged by adjustment for CVL or WM volume. T2DM independently associated with worse scores in RCFT copy ($P < 0.001$), delayed recall ($P < 0.001$) and longer time to complete the Stroop dot-test (P = 0.004). Longer duration T2DM (> 15y, n = 157) associated with poorer scores in RCFT copy (P = 0.03), digit symbol coding (P = 0.001), and symbol search (P = 0.001) T2DM, MRI & Cognition when adjusting for hippocampal and GM volume associations was attenuated by in RCFT copy (by 36.2%), RCFT delayed recall (by 54.9%), and Stroop dot (by71.7%) scores. Only very small additional changes in were observed with WMH vol. (< 9.4%), WM volume (< 1%), or infarcts (< 17.2%).
41.	Musen et al. (2012)	10	11	Structural: hippocampal volume FMRI: DMN	3 T Tim Trio SIEMENS; **BOLD:** TR/TE = 3000/30 ms; flip angle = 90°; whole brain volumes with 26 contiguous; slice thickness = 5 mm; transverse slices; no interslice gap; resolution = 3.125 × 3.125 mm inplane **3D MPRAGE:** matrix = 256 × 256; FOV = 25.6 cm; 128 slices; slice thickness = 1.33 mm; flip angle = 12°; TE/TR = 2.74/2100 ms	*t*-test (clinical/demographic param) GLM to asses functional connectivity βweight Pearson correlation to determine whether hippocampal volume and HOMAIIR were correlated with βweight	Reduced functional connectivity between PCC and other DMN regions. HOMA inversely correlated with βweight for connectivity between PCC regions involved in DMN: right inferior frontal gyrus r = 0.90, P = 0.035 and right precuneus r = 0.81, P = 0.097. Controlling for full scale/verbal IQ did not influence results. No group effects on brain structure or cognition. No differences in hippocampal volume. Diabetes duration was associated with any outcomes.
42.	Novak et al. (2006)	28	22	Structural: WMH Perfusion: Blood flow velocities	3.0 Tesla MRI; **T_1 IR-FRG; FLAIR; T_2 FSE.** Parameters not defined	Regression analysis	WMH volume was negatively correlated with baseline BFV ($P < 0.0001$). A regression model revealed that baseline BFVs were negatively associated with periventricular WMHs, HbA1c (A1C), and inflammatory markers and positively associated with systolic blood pressure ($R^2 = 0.86$, $P < 0.0001$). Microvascular disease in type 2 diabetes, which manifests as white matter abnormalities on MRI, is

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Table 1 (*continued*)

	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
							associated with reduced cerebral BFVs, increased resistance in middle cerebral arteries, and inflammation.
43.	Novak et al. (2011)	71	76	Structural: GM, WM, CSF, WMH Perfusion: Vasoconstriction reactivity	3 T GE **MPRAGE**: **FLAIR**: and 3D **ASL.** Parameters not defined	Least square models	Diabetic subjects with greater vasoconstriction reactivity, more atrophy, depression, and slower walking. Adhesion molecules specifically related to GM atrophy. (P = 0.04) and altered vasoreactivity (P = 0.03) in the diabetic and control groups. Regionally, sVCAM and sICAM were linked to exaggerated vasoconstriction, blunted vasodilatation, and increased cortical atrophy in the frontal, temporal, and parietal lobes (P = 0.04–0.003). sICAM correlated with worse functionality.
44.	Novak et al. (2011)	15	14	Perfusion: rCBF	Parameters not defined	Between group oneway ANOVA, nonparametric tests, and LS models	Diabetic subjects had greater vasoconstriction reactivity, more atrophy, depression, and slower walking. Adhesion molecules were specifically related to grey matter atrophy (P = 0.04) and altered vasoreactivity (P = 0.03) in the diabetic and HC groups. Regionally, sVCAM and sICAM were linked to exaggerated vasoconstriction, blunted vasodilatation, and increased cortical atrophy in the frontal, temporal, and parietal lobes (P = 0.04–0.003). sICAM correlated with worse functionality.
45.	Raji et al. (2010)	94	94	Structural: GM, WM	1.5 T – Signa GE; **SPGR**: TE/TR = 5/25 ms; FA = 40°; NEX = 1; size = 0.98 × 0.98 mm^2; FOV = 250 × 250 mm; acquisition matrix; slice thickness = 1.5/0 mm	ANCOVA model controlling for age, gender, and race,	Lower GM and WM.
46.	Reijmer et al. (2013a)	35	35	Diffusion: MD, FA Structural: WMH, Infarcts	3 T – Intera Philips; **SSEPI:** 48 contiguous slices; voxel size = 1.72 × 1.72 × 2.50 mm^3; TR = 6638 ms; TE = 73 ms; flip angle = 90°; 45 isotropically distributed diffusionsensitizing gradients with b value = 1200 s/mm^2 and one b = 0 s/mm^2 (3 averages). TA = 5min32s. **FLAIR:** 48 continuous slices; voxel size = 0.96 × 0.95 × 3 mm^3; TR = 11,000 ms; TE = 125 ms; IT = 2800 ms	Independentsamples *t*-test MannWhitney *U* test for nonparametric data, Linear regression analyses. Linear regression analyses	MD significantly increased in all tracts in both hemispheres (P < 0.05). FA difference between group was located in uncinate fasciculus (P = 0.046). MD changes were associated with slowing information processing speed. Worse memory performance was noticed after adjustment for age, sex and IQ (group x MD interaction, all P < 0.05). No association with WMH load presence of cerebral infarcts and diabetes duration. HbA1c associated with worse executive functioning in T2DM (−0.42 [−0.89 to −0.15], P = 0.01). Trend between HbA1c levels and memory (−0.28 [−0.68 to 0.002], P = 0.05) and higher MD in the ILF (0.28 [0.00–0.56], P = 0.05).
47.	Reijmer et al. (2013b)	63	61		3 T PHILIPS; **SSEPI:** 192 contiguous slices; voxel	Cognitive testing,, IQ with Dutch version of the	In T2DM patients network parameters associated with slowing of information

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Table 1 (*continued*)

	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
				Structural: WMH Functional: lacunar infarcts	size = 1.00 × 1.00 × 1.00 mm^3; 45 isotropically distributed diffusion sensitizing gradients with b value = 1200 s/mm^2 and one b = 0 s/mm^2 **FLAIR:** 48 continuous slices; voxel size = 0.96 × 0.95 × 3 mm^3; TR/TE = 11,000/125 ms; IT = 2800 ms	national adult reading test, information processing speed by TrailMaking Test, Stroop ColourWord Test and subtest Digit Symbol of the Wechsler Adult Intelligence Scale III Network measures using the brain connectivity toolbox Between group differences in the brain WM with independent sample tests Zscores	processing. No correlation between network measures and memory or executive functioning. No relation between network measures and cognitive performance within the control group WMH load and lacunar infarcts associated with reduced clustering, reduced global efficiency, and increased path length in patients.
48.	Reinhard et al. (2012)	20	26	Structural: WMH	3 T Trio Magnetom SIEMENS; **3D**: 192 sagittal slices; matrix = 256 × 256; **T_1:** TR/TE = 1550/3.04 ms; TI = 800 ms; flip angle = 9°; voxel size = 1 × 1 × 1 mm^3 **T_2:** TR/TE = 3000/354 ms; FOV = 282 mm; voxel size = 1.1 × 1.1 × 1.1 mm^3 **FLAIR:** TR/TE = 6000/353 ms; TI = 2200 ms; FOV = 282 mm; voxel size = 1.1 × 1.1 × 1.1 mm^3	Linear regression analysis, univariate analysis	PNTproBNP was associated with WMH in linear regression analysis adjusted for CV risk factors (r = 0.94, p = 0.001) and with BPF in univariate analysis (r = 0.57, p = 0.009). Patients divided into groups of increased PNTproBNP levels were paralleled with increased WMH volumes(geometric mean[SD]; (2.86[5.11] ml and 0.76[2.49] ml compared to patients with low PNTproBNP 0.20[2.28] ml, p = 0.003)) and also when adjusted for age, sex and presence of CAD (p = 0.017). The association was strengthened by CV risk factors and we did not find a common heart or brain specific driver of both PNTproBNP and WMH. Patients and particular patients with CAD had higher WMH, however no longer after adjustment for age and sex.
49.	Rusinek et al. (2015)	23	37	Perfusion: CBF	3 T Tim Trio SIEMENS; Parameters not given	A general linear model to identify factors correlated with GM CBF.	CBF decrease of 4.4 ml/100 g per/min (~7.5% lower) in IR compared to HC (P = 0.005), with no significant hypoperfusion in TDM (P = 0.312) No group interaction for any other individual predictors of cortical CBF.
50.	Samaras et al. (2014)	33	279	Structural: VBM	3 T Intera Quasar PHILIPS; 3 T Achieva Quasar Dual scanner PHILIPS; **T_1:** TR/TE = 6.39/2.9 ms; flip angle = 8°; matrix size = 256 × 256; FOV = 256 × 256 × 190; slice thickness = 1 × 1 × 1 mm^3; no gap	Group comparisons with ANCOVA, mood score and APOE ε4; cognition included as a covariate. Brain volumes were examined using ANCOVA	Diabetes was associated with a greater decline in global cognition at 2 year compared to HC. Greater decline in executive function compared to baseline diabetes. Baseline diabetes are significantly associated with CSF volumes increase, with trends for greater 2 year decline in TBV, hippocampal, parahippocampal and precuneus volumes, compared no diabetes. Comparing diabetes to NFG subjects only (over 2 years). Baseline diabetes are associated with significantly greater decline in TBV. Baseline diabetes are associated with greater decline in frontal lobe and precuneus volumes. Glucose disorders and

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	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
							changes. Incident glucose disorders (diabetes 5.8% (n = 18), IFG 12% (n = 38)) are associated with significantly greater decline in TBV. Both groups were similar in the 2 year changes in TBV observed. Inflammatory markers, oxidative metabolism byproducts and APOE genotype. Baseline diabetes had significantly lower total and HDL cholesterol and higher triglycerides, insulin, byproducts of oxidative metabolism (urate, malondialdehyde an homocysteine), VCAM and IL6. Carrier frequency of the Alzheimer's disease genotypes APOE ε3/4 and 4/4 are similar in all groups. No associations between hypoglycaemia frequency and 2 year change in cognitive domains. Dietalonetreated diabetes is associated with 2fold greater decline in TBV, compared to medication treated diabetes (-68.7 ± 0.4 vs. $-36.7 \pm 0.8\,mm^3$, respectively, $p = 0.04$). Dietalone participants had higher LDL (2.9 ± 0.2 vs. 2.2 ± 0.1 mmol/l, $p = 0.005$), lower triglycerides (1.0 ± 0.1 vs. 1.4 ± 0.1 mmol/l, $p = 0.04$), lower BMI (27.2 ± 1.0 vs. $29.9 \pm 0.06\,kg/m^2$, $p = 0.04$).
51.	Tiehuis et al. (2008)	98	47	Perfusion: Cerebral blood flow	1.5 T PHILIPS Medical Systems; Axial **T_1:** TR/TE = 234/2 ms; **IR:** TR/TE = 2900/22 ms; **FLAIR:** TR/TE/TI = 6000/2000/100 ms; slice thickness = 4 mm; no gap; 38 slices; FOV = 230 × 230 mm^2 matrix = 256 × 256	Linear regression analysis	Patients with type 2 diabetes performed worse on neuropsychological tests ($p < 0.05$). Total CBF per 100 ml brain parenchyma volume did not differ between participants with and without diabetes (difference $-2.3\,ml\,min^{-1}\,100\,ml^{-1}$; 95% CI −6.0, 1.3). In the entire group, total CBF per 100 ml brain parenchyma volume was positively associated with cognitive functioning (0.09 SD increase in composite z score per $10\,ml\,min^{-1}\,100\,ml^{-1}$ increase in relative total CBF). This association was not affected by type 2 diabetes.
52.	van Bussel et al. (2015)	39	34	Structural: Diffusion/ Perfusion	3 T Achieva TX PHILIPS; **3D T_1**: TR/TE = 8.1/3.7 ms; 1.00 mm isotropic voxel; 170 continuous slices; matrix size = 240 × 240; TA = 7:56 min **SSEPI:** TR/TE = 6800/84 ms; 2.4 mm isotropic voxel; TI = 2230 ms; TA = 5:13 min.	T-tests, χ^2 test for demographic clinical group differences Linear regression analyses	Worse performance on WLT (P = 0.016) and on baseline MMSE (P = 0.023), but not on the repeated MMSE (P = 0.366), and the recall words learning (verbal) memory task (WLT recall score, P = 0.178) Increased perfusion fraction f (P = 0.022). D increased with lower memory performance (P = 0.021) and age ($\beta = 0.344$, P = 0.018) Blood flow–related fD^* increased with lower memory performance (P = 0.038). No significant associations were observed for D^*. Increased perfusion fraction f with

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	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
							higher FBG levels (P = 0.031) Blood flow–related fD* increased with higher FBG levels (P = 0.020) and with lower memory performance (P = 0.041). Interaction analysis (FBG levels × memory performance) revealed a significant interaction for D* (β = 0.273, P = 0.038) and fD* (β = 0.278, P = 0.018). HbA1c did not show any significant associations with IVIM measures.
53.	van Harten et al. (2007)	92	44	Structural: Periventricular hyperintensities, WML, cerebral atrophy, lacunar infarcts	1.5 T GE; Parameters not defined.	Multiple linear regression analysis	Neuropsychological scores were worse for each cognitive domain except for memory functions after adjustment for hypertension in a group of elderly patients with type 2 DM compared to HC subjects. Only PVH were independently associated with motor speed, whereas all other MRI measures were not independently associated with cognitive Impairment. Interactions between the different MRI measures were not present. Glycosylated haemoglobin (HbA1c) and duration of DM were significantly associated with cognitive dysfunction.
54.	Wang et al. (2014)	26	26	RS-FMRI: ALFF	3 T Achieva PHILIPS; **EPI:** TR = 2000/30 ms; 33 slices; slice thickness = 5 mm; gap = 0 mm; FOV = 192 × 192 mm^2; matrix = 64 × 64; flip angle = 90°; TA = 7 min. **Turbofield echo:** TR/ = 7.7/3.8 ms; slices = 180; slice thickness = 1 mm; gap = 0 mm; flip angle = 80°; acquisition matrix = 252 × 227; FOV = 250 × 250 mm^2 and TA = 2 min58 s. **T_2FSE:** TR/TE = 2000/80 ms **FLAIR:** TR/TE = 9000/140 ms; slice thickness = 5 mm; 2 mm gap	Group differences with *t*-test, Wilcoxon two sample test for data that did not achieve normal distribution after logarithm transformation, χ^2test for proportions. Linear correlations	Lower MoCA (p = 0.007) and CDT (p = 0.002) scores, after correcting for age and education MMSE test did not significantly differ between the two groups (p > 0.05). Significantly decreased ALFF in frontal and parietal lobes, bilateral thalami, posterior lobe of cerebellum and increased ALFF in the visual cortices. Lower ALFF in the left subcallosal gyrus correlated with lower ABI (r = 0.481, p = 0.020). Lower ALFF in bilateral medial prefrontal gyri correlated with higher UACR (r = 0.418, p = 0.047). Increased ALFF values in visual cortices were found to negatively correlate with MoCA scores. No difference in WMLs and lacunar infarcts (p > 0.05).
55.	Wang et al. (2015)	188	266	Spectroscopy: ^{1}H MRS STEAM	3 T – Intera Achieva PHILIPS; **T_2:** TR/TE = 5500/130 ms; slice thickness = 6 mm; gap = 1 mm **STEAM**: TE/TR = 9.4/2000 ms; NEX = 12; TA = 4 min348 s.	*t*-tests, χ^2test Multiple liner regression analyses	Significantly lower scores for MMSE and MoCA than did the control group (p < 0.05), but no MQ diff. T2DM negatively affected scores of MMSE, subtests (i.e., attention and language) of MMSE, MoCA, and subtests (i.e., visuospatial/ executive reasoning, attention, and language skills) of MoCA (p < 0.05). T2DM positively affected the concentrations of Cr and mI in the left hippocampus (p < 0.05). T2DM did not affect left frontal lobe NAA, Cho, Cr, and mI levels and left hippocampal NAA and Cho. Significant negative

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	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
							correlation between left hippocampal mI levels and language scores of MoCA. Significant negative correlation between left hippocampal Cr and visuospatial/executive MoCA scores.
56.	Wisse et al. (2014)	120	502	Structural: VBM	1.5 T – Philips; **Axial T1 IR**: TR/TE/TI: 2919/22/410 ms; **FLAIR:** TR/TE/TI: 6000/100/2000 ms; Both 38 contiguous slices; 0.9 × 0.9 × 4.0 mm^3 voxels 3 T – Philips; Axial **T_1 IR**: TR/TE/TI = 4416/15/400 ms; 48 contiguous slices; 1 × 1 × 3 mm^3 voxels Sagittal **T_1:** TR/TE = 7.2/2.9 ms; 192 contiguous slices; resolution = 1 × 1 × 1 mm^3	Linear regression analyses	Significantly smaller TBV relative to ICV than HC (mean diff: −1.24, 95% CI: −1.63; −0.86). Patients with T2DM relative to HC did not have smaller HV relative to ICV (mean diff: 0.00, 95% CI: −0.01; 0.00), nor did they have a smaller HV relative to TBV (mean diff: 0.01, 95% CI: −0.01; 0.02). HbA1c was not associated with any of the brain volume measures. Brain volume measures were not associated with memory performance in patients with T2DM.
57.	Xia et al. (2015a)	38	40	Perfusion: CBF	3 T Tim Trio SIEMENS**; 3D T_1:** TR/TE = 1900/2.48 ms; slice thickness = 1 mm; 176 slices; no gap; flip angle = 90°; FOV = 250 × 250 mm^2; matrix = 256 × 256 **Pulsed ASL** (PICORE Q2T): TR/TE = 4000/12 ms; FOV = 220 × 220 mm^2; matrix = 64 × 64; slice thickness = 4 mm; 1 mm gap; TI_1 = 600 ms; TI_2 = 1600 ms. TA = 45 min; including perfusion; anatomic; and other scans for BOLD	Differences between groups: *t*-test, nonparametric Mann–Whitney *U* test, χ^2 test, Bonferroni correction Betweengroup differences in brain volumes with 1 way ANOVA	Worse performance on all neuropsychological tests (significant differences in CFTcopy, CFTdelay, DST, and TMTB ($P < 0.05$)). No significant structural changes in brain regions ($P > 0.05$): GMV, WMV, and BPV not different. Decreased CBF, primarilythe visual area and DMN, including the right middle occipital gyrus, bilateral IPL, and right precuneus ($P < 0.01$, corrected). Relative CBF in the middle occipital gyrus was associated with CFTcopy scores (r = 0.392, P = 0.020), relative CBF in the bilateral IPL was correlated with TMTB scores (r = 0.351, P = 0.039), and relative CBF in the right precuneus correlated with DST scores (r = 0.371, P = 0.28). DBP inversely correlated with CBF in the middle occipital gyrus (r = 0.361, P = 0.033). DBP (r = 0.405, P = 0.016) and SBP (r = 0.343, P = 0.044) inversely correlated with CBF in precuneus.
58.	Xia et al. (2013)	28	29	RS-FMRI: ALFF	3 T Tim Trio SIEMENS; **EPI:** TR/TE = 2000/25 ms; slices = 36; thickness = 4 mm; 0 mm gap; FOV = 240 × 240 mm; matrix size = 64 × 64; flip angle = 90° **3D T_1:** TR/TE = 1900/TE ms; TE = 2.48 ms; 176 slices; slice thickness = 1 mm; no gap; flip angle = 90°; matrix size = 256 × 256; FOV = 250 × 250 mm^2; TA = 2min24s	*t*-test, χ^2test, Monte Carlo simulation.	T2DM patients performed poorer on CFT, TMTA, TMTB and CDT ($p < 0.05$) which may be specific indicators of attention, memory, and visual function. Significantly decreased ALFF in bilateral middle temporal gyrus (MTG), left fusiform gyrus, left middle occipital gyrus, right inferior occipital gyrus; Increased ALFF values in both the bilateral cerebellum posterior lobe and right cerebellum culmen. Inverse correlation between the ALFF values in MTG and both HbA1c (r = 0.451, p = 0.016) and the score of Trail Making TestB (r = 0.42, p = 0.026). Cpeptide level and pancreatic bcell function

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	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
							had a positive correlation (r = 0.429, p = 0.023; r = 0.453, p = 0.016, respectively) with the ALFF in MTG.
59.	Xia et al. (2015b)	25	26	Structural: WMH, lacunar infarcts RS-FMRI: Functional connectivity	3 T Tim Trio SIEMENS; **3D T_1:** TR/TE = 1900/2.48 ms; slice thickness = 1 mm; 176 slices; no gap; flip angle = 90°; FOV = 250 × 250 mm^2; matrix size = 256 × 256 **EPI:** TR/TE = 2000/25 ms; slice = 36; slice thickness = 4 mm; no gap; FOV = 240 × 240 mm^2; matrix = 64 × 64; flip angle = 90°	ANOVA, post hoc *t*-test for means and χ^2test for proportions between groups Z values to investigate associations	No significant difference in age, sex, education level, BMI, blood pressure, fasting Cpeptides, triglyceride, intima media thickness, presence of WMH and lacunar infarcts. Significant differences in Trail Making Test B (TMTB) ($p < 0.05$). Significant differences in functional connectivity of left hippocampus (One-way ANOVA) with: left insula, left MFG, bilateral IPL, bilateral calcarine, and left lingual gyrus. In the right hippocampus: left IFG, right MFG, right IPL, bilateral calcarine, right lingual, and right precuneus. T2DM + poorly controled cholesterol show signification correlations between clinical data (LDL/HDL, TMTB scores, waisthip ratio) and functional connectivity of left hippocampus left MFG (r = −0.607, p = 0.001; r = −0.442, p = 0.027;r = −0.416, p = 0.039, respectively) and functional connectivity of right hippocampus MFG (r = 0.418, p = 0.038; r = 0.552, p = 0.004, respectively).
60.	Xia et al. (2015c)	30	28	FMRI: Functional connectivity Structural: VBM	3 T Tim Trio SIEMENS; **FLAIR:** TR = 8500/94 ms; 20 slices; slice thickness = 5 mm; voxel size = 1.3 × 0.9 × 5 mm^3; **EPI:** TR = 2000/25 ms; 36 slices; slice thickness = 4 mm; no gap; FOV = 240 × 240 mm^2; matrix = 64 × 64; flip angel = 90°; **3D T_1** axial images: TR = 1900/2.48 ms; 176 slices; thickness = 1 mm; no gap; flip angle = 90°; matrix = 256 × 256; FOV = 250 × 250 mm^2; TA 744 s	*t*-test for means and χ^2test log HOMA-IR to investigate associations, Bonferroni correction	Groups did not differ significantly in age, sex, education, smoking, BMI, blood pressure, lipid content, blood pressure and cholesterol lowering medication intake, MMSE, MoCA. Patients scored lower then healthy controls on AVLTimmediate recall, TMTB, and DST ($p < 0.05$). GM, WM, and brain parenchyma volumes of two groups were not significantly different, but indices of T2DM were slightly lower. Significantly lower interhemispheric connectivity in MTG, middle frontal gyrus, superior frontal gyrus (SFG), inferior parietal lobule, and anterior cingulate gyrus. Interhemispherci connectivity in MTG and SFG are inversely correlated with TMTB (r = −0.404, p = 0.027; r = −0.544, p = 0.002, resp.) not significant after Bonferroni correction. HOMA-IR is negatively correlated with interhemispheric connectivity in MTG (r = −0.528, p = 0.003). No correlation was detected between HOMA-IR and neuropsychological.
61.	Xia et al. (2015d)	38	32	FMRI	3 T Tim Trio SIEMENS; **FLAIR:** TR = 8500/94 ms; 20 slices; slice thickness = 5 mm; voxel	*t*-test MannWhitney *U* test for asymmetrically distributed	Decreased rsFC in the left middle. Frontal gyrus (MFG) and bilateral inferior parietal lobe (IPL) of the DAN, as well as the left IPL

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Table 1 (*continued*)

	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
					size = 1.3 × 0.9 × 5 mm^3 **EPI:** TR = 2000/25 ms; 36 slices; slice thickness = 4 mm; no gap; FOV = 240 × 240 mm^2; matrix = 64 × 64; flip angel = 90°; **Rs-FMRI:** TA = 14 min:23 s; T_1 spanning; TR = 1900/2.48 ms; 176 slices; slice thickness = 1 mm; no gap; FA = 90°; FOV = 256 × 256 mm^2	variables, and a χ^2test for categorical variables.	and right MFG/IFG of the VAN in T2DM patients. rsFC of the left MFG was inversely correlated with the Trail Making TestB scores; the rsFC of the left IPL was positively correlated with the Digit Span Test scores but negatively correlated with HbA1c; and the rsFC in the right precuneus was positively associated with cognitive performance (without Bonferroni correction).
62.	Yang et al. (2015)	20	26	Structural: MTR	3 T Achieva PHILIPS; **SPGRE** with multishot EPI readout: TR/TE = 64/15 ms; flip angle = 9°; FOV = 24 cm; 67 axial slices; slice thickness = 2.2 mm; no gap; EPI factor = 7; voxel size = 0.83 × 0.83 × 2.2 mm^3; with a nonselective 5 lobed SincGauss offresonance MT prepulse B1/Df/duration = 10.5 mT/1.5 kHz/ 24.5 ms **MPRAGE:** TR/TE = 8.4/3.9 ms; FA = 8°; FOV = 24 cm; 134 axial slices; no gap; voxel size = 0.83 × 0.83 × 1.1 mm^3. **FLAIR FSE**: TR/TI/TE = 11000/2800/68 ms; FOV = 24 cm; 67 axial slices/no gap; voxel size = 0.83 × 0.83 × 2.2 mm^3	univariate ANOVA for continuous variables and for χ^2test categorical variables. univariate ANCOVA controlling for age. Correlations using partial Pearson producmoment correlations.	Group differences No significant differences in age, sex race, handedness, education, IQ, MMSE, HAMD, DMI, blood pressure, LDL and mFSRP. No significant group difference in neuropsychological task performance in the three domains Significant differences HDL ($F = 19.406$, df = 1, 44, $P < 0.001$), CIRS ($F = 15.812$, df = 1, 44, $P < 0.001$), FSRP ($F = 8.848$, df = 1, 44, $P = 0.005$) and HbA1c MTR significantly lower in bilateral dACC ($F = 6.082$, df = 1, 44, $P = 0.018$) and right hCaud ($F = 5.416$, df = 1, 43, $P = 0.025$). MTR and T2DMrelated clinical measures. MTR negatively correlated with HbA1c in bilateral dACC (left: $r = 0.401$, df = 43, $P = 0.006$ and right: $r = 0.412$, df = 43, $P = 0.005$), bilateral rACC (left: $r = 0.350$, df = 43, $P = 0.018$,& right: $r = 0.329$, df = 43, $P = 0.027$), and right hCaud ($r = 0.323$, df = 43, $P = 0.031$). Significant correlation between right rACC MTR and FSRP (left: $r = 0.344$, df = 43, $P = 0.021$, right: $r = 0.371$, df = 43, $P = 0.012$). No significant correlation between MTR and duration of T2DM ($P > 0.07$), SBP ($P > 0.08$), DBP ($P > 0.13$), BMI ($P > 0.39$), HDL cholesterol ($P > 0.19$), and LDL cholesterol ($P > 0.12$) in T2DM. MTR and Neurophisiological task. Learning and memory Z score was positively correlated with bilateral rACC MTR in T2DM (left: $r = 0.595$, df = 16, $P = 0.009$ and right: $r = 0.811$, df = 16, $P < 0.001$). Right rACC MTR also positively correlated with executive function Z score in T2DM ($r = 0.540$, df = 15, $P = 0.025$).

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	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
63.	Yau et al. (2009)	24	17	Structural: WM	1.5 T Avanto SIEMENS; **T_1 MPRAGE**: TR = 1300/4.38 ms; TI = 800 ms; FOV = 250 × 250; 196 slices; slice thickness = 1.2 mm; NEX = 1; flip angle = 15°; coronal plane; **T_2:** TR = 9000/94 ms; TI = 2000 ms; FOV = 210 × 210; 50 slices; slice thickness = 3 mm; **FLAIR:** TR = 9000/97 ms; FOV = 210 × 210; 1 average and 2 concatenations; flip angle = 145° **DTI:** echo planar: TR = 6100/75 ms; delay in TR = 0; b values = 0; 1000 s/ mm^2; 6 directions; FOV = 210 × 210; 4 averages and 1 concatenation; 50 axial slices; voxel size = 1.64 × 1.64 × 3 mm^3	Hierarchical regression analysis	impairment in declarative memory among diabetic subjects and in some preliminary support to suggest a possible blunting of the memory facilitation by emotional material among female but not male diabetics; first DTI assessment among individuals with T2DM, which after accounting for overt WM damage, revealed diffuse but predominantly frontal and temporal WM microstructural abnormalities, with e × tensive involvement of the temporal stem. Hierarchical regression analyses demonstrated that immediate, but not delayed, emotional memory performance was explained by temporal stem FA, independent of age, poor metabolic regulation, and systolic blood pressure. Given that the temporal lobe memory networks appear to be particularly vulnerable to the deleterious effects of T2DM, this may help explain the observed memory impairments among diabetics.
64.	Yau et al. (2014)	46	50	Structural: WMH, VBM Diffusion: MD, FA	1.5 T Avanto SIEMENS; **MPRAGE**: TR = 1300/4.38 ms; TI = 800 ms; FOV = 250 × 250; 196 coronal slices; slice thickness = 1.2 mm; no gap; NEX = 1; flip angle = 15°	Group differences using independent samples *t*-test, χ^2test for categorical variables. MannWhitney *U* test, BonferroniHolm stepdown test VANCOVA, Spearman's correlation analyses	Neuropsychological:T2DM had significantly lower estimated IQ scores and scored consistently lower across all verbal memory WM FA: VANCOVA analysis identified 15 significant WM clusters (3471 voxels or 3.47 cc in volume, $p < 0.01$), 13 demonstrated significant FA reductions in T2DM (3228 voxels or 3.23 cc in volume), independent of age and WMH. Clusters were located in left hemisphere (70%), specifically temporal regions involved in auditory memory processing, including bilateral arcuate fasciculi, left superior temporal WM, right middle temporal WM. GM MD: VANCOVA revealed 22 clusters of significant MD elevation in T2DM GM relative to HC ($p < 0.01$). Brain volume & cortical thickness: groups did not differ in ICV volume or ICVadjusted global atrophy. Only average ICVadjusted hippocampal volume was significant, showing smaller volumes in T2DM. Result remained significant after accounting for multiple comparisons (p = 0.01). Brain volume, cortical thickness and cognitive results remained the same even after controlling for age, sex and inflammation Temporal lobe & verbal memory: Spearman's correlation found no relationship between ICVadjusted average

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	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
							hippocampal volume and composite scores for verbal memory immediate or delayed recall in T2DM. No correlation was found even when examining left or right hippocampal volume separately. Only MD value of left PHG MD cluster correlated negatively and significantly with verbal memory immediate, $rs(25) = -0.54$, $p < 0.01$ and delayed recall composite scores, $rs(25) = -0.44$, $p < 0.05$. Associations remained significant after controlling for age and sex.
65.	H. Zhang et al. (2015)	14	14	RS-FMRI	3 T Signa HDxt General electric; **MPRAGE:** TR = 6.6/2.8 ms; flip angle = 15°; BW = 31.25 kHz; FOV = 24; slice thickness = 3 mm; 52 slices; matrix = 192 × 256; **EPI:** BOLD contrast; TR = 3000 ms; TE = 27 ms; flip angle = 60°; FOV = 25; slice thickness = 5 mm; 30 slices; matrix = 64 × 64; NEX = 1	Pearson correlation, Onesample Student *t*-tests, two sample	Lower global GM volume (P = 0.03), fewer years of education (P = 0.03), worse executive function (P = 0.004) and verbal memory (P < 0.002). Hippocampal volumes were similar between groups Insulin increased connectivity between the medial frontal cortex (MFC), right (R)IPC, PCC, and ACC and hippocampal regions, compared placebo rs connectivity after insulin administration: Diabetes group still had worse functional connectivity in the MFC as compared with HC but these differences are less prominent than after placebo administration Smaller cluster of voxels within MFC functionally connected with right hippocampus, compared to HC (47% decrease; P = 0.019; zvalue P = 0.31), similair trend with left hippocampus Larger cluster of connectivity between right hippocampus and the PCC as compared with HC (29% increase; P = 0.047; z value P = 0.09), similair trend with left hippocampus Cluster size differences between groups decreased by 44% in MFC and by 95% in ACC rs connectivity and cognition after insulin admnistration: Better performance on verbal fluency category associated with stronger average connectivity between right hippocampal region and ACC ($R^2_{adj} = 0.28$; P = 0.02) Verbal fluency associated with lower connectivity coefficient between left hippocampal region and MFC ($R^2_{adj} = 0.43$; P = 0.04) but not with cluster size rs connectivity and cognition after placebo administration BVMTR Total recall scores associated with lower connectivity between left hippocampal region and ACC ($R^2_{adj} = 0.45$; P = 0.04) and lower connectivity with RIPC ($R^2_{adj} = 0.44$; P = 0.03)

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	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
							BVMTR Learning T scores were also associated with lower average coefficients of connectivity between the right hippocampal region and the IPC (R^2_{adj} = 0.60; P = 0.01) rs connectivity and glycaemic HC. No significant relationship between HbA1c and resting-state connectivity after insulin administration.
66.	Zhang et al. (2014)	25	29	Structural: VBM	3 T – Tim Trio Siemens; **FLAIR T_1; T_2 MPRAGE:** TR = 1900 ms; TE = 2.52 ms; flip angle = 9°; slice thickness = 1 mm; matrix size = 256 × 256; voxel size = 1 × 1 × 1 mm^3; 176 slices	One way ANOVA,twotailed *t*-test, Chisquare tests , ANCOVA, univariate tests Bonferroni	No significant differences were identified for age, gender, educational level, duration of diabetes, age at diagnosis, HbA1c, BMI, WHR, MMSE and WM volume Significantly reduced total GM volumes (both P < 0.05) compared with the HC (620.24 ± 4.08 ml) Decreased GM volume in the superior temporal gyrus and MTG, fusiform gyrus, superior and medial frontal gyrus, middle occipital gyrus, precuneus, angular gyrus and bilateral cingulate regions.
67.	Y.-W. Zhang et al. (2015)	80	80	Structural: VBM	3 T Tim Trio Siemens; **MPRAGE:** TR = 1900 ms; TE = 2.52 ms; flip angle = 9°; slice thickness = 1 mm; FOV = 256 × 256 mm^2; matrix size = 256 × 256; voxel size = 1 × 1 × 1 mm^3; 176 slices	*t*-tests, χ^2test, Partial correlation, MANCOVA, ANOVA	No significant differences in cholesterol level, blood pressure, MMSE, BMI (P > 0.05). Significantly lower MoCA (P < 0.001). Partial correlation analysis found HbA1c was negatively correlated with MoCA score (r = −0.24, P = 0.032), mainly in delayed recall (r = −0.309, P = 0.006). No significant differences observed in GM (F = 2.877; P = 0.092), WM (F = 0.002; P = 0.969) volume, and WMHr (t = −0.925; P = 0.357) or TIV (F = 0.616; P = 0.434). Hippocampi volume significantly smaller (left (F = 4.543; P = 0.035) and right (F = 6.081; P = 0.015)). HbA1c negatively correlated with hippocampal volume (r = −0.267, P = 0.02). In hippocampal subfield, CA1 (F = 8.126; P = 0.005) and subiculum (F = 5.686; P = 0.018) volumes were significantly smaller. CA1 and subiculum volume positively correlated with MoCA (r = 0.516, P < 0.001; r = 0.307, P = 0.007).

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	Study	T2DM	HC	Imaging modality	MRI parameters	Method for testing relationships between measures	Relationship between physiological/ cognitive and imaging parameters
68.	Zhou et al. (2014)	14	17	Rs-fMRI: ALFF	3 T Siemens; **EPI:** TR = 2000 ms; TE = 40 ms; flip angle = 90°; 28 slices; slice thickness = 4 mm; gap = 1 mm; voxel size = 4 × 4 × 4 mm^3; matrix size = 64 × 64. TA = 478 s	ANCOVA	Decreased ALFF in left middle frontal gyrus, precuneus, left cuneus and precneus, and insula. Increased ALFF in fusiform and temporal gyrus. Positive correlations between left fusiform gyrus, left parahippocampal gyrus, and the Stroop test; and between the left paracentral gyrus, precuneus, superior parietal gyrus, and TMT-test. Negative correlations were found between the left fusiform gyrus, left parahippocampal gyrus, and MMSE; and between left paracentral gyrus, precuneus, superior parietal gyrus, and SDMT.

AD = Axial Diffusion; ALFF = Amplitude Lowfrequency Fluctuations; ANCOVA = Analysis of covariance; ASL = arterial spin labelling; BOLD = blood oxygenation level dependent; CBF = Cerebral Blood Flow; DTI = diffusion tensor imaging; EPI = echo planar imaging; FA = fractional anisotropy; FAIR = flow-sensitive alternating inversion recovery; FLAIR = fluid attenuation inversion recovery; fMRI = functional Magnetic Resonance Imaging; FOV = field of view; FSE = fast spin echo; FSPGRE = fast SPGRE; GM = Gray Matter; GE = General Electric; GRE = Gradient Echo; HC = Healthy control; IR = inversion recovery; IRFGE = Inversion Recovery fastgradient echo; MD = mean diffusivity; MPRAGE = magnetization prepared rapid acquisition gradient echo; MTR = Magnetisation Transfer Ratio; MANCOVA = Multivariate ANCOVA; NEX = number of excitations; PD = proton density; RD = Radial Diffusion; Rs-fMRI = Resting state fMRI; SPGRE = spoiled gradient echo; STEAM = single voxel stimulated echo acquisition mode; taskfMRI = task fMRI; T2DM = Type 2 Diabetes Mellitus; T = tesla; TE = echo time; TR = repetition time; VBM = Voxel based morphometry; WM = White Matter; WMH = White Matter Hyperintensities.

of GM. Last et al. (2007) showed that hypoperfusion in the frontal region was associated with GM atrophy. In their work, Raji et al. (2010) reported that BMI is negatively correlated to brain atrophy. Climie et al. (2014) investigated the hemodynamic and GM structure at rest and during exercise, and showed that GM volume was inversely associated with aortic pulse wave velocity (aPWV) in T2DM patients. Furthermore, it was found that this remained associated following adjustments for age, sex, antihypertensive medication, BMI, albumin, and cholesterol. Another study of García-Casares et al. (2014a) reported a negative correlation between HbA1c levels and GM density in the right medial prefrontal cortex and the left angular gyrus. Mehta et al. (2014) investigated GM volume atrophy which was associated with an increase urine albumin to creatinine ratio (UACR), a marker of kidney disease observed in diabetes, and showed a significant correlation in the frontal lobe irrespective of disease duration, HbA1c level, or hypertension. X. Cui et al. (2014) reported that GVC_2 values were negatively correlated with lower GM volumes in T2DM patients, whereas, after controlling for GVC_2 variability measures, other glucose variables, including HbA1c and FPG, were not found to be independently associated with brain volume outcomes. Novak et al. (2011) related GM atrophy to increased sICAM within the diabetic group. The work of Moran et al. (2013) revealed an association between more cerebral infarcts and lower total GM and WM in T2DM patients with GM loss being evident mainly in the medial temporal, anterior cingulate, and medial frontal lobes, whereas loss of WM was seen in the frontal and temporal regions. A. Kumar et al. (2008) noticed a negative correlation between cerebrovascular risk factors and GM volumes. Other studies reported no significant correlations between GM volume atrophy and HbA1c, age, education, disease duration, stroke, myocardial infarction, hypertension, apolipoprotein E (ApoE) e4, cholesterol, BMI, urine protein (UP), creatinine clearance rate (CCr), or FPG (Z. Chen et al., 2014; X. Cui et al., 2014; Falvey et al., 2013; Zhang et al., 2014).

Cortical and subcortical atrophy were investigated in eight studies (Brundel et al., 2010; Z. Chen et al., 2015, 2014; R. Kumar et al., 2008; Manschot et al., 2008, 2007, 2006; Yau et al., 2014). Yau et al. (2014) reported no cortical thinning in T2DM patients, although seven studies reported the observation of significant changes in T2DM patients compared to HC: three (R. Kumar et al., 2008; Manschot et al., 2006, 2007), four (Brundel et al., 2010; Z. Chen et al., 2015, 2014; Manschot et al., 2007) and one (Manschot et al., 2008) of them reported positive, negative and no significant correlations when compared to clinical parameters, respectively. Cortical atrophy positively correlated with hypertension in the study of R. Kumar et al. (2008), as well as with retinopathy and cerebral infarcts in the study of Manschot et al. (2007). This result was already demonstrated in a previous publication of the same authors (Manschot et al., 2006), where cortical and subcortical atrophy correlated additionally with age, intelligence quotient (IQ), and cerebral infarcts. Brundel et al. (2010) found a significant association between cortical atrophy and cerebral small vessel diseases. Z. Chen et al. (2015) reported cortical thinning in diabetic brains, and in one of their previous studies, they found that this atrophy could not be recovered after insulin therapy (Z. Chen et al., 2014). Manschot et al. (2007) determined a negative correlation between lipid-lowering drugs and reduced cortical atrophy. In another work, the same group observed no correlation between cortical atrophy in comparison to neuropathy (Manschot et al., 2008).

Seventeen studies (Brundel et al., 2014, 2010; Y.-C. Chen et al., 2014; Falvey et al., 2013; Jongen et al., 2007; R. Kumar et al., 2008; Last et al., 2007; Laugesen et al., 2013; Manschot et al., 2008, 2007, 2006; Moran et al., 2013; Novak et al., 2006; Reijmer et al., 2013a; Reinhard et al., 2012; Wang et al., 2014; Y.-W. Zhang et al., 2015) focussed on white matter lesions (WMLs) or white matter hyperintensities (WMHs). Twelve studies (Brundel et al., 2014, 2010; Y.-C. Chen et al., 2014; Falvey et al., 2013; R. Kumar et al., 2008; Manschot et al., 2008, 2007, 2006; Moran et al., 2013; Reijmer et al., 2013a; Wang et al., 2014; Y.-W. Zhang et al., 2015) compared T2DM patients

and HCs and could not identify significant changes due to the pathology. Three studies (Jongen et al., 2007; Laugesen et al., 2013; Reinhard et al., 2012) revealed positive, and two studies (Last et al., 2007; Novak et al., 2006) showed negative correlations. Jongen et al. (2007) identified a positive correlation between age and WML whereas Reinhard et al. (2012) found higher WMH to be related to higher plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, which is considered to be a reliable predictor of cardiovascular mortality in diabetics. Laugesen et al. (2013) reported that the pulse wave velocity (PWV) significantly correlated with the presence of WMLs. In the work of Last et al. (2007), WMHs were reported to negatively correlate with reduced CO_2 reactivity in HC; with WMHs contributing to regional differences in vasoreactivity in the T2DM group. Novak et al. (2006) observed a negative correlation between mean blood flow velocities (BFVs) and normalised WMHs or periventricular WMH (PWMH) volumes.

Two of the included studies observed relationships between cerebral blood flow (CBF) and clinical parameters in T2DM (Last et al., 2007; Tiehuis et al., 2008). Tiehuis et al. (2008) reported hypertension and diastolic blood pressure as predictors for high CBF. Moreover, Last et al. (2007) found retinopathy and hypertension to be associated with lower CBF during hypercapnia and, in addition, hypocapnia and higher BMI were related to lower CBF.

Infarcts, as a cerebrovascular lesion marker of small vessel disease, were investigated in seven manuscripts (Brundel et al., 2014; Y. Chen et al., 2015; Laugesen et al., 2013; Moran et al., 2013; Reijmer et al., 2013a; Wang et al., 2014; Xia et al., 2015b). Although changes were identified in HC compared to T2DM patients, only one study showed a positive correlation between the prevalence of cerebral infarctions with the PWV (Laugesen et al., 2013). The other six studies revealed no significant associations between infarcts and clinical parameters (Brundel et al., 2014; Y. Chen et al., 2015; Moran et al., 2013; Reijmer et al., 2013a; Wang et al., 2014; Xia et al., 2015b). Notably, a study that employed ultra-high fields (i.e., 7 T) to investigate microinfarcts and the occurrence of microbleeds in T2DM patients, could not reveal any significant association (Brundel et al., 2014).

Six studies have used diffusion MRI to track microstructural changes affecting the brain in T2DM (Falvey et al., 2013; Hoogenboom et al., 2014; Hsu et al., 2012; Reijmer et al., 2013a; van Bussel et al., 2015; Yau et al., 2014). Intra-voxel incoherent motion was used by van Bussel et al. (2015) to examine the microvasculature and parenchymal microstructure of the hippocampus, showing an increased blood perfusion volume and an increased blood flow associated with higher FPG levels. Hoogenboom et al. (2014) reported a positive correlation between low FA values in the UF and the serum creatinine level. Hsu et al. (2012) observed that the MD of the brain parenchyma was significantly increased compared to controls and was positively correlated with disease duration. Additionally, within these regions, a significant association between disease duration and microstructural properties in several brain regions, including cerebellum, temporal lobe WM, right caudate, cingulate gyrus, pons, and parahippocampal gyrus, was revealed. Furthermore, MD, AD and transverse diffusivity (TD) was negatively correlated with triglyceride. Falvey et al. (2013), reported that decreased FA in the WM was negative correlated with depression, stroke, and myocardial infarction. Hoogenboom et al. (2014) reported that a low FA in the cingulate bundle negatively correlates with BMI. Yau et al. (2014) reported a significant mean diffusivity (MD) elevation of the GM region in T2DM patients, in addition to a significant reduction in FA of the WM, independent of age and WMH load, but no significant correlation was found. Reijmer et al. (2013a) found no relation between the duration of diabetes and DTI parameters.

Fifteen functional connectivity (FC) studies, using functional MRI (fMRI), reported diverse brain distortions in T2DM patients (Y. Chen et al., 2015, 2014; Y.-C. Chen et al., 2014; Cui et al., 2015; Y. Cui et al., 2014; He et al., 2015; Hoogenboom et al., 2014; Marder et al., 2014; Musen et al., 2012; Wang et al., 2014; Xia et al., 2015c, 2015b, 2015d, 2013; H. Zhang et al., 2015). They all revealed functional differences in T2DM patients compared to HC. H. Zhang et al. (2015) used insulin therapy to assess the evolution of FC, which showed a positive correlation with stronger average connectivity between the right hippocampal region and the anterior cingulate cortex (ACC) after insulin administration. Y. Chen et al. (2015) showed that T2DM was linked to several FC disruptions, showing a higher connectivity within the default mode network (DMN), left frontal-parietal network (LFPN), and the sensorimotor network. This abnormal FC was correlated with fasting glucose levels. Xia et al. (2013) reported that both C-peptide level and pancreatic β-cell function had a positive correlation with the amplitude of low-frequency fluctuations (ALFF). He et al. (2015) also found a significant positive correlation between HbA1c levels and brain activations in the anterior cingulate cortex and bilateral dorsolateral prefrontal cortex (DLPFC) in patients with T2DM. Regarding negative correlations, Musen et al. (2012) determined an FC between posterior cingulate cortex (PCC) and other DMN regions (e.g., right inferior frontal gyrus (IFG), precuneus) which was inversely associated with the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), independently of disease duration. Xia et al. (2015c) showed a significant negative correlation relating strong insulin resistance to FC in the MTG of T2DM patients. Furthermore, log HOMA-IR was also negatively correlated with interhemispheric connectivity in the MTG. Xia et al. (2013) reported a significantly decreased ALFF in bilateral MTG, the left fusiform gyrus, the left middle occipital gyrus, and the right inferior occipital gyrus, while increased ALFF values were observed in both the bilateral cerebellum posterior lobe and the right cerebellum in T2DM patients compared to HC. Furthermore, in another publication (2015d), they showed that T2DM and poorly controlled cholesterol levels leads to significant correlations between low-density lipoprotein (LDL), high-density lipoprotein (HDL), waist-hip ratio, and FC of the bilateral hippocampus middle front gyrus (MFG). Cui et al. (2015) showed increased FC in the anterior DMN bilateral superior frontal gyrus (SFG) and decreased FC in the anterior DMN (PCC and precuneus). FC strength in the posterior DMN was negatively correlated with HOMA-IR, and hypoconnectivity in the PCC was related to higher IR levels. However, no correlation was observed between the glycaemic control and functional changes. In a previous work (Y. Cui et al., 2014), they could already identify a negative correlation between HOMA-IR and the neural activity in the parieal, frontal and temporal lobes, and the lingual gyrus. Wang et al. (2014) observed a significantly decreased ALFF in the frontal and parietal lobes, bilateral thalami, and the posterior lobe of the cerebellum. In contrast, increased ALFF was found in the visual cortices. Lower ALFF values in the bilateral medial prefrontal gyri correlated with a higher urinary albumin-creatinine ratio. Additionally, several studies evaluated DMN connectivity, showing abnormal activation/deactivation in different brain regions. PCC connectivity was also investigated by Y.-C. Chen et al. (2014), showing a significant decrease in FC between the PCC and right MTG, the left lingual gyrus, the left middle occipital gyrus, and the left precentral gyrus, while increased FC of PCC was observed in the left cerebellum posterior lobe, the right SFG, and the right MFG. In addition, a negative correlation between PCC right MTG connectivity and HOMA-IR was reported. One task fMRI study reported an association between plasma glucose level (> 11 mmol/L) and reduced deactivation of DMN regions during both encoding (i.e., cuneus, precuneus) and recognition (i.e., MTG) (Marder et al., 2014). Xia et al. (2013) reported a significantly decreased ALFF in bilateral MTG, the left fusiform gyrus, the left middle occipital gyrus, and the right inferior occipital gyrus, while increased ALFF values have been observed in both the bilateral cerebellum posterior lobe and the right cerebellum in T2DM patients compared to HC. Another work of Xia et al. (2015b) reported a negative correlation between the resting-state FC of the left inferior parietal lobe (IPL) and HbA1c levels. However, H. Zhang et al. (2015) found no significant relationship between HbA1c and resting-state connectivity after insulin administration. Hoogenboom et al. (2014) observed stronger FC in HC

compared to T2DM patients without any correlation to a clinical variable. Y. Chen et al. (2014) reported that worse executive and memory abilities of T2DM patients with high WM loads was correlated with low activation of the left MFG and SFG.

3.2.2. Relationships between imaging parameters and cognitive functioning in T2DM patients

In the manuscripts included for this systematic review, cognitive functioning was mainly investigated in two ways. First, neuropsychological test batteries were administered, which included questionnaires and/or reaction time tasks. Second, experimental paradigms were conducted during fMRI measurements.

Two studies (Ajilore et al., 2010; Yau et al., 2014) examined the relationship between cortical thickness and performance on neuropsychological test batteries, both of them showing changes associated with T2DM. Ajilore et al. (2010) focused on attention and executive functions and identified a significant positive correlation between better performance and higher values of cortical thickness. Yau et al. (2014) focused on verbal memory impairments by assessing the cortical thickness of the frontal and temporal lobe structures. They showed that the T2DM group had significantly lower estimated IQ scores and scored consistently lower across all verbal memory measures. After controlling for multiple comparisons, all results remained significant, with the exception of the California Verbal Learning Test (CVLT), Short Delay Cued Recall, and Wechsler Memory Scale Revised (WMS-R) Verbal Paired Associates Immediate Recall measures (Yau et al., 2014).

Eleven studies investigated the relationship between hippocampal volume and subjects' performance in neuropsychological tests (Ajilore et al., 2015; García-Casares et al., 2014b; Gold et al., 2007; Hayashi et al., 2011; Moran et al., 2013; Wang et al., 2015; Wisse et al., 2014; Yau et al., 2014; H. Zhang et al., 2015; Zhang et al., 2014; Zhou et al., 2014). One study (Wisse et al., 2014) showed that patients with T2DM did not have reduced hippocampal brain volumes, as compared to controls. However, three manuscripts determined positive correlations (Ajilore et al., 2015; Zhang et al., 2014; Zhou et al., 2014). Ajilore et al. (2015) observed that subjects with diabetes and depression performed significantly worse on verbal list learning, compared to HC. In addition, the hippocampal volume was a strong predictor of performance in HC, while age and hippocampal volume were strong predictors in subjects with T2DM. Age was a significant predictor of verbal learning performance in subjects with diabetes and depression (Ajilore et al., 2015). Zhang et al. (2014) included T2DM patients with and without mild cognitive impairment (MCI) and reported that for T2DM patients without MCI, reduced GM in the limbic system (i.e., hippocampus, parahippocampal gyrus, amygdala, and uncus) correlated positively with the total Montreal Cognitive Assessment (MoCA) score. Zhou et al. (2014) reported a significant positive correlation between the left parahippocampal gyrus and the Stroop test, as well as negative correlations with the Mini-Mental-Status Examination (MMSE) score. Negative correlations between MD values of the left parahippocampal gyrus and verbal memory were reported by Yau et al. (2014). Gold et al. (2007) could not establish a significant correlation between hippocampal volume and memory tests, but Hayashi et al. (2011) reported that worse memory performance was correlated with diminished hippocampal volume. García-Casares et al. (2014b) concluded that worse executive and memory functioning correlated predominantly with less GM density and reduced glucose metabolism in the temporal region (i.e., middle gyrus, parahippocampus, and uncus). In the report of Moran et al. (2013), T2DM was associated with poorer visuospatial construction, planning, visual memory, and speed. This was found to be independent of age, sex, education, and vascular risk factors. When adjusting for hippocampal and GM volumes, the strength of these associations was attenuated by almost one-half, but remained unchanged when adjusting to cerebrovascular lesions or WM volume. Additionally, longer duration of the disease was significantly associated with poorer scores in the Rey-Osterrieth Complex Figure (RCFT), digit symbol coding, and symbol search. Wang et al. (2015) found a significant negative correlation between left hippocampal myoinositol levels and language scores, as well as between left hippocampal creatine levels and visuospatial/executive scores in patients with T2DM. Yau et al. (2014) reported no relationship between hippocampal volume and composite scores for verbal memory (immediate or delayed recall) in T2DM patients, even when examining the left or right hippocampal volume separately. H. Zhang et al. (2015) could not associate the hippocampal atrophy in T2DM patients to any cognitive impairment.

CSF association with cognition was investigated in two publications (Jongen et al., 2007; R. Kumar et al., 2008). Neither study was able to find any significant correlations with cognitive parameters, such as immediate recall, which was assessed using the CVLT.

GM and WM volume were of interest in eight studies (X. Cui et al., 2014; García-Casares et al., 2014b; Jongen et al., 2007; R. Kumar et al., 2008; Mehta et al., 2014; Moran et al., 2013; Zhang et al., 2014; Y.-W. Zhang et al., 2015). With respect to cognition, Y.-W. Zhang et al. (2015) found no differences in GM in T2DM patients. A study revealing a positive correlation showed worse performance in a cognitive test battery associated with reduced total brain volume (Jongen et al., 2007). A. Kumar et al. (2008) and R. Kumar et al. (2008) was able to predict GM volume based on performance during recall memory tasks (R. Kumar et al., 2008). In the study of Moran et al. (2013), T2DM was associated with poorer visuospatial construction, planning, visual memory, and speed. This was found to be independent of age, sex, education, or vascular risk factors. Moreover, the strength of these associations was attenuated by almost one-half when adjusted for hippocampal and GM volumes. X. Cui et al. (2014) showed that worse executive functions and memory functioning was also predominantly correlated with less GM density. Similar results were published by García-Casares et al. (2014b). Negative associations to cognitive impairment were published by Zhang et al. (2014), showing that the combined effect of T2DM and MCI exhibited reduced GM in the limbic system and MTG region. Referring to Mehta et al. (2014), subclinical albuminuria ($\geq$5 mg/g) was associated with lower GM volume and was shown to have a clinical impact on cognitive function (i.e., worse executive function) in older diabetic patients, independently of diabetes control and hypertension.

Four of the included studies determined the relationship between cognitive processing and cortical and subcortical atrophy exhibiting changes associated with T2DM (R. Kumar et al., 2008; Manschot et al., 2006; van Harten et al., 2007; Yau et al., 2014). All these four studies identified negative correlations to attention and executive function, information processing speed, abstract reasoning, and visuoconstruction. Only Manschot et al. (2006) made an association between cortical atrophy and information processing speed. Van Harten et al. (2007) found mental speed to be related to global atrophy and R. Kumar et al. (2008) determined a significant interaction between an atrophy ratio and subjects' performances on Purdue Pegboard tests. Yau et al. (2014) reported that from temporal cortical clusters, shown to be affected on the diffusion tensor imaging (DTI) analyses, only the MD values of the left parahippocampal gyrus (PHG), which represented the most extensive GM microstructural abnormalities found in the temporal lobe, correlated significantly with both immediate and delayed recall of verbal memory.

Four studies reported WML to be present in T2DM patients as compared to HC and focussed on the link between WML and cognitive functioning (Jongen et al., 2007; Manschot et al., 2006, 2008; van Harten et al., 2007). Jongen et al. (2007) showed worse cognitive performance to be correlated to larger WML volume. Manschot et al. (2006) observed a significant negative correlation between attention and executive functioning and periventricular WML (PWML), as well as between information processing speed and PWML and DWMLs. However, they were unable to confirm their findings in a later publication in 2008 (Manschot et al., 2008). Similarly, Van Harten et al. (2007) did not find any significant correlations to deep WMLs (DWMLs).

WMHs were investigated in six studies (Bruehl et al., 2009a; Falvey

et al., 2013; R. Kumar et al., 2008; Moran et al., 2013; Reijmer et al., 2013a, 2013b). Five of these studies did not find any significant differences with respect to WMH between T2DM patients and HC (Bruehl et al., 2009a; Falvey et al., 2013; R. Kumar et al., 2008; Moran et al., 2013; Reijmer et al., 2013a). The study of Reijmer et al. (2013b) identified a positive correlation relating a high WMH load to increased information processing, whereas WMH load was negatively correlated with clustering and global efficiency.

The association between CBF and perfusion and cognitive function was investigated in four studies (Novak et al., 2014; Rusinek et al., 2015; Tiehuis et al., 2008; Xia et al., 2015d). Rusinek et al. (2015) showed a positive correlation between CBF and a verbal fluency score, even though hypoperfusion was more significant in the IR group than in T2DM patients. A study by Tiehuis et al. (2008) reported a significant positive association between CBF and performance on neuropsychological tests. Using insulin therapy, a longitudinal study showed an increase of perfusion after insulin administration, located mainly in the insular cortex, compared to the control group (Novak et al., 2014). Here, cognitive performance after insulin administration was related to regional vasoreactivity by Novak et al. (2014). An improvement of visuospatial memory after insulin administration in T2DM patients was correlated with vasodilatation in the middle cerebral artery territory. Xia et al. (2015d) observed that T2DM patients performed worse than the HC regarding all neuropsychological tests. Significant differences were found in Complex Figure test (CFT)-copy, CFT-delay, digital span test (DST), and trail making test (TMT)-B, in addition to a decreased CBF, primarily located in the visual area (i.e., parietal and occipital lobe). Further analysis showed that relative CBF in the middle occipital gyrus (MOG) was associated with CFT-copy scores, relative CBF in the bilateral inferior parietal lobe was correlated with TMT-B scores, and relative CBF in the right precuneus correlated with DST scores in T2DM patients (Xia et al., 2015d).

The relationship between diffusion measures and cognition was the focus in three studies (Reijmer et al., 2013a; van Bussel et al., 2015; Yau et al., 2009). Yau et al. (2009) reported that performance in memory tests correlated positively with FA. This was in line with the findings of Reijmer et al. (2013a), where a positive association on information processing speed in the right UF and a negative association between MD of both UF ILF and splenium of the corpus callosum as well as information processing speed and memory independently of age was noticed. Van Bussel et al. (2015) reported that T2DM patients performed worse on word learning (verbal) memory tasks (WLT) and on baseline MMSE, but not on the repeated MMSE or the recall WLT score. Additionally, diffusion (D) and blood flow–related microvascular pseudo diffusion (fD^*) increased with lower memory performance and interaction analysis (fasting blood glucose (FBG) levels × memory performance) revealed a significant interaction for pseudo diffusion coefficient (D^*), which reflects the incoherent motion of water molecules in the microvasculature, and fD^*.

Two studies investigated the relationship between fMRI-BOLD and clinical parameters in T2DM patients (Chechlacz et al., 2009; He et al., 2015). He et al. (2015) found significant positive correlations between HbA1c and the BOLD response in some brain regions (e.g., ACC and DLPFC) during a 2-back task. Chechlacz et al. (2009) revealed that increased activation to food within the insula and orbitofrontal cortex was positively correlated with external eating, dietary self-efficacy, and dietary self-care. In contrast, responses within subcortical structures (e.g., amygdala and basal ganglia) were positively correlated with emotional eating and rated appetite for the food stimuli, and negatively correlated with dietary self-care.

Two studies looked at the caudate magnetisation transfer (MT) and calculated a ratio, both exhibiting changes related to T2DM (Elderkin-Thompson et al., 2009; Yang et al., 2015). Yang et al. (2015) used MT to investigate three major cognitive domains: learning and memory, attention information processing, and executive function. It was shown that the learning and memory Z score was positively correlated with bilateral rostral anterior cingulate cortex MTR in T2DM. Right rostral anterior cingulate cortex Magnetisation Transfer Ratio (MTR) also correlated positively with the executive function Z score in T2DM patients. Elderkin-Thompson et al. (2009) reported that the MT ratios of the caudate and putamen correlated with a cognitive index (based on the cognitive performance of the subjects). They highlighted their finding that the caudate MT ratio correlations were stronger among diabetics than HC.

Franke et al. (2013) correlated a parameter depicting the age of the patients' brain with cognitive performance. Their results revealed that an abnormal advance of this parameter in T2DM patients correlated with worse verbal fluency, more severe depressive symptoms and increased risk of dementia. The brain age parameter increased with disease duration and higher FBG levels.

4. Discussion

We performed a systematic review of literature investigating what MRI can reveal about the brain of T2DM patients. In relation to our principle aim, to investigate whether there are relationships between imaging and clinical parameters as well as between imaging and cognitive functioning in these patients, we found positive, negative and non-significant associations in the reviewed literature. As a spin-off, we could determine whether imaging per se could diagnose significant changes in the brain of T2DM patients as compared to HC, and whether these could be linked to clinical symptoms and/or cognitive deficits. The findings and their implications are discussed in a broader context below.

4.1. Relevant findings

MRI could reveal significant structural changes in the brain of T2DM patients and link its parameters to clinical variables. For example, brain atrophy in T2DM patients was strongly correlated to clinical values. This observation might be due, in part, to the large number of studies that reported changes in structural imaging in T2DM. Mostly, statistically significant correlations were observed between decreased volumes in specific brain regions and BMI, HbA1c level, disease duration, hypertension, and small vessel diseases. To give an example, a reduced hippocampal volume was related to an increased BMI, HbA1c and disease duration in several studies (e.g., Bruehl et al., 2009a, 2009b; Hayashi et al., 2011; Y.-W. Zhang et al., 2015). Similarly, increases in the amount of CSF positively correlated with high BMI, HbA1c, and also disease duration (e.g., R. Kumar et al., 2008; Last et al., 2007; Lee et al., 2013). In addition, clinical measures used to indicate cerebral small vessel diseases, i.e., CAR, GVC, blood pressure, FPG levels, and hypertension were also related to GM, WM, CBF, cortical and subcortical atrophy, as well as abnormal FC and high values of fasting glucose (e.g., Brundel et al., 2010; X. Cui et al., 2014; Y. Cui et al., 2014; García-Casares et al., 2014a; Jongen et al., 2007; R. Kumar et al., 2008; Last et al., 2007; Mehta et al., 2014; Raji et al., 2010; Yau et al., 2014). For example, hypertension was negatively correlated with reduced GM (e.g., Mehta et al., 2014), whereas an increase in small vessel disease was negatively correlated with cortical and subcortical atrophy (e.g., Brundel et al., 2010). Diffusion measurement findings determined decreased FA values as a sign of loss of fibre density, which was positively correlated with serum creatinine levels and negatively correlated to BMI (e.g., Hsu et al., 2012). Moreover, insulin therapy was reported to produce some recovering effects on brain distortions related to T2DM. Some of the reviewed studies reported improvements after one year of treatment (e.g., Z. Chen et al., 2015, 2014; Hayashi et al., 2011). Thus, our finding confirms the assumption that insulin might provide a brain protection mechanism and could be used successfully in the treatment of T2DM. Furthermore, the systematic review reveals that most of the studies focussing on WMLs and WMHs could not identify significant associations to T2DM (e.g., Brundel et al., 2014; Cui et al.,

2015; Falvey et al., 2013; R. Kumar et al., 2008; Moran et al., 2013; Reijmer et al., 2013b; Wang et al., 2014). In the case of existing differences between HC and patients, relevant correlations rather involved clinical variables such as age, reduced CO_2 vasoreactivity or blood flow velocities (e.g., Jongen et al., 2007; Last et al., 2007; Laugesen et al., 2013; Novak et al., 2006) than the well-known diabetes-related factors, such as FPG, HbA1c levels and BMI (e.g., Reijmer et al., 2013b). Notably, the prevalence of cerebral infarcts did not correlate with any of the investigated clinical variables of T2DM patients (e.g., Brundel et al., 2014; Y. Chen et al., 2015; Moran et al., 2013; Reijmer et al., 2013b; Wang et al., 2014; Xia et al., 2015b). Several studies highlighted the reduction of FC in T2DM and its association with clinical variables: Beside the strong negative correlations found between reduced connectivity and low values of HOMA-IR (e.g., Y.-C. Chen et al., 2014; Cui et al., 2015; Musen et al., 2012; Xia et al., 2015c), FC also correlated negatively with insulin resistance (e.g., Xia et al., 2015c) and HbA1c (e.g., Xia et al., 2013). Positive correlations were found between increased FC and the positive effects of insulin therapy, as well as abnormal FC and high values of fasting glucose (e.g., H. Zhang et al., 2015).

Regarding functional changes of the patients' brains, cognitive impairment prevails as being clinically important for T2DM patients as they are more prone to cognitive decline compared with people without diabetes (Biessels et al., 2014). There is evidence that there is an association between the regulation of glucose and cognitive distortions, namely that high HbA1c concentration and glucose variability are negatively associated with cognitive function (Geijselaers, 2015), although their precise role is still debated. The present systematic review points out that MRI could reveal significant differences in various cognitive parameters between T2DM patients and HC. Concerning the relationship between imaging parameters and variables of cognitive function, the study results are not homogeneous but they do show a clear trend. In most of the studies, reduced GM and WM volume were associated with worse cognitive performance, e.g. less GM density was linked to worse executive functions and memory performance in T2DM patients (e.g., X. Cui et al., 2014; García-Casares et al., 2014b). Subcortical atrophy could, for example, be correlated with information processing speed, abstract reasoning, and visuoconstruction (e.g., A. Kumar et al., 2008; R. Kumar et al., 2008; Yau et al., 2014). Furthermore, cortical thickness was positively associated with attention capabilities and executive functions (e.g., Ajilore et al., 2010). Concerning the performance on neuropsychological test batteries, T2DM patients performed significantly worse on tests such as the Complex Figure or the digit span test (e.g., Xia et al., 2015d). FMRI could reveal significant differences between T2DM patients and HC in task dependent brain areas (e.g., He et al., 2015; Chechlacz et al., 2009). However, the interpretation of the findings remains complex, due to the variety of MRI methods and cognitive tasks employed (see *limitations* below).

4.2. Limitations and future directions

The following limitations have to be highlighted. The reviewed manuscripts covered a wide range of imaging methods, brain regions, cognitive capabilities, and clinical parameters related to T2DM. Mainly, our concerns refer to the inconsistencies regarding the experiments' setups that make it difficult to draw conclusions. For example, the tasks assessed during fMRI or during the administration of cognitive test batteries varied across studies. Moreover, the same holds for the diversity of the imaging methods applied, e.g., quantitative or qualitative MRI and the magnetic field strength (see Table 1). In addition, the analyses methods vary, i.e. while some studies were focussing on regions of interest, some analyses covered the whole brain. Regarding the statistical analyses of associations between imaging parameters and clinical variables or cognitive functioning, different approaches to correlation were also used across the studies, e.g. bivariate Pearson's correlation or multiple regression. Although the diversity of the studies certainly is favoured, the inconsistencies become problematic when comparing the results. Furthermore, it seems that in some result sections, non-significant correlations were not explicitly stated or discussed, despite possibly being very informative for the reader. Finally, most studies did not consider gender differences. This represents a shortfall as previous studies have been able to identify gender differences in T2DM brain atrophy (Hempel et al., 2012) and the influence of sex specific hormones on glucose homeostasis (Varlamov et al., 2014). Thus, in order to draw valid conclusions about structural or functional brain distortions in T2DM, gender should be considered at least as a covariate when interpreting the results.

4.3. Conclusion

The reported results provide clear evidence that the deregulation in glucose metabolism associated with T2DM has an impact on the human brain. Notably, although the associations between imaging, clinical and cognitive variables are not fully homogeneous, they do show a clear trend towards a link between altered brain structure and worse cognitive processing. Nevertheless, the heterogeneity seen in the findings might be explained by the patient selection criteria, such as medication, treatment, disease duration and the demographic characteristics. Therefore, in addition to the imaging methodology used, subjects' selection criteria can play a critical role if not considered carefully. Furthermore, T2DM is a metabolic disease characterised by a strong association with both microvascular and macrovascular complications leading to multiorgan dysfunction and tissue damage. Thus, risk factors for vascular disease in people with T2DM, including hyperglycemia, IR, dyslipidemia, hypertension and obesity must be carefully taken into account when investigating the brain abnormalities and cognitive functions affecting this population. In short, the results highlight the heterogeneity in the methods used across manuscripts in terms of imaging technique, data analysis methods and the clinical variables assessed. This heterogeneity makes it difficult to draw firm conclusions. Replication is a critical necessity as future studies in this research area would profit from standardised methods (and data analyses standards) for combining different types of imaging data. Multimodal imaging would be a powerful tool to develop a body of knowledge in this area and to overcome the existing inconsistencies across studies.

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Appendix A. Supplementary material

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