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Brain microstructural abnormalities in type 2 diabetes mellitus: A systematic review of diffusion tensor imaging studies

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is associated with deficits in the structure and function of the brain. Diffusion tensor imaging (DTI) is a highly sensitive method for characterizing cerebral tissue microstructure. Using PRISMA guidelines, we identified 29 studies which have demonstrated widespread brain microstructural impairment and topological network disorganization in patients with T2DM. Most consistently reported structures with microstructural abnormalities were frontal, temporal, and parietal lobes in the lobar cluster; corpus callosum, cingulum, uncinate fasciculus, corona radiata, and internal and external capsules in the white matter cluster; thalamus in the subcortical cluster; and cerebellum. Microstructural abnormalities were correlated with pathological derangements in the endocrine profile as well as deficits in cognitive performance in the domains of memory, information-processing speed, executive function, and attention. Altogether, the findings suggest that the detrimental effects of T2DM on cognitive functions might be due to microstructural disruptions in the central neural structures.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder, leading to severe multi-systemic impairments. Over the past three decades, the worldwide prevalence of diabetes mellitus has doubled, and it has become the seventh cause of disability and decreased quality of life (Dickens et al., 2011; Novoselova et al., 2014; Wood et al., 2016). In addition to well-known vascular complications, T2DM is associated with deficits in higher-level cognitive functions of the brain (Miles and Root, 1922). Epidemiological studies have shown that patients with T2DM have a 1.2–1.5-fold higher chance of cognitive dysfunction (Cukierman et al., 2005). Although the underlying mechanisms responsible for cognitive decline in T2DM are currently ambiguous, it is postulated that hyperglycemia, insulin resistance, oxidative stress, and neuroinflammation might play a role (Feinkohl et al., 2015; Geijselaers et al., 2015). Recently, there has been an increasing interest in comprehending the connection between T2DM and other dementing disorders of the brain. For a long time, T2DM has been recognized as an essential risk factor for vascular dementia (Prince et al., 2014), and is estimated to confer an increased risk of Alzheimer's disease (Cheng et al., 2012). Previous studies have suggested that the underlying mechanisms and risk factors for aging and Alzheimer's disease are, to some extent, overlapping with those of T2DM (Debette et al., 2011; Exalto et al., 2012). T2DM and Alzheimer's disease might constitute a spectrum of cognitive decline, characterized by accelerated progression of aging processes (Biessels and Reijmer, 2014; Geijselaers et al., 2015). However, the interconnection between these two disorders is not fully known.

During the past recent years, several neuroimaging studies with different modalities have demonstrated that T2DM is accompanied by structural and functional abnormalities in various regions of the brain (Yau et al., 2010; Bruehl et al., 2011). It is shown that patients with T2DM have decreased volume of the hippocampus and prefrontal region. Lower levels of total cortical volume and mean cortical thickness are also documented in both hemispheres of these patients (Anan et al., 2010; Brundel et al., 2010; Chen et al., 2012; Moulton et al., 2015). Moreover, loss of grey matter (GM) in the temporal and precentral gyri is represented in voxel-based morphometry of patients with T2DM (Chen et al., 2012). Both task-based and resting-state functional magnetic resonance imaging (MRI) studies have revealed that T2DM is associated with decreased connectivity in the default mode network and reduced activation in many task performances. These changes have been closely related to weaker cognitive function (for review refer to (Macpherson et al., 2017)).

Diffusion tensor imaging (DTI) is an MRI-based technique, which can reveal the alterations in the microstructure of cerebral tissue,

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subcortical structures, and specifically interconnecting white matter (WM) tracts (Basser et al., 1994). DTI quantifies the directionality and magnitude of three-dimensional random diffusion of water molecules in soft tissues. In free space, water molecules diffuse evenly in all directions, known as isotropic diffusion. However, in the presence of barriers, such as neural membranes and myelin sheets, the movement of water molecules is biased toward a specific direction (e.g. alongside the axons), defined as anisotropic diffusion (Beaulieu, 2002). The main metrics of DTI are fractional anisotropy (FA) and mean diffusivity (MD). FA indicates the degree of anisotropic movement of water molecules, while MD measures the average movement of water molecules in three possible dimensional directions. Decreased level of FA and increased value of MD are generally indicative of lower microstructural integrity within neural structures. However, in some cases, other unrelated causes might also be responsible for the altered level of diffusivity measures, such as inflammation-induced changes in fiber density or diameter and the presence of complex crossing fibers and branches (Song et al., 2002; Alba-Ferrara and de Erausquin, 2013; Jeurissen et al., 2013). Radial diffusivity (RD) and axial diffusivity (AD) are two supplementary indices, which measure the movement of water molecules respectively perpendicular and alongside to the nerve fibers (Pierpaoli and Basser, 1996). AD is supposedly linked with the axonal damage and fragmentation, and RD primarily reflects the myelin sheath integrity. This strict attribution of AD and RD to specific neuropathology is, however, confronted by the evidence of changes in RD due to the dynamics in axonal density and diameter (Wheeler-Kingshott and Cercignani, 2009). Therefore, the diffusivity measures should be interpreted with caution regarding the underlying neuropathology.

The quantitative nature of DTI has led to its application in the evaluation of WM microstructure in various central nervous system disorders, particularly dementing diseases (Chua et al., 2008a; Morand et al., 2018). Microstructural deficits indicated by DTI metrics constitute a sensitive marker of cognitive decline due to aging and Alzheimer's disease (Charlton et al., 2006; Chua et al., 2008b; Schiavone et al., 2009). Of significant importance, DTI indices have been correlated with cognitive impairment, even when there is no sign of macrostructural abnormalities, such as decreased GM volume and atrophy of brain structures (Schiavone et al., 2009; Venkatraman et al., 2011; Zhuang et al., 2012). Altogether, DTI appears to be an applicable tool for detecting early changes in neurodegenerative disorders.

Herein, we aimed to explore the extent of diabetes impact on the measures of neural integrity and cerebral network organization. We systematically reviewed DTI studies of the brain microstructure in patients with T2DM. We have also discussed the preliminary evidence, linking DTI metrics with endocrine profile and cognitive performance.

2. Search strategy and study identification

PubMed and Embase were selected to search for relevant articles, published between the earliest record and January 1st, 2019. The search strategy and study screening were in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search terms used for each database can be found in supplementary 1. All full-text articles, which had investigated the brain microstructure in patients with T2DM using DTI technique were included in this systematic review. Animal studies or articles in a language other than English were not the targets of this review. Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) was used to organize the identified articles. HSM and MHA independently conducted the title/abstract and full-text screening. A mutual discussion by all reviewers obviated the conflicts. In order to find all eligible articles, the references of the included articles were reviewed by HSM and FGS. In case two or several studies had overlapping study participants, the study with more participants was selected. The detailed process of searching and selection is illustrated in Fig. 1.

3. Result

A total of 29 DTI studies are included in this review, which are all cross-sectional in design. An overview of demographic and endocrine data of the participants in each study is presented in Table 1. The distribution of key demographic, endocrine, and methodological features is illustrated in Fig. 2. Most studies were conducted in the USA and China and over recent years since 2016. Variations in the sample size versus the age difference of participants are clearly depicted in Fig. 2a. In most cases, the participants are middle-aged or elderly individuals, except for three studies which have conducted on juveniles (Yau et al., 2010; Rofey et al., 2015; Nouwen et al., 2017). Disease duration ranges from less than a year to over five decades among studies. All studies have included participants comparable regarding age, gender, and education, except for two studies, whose participants are different based on gender (Falvey et al., 2013) or education (Groeneveld et al., 2018). In regard with lipid profile, blood pressure, and body mass index (BMI), some studies have reported significant differences between patients with T2DM and controls, while other studies have included participants comparable regarding these baseline variables (Table 1). Most studies have also tried to control for these covariates to some extent in between-groups or correlation analyses. Except for three studies (Falvey et al., 2013; Rofey et al., 2015; Sun et al., 2018), all studies have measured Hb1Ac (%) with an average ranging from 6.7 to 10.7 for patients with T2DM and from 5.29 to 5.9 for non-diabetic controls (Fig. 2b). Fasting blood sugar (FBS) is also provided in all but five studies (Falvey et al., 2013; Zhang et al., 2013; Rofey et al., 2015; Groeneveld et al., 2018; Sun et al., 2018), ranging from 6.7 to 10.29 for patients with T2DM and from 3.8 to 5.5 for non-diabetic controls (Fig. 2c). In ten studies, some diabetic patients were on insulin treatment. In addition, some studies have excluded patients with experience of hypoglycemic events to eliminate the possible confounding effect of this episodic condition on the neural structure. All studies which have investigated the classical MRI markers of small vessel disease, i.e., WM hyperintensities and lacunar infarcts, have reported no difference between their case and control groups.

Twenty-five articles have investigated the conventional DTI diffusion metrics, i.e., FA, MD, AD, or RD, while three studies have conducted graph theory to analyze WM topological network using DTI data. Finally, one study (Kim et al., 2016) has surveyed both analytical methods in patients with T2DM. Table 2 summarizes the DTI findings in between-group comparisons. Among DTI analytical methods, whole-brain tract-based spatial statistics (TBSS) method is adopted more frequently to reveal the extent of diabetic damage on the neural microstructure (Fig. 2d). FA is the most common measure investigated by the reviewed studies (Fig. 2e), though many studies have applied overlapping methods and measures. While most of the studies have surveyed the whole brain or multiple major WM tracts, four studies have only examined the hippocampus (van Bussel et al., 2016), anterior limb of the internal capsule (ALIC) (Zhang et al., 2013), corpus callosum (CC) (Yu et al., 2018), or cerebellum (Fang et al., 2017) as their regions or tracts of interest. All studies have investigated the abnormalities in the microstructural integrity or network organization of brain microstructure in patients with T2DM compared to those without T2DM, except the study by Groeneveld et al. (2018), which has investigated patients with T2DM with and without cognitive impairment. Of note, a handful of studies have specifically examined the relative impact of diabetes and obesity (Yau et al., 2010; Rofey et al., 2015; van Bloemendaal et al., 2016; Nouwen et al., 2017; Yoon et al., 2017), major depression (Zhang et al., 2013), hypertension (HTN) (Yau et al., 2013), cognitive impairment (Xiong et al., 2016; Groeneveld et al., 2018), or stroke (Yu et al., 2018) on neural structure by additional comparison of participants with and without these common comorbidities. Ten studies have explored the possible association between DTI metrics and cognitive function in T2DM, while sixteen studies have tried to elucidate the contribution of different demographic, metabolic,

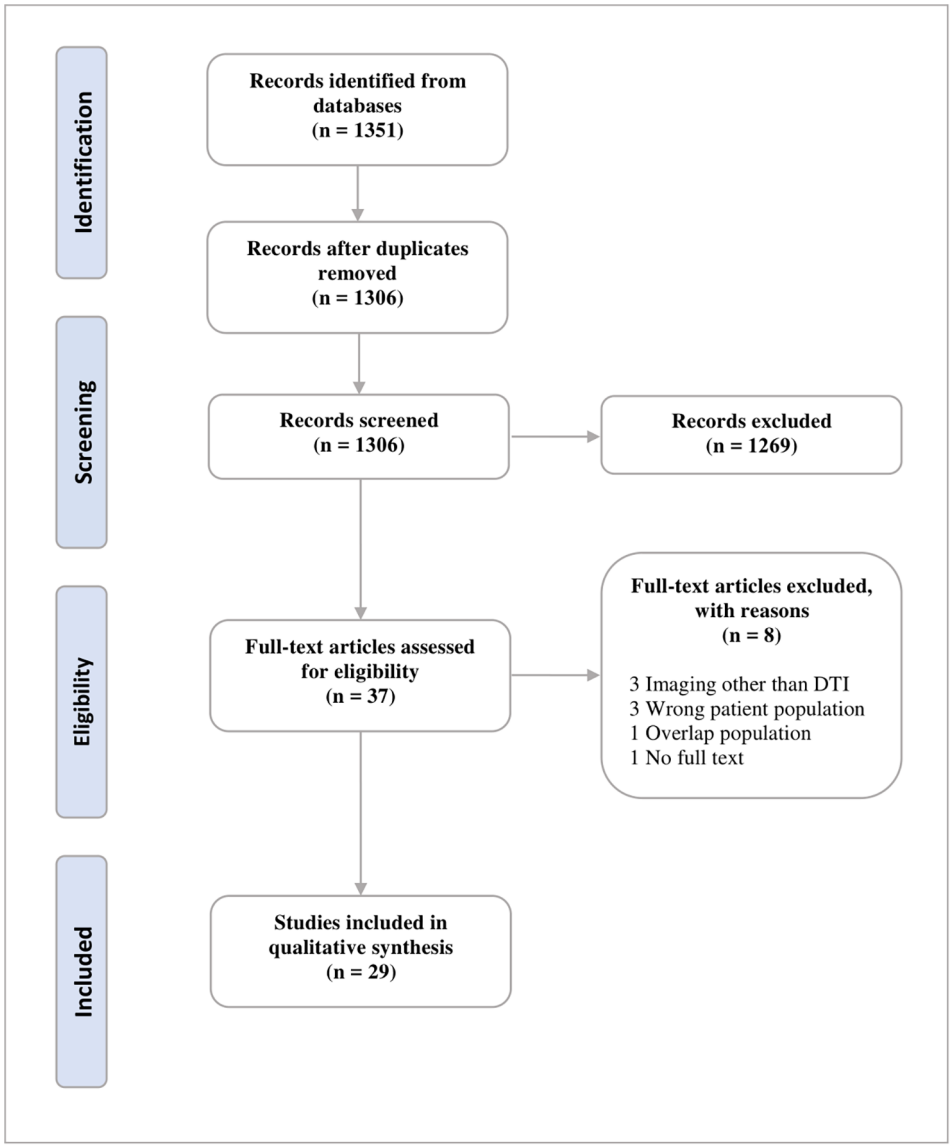

Fig. 1. RISMA flow diagram for DTI in T2DM.

and clinical parameters in altered neural microstructure in diabetic patients. Cognitive findings and the correlation of DTI measures with cognitive and clinical profile in T2DM are summarized in Table 3.

Quantitative analysis is essential for a definite conclusion about the extent of microstructural disruptions in T2DM. However, numerous study-to-study variations in the methods of DTI analysis have made it unfeasible to implement meta-analysis on the diffusion data in this review.

3.1. Overview of microstructural abnormalities in T2DM

As shown in Table 2, global or voxel-wise whole-brain analyses have revealed a quite consistent pattern of reduced FA and increased MD, AD, and RD in the GM and WM of adolescent, middle-aged or elderly patients with T2DM and diverse socio-demographic and clinical variables compared to healthy controls. Several studies have also tracked the changes in major WM tracts with similar results throughout the brain. In addition, diabetic patients with a comorbid feature of obesity, HTN, cognitive decline, depression, or stroke have shown a further reduction in the GM/WM integrity compared to diabetic patients without these comorbidities or compared to non-diabetic controls with mentioned conditions. Reports of higher FA or lower MD in diabetic patients compared to healthy controls are scarce and only limited to small clusters identified by voxel-wise analysis of covariance (VANCOVA) method (Yau et al., 2010, 2014). Moreover, Yau et al. (Yau et al., 2009, 2010) and Nouwen et al. (Nouwen et al., 2017) have reported left dominant findings in the frontotemporal lobes and their associated fibers in T2DM. Nonetheless, microstructural disruption was mostly widespread and involved both hemispheres in almost all other studies. Therefore, the damage seems to be extensive and without favored laterality in affecting left or right hemispheres. Zhang et al. (2016b) have also found no difference between FA of left and right-sided regions in T2DM. Further studies equating the diffusivity between left and right hemispheres could bring more reliable evidence for this pattern of involvement.

Only half of the reviewed studies have examined the between-group differences of complementary diffusion parameters, i.e. AD and RD. The results regarding which measure mainly derives the reduced FA or increased MD are mixed. Using voxel-based analysis (VBA) (Hsu et al., 2012), TBSS (Xiong et al., 2016), tractography (Reijmer et al., 2013a; Sun et al., 2018), or region of interest (ROI) (Xie et al., 2017; Sun et al., 2018), some studies have found increases in both RD and AD in the regions or tracts with reduced FA or increased MD. However, alterations only in RD (Zhang et al., 2013, 2014; Nouwen et al., 2017; Yu

Table 1
Overview of reviewed articles; Demographic and endocrine profile.

	Study	Study groups (special characteristics or exclusion criteria)	N (with DTI*)/ male	Age (years) (mean ± SD)	T2DM Duration (years) (mean ± SD)	FBS (mmol/L) (mean ± SD)	HbA1c (%) (mean ± SD)	DM med	N with high BP (on anti-HTN Tx)	Matched in:	Differed in: #
				Diffusion Studies							
1	Yau et al. 2009	T2DM HC (no obvious vascular pathology, significant WM disease or psychiatric disorder)	24 (22)/13 17 (16)/8	57.21 ± 8.05 56.44 ± 6.94 **(middle-aged and elderly)**	7.94 ± 5.64	7.90 ± 3.05 4.36 ± 0.40	7.83 ± 1.88 5.37 ± 0.42	No Hx of insulin Tx	16 (16) 2 (1)	age, gender, education, TC, LDL, TG, DBP, fibrinogen	FBS, fasting insulin, HbA1c, QUICKI score, SBP, HDL, BMI
2	Yau et al. 2010	Obese with T2DM Obese without T2DM (no obvious vascular pathology, significant WMH or psychiatric disorder)	18/- 18 (16)/-	16.46 ± 1.89 17.16 ± 1.45 **(adolescent)**	2.61±1.90	8.37 ± 4.79 4.16 ± 0.43	8.32 ± 2.87 5.29 ± 0.33	–	5 (1) 4 (0)	age, gender, ethnicity, school grade, SES, BMI, CRP, waist circumference, waist–height ratio, sleep apnoea self-rating, LDL, TC	FBS, fasting insulin, HOMA-IR, HbA1c, TG, HDL
3	Hsu et al. 2012	T2DM HC (no significant cognitive impairment, HTN, CVA, MI, major neurologic or psychiatric disease, significant WMH or macrostructural brain abnormalities)	40/25 97/54	56.8 ± 5.5 56.2 ± 4.7 **(middle-aged)**	5.1 ± 4.7	7.84 ± 2.45 5.01 ± 0.56	7.7 ± 1.7 5.5 ± 0.3	No Hx of insulin Tx and hypoglycaemic episode	0 (0) 0 (0)	age, gender, TC, LDL	FBS, HbA1c, BMI, SBP, DBP, TG, HDL
4	Falvey et al. 2013	T2DM HC (Some participants with Hx of MI, stroke, HTN, or depression)	85/46 223/81	83.3 ± 3.1 83.3 ± 2.6 **(elderly)**	–	–	–	–	65 (-) 153 (-)	age, education, depression score, modified MMSE score, Apo E4, Hx of stroke, MI, HTN	ethnicity (more blacks in T2DM), BMI, gender (more males in T2DM)
5	Reijmer et al. 2013 (a)	T2DM HC (non-demented well-controlled DM; no ischemic attack, stroke, neurologic disorder, psychiatric disorder requiring hospitalization, or alcohol abuse)	35/20 35/21	71.1 ± 4.6 71.0 ± 4.6 **(elderly)**	8.6 (range: 1–51)	7.8 ± 1.8 5.5 ± 0.6	6.8 ± 0.8 5.7 ± 0.4	–	- (77) - (49)	age, gender, education, SBP, DBP	FBS, HbA1c, BMI, TC, Antihypertensive med, Cholesterol-lowering drugs
6	Yau et al. 2013	HTN/T2DM HTN/non-T2DM (no psychiatric illness or significant vascular disease; no significant CAD; no Hx of stroke, head trauma, or brain tumor; BP<150/90)	22/11 11/8	58.36 ± 7.91 62.38 ± 7.32 **(middle-aged and elderly)**	–	8.01 ± 3.26 4.40 ± 0.62	7.89 ± 1.90 5.64 ± 0.19	Not currently on insulin Tx	29 on anti-HTN Tx	age, gender, education, ethnicity, SBP, DBP, TG, HDL	FBS, HbA1c, BMI
7	Aifeng Zhang et al. 2013	T2DM with MDD T2DM without MDD HC (no Hx of unstable cardiac, neurological and other psychiatric disease, head trauma, or substance abuse)	22/11 24/14 42/20 (9 subjects not in DTI analysis)	56.05 ± 9.40 62.54 ± 11.38 57.52 ± 16.0 **(middle-aged and elderly)**	8.9 ± 7.2 9.4 ± 7	–	7.88 ± 2.12 7.15 ± 0.97 5.63 ± 0.42	18 19 3 on endocrine/ metabolism med	– –	age, gender, education, SBP, DBP, LDL, BMI	HbA1c, HDL, more diabetic duration in T2DM without MDD
8	Hoogenboom et al. 2014	T2DM HC (right-handed; no Hx of stroke, MI, or substance abuse (excluding nicotine); no psychiatric, sleep, eating or learning disorder; BMI<40)	18/11 19 (18)/11	56.2 ± 6.3 53.1 ± 6.2 **(middle-aged)**	10.5 ± 6.9	8.76 ± 4.93 4.49 ± 0.38	7.5 ± 1.8 5.6 ± 0.3 (lifetime HbA1c for T2DM: 7.1 ± 1.3)	Some on insulin Tx; No use of insulin-sensitizing meds	- (6) - (2)	age, gender, ethnicity, education, BMI, smoking Hx, blood pressure meds, fasting serum insulin, SBP, DBP, TC, HDL, LDL	FBS, HbA1c, HOMA-IR, cholesterol meds, serum creatinine, TG
9	Yau et al. 2014	T2DM HC (no psychiatric illness or significant vascular disease; no significant CAD; no Hx of stroke, head trauma, or brain tumour; BP<150/90; 26 T2DM and 6 HC obese)	46/22 50/21 (with DTI: 29/14 27/12)	58.79 ± 8.20 58.80 ± 7.91 **(middle-aged and elderly)**	7.48 ± 6.69	7.90 ± 3.03 4.31 ± 0.50	7.84 ± 1.86 5.32 ± 0.43	No Hx of insulin Tx	32 (29) 17 (5)	age, gender, education, ethnicity, DBP, SBP, CRP	FBS, HbA1c, fasting insulin, QUICKI score, BMI, HDL, TG, fibrinogen, lower TC and LDL in T2DM
10	Junying Zhang et al. 2014	T2DM HC (no Hx of neurological or psychiatric disease including stroke, dementia, or TIA)	38/18 34/17	65.11 ± 7.40 62.85 ± 5.92 **(middle-aged and elderly)**	5.28 ± 2.13	7.25 ± 2.54 4.88 ± 0.51	7.05 ± 5.50 5.50 ± 0.36	13 T2DM on insulin Tx, the rest on oral hypoglycemic agents	7 (-) 6 (-)	age, gender, education, TC, HDL, LDL, BMI,	HbA1c, FBS, TG
11	Rofey et al. 2015	T2DM Obese without T2DM HC (no traumatic brain injury, cardiovascular or psychiatric disease, no medical condition affecting body weight, no Hx of bariatric surgery)	5/1 5/3 5/4	18 ± 1.4 15.4 ± 2.2 14.5 ± 2.5 **(adolescent and youth)**	7 years for all/ age at onset: 11 for all	–	–	All T2DM on metformin	– –	gender, ethnicity, SES, BMI (comparing T2DM or obese with HC)	BMI (comparing T2DM and obese), all in tanner stage IV-V
12	Raffield et al. 2016	T2DM HC (high rates of obesity, HTN and CVD in T2DM and HC; most HC= DM siblings; creatinine<2)	682/312 102/35	65.78 ± 9.84 66.65 ± 10.04 **(middle-aged and elderly)**	15.2 ± 7.73	8.14 ± 3.00 5.40 ± 0.55	7.49 ± 1.44 5.87 ± 0.3	33.3 % on insulin Tx, 65.3% on oral med	- (470) - (50)	–	–
13	Tan et al. 2016	T2DM HC (well-controlled DM; no Hx of dementia, psychiatric disease, HTN, HLP, stroke, CVD, TIA in past 2 years, epilepsy, organic lesions in brain, head trauma, brain surgery, severe liver, kidney, or heart disease, alcohol or tobacco abuse)	48/18 48/26	57.5 ± 2.32 55.7 ± 2.40 **(middle-aged)**	–	8.1 ± 2.3 5.34 ± 0.42	7.3 ± 0.44 5.6 ± 0.21	–	0 0	age, gender, education, TC, LDL, HDL, SBP, DBP, TG	FBS, HbA1c, BMI
14	Van Bloemendaal et al. 2016	Obese with T2DM Obese without T2DM HC (right-handed; no CVD, micro-albuminuria, neurological or	16/8 16 (15)/8 16 (15)/8	61.4 ± 1.5 57.7 ± 2.2 57.3 ± 1.9 **(middle-aged)**	median (interquartile range): 7.0 (4.25- 10.75)	8.4 ± 0.5 5.3 ± 0.1 5.2 ± 0.1	6.9 ± 0.22 5.5 ± 0.06 5.5 ± 0.03	8 on metformin 8 on metformin + sulfonylurea	- (12) - (3)	age, gender, DBP	T2DM vs. others: FBS, HbA1c, SBP, TG, insulin levels, lower TC and LDL; Obese with or without T2DM vs. HC: higher BMI and wait circumference, lower HDL

(*continued on next page*)

Table 1 (*continued*)

		psychiatric disorder, substance abuse or use of any centrally acting agents)									
15	Van Bussel et al. 2016	T2DM HC (no Hx of stroke or neurological disease, no mild cognitive impairment, dementia, or metabolic syndrome)	40/- 38/-	lower cognition: 61.1 ± 9.5/ higher cognition: 62.7 ± 6.7 **(middle-aged and elderly)**	9.9 ± 6.8	7.5 ± 1.2 5.1 ± 0.3	6.7 ± 0.5 5.6 ± 0.4	75% on oral med, 2.5% on insulin Tx, 10% on insulin and oral med	_ _	Participants with higher and lower cognition: age, gender, education	FBS, HbA1c, BMI, DBP, SBP,
16	Xiong et al. 2016	T2DM-MCI T2DM-NC HC (right-handed; no organic lesion in brain, no Hx of stroke, epilepsy, head trauma, or brain surgery; BP<160/100; mild or no HLP)	20/8 22/7 26/9	62.75 ± 5.93 59.05 ± 6.22 59.88 ± 6.17 **(middle-aged and elderly)**	9.02 ± 7.95 5.28 ± 4.52	9.94 ± 2.07 10.29 ± 3.35 5.22 ± 0.65	8.22 ± 1.60 6.98 ± 1.26 5.39 ± 0.41	1 T2DM-NC and 3 T2DM-MCI on insulin Tx	5 6 3	age, gender, education, BMI, HLP, HTN, FH of T2DM within 3 generations, FBS, Activities of Daily Living (Barthel index), Hachinski Ischemic Score, disease duration, insulin use, microvascular complications between T2DM-NC and MCI	T2DM-MCI > T2DM-NC > HC: HbA1c
17	Jian-Hui Zhang et al. 2016	T2DM HC (right-handed; no Hx of CVD, HTN, MI, IHD, TIA, stroke, hepatic or renal dysfunction, psychiatric or neurological disorder, substance/alcohol abuse, or diabetic peripheral neuropathy)	22/10 25/11	72.32 ± 7.05 71.75 ± 6.84 **(elderly)**	9.8 ± 2.58	8.5 ± 2.3 5.1 ± 0.8	7.86 ± 1.43 5.62 ± 0.42	Only on biguanide or alpha glycosidase inhibitor	0 0	age, gender, education	FBS, HbA1c, higher plasma CML
18	Fang et al. 2017	T2DM HC (right-handed; no Hx of HTN, stroke, alcoholism, smoking, head injury, neurological or psychiatric disorders)	48/18 48/25	57.5 ± 7.9 55.7 ± 8 **(middle-aged)**	6.5 ± 3.3	6.7 ± 2.1 3.8 ± 1.2	8.0 ± 1.5 5.7 ± 1.3	All on oral med	0 0	age, gender, education, TG, TC, HDL, LDL	FBS, HbA1c, BMI
19	Nouwen et al. 2017	T2DM Obese without T2DM HC (no major medical condition (other than PCOS and hirsutism), learning disability, major change in diabetic Tx in last 6 months, or diabetic complications; 6 obese without T2DM with impaired glucose tolerance)	13 (12)/1 13/3 20/6	16.0 ± 1.6 15.0 ± 1.9 16.1 ± 1.9 **(adolescent)**	2.56 ± 1.9	8.87 ± 3.87 (n=9) 4.95 ± 0.56 4.78 ± 0.49 (n=19)	7.80 ± 1.97 5.55 ± 0.39 5.29 ± 0.33	3 on insulin and oral med, 7 on oral med only; 1 in obese group on metformin	_ _	age, ethnicity	FBS, OGTT, HbA1c, fasting insulin, HOMA-IR, BMI, c-peptide
20	Xie et al. 2017	T2DM HC (right-handed; no cognitive impairment, microvascular complications, psychiatric or neurologic disorders, CVA, alcohol or substance abuse, or FH of HTN/ HLP/ dementia)	58/34 58/35	56.09 ± 8.16 54.66 ± 7.03 **(middle-aged)**	7.5 ± 5.8	8.06 ± 2.81 5.13 ± 0.65	8.35 ± 2.10 5.56 ± 0.33	9 on insulin Tx, 29 on oral med, 14 on both; no Hx of hypoglycemia during past 2 years	_ _	age, gender, education, BMI, SBP, DBP, TG, TC, LDL	FBS, HbA1c, HDL
21	Yoon et al. 2017	Overweight-obese T2DM Normal-weight T2DM HC (early stages of DM (<5 years) with no chronic diabetic macro-and micro-vascular complications; no major medical, neurological or psychiatric disorders, no MI or CVD)	50/25 50/25 50/25	49.0 ± 7.4 49.3 ± 8.1 49 ± 7.8 **(middle-aged)**	1.88 ± 1.5 1.78 ± 1.5	7.94 ± 2.06 7.41 ± 2.40 5.24 ± 0.21	7.28 ± 1.43 6.95 ± 1.43 5.29 ± 0.15	No Hx of insulin Tx or hypoglycemic episode (All on lifestyle modification or oral med)	- (14) - (14) - (0)	age, gender, education, smoking Hx, DBP, SBP, HTN med, TC, TG, HDL, LDL, HLP med; disease duration, FBS, HbA1c, HOMA-IR, CRP between two T2DM subgroups	BMI, T2DM>HC: FBS, HbA1c overweight-obese T2DM > normal-weight T2DM: fasting C-peptide
22	Groenevel d et al. 2018	T2DM with cognitive impairment T2DM without cognitive impairment (22 with MCI, 3 with early dementia of which 2 met criteria for Alzheimer and 1 for vascular dementia)	25/15 23/15	76.4 ± 5.0 76.5 ± 4.8 **(elderly)**	7.7 ± 6.1 6.2 ± 5.1	_	6.9 ± 0.90 6.5 ± 0.53	1st group: 15 on oral med, 9 on insulin 2nd group: 20 on oral med, 3 on insulin	23 (-) 19 (-)	Age, gender, BMI, HTN, hypercholesterolemia, diabetes duration, diabetic Tx, ever smoked, Hx of stroke, atherosclerotic disease	T2DM with cognitive impairment: lower education, higher geriatric depression score, HbA1c
23	Sun et al. 2018	T2DM HC (no Hx of brain disease, systemic disease, or alcohol or drug abuse; BP<140/90; all subjects with intact cognition)	12/4 24/8	67.33 ± 4.72 66.67 ± 5.42 **(middle-aged and elderly)**	7.92±5.30	_	_ _	_ _	6 18	age, gender, education, BMI, HTN	No difference
24	Xiong et al. 2018	T2DM HC (no lesions in brain, systemic organic disease, or moderate to severe HTN; no Hx of stroke, epilepsy, head trauma or head surgery; 4 T2DM with very mild retinopathy and neuropathy; HC without FH of DM)	30/13 28 (26)/10	60.6 ± 6.01 58.5 ± 6.22 **(middle-aged and elderly)**	7.49 ± 7.31	9.67 ± 2.63 5.20 ± 0.67	7.53 ± 1.59 5.37 ± 0.40	4 T2DM on insulin Tx	5 (-) 3 (-)	age, gender, education, BMI, HTN, HLP	FBS, HbA1c, ppBS
25	Yu et al. 2018	Stroke-T2DM stroke HC (first-ever ischaemic stroke in the vascular territory of unilateral MCA, 3-7 days after onset, no Hx of neurologic or psychiatric disorders, no stroke lesion in CC and primary sensorimotor cortex)	26/15 19/8 14/6	62.3 ± 11.6 58.0 ± 13.3 57.6 ± 8.8 **(middle-aged and elderly)**	7.3 ± 4.2	9.2 ± 3.8 5.3 ± 0.8 _	8.4 ± 1.7 5.9 ± 0.7 _	_	17 (-) 13 (-)	age, gender, HTN, HLP, smoking, drinking	FBS, HbA1c
Network Studies											
1	Reijmer et al. 2013 (b)	T2DM HC (well controlled DM, no dementia (MMSE>26), neurologic disease including TIA, stroke, psychiatric disease requiring hospitalization, or alcohol abuse)	55/33 50/32	70.9 ± 4.4 70.9 ± 4.5 **(elderly)**	Mean: 8 Range: 1-51	7.8 ± 1.7 5.5 ± 0.6	6.7 ± 0.7 5.7 ± 0.4	_	- (42) - (26)	age, gender, education, SBP	FBS, HbA1c, lower TC in T2DM, anti-hypertensive med, cholesterol lowering med,

(*continued on next page*)

Table 1 (*continued*)

2	Kim, et al. 2016	T2DM HC (right-handed; poor-controlled DM with microvascular complications; no Hx of serious head injury, TIA, stroke, other neurological illness, psychiatric disorder, heart disease, learning disability, severe hypoglycemia, alcohol or substance dependence in last 3 months)	20/9 20/9	54.6 ± 2.3 54.3 ± 2.4 **(middle-aged)**	12.1 ± 6.5	10.0 ± 1.04 5.19 ± 0.13	10.7 ± 0.3 5.9 ± 0.1	–	–	age, gender, education, BMI, SBP, DBP, TC	FBS, HbA1c, more smoking Hx in T2DM
3	Junying Zhang, et al. 2016	T2DM HC (right-handed, no Hx of neurological or psychiatric disease including stroke, dementia, or TIA, CHD, HTN, or alcoholism)	38/18 34/17	65.11 ± 7.40 62.85 ± 5.92 **(middle-aged and elderly)**	5.28 ± 2.13	7.25 ± 2.54 4.88 ± 0.51	7.05 ± 5.50 5.50 ± 0.36	13 T2DM on insulin, 27 on oral med	0 0	age, gender, education, TC, HDL, LDL, BMI,	FBS, HbA1c, TG
4	Yang Zhang, et al. 2018	T2DM HC (right-handed, no obvious vascular pathology, psychiatric and neurologic disorder, alcohol or drug abuse, T2DM-microvascular complications, CVA, MI, PVD, HLP, severe hypoglycemia during last 2 years, or FH of dementia; MMSE > 26)	57/33 57/24	55.98 ± 8.19 54.46 ± 6.93 **(middle-aged)**	7.73 ± 5.78	8.09 ± 2.82 5.14 ± 0.65	8.38 ± 2.10 5.56 ± 0.33	–	7 (-) 5 (-)	age, gender, education, BMI, BP, TC, TG, LDL	FBS, HbA1c

T2DM: Type 2 diabetes mellitus; HC: healthy control; DTI: diffusion tensor imaging; SD: standard deviation; med: medication; HX: history; Tx: treatment; FH: family history; SES: socioeconomic status; MMSE: mini mental state examination; BMI: body mass index; FBS: fasting blood sugar; HbA1c: hemoglobin A1c; OGTT: oral glucose tolerance test; ppBS: postprandial blood sugar; QUICKI: Quantitative Insulin Sensitivity Check Index; HOMA-IR: homeostatic model assessment-insulin resistance; TC: total cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglyceride; HLP: hyperlipoproteinemia; CRP: C-reactive protein; Apo E4: apolipoprotein E4; CML: Nε-(Carboxymethyl) lysine; BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; HTN: hypertension; IHD: ischemic heart disease; MI: myocardial infarction; CAD: coronary artery disease; CVA: cerebrovascular accident; CVD: cerebrovascular disease; TIA: transient ischemic attack; MCA: middle cerebral artery; MDD: major depressive disorder; NC: normal cognition; MCI: mild cognitive impairment; PCOS: polycystic ovary syndrome; WMH: whiter matter hyperintensities.

–: No data presented, or the measure not investigated.

*Mentioned only if the whole number of participants did not undergo DTI assessment.

#All data of metabolic derangement are higher in T2DM compared to controls, except HDL, which is lower in T2DM, or mentioned otherwise.

Please note that in case of any discrepancy between texts of the reviewed articles and their presenting tables, we have relied on the data in the (supplementary) tables.

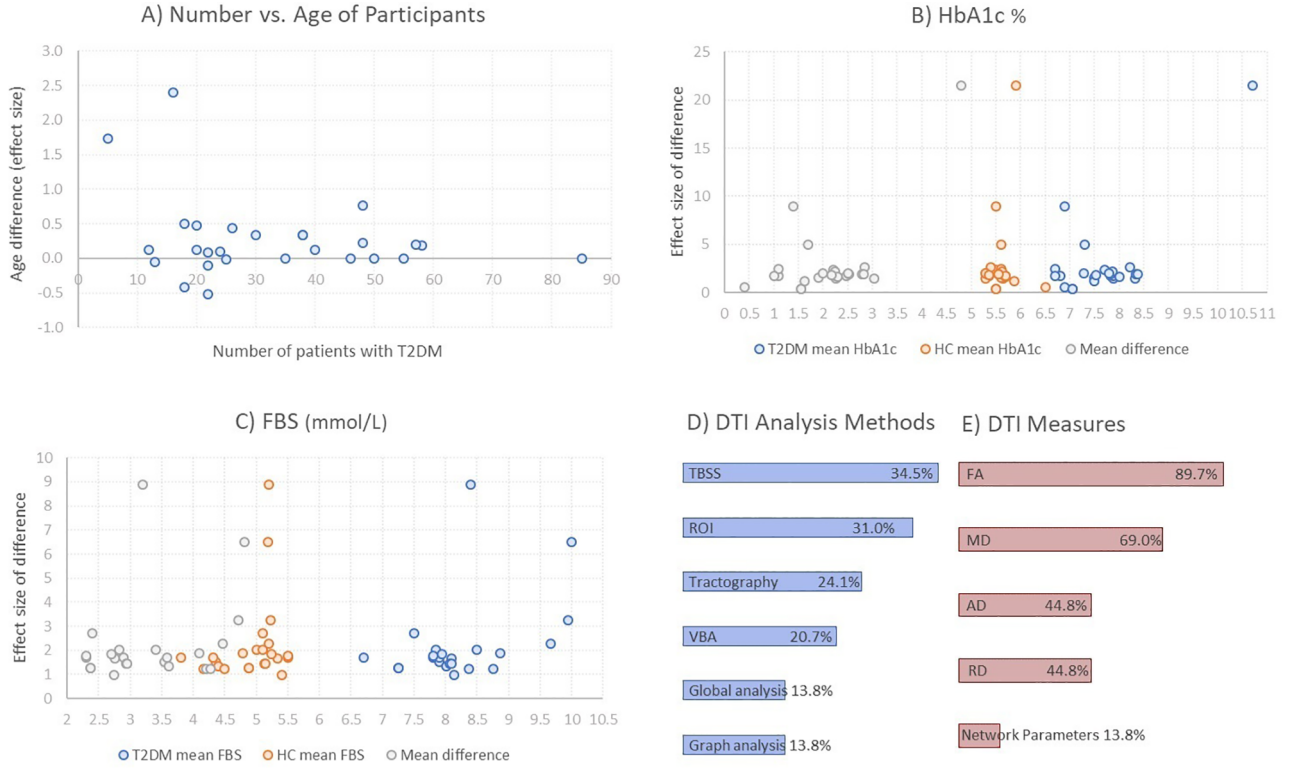

Fig. 2. Key features of reviewed studies. (A) Scatter plot showing number of patients with T2DM against age difference (effect size) between T2DM and control groups; (B and C) Scatter plots of HbA1c and fasting blood glucose (FBS) difference between T2DM and control subjects; (D) Proportion of different methods of imaging analysis applied by reviewed studies; (E) Proportion of different DTI measures investigated by reviewed studies.

For simplicity, only two main study groups (first group in Table 1, in case of multiple groups, versus HC) are illustrated for A, B, and C. Case and control groups of Groeneveld et al. (2018) were: T2DM with (n = 25, age: 76.5 ± 5) and without (n = 25, age: 76.5 ± 4.8) cognitive impairment. In order to present a better look on the scatter plot, the sample size of Raffield et al. (2016) (n = 682) is not shown in A. One study might have applied more than one method for analysis or reported more than one measure, thus the sum of percents might exceed 100%.TBSS: tract-based spatial statistics; ROI: region of interest; VBA: voxel-based analysis; FA: fractional anisotropy; MD: mean diffusivity; AD: axial diffusivity; RD: radial diffusivity.

Table 2
Overview of reviewed articles; DTI analysis and between-group diffusion/network findings.

Diffusion Studies								
		DTI analysis		Between-groups findings (T2DM vs. HC)				
Study		Field Strength/b value (s/mm²)	Method of analysis: studied tracts/regions	Lower FA	Higher MD	Higher AD	Higher RD	Other imaging findings
1	Yau et al. 2009	1.5T/ 1000	**VANCOVA**: voxel-wise whole brain WM **ROI**: temporal stem	**VANCOVA:** 11/12 clusters in all four lobes but predominantly in frontal and temporal WM and largest in L-temporal stem/ **Clusters:** L-temporal Stem, L-frontal temporal region, L-parietal region, L-middle temporal region, R-prefrontal region, R-EC **ROI**: temporal stem	–	–	–	**Periventricular or deep WM hyperintensities:** no difference
2	Yau et al. 2010	1.5T/ 1000	**VANCOVA**: voxel-wise whole brain WM FA and GM MD	**5 clusters; largest:** L-temporal stem, R-cingulate WM, L-cerebral peduncle; 1 small cluster with higher FA, 5 clusters with higher FA or lower MD	**27 clusters; largest:** R-STG, L-prefrontal cortex, R-parietal cortex	–	–	**WM volume:** reduced in whole brain and frontal lobe; **CSF volume:** enlarged in whole brain and frontal lobe; **GM volume** no obvious reduction
3	Hsu et al. 2012	1.5T/ 1000	**Global analysis** **VBA**: whole brain	Trend in lower global FA **VBA: 2 clusters** in bilateral frontal WM	Increased global MD **VBA: 12 Clusters:** bilateral anterior and posterior lobes of cerebellum, bilateral temporal lobe WM, L-PHG, L-fusiform gyrus, L-cuneus WM	Trend in higher global AD **VBA:** Same as MD	Increased global RD **VBA:** Same as FA and MD	**WMH:** no difference **GM, WM, CSF volume**: no difference
4	Falvey et al. 2013	3T/ 1000	**Global analysis** **ROI**: hippocampus, entorhinal cortex, posterior cingulate, DLPFC, posterior parietal cortex, striatum (putamen, caudate, pallidum)	Decreased global WM FA	No difference in global GM MD **ROI**: Hippocampus, L-posterior cingulate, DLPFC, trend in R-posterior cingulate and R-putamen	–	–	**GM volume:** reduced in whole brain and putamen, trend in L-DLPF and L-striatal GM; **total brain volume:** reduced; **cerebral atrophy:** greater; **WMH:** no difference
5	Reijmer et al. 2013 (a)	3T/ 1200	**Fiber tractography**: SLF, UF, ILF, gCC, sCC	R-UF	SLF, UF, ILF, sCC	SLF, UF, L-ILF, sCC, trend in R-ILF	SLF, UF, L-ILF, trend in R-ILF	markers of vascular injury (**WMH**, **lacunar and large vessel infarcts**): no difference; **tract**s of interest **volume:** no difference
6	Yau et al. 2013	-/ 1000	**VANCOVA**: voxel-wise whole brain WM	HTN with T2DM < HTN without T2DM: **16 clusters:** R-IC, EC, medial cerebellar WM, parietal WM, AF, L-calcarine fissure WM, L-CC, L-occipital lobe, temporal lobe, L-frontal lobe	–	–	–	**Periventricular or deep WM hyperintensities:** no difference
7	Aifeng Zhang et al. 2013	3T/ 700	**FACT**: ALIC	T2DM with MDD < HC: R-ALIC trend in diabetes effect in L-ALIC	No significant difference	No significant difference	T2DM with MDD > HC: R-ALIC (trend)	**WMH:** no difference
8	Hoogenboom et al. 2014	3T/ 1000	**Streamline tractography**: Cingulum, UF, SLF	cingulum, UF (Shorter fiber length but the same fiber volume in cingulum, UF and SLF)	No significant difference	trend in **lower AD** in cingulum	No significant difference	**FC:** reduced in DMN between posterior cingulate and both L-fusiform and L-medial frontal gyrus in T2DM; FA of cingulum correlated with FC between posterior cingulate and medial frontal gyrus for combined groups
9	Yau et al. 2014	1.5T/ 1000	**VANCOVA**: voxel-wise whole brain WM FA and GM MD	**13 Clusters:** Extensive abnormalities in temporal WM (AF, L-superior and R-middle temporal WM), L-SLF, L-temporal stem, L-occipital WM, parietal WM, R-medial occipito-temporal WM, prefrontal WM, occipital WM; 70% of clusters in L-hemisphere; frontal lobe largely unaffected **Higher FA:** 4 small clusters in R-ALIC and R-frontal WM	**23 Clusters:** 10 in temporal lobe (Heschl's gyri, PHG, fusiform areas, R-insular cortex), 5 in occipital lobe (calcarine fissure), R-PHG/cerebellum, 5 in R-prefrontal cortex, and 2 in L-parietal cortex. **Lower MD:** 3 small clusters in occipital lobe	–	–	**Intracranial vault volume**: no difference; **global atrophy:** no difference; **hippocampal volume**: reduced in T2DM; **cortical thickness** and **frontal and temporal lobes volume:** no difference
10	Junying Zhang et al. 2014	3T/ 1000	**TBSS**: whole brain WM **ROI**: 40 WM tracts within the cerebrum	**TBSS:** gCC, bCC, sCC; CR; ALIC, PLIC, retro-lenticular part of IC, PTR, cingulum (L-cingulate gyrus), L-cingulum (hippocampal part), SLF, SS (including ILF and IFOF), SFOF, EC, fornix/stria terminalis, UF, tapetum; **ROI:** gCC, bCC, sCC, L-ALIC, L-SS, L-EC, R-SLF, L-UF, tapetum	**TBSS**: gCC, bCC, sCC; CR; EC, ALIC, L-PLIC, retro-lenticular part of IC, PTR, cingulum (cingulate gyrus), SLF, tapetum; **ROI**: no significant difference	**TBSS and ROI:** no significant difference	**TBSS**: gCC, bCC, sCC, CR, IC (except R-PLIC), PTR, cingulum (cingulate gyrus), SLF, SS, EC, fornix/stria terminalis, UF, tapetum, R-SFOF; **ROI**: no difference	–
11	Rofey et al. 2015	-/ 1000	**Voxel-wise deterministic tractography**: frontal cortico-striatal pathways between MFG and striatal nuclei (caudate, thalamus and putamen)	Only before controlling for BMI: T2DM<obese<HC: generalized FA in right cortico-striatal pathways (DLPFC to caudate and putamen) (trend in left side) and thalamic pathways (DLPFC to thalamus)	–	–	–	**GM volume:** T2DM<obese<HC: caudate volume and thalamus volume and a trend in all other GM structures

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Table 2 (*continued*)

12	Raffield et al. 2016	two 1.5T, one 3T (15 subjects)/ 1000	**Global analysis:** GM FA and MD, WM FA and MD	Lower FA in WM and GM	Higher MD in WM and GM	–	–	**WM volume:** reduced, **WM lesion volume:** increased
13	Tan et al. 2016	3T/ 1000	**TBSS**: whole brain WM	Vermis cerebella, CC, bilateral thalami (including fornix, ATR, and PTR), cingulum-frontal lobe, R-cingulum-parietal lobe, R-frontal lobe (including R-UF), bilateral parietal lobes (including SLF and ILF)	R-MTG (including UF and ILF), bilateral thalami (including fornix, ATR, and PTR)	Bilateral thalami (including fornix, ATR, and PTR), L-cingulum-frontal lobe	No significant difference	**WMH** and **lacunar infarcts:** no difference; No specific lesions on conventional MR scans of any of the subjects;
14	Van Bloemendaal et al. 2016	3T/ 1000	**TBSS**: whole brain WM	No significant difference	No significant difference	Obese T2DM < HC: R-CST, R-IFOF, R-SLF, R-forceps major; Obese without DM < HC: trend in a cluster of voxels on L-forceps major	No significant difference	**WM lesions:** no difference; **WM volume:** T2DM < HC in R-IPL and L-EC, obese without DM < HC trend in L-EC
15	Van Bussel et al. 2016	3T/ 1500	**Probabilistic tractography**: hippocampus **Connectivity (tract volume)**: hippocampus to frontal lobe, parietal lobe, temporal lobe, subcortical gray matter	**Tractography**: lower hippocampal FA which did not remain significant after adjustment for covariates; **Connectivity:** fewer WM connections between hippocampus and frontal lobe; Fewer WM connections between hippocampus and temporal lobe in participants who scored lower on memory function, regardless of T2DM	**Tractography**: higher hippocampal MD which did not remain significant after adjustment for covariates	–	–	**WM lesion volume**: increased; **Hippocampal volume:** reduced in L-hippocampus (trend)
16	Xiong et al. 2016	3T/ 1000	**TBSS**: whole brain **ROI** (FA and MD): ALIC, cingulum (cingulate gyrus and hippocampus), ACR, SCR, PCR, gCC, bCC, sCC, EC, PTR (including optic radiation), rIC, SS (including ILF and IFOF), cerebellar peduncle, CST, MCP, PCT	**TBSS**: T2DM-MCI < T2DM-NC: 7.3% of parcellated regions, T2DM-MCI < HC: 36.6% of parcellated regions; **ROI**: T2DM-MCI < T2DM-NC: L-EC, L-ALIC, ACR, L- PTR, cingulum (hippocampus); T2DM-NC < HC: R-CST, R-cerebellar peduncle	**TBSS**: T2DM-MCI > T2DM-NC: 24.9% of parcellated regions, T2DM-MCI > HC: 58.8% of parcellated regions; **ROI**: T2DM-MCI > T2DM-NC: L-EC, L-rIC, L-SCR, R-SS; T2DM-NC > HC: R-rIC and R-EC	**TBSS:** T2DM-MCI > HC: several regions (shown on figures, not specified)	**TBSS:** T2MD-MCI > T2MD-NC: main mediator of FA and MD differences between these two groups relative to AD, T2DM-NC > HC: several regions, including EC, temporal WM, R-frontal WM and CR	–
17	Jian-Hui Zhang et al. 2016	3T/ 1000	**TBSS**: whole brain WM	temporal lobe WM, hippocampus, parietal WM, bCC, sCC, cingulum, SLF, and IFOF (No difference between FA of left- and right-sided regions in either group)	–	–	–	No obvious abnormality in conventional MRI structural images
18	Fang et al. 2017	3T/ 1000	**Deterministic tractography**: cerebellar and cerebrocerebellar circuits	Cerebrocerebellar circuit: from anterior cerebellum crus to precentral, superior frontal, R-superior parietal and precuneous gyri; from R-precuneous and R-thalamus to R-cerebellar hemisphere; Cerebellar circuit: mainly from cerebellum IX to vermis	–	–	–	–
19	Nouwen et al. 2017	3T/ 1500	**TBSS**: whole brain WM	T2DM < HC: L-CST, medial CC, L-fornix, L-thalamic radiation, L-rIC, L-IFOF, R-ACR, gCC, L-UF, L-bCC, cingulum, and L-anterior EC	No significant difference	No significant difference	Regions of reduced FA mainly driven by RD increase	**GM volume:** T2DM < HC: caudate and putamen, Obese without T2DM < HC: R-hippocampus, L-putamen, L-caudate, amygdala, T2DM + Obese without T2DM < HC: putamen, caudate, L-amygdala and L-thalamus, no difference between T2DM and obese without T2DM
20	Xie et al. 2017	3T/ 1000, 2000	DTI and DKI: **VBA:** whole brain WM (FA, MD, MK) **ROI:** each cluster with significant intergroup difference on VBA (AD, RD, AK, RK)	**DKI**: R-prefrontal WM, sCC **DTI**: sCC	**DKI**: prefrontal WM, R-superior temporal WM, sCC, pons, L-EC **DTI**: superior and inferior R-prefrontal WM and L-EC	prefrontal WM, sCC, R-superior temporal WM, L-EC, pons	prefrontal WM, sCC, R-superior temporal WM, L-EC, pons	**MK, AK and RK:** lower in sCC and pons; (no difference in any diffusion or kurtosis metrics between T2DM separated based on insulin treatment)
21	Yoon et al. 2017	1.5T/ 1000	**Global WM analysis** **TBSS**: WM in temporal, prefronto-parietal, motor and occipital regions **ROI**: SLF, ILF, UF, cingulum, CC	Total T2DM < HC: **global** WM FA **TBSS**: total T2DM < HC: L-SS, L-IFOF, L-UF, CST (R-frontal and temporal regions), CC (frontal, L-parietal regions), ant thalamic radiation, ACR, SCR, cerebellar WM, forceps minor, optic radiation, EC, R-parietal WM, R-temporal WM **ROI:** overweight-obese T2DM < HC: ILF, IFOF, cingulum, CC Normal-weight T2DM < HC: IFOF, UF, cingulum overweight-obese T2DM < normal-weight T2DM: prefrontoparietal WM	–	–	–	**GM thickness:** overweight/obese T2DM < normal-weight T2DM: global and in temporal, motor and prefrontoparietal ROIs, total T2DM < HC: in clusters in temporal, prefrontoparietal, motor and occipital cortices

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Table 2 (*continued*)

22	Groeneveld et al. 2018	3T/ 1200	**Fiber tractography**: whole brain WM	No significant difference in FA-weighted WM connectivity	Trend in higher MD-weighted WM connectivity in T2DM with cognitive impairment compared to without (topographically unrelated to GM atrophy)	–	–	in T2DM with cognitive impairment < without: **Total brain volume** **GM volume:** in total and predominantly in R-temporal cortex and subcortical regions **WM volume:** no difference **WMH and vascular lesions:** no difference
23	Sun et al. 2018	3T/ 1000	**TBSS:** whole brain WM **ROI:** JHU atlas	**TBSS:** extensive WM impairment including CC, cingulum, CST, IC, EC, ACR, PCR, fornix, PTR, SCP, tapetum, etc **ROI:** gCC, bCC, L-CST, L-SCP, L-PTR (bCC most heavily impaired structure) (Decreased FA in L-PTR closely related with decreased L-hippocampal FC to L-caudate and frontal cortex in T2DM)	**TBSS:** same as FA **ROI**: bCC, sCC, R-ACR, SCR, PCR, R-cingulum (Increased MD in sCC closely related with the decreased R-hippocampal FC to L-caudate, R-cingulate cortex and R-frontal cortex in T2DM)	**TBSS:** same as FA **ROI:** bCC, sCC, R-ACR, SCR, PCR	**TBSS:** in restricted brain regions **ROI:** bCC, sCC, R-ACR, SCR, PCR	**Total brain, GM, WM, CSF volume:** no difference **Regional GM volume**: no difference **Hippocampal FC** to anterior cingulate cortex, olfactory cortex, caudate nucleus and frontal cortex (including dorsolateral, medial and orbital part of SFG, gyrus rectus, orbital part of MFG and IFG): T2DM < HC
24	Xiong et al. 2018	3T/ 1250, (kurtosis metrics: 1250 and 2500)	DKI: **TBSS**: whole brain WM **ROI**: 48 regions of JHU WM tractography atlas and in GM nuclei (FA and MK): thalamus, caudate, Globus pallidus, putamen	**TBSS:** 29.6% of whole brain WM; **ROI:** 13/48: ACR, SCR, EC, cingulum (hippocampus), L-cingulum (cingulate gyrus), SFOF, L-UF, R-cerebral peduncle; in **GM nuclei**: L-caudate	**TBSS: T2DM < HC:** 30.4% of whole brain WM; **ROI:** 17/48: gCC, R-PLIC, rIC, R-ACR, PCR, L-EC, cingulum (hippocampus), L-cingulum (cingulate gyrus), SS, SFOF, L-UF, MCP	–	–	**TBSS:** MK: 35.4%; AK: 10.5% ; RK: 26.0% of whole brain WM; MK reduction contributed more by decreased RK; **ROI:** ↓MK: 27/48: gCC, bCC, ALIC, PLIC, ACR, SCR, PCR, R-EC, L-cingulum (cingulate gyrus), cingulum (hippocampus), SLF, SS, R-UF, R-SCP, MCP, tapetum, PCT, fornix; **in GM nuclei:** thalamus and caudate; ↓AK: R-rIC, PCR, R-PTR, SLF, SS, R-UF, MCP, fornix; ↓RK: L-SFOF, L-tapetum and underlined regions for MK
25	Yu et al. 2018	3T/ 1000	**ROI**: five subregions of CC	iCC in stroke-T2DM compared to both stroke patients and HC and also in poorly recovered patients (lower FA of iCC correlated with decreased inter-hemispheric primary sensorimotor FC in all and in T2DM)	No significant difference	No significant difference	iCC	**inter-hemispheric primary motor FC:** only different in stroke-T2DM < HC; **inter-hemispheric primary sensory FC**: stroke-T2DM < stroke and HC

Network Studies

Study		Network analysis		Between-groups findings (T2DM vs. HC)							
				Global Parameters						Nodal parameters	Other imaging findings
				Network Segregation		Network Integration			Balance		
		Field Strength/ b value (s/mm²)	Method of analysis	Clustering coefficient (γ)	local efficiency	Strength	Shortest path length (λ)	Global efficiency	Small-worldness (σ: γ/ λ)		
1	Reijmer et al. 2013 (b)	3T/ 1200	**Graph theoretical analysis and Fiber tractography:** 90 nodes (cerebellum excluded)	↓	No difference	–	↑	↓	–	–	**WMH, lacunar/cortical infarct**: no difference (between-group differences of network parameters independent of WMHs and infarcts) (WMH and lacunar infarcts associated with reduced clustering, reduced global efficiency, and increased path length in T2DM)
2	Kim et al. 2016	3T/ 1000	**Graph theoretical analysis**: 144 nodes **Deterministic fiber tractography**: whole brain **TBSS**: whole brain WM	No difference	–	No difference	↑	↓	No difference	–	**Global WM FA**: no difference **TBSS**: lower FA in distributed WM; peak clusters in: PTR including optic radiation, R-rIC, sCC, R-fornix/stria terminalis, R-SS (including ILF and IFOF), R-EC; MD, AD, RD: No difference **Fiber tractography:** no difference found
3	Junying Zhang et al. 2016	3T/ 1000	**Graph theoretical analysis and Deterministic tractography**: 60 nodes	No difference	↓	↓	↑	↓	↓	↓ Nodal efficiency in frontal (SFG, medial orbital, R-RO), limbic (L-anterior cingulate and paracingulate gyri), and parietal (R-lPL) regions; Trend in L-olfactory cortex (frontal), R-MFG (frontal), L-postcentral gyrus (parietal); No damaged hub nodes in T2DM	**GM volume**: no difference in total, trend in lower volume in R-STG and L-dorsolateral SFG, and higher volume in L-angular gyrus
4	Yang Zhang, et al. 2018	3T/ 1000	**Graph theoretical analysis**: 90 nodes	↑	No difference	–	↑	No difference	No difference	↓ Global efficiency in R-hippocampus, R-amygdala, and L-pallidum ↓ Local efficiency in L-post central gyrus and R-SPT ↑ Nodal degree in R-IFG	–

T2DM: Type 2 diabetes mellitus; HC: healthy control; MRI: magnetic resonance imaging; DTI: diffusion tensor imaging; DKI: diffusion kurtosis imaging; FA: fractional anisotropy; MD: mean diffusivity; AD: axial diffusivity; RD: radial diffusivity; MK: mean kurtosis; AK: axial kurtosis; RK: radial kurtosis; FC: functional connectivity; WM: white matter; WMH: WM hyperintensities; GM: grey matter; CSF: cerebrospinal fluid; VBA: voxel-based analysis; ROI: region of interest; VANCOVA: voxel-wise

analysis of covariance; TBSS: tract-based spatial statistics; FACT: fiber assignment by continuous tractography; BMI: body mass index; HTN: hypertension; MDD: major depressive disorder; NC: normal cognition; MCI: mild cognitive impairment.
L-: left; R-: right; STG/MTG: superior/middle temporal gyrus; SPT: superior pole of the temporal lobe; SFG/MFG/IFG: superior/middle/inferior frontal gyrus; DLPFC: dorsolateral prefrontal cortex; IPL: inferior parietal lobe; PHG: parahippocampal gyrus; SLF/ILF: superior/inferior longitudinal fasciculus; UF: uncinate fasciculus; AF: arcuate fasciculus; CC: corpus callosum; gCC/bCC/sCC/iCC: genu/body/splenium/isthmus of corpus callosum; EC: external capsule; IC: internal capsule; ALIC/PLIC/rIC: anterior limb/posterior limb/retrolenticular part of internal capsule; ATR/PTR: anterior/posterior thalamic radiation; CR: corona radiata; ACR/PCR/SCR: anterior/posterior/superior corona radiata; SS: Sagittal stratum; SFOF/IFOF: superior/inferior fronto-occipital fasciculus; CST: corticospinal tract; MCP: middle cerebellar peduncle; PCT: pontine crossing tract; RO: rolandic operculum; JHU: John Hopkins University; DMN: default mode network.
–: No data presented, or the measure not investigated. Texts in red represent the counterintuitive results of higher FA, or lower MD/AD/RD in T2DM compared to HC. Only statistically significant results are reported. If the results are statistically corrected, only corrected ones are reported, unless mentioned otherwise.
Please note that in case of any discrepancy between text of the reviewed articles and their presenting tables, we have relied on the data in the (supplementary) tables.

et al., 2018), or only in AD (Tan et al., 2016; van Bloemendaal et al., 2016), or even none of them (Hoogenboom et al., 2014; Zhang et al., 2014; Kim et al., 2016) are also noticed by various methods of analysis. Neuronal loss (Zhao et al., 2011; Ramos-Rodriguez et al., 2013), disorganized myelin (Cermenati et al., 2017; Nam et al., 2018), axonal shortening (Yermakov et al., 2018) and decreased dendritic density (Stranahan et al., 2009) are all described in the brains of rodent models of T2DM. However, by assuming RD as the main index of myelin integrity and AD as an index of axonal integrity, the relative vulnerability of the axonal and myelin structures to metabolic derangement in T2DM remains unclear.

All four studies using graph theoretical network analysis (Zhang et al.; Reijmer et al., 2013b; Kim et al., 2016; Zhang et al., 2016a) have described disruptions in network integration parameters, reflected by longer characteristic path length (λ) and lower global efficiency. These parameters represent the slower speed and lesser capacity of a network to exchange information, respectively. In other words, it seems that remote brain regions do not interact efficiently due to the impact of T2DM. However, indicators of local information integration capability, i.e. clustering coefficient and local efficiency, did not show a consistent pattern in T2DM. In the first investigation of network characteristics in T2DM, Reijmer et al. (2013b) found lower clustering coefficient in well-controlled diabetic patients compared to healthy controls, while later, Zhang et al. reported higher values for this index in patients free of clinical vascular complications. The two other studies, however, have not detected any difference in local parameters in T2DM. More studies are clearly needed to assume a reliable conclusion about the impact of T2DM on the topological properties of the brain network.

Worthy of note, DTI has detected microstructural abnormalities even in the absence of atrophies or gross vascular pathologies, such as differences in WM hyperintensities or cortical/lacunar infarcts. The superiority of DTI was similarly evident in studying patients with well-controlled DM, including those with less than five years of disease duration, or without any macro- or microvascular complications or cognitive deficit (Table 2).

3.2. Between-group differences: Lobar cluster

Compared to non-diabetic controls, major voxels with lower levels of microstructural integrity are frequently reported to be predominantly located in the frontal, temporal and parietal cortical and subcortical regions in patients with T2DM (Fig. 3). This pattern is also replicated by decreased nodal efficiency of these areas in the topological network analysis (Zhang et al.; Zhang et al., 2016a).

Whole-brain between-group comparison of DTI measures by VBA or VANCOVA has always confirmed extensive disruptions in the microstructural integrity of the frontal and temporal lobes. In particular, T2DM patients had lower FA in the right (Tan et al., 2016; Xiong et al., 2016), left (Yau et al., 2013), or bilateral (Yau et al., 2009; Hsu et al., 2012) frontal WM. Notably, different modes of analysis have consistently reported the microstructural disruption of cortical and subcortical regions of the prefrontal area in patients with T2DM (Yau et al., 2010, 2014; Falvey et al., 2013; Xie et al., 2017). Tractography has also revealed disruptions, reflected by FA reductions, in the prefrontal-striatal (Rofey et al., 2015) and frontal-cerebellar pathways (Fang et al., 2017). Microstructurally abnormal clusters have also been identified within the temporal lobe (Yau et al., 2009, 2013; Hsu et al., 2012; Zhang et al., 2016b; Yoon et al., 2017) and more specifically in the superior (Yau et al., 2010; Yau et al., 2014; Xie et al., 2017) and middle (Yau et al., 2009, 2014) temporal regions. Structures within the temporal lobe, such as the left temporal stem, hippocampus, and parahippocampal (PHG), insular, fusiform, and Heschl's gyri (Yau et al., 2009, 2010, 2014; Falvey et al., 2013) are also found with lower diffusion parameters in T2DM. In addition, van Bussel et al. have demonstrated lower hippocampal WM connections with the frontotemporal region in patients with relatively well-controlled T2DM compared to healthy controls (van Bussel et al., 2016).

The parietal lobe signifies the most predominant region with microstructural disruption after the frontotemporal region. Several studies have found reduced FA values in parietal WM in patients with T2DM (Yau et al., 2013, 2014; Zhang et al., 2016b; Yoon et al., 2017). Besides, the parietal cortex was demonstrated to have higher levels of MD in these patients (Yau et al., 2010, 2014).

Important to note, decreased integrity in each lobe was not always in parallel to reductions in GM thickness or WM volume. Microstructural disruptions occurred somehow independent of gross morphological damage (Table 2).

3.3. Between-group differences: White matter cluster

Altered diffusivity in the major association fibers interconnecting frontal, temporal and, less predominantly, parietal regions is reflected in several whole-brain voxel-based studies or other regions/tracts of interest analytical methods.

As depicted in Fig. 3, uncinate fasciculus (UF) together with the external capsule are of the most consistently reported tracts with microstructural abnormality in T2DM. UF connects the prefrontal cortex with parts of the limbic system in the temporal lobe, such as the hippocampus and amygdala. It also forms one of the major bundles of the temporal stem (Kier et al., 2004) and external capsule (Panesar et al., 2017). The cingulum is another important limbic structure, which expands from the frontal lobe to the temporal lobe and forms a C-like structure right above the CC. The cingulum is an essential railway between the cingulate gyrus and prefrontal cortex and hippocampus (Leech et al., 2012). Several studies using different modes of DTI analysis have consistently reported that T2DM is associated with microstructural abnormalities in the cingulum and CC (see the Table in Fig. 3 for relevant references). In addition, disruptions in different subregions of CC, including genu (Zhang et al., 2014; Nouwen et al., 2017; Xiong et al., 2018), body (Zhang et al., 2014, 2016b; Nouwen et al., 2017), isthmus (Yu et al., 2018), and splenium (Reijmer et al., 2013a; Zhang et al., 2014, 2016b; Kim et al., 2016; Xie et al., 2017) have been

Table 3
Overview of reviewed articles; Cognitive findings and correlation of diffusion/network parameters with cognitive and metabolic profile.

	Study	Cognitive findings		Association between diffusivity/network metrics and metabolic profile of T2DM
		Cognitive function in T2DM vs. HC	Investigated correlation of diffusivity/network metrics with cognitive functions: • Significant findings	
	Diffusion Studies			
1	Yau et al. 2009	Impaired immediate and delayed neutral and emotional memory; Blunted memory facilitation by emotional material among female but not male diabetics; No significant difference: IQ, working and episodic memory (CVLT and WMS-R scores), sustained attention (DSST) and verbal fluency (COWAT)	FA of temporal stem with emotional and neutral memory (immediate and delayed): • Lower FA of L-temporal stem: worse immediate, but not delayed, emotional memory	• No relation between FA in temporal stem and age, QUICKI score (higher score: better insulin function), or systolic BP
2	Yau et al. 2010	Lower intellectual functioning, IQ, verbal memory and psychomotor efficiency; Trends for lower executive function, reading and spelling	_	_
3	Hsu et al. 2012	_	_	• Higher global mean MD, AD, RD: lower TG; • Higher global mean MD, RD: lower BMI; • Higher disease duration: higher MD, AD, RD globally and in 30 clusters, largest of which are in L-IFG WM, L-MFG WM, R-cingulate gyrus WM, R-caudate, R-STG WM, L-precuneus, pons WM, L-parietal lobe WM, L-fusiform gyrus WM; • Higher disease duration: lower FA and higher AD and RD in bilateral posterior cerebellar lobes, R-MFG WM • Higher disease duration: higher FA and AD and lower RD in L-brainstem, R-lentiform nucleus, bilateral MFG WM
4	Falvey et al. 2013	No difference in MMSE score	_	_
5	Reijmer et al. 2013 (a)	No difference in IQ, MMSE, verbal memory (RAVLT), information-processing speed (TMT-A, DSST, stroop part 1,2), attention (TMT B/A) and executive function (category and verbal fluency, stroop part3)	Significantly different between-groups DTI parameters or WMH and infarcts with verbal memory, information-processing speed, attention and executive function: • Higher MD of UF, ILF, sCC: worse information-processing speed only in T2DM; • Higher MD of ILF: worse memory only in T2DM; • Lower FA of UF: worse information-processing speed only in T2DM	• Higher HbA1c: worse executive functioning in T2DM •Trend between higher HbA1c and higher MD of ILF and worse memory; • No relation between duration of T2DM and cognition or DTI parameters
6	Yau et al. 2013	_	_	_
7	Aifeng Zhang et al. 2013	_	_	• Higher HbA1c in all diabetics: lower FA of L-ALIC, higher RD of L-ALIC (trend); • Higher HbA1c in T2DM with MDD: higher RD of R-ALIC; • Higher HbA1c in T2DM without MDD: lower FA of L-ALIC
8	Hoogenboom et al. 2014	Lower full-scale IQ, worse executive function (verbal fluency) and memory (RAVLT-immediate recall); No significant difference: Information-processing speed (Grooved Pegboard), trail making number-letter switching, HDRS, RAVLT-delayed recall and psychomotor speed	FA of UF and cingulum with executive function, memory, and psychomotor speed performance: • Lower FA of UF: slowing of information-processing speed in T2DM and HC; • Lower FA of cingulum: higher delayed memory scores only in T2DM	• Age, education, diabetes duration, lifetime HbA1c and HOMA-IR not correlated with FA of cingulum and UF; • Higher HbA1c: higher FA of UF in T2DM and HC; • Higher serum creatinine level: lower FA of UF only in T2DM; • Higher BMI: lower FA of cingulum only in T2DM; • Higher FBS: lower FA of cingulum in combined groups
9	Yau et al. 2014	lower estimated IQ and verbal memory immediate and delayed recall (CVLT, WMSR, and GMT scores)	Intracranial vault-adjusted hippocampal volume and FA of AF, superior temporal WM, L-temporal stem, MD of L-PHG, bilateral Heschl's gyri with verbal memory in T2DM: • Higher MD of L-PHG: worse immediate and delayed recall of verbal memory	_
10	Junying Zhang et al. 2014	Worse executive function (Stroop C-B time), spatial processing (ROCF-copy), attention (SDMT), and working memory (digit span, backward recall); No significant difference: general mental status (MMSE), episodic memory (AVLT, ROCF-recall), language (BNT, CVFT), logical reasoning (similarity)	FA of gCC, bCC, sCC, L-ALIC, L-SS, L-EC, R-SLF, L-UF, and tapetum with executive function, spatial processing, attention, and working memory: • Lower FA of L-EC and (trend in) L-ALIC: worse executive function (Stroop C-B time) only in T2DM	_
11	Rofey et al. 2015	_	_	_
12	Raffield et al. 2016	lower scores on DSST, modified MMSE, RAVLT; Same in Stroop, semantic and phenomic fluency	_	• No association between FBS, HBA1c, diabetes duration and GM/WM volume, WM lesion volume, GM cerebral blood flow, FA and MD of WM and GM in T2DM; • Pulse pressure associated with WM and GM volume, cerebral blood flow, FA of WM and GM in T2DM (direction not specified); • Hx of CVD associated with GM/WM volume, WM lesion volume, GM cerebral blood flow, FA and MD of WM and FA of GM (direction not specified)
13	Tan et al. 2016	_	_	_
14	Van Bloemendaal et al. 2016	_	_	• Lower AD in differed voxels in T2DM compared to HC: higher BMI, FBS, fasting insulin levels and HbA1c, trend in HDL, (independent predictor: higher BMI); • Lower WM volume in L-EC cluster: higher age, BMI, FBS, insulin levels, HbA1c, and being male (independent predictors: age and BMI) • Lower WM volume in R-IPL cluster: higher age, BMI, insulin levels, HbA1c, and being male (independent predictors: gender, age and BMI) • Second-level whole-brain analysis did not show any correlations between WM integrity/volume and FBS or fasting plasma insulin

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Table 3 (*continued*)

15	Van Bussel et al. 2016	Lower WLT (verbal memory) and MMSE	FA and MD of hippocampus, tract volume of hippocampus to subcortical GM, frontal, parietal, temporal and occipital lobes with verbal memory (WLT total score): • Positive association between tract volume from hippocampus to temporal lobe and memory performance	• Higher FBS and HbA1c: trend in lower tract volume from hippocampus to frontal lobe
16	Xiong et al. 2016	Lower MMSE and MoCA and AVLT scores	_	_
17	Jian-Hui Zhang et al. 2016	Lower MMSE and MoCA scores	_	• Higher Nε-(carboxymethyl)-lysine level: lower average FA values in whole brain WM and lower MoCA scores (but not MMSE scores) in T2DM
18	Fang et al. 2017	_	_	• Longer disease duration: lower connectivity between R-superior frontal gurys to R-cerebellar crus II, R-precuneus to R-cerebellar crus II, L-cerebellar lobule IX to vermis lobule VIII; • No association between FBS or HBA1c with cerebellar connectivity
19	Nouwen et al. 2017	_	_	• Higher BMI: lower GM density in L-caudate, L-amygdala, L-hippocampus in all subjects together • Higher BMI, HbA1c or HOMA-IR: higher RD (none were independent predictors after adjustment for age); • No correlation between duration of diabetes and GM density or FA, MD, AD, RD; • Higher BMI, higher HOMA-IR (only independent predictor after adjustment for age): lower FA; • No correlation between HBA1c and FA
20	Xie et al. 2017	No significant difference: MMSE, depression and anxiety scores (SDS, SAS), short- and long-term memory (AVLT), working memory (DFT, DBT), executive function (WCST), attention (ANT) and Information-processing speed (TMT-A)	DTI (FA, MD, AD, RD) and DKI metrics (MK, AK, RK) within all ROIs with cognitive variables: • Lower FA of R-prefrontal WM: longer reaction time of the Attention Network Test in T2DM; • Higher RD of R-prefrontal WM: longer reaction time of Attention Network Test in T2DM	• Longer disease duration: higher MD, AD, RD of superior R-prefrontal WM in T2DM; • No correlations between kurtosis metrics and cognitive/clinical variables in T2DM and HC
21	Yoon et al. 2017	Total T2DM vs HC: worse memory and psychomotor speed but same executive function; worse psychomotor speed in overweight-obese T2DM vs normal-weight T2DM	_	• Longer disease duration: lower global WM FA and FA of temporal and occipital ROIs and slower psychomotor speed only in overweight/obese T2DM; • Higher HOMA-IR: lower global mean GM thickness, but not associated with global mean FA in first 2 years of diagnosis; • Relationship between disease duration and mean FA for temporal and occipital ROIs in overweight/obese T2DM differed from normal-weight T2DM
22	Groeneveld et al. 2018	Lower scores in T2DM with cognitive impairment compared to without: MMSE, memory (RAVLT, ROCF), information processing speed (Symbol Digit substitution Test, Stroop Color-Word Test 1 and 2, TMT-A), visuoperception and construction (JLO, ROCF-copy), working memory (Digit span), attention and executive function (letter fluency, category fluency, Stroop Color Word Test 3/2) No significant difference: TMT-A, TMT B/A	Total brain volume and GM volume with memory, information processing speed, visuoperception and construction, working memory, attention and executive function: • Lower GM volume: worse information processing speed	• No relation between HbA1c and total brain volume and GM volume
23	Sun et al. 2018	No difference in MoCA and MMSE	_	_
24	Xiong et al. 2018	Lower scores on MMSE, MoCA, Hachinski test (for vascular dementia), verbal memory (AVLT); Same daily life abilities (Activity of Daily Living)	ROI-based MK of corona radiata, CC, IC, EC, and cingulum with cognitive scores in T2DM: • Lower MK in cingulum (hippocampus): lower MMSE and MoCA scores	• Longer disease duration: lower MK in gCC and anterior corona radiata; • Correlations between ROI-based MK of corona radiata, CC, IC, EC, and cingulum with disease duration, HbA1c for all T2DM were not significant
25	Yu et al. 2018	_	_	• Lower inter-hemispheric motor FC: poorer clinical outcome after stroke • Higher HbA1c: lower FA of iCC • No correlations between the duration of diabetes and FPG with FA of iCC
			Network Studies	
1	Reijmer et al. 2013 (b)	Same IQ and MMSE Applied cognitive tests: Information processing speed (TMT, Stroop Color–Word Test, Wechsler Adult Intelligence Scale III) Verbal memory (AVLT) Executive function (TMT-B/A, Stroop Color–Word Test, Verbal Fluency)	Clustering coefficient, global efficiency, path length, total strength of the network with information processing speed, memory, executive function: • Lower clustering coefficient, lower global efficiency, higher path length: worse information processing speed only in T2DM; Correlation remained significant after adjusting for WMH, but lacunar infarcts partly attenuated this relationship	_
2	Kim et al. 2016	_	_	• Higher HbA1c: longer network path length and lower global efficiency • No significant association between HbA1c and clustering coefficient, modularity, and small-worldness • No significant association between FBS and network parameters • No significant association between age, disease duration, BP, TG, TC, and presence of microvascular complications with network parameters • Higher HbA1c: lower FA in PTR including optic radiation, rIC, sCC, R-fornix/ stria terminalis, R-EC, R-SS (including ILF and IFOF) in T2DM and only in TBSS; • Higher FBS: lower FA in rIC, sCC, R-fornix/ stria terminalis, R-EC in T2DM and only in TBSS • No significant association between HbA1c, FBS and FA in global and tractography analyses
3	Junying Zhang et al. 2016	Worse visual special processing (R-O copy), executive function (Stroop C-B Time), attention (SDMT), working memory (backward recall); No difference in MMSE, episodic memory (AVLT), special processing (clock drawing	Global and nodal network parameters with AVLT, ROCF-delay, ROCF-copy, CDT, TMT-A, TMT B/A, BNT, CVFT, SDMT, backward recall, Stroop C-B time: • Lower global efficiency, local efficiency, strength, and nodal efficiency of R-RO,	_

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Table 3 (*continued*)

		test), executive function (TMT B/A), language (BNT, CVFT), attention (TMT-A) Lower scores in T2DM in ROCF-copy, SDMT, backward recall; Higher scores in T2DM in Stroop C-B time	longer path length: higher Stroop C-B time (executive function) in T2DM; • Lower strength and local efficiency: higher Stroop C-B time in HC	
4	Yang Zhang et al. 2018	No difference in MMSE, memory (AVLT), working memory (DFT, DBT, SWM), attention (RT and ACC of ANT), information processing speed (TMT-A), depression (SDS), anxiety (SAS)	Global and nodal network parameters with cognitive tests: • Higher path length: lower ACC of SWM only in T2DM; • Lower clustering coefficient: lower RT of ANT only in T2DM; • Lower nodal global efficiency in R-hippocampus: lower DBT only in T2DM, • Lower nodal local efficiency in R-SPT: lower ACC of ANT, DFT and DBT only in T2DM	No significant association between network parameters and disease duration and blood glucose level

IQ: intelligence quotient; MMSE: mini mental state examination; MoCA: Montreal cognitive assessment; RAVLT: Rey auditory verbal learning test; AVLT: auditory verbal learning test; CVLT: California verbal learning test; DSST: digit symbol substitution test; WMS: Wechsler memory scale; COWAT: controlled word association test; GMT: Guild Memory Test; ROCF: Rey-Osterrrieth complex figure; WCST: Wisconsin card sorting test; CDT: clock-drawing test; TMT: trail making test; BNT: Boston naming test; CVFT: category verbal fluency test; SDMT: symbol digit modalities test; ACC of ANT: accuracy rate of attention network test; RT of ANT: reaction time of attention network test; SWM: spatial working memory; SAS: self-rating anxiety scale; SDS: self-rating depressive scale; DFT: digit forward test; DBT: digit backward; JLO: judgment of line orientation; HDRS: Hamilton Depression Rating Scale; WLT: Word Learning Test; WRAT: Wide Range Achievement Test; WRAML: Wide Range Assessment of Memory and Learning

–: No data presented, or the measure not investigated. Texts in red represent the counterintuitive results of higher FA, or lower MD/AD/RD correlated with poorer cognition or worse metabolic profile.

Other abbreviations are represented in Table 2 footnote.

Only statistically significant results are reported. If the results are statistically corrected, only corrected ones are reported, unless mentioned otherwise.

Please note that in case of any discrepancy between text of the reviewed articles and their presenting tables, we have relied on the data in the (supplementary) tables.

specified in patients with T2DM.

Several studies support the extension of WM impairments in T2DM to other association fibers, which pass through the temporal lobe, such as inferior longitudinal fasciculus (ILF) and inferior fronto-occipital fasciculus (IFOF). Superior longitudinal fasciculus (SLF), which passes through the frontal and parietal lobes to reach the occipital lobe is another frequently reported tract in patients with T2DM (Table in Fig. 3).

Corona radiata and its subsequent radiation, the internal capsule, along with the corticospinal tract which constitutes the major part of these tracts, are the most frequently described WM projection fibers with impaired integrity in diabetic patients. Anterior (Zhang et al., 2014; Nouwen et al., 2017; Yoon et al., 2017), posterior (Zhang et al., 2014), and superior (Zhang et al., 2014; Yoon et al., 2017) corona radiata seem to be relatively vulnerable to the destructive effects of T2DM. The contribution of diabetes in WM impairment of the internal capsule involves the anterior limb (Zhang et al., 2013, 2014; Xiong et al., 2016), posterior limb (Zhang et al., 2014; Xiong et al., 2018), and retrolenticular part (Zhang et al., 2014; Kim et al., 2016; Xiong et al., 2016; Nouwen et al., 2017) of this structure.

Other than the abovementioned WM structures, decreased FA or increased MD, AD, or RD in the forceps major (van Bloemendaal et al., 2016) and minor (Yoon et al., 2017), arcuate fasciculus (Yau et al., 2013, 2014), superior fronto-occipital fasciculus (Zhang et al., 2014), and optic radiation (Kim et al., 2016; Yoon et al., 2017) are noticed by several methods of DTI analysis in patients with T2DM compared to non-diabetic controls.

As mentioned previously, quantitative meta-analysis is a prerequisite for a definite conclusion about the reliability and extent of microstructural disruption in the WM structures, which is impractical here, due to different methods of analysis. Consequently, the relative vulnerability of different WM fibers to the damage of metabolic derangement in T2DM cannot be determined by a simple constellation of the findings of reviewed studies. Even so, it seems that the microstructural disruption in T2DM spans throughout the brain, but the frequency of results suggest that the frontotemporal association fibers followed by the parietal association fibers might be specifically more susceptible to the damage caused by diabetes mellitus. Fewer reports of altered diffusivity in the occipital region and splenium of the CC suggest that either more posterior regions of the brain are not immune to the pathological damage.

3.4. Between-group differences: Subcortical cluster

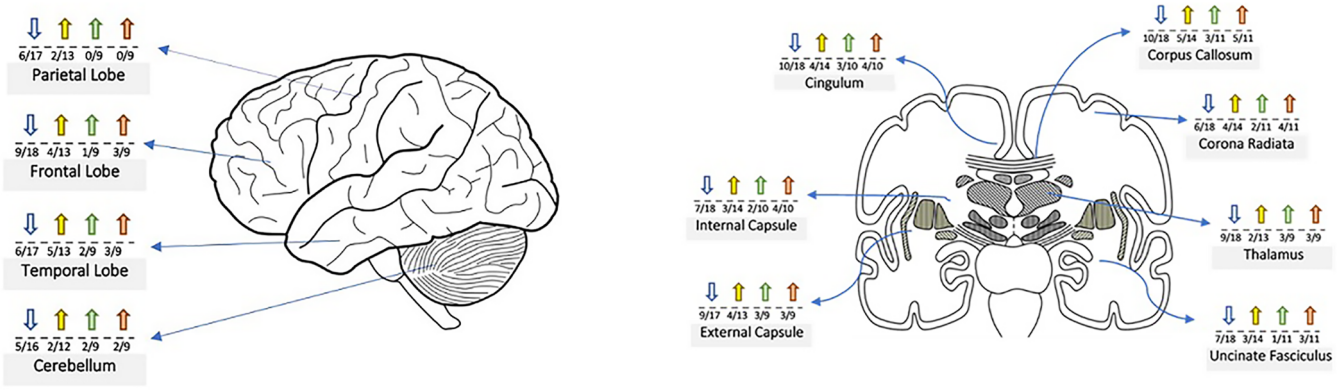
Given the multiple reports of lower integrity in the thalamus and its WM radiations, including anterior and posterior thalamic radiations (ATR and PTR) and fornix (Fig. 3), T2DM might increase the risk of damage to this major neural gateway. Thalamus is interconnected with the medial temporal lobe through the fornix and with the frontal lobe and cingulate gyrus via ATR. PTR serves the bridge from the thalamus to the parietal and occipital regions. Rofey et al. (2015) showed that generalized FA (gFA) is significantly reduced in the pathway between dorsolateral prefrontal cortex to the thalamus in association with T2DM and obesity.

Moreover, overall findings suggest a possible relationship between T2DM and the microstructure of hippocampus and its associated limbic structures, such as PHG and cingulate gyrus. In this context, the hippocampus was found with decreased FA (van Bussel et al., 2016; Zhang et al., 2016b), or increased MD (Falvey et al., 2013; van Bussel et al., 2016) in patients with T2DM. However, after adjustments for confounding factors, there was no significant association between FA or MD levels and status of T2DM in one study (van Bussel et al., 2016). Furthermore, increased levels of MD in PHG (Hsu et al., 2012; Yau et al., 2014) and cingulate gyrus (Falvey et al., 2013) have been detected in patients with T2DM. The graph-theoretical approach also demonstrated decreased nodal efficiency for the hippocampus (Zhang et al.), amygdala (Zhang et al.), and cingulate gyrus (Zhang et al., 2016a), suggesting network disorganization in these structures in diabetic patients.

In contrast to the abovementioned structures, the results regarding other subcortical structures, including putamen and caudate, are not so strong (Falvey et al., 2013; Rofey et al., 2015).

3.5. Between-group differences: Cerebellar cluster

Several studies have reported significant between-group differences regarding the microstructural integrity of the cerebellum (Fig. 3). It has been reported that compared to controls, patients with T2DM have



Cluster	Region/tract	↓ FA	↑ MD	↑ AD	↑ RD
Lobar Cluster	Frontal GM/WM	Yau 2009; Hsu 2012; Yau 2013; Yau 2014; Rofey 2015; Tan 2016; Fang 2017; Xie 2017; Yoon 2017	Yau 2010; Falvey 2013; Yau 2014; Xie 2017	Xie 2017	Hsu 2012; Xiong 2016; Xie 2017
	Parietal GM/WM	Yau 2009; Yau 2013; Yau 2014; Jian-Hui Zhang 2016; Fang 2017; Yoon 2017	Yau 2010; Yau 2014	-	-
	Temporal GM/WM	Yau 2009; Yau 2010; Yau 2013; Yau 2014; Jian-Hui Zhang 2016; Yoon 2017	Yau 2010; Hsu 2012; Yau 2014; Tan 2016; Xie 2017	Hsu 2012; Xie 2017	Hsu 2012; Xiong 2016; Xie 2017
Cerebellar Cluster	Cerebellum	Yau 2013; Tan 2016; Xiong 2016; Fang 2017; Yoon 2017	Hsu 2012; Yau 2014	Hsu 2012; Xiong 2016	Hsu 2012; Xiong 2016
White matter Cluster	Cingulum	Yau 2010; Hoogenboom 2014; Junying Zhang 2014; Tan 2016; Jian-Hui Zhang 2016; Xiong 2016; Nouwen 2017; Yoon 2017; Sun 2018; Xiong 2018	Falvey 2012; Junying Zhang 2014; Sun 2018; Xiong 2018	Tan 2016; Xiong 2016; Sun 2018	Junying Zhang 2014; Xiong 2016; Nouwen 2017; Sun 2018
	Corpus Callosum	Yau 2013; Junying Zhang 2014; Tan 2016; Jian-Hui Zhang 2016; Nouwen 2017; Xie 2017; Yoon 2017; Sun 2018; Yu 2018; Kim 2016	Reijmer 2013; Junying Zhang 2014; Xie 2017; Sun 2018; Xiong 2018	Reijmer 2013; Xie 2017; Sun 2018	Junying Zhang 2014; Nouwen 2017; Xie 2017; Sun 2018; Yu 2018
	Internal Capsule	Yau 2013; Aifeng Zhang 2013; Junying Zhang 2014; Kim 2016; Xiong 2016; Nouwen 2017; Sun 2018	Junying Zhang 2014; Xiong 2016; Xiong 2018	Xiong 2016; Sun 2018	Aifeng Zhang 2013; Junying Zhang 2014; Xiong 2016; Nouwen 2017
	External Capsule	Yau 2009; Yau 2013; Junying Zhang 2014; Kim 2016; Xiong 2016; Nouwen 2017; Yoon 2017; Sun 2018; Xiong 2018	Junying Zhang 2014; Xiong 2016; Xie 2017; Xiong 2018	Xiong 2016; Xie 2017; Sun 2018	Xiong 2016; Nouwen 2017; Xie2017
	Uncinate Fasciculus	Reijmer 2013; Hoogenboom 2014; Junying Zhang 2014; Tan 2016; Nouwen 2017; Yoon 2017; Xiong 2018	Reijmer 2013; Tan 2016; Xiong 2018	Reijmer 2013	Reijmer 2013; Junying Zhang 2014; Nouwen 2017
	Corona Radiata	Junying Zhang 2014; Xiong 2016; Nouwen 2017; Yoon 2017; Sun 2018; Xiong 2018	Junying Zhang 2014; Xiong 2016; Sun 2018; Xiong 2018	Xiong 2016; Sun 2018	Junying Zhang 2014; Xiong 2016; Nouwen 2017; Sun 2018
	Superior Longitudinal Fasciculus	Yau 2014; Junying Zhang 2014; Tan 2016; Jian-Hui Zhang 2016	Reijmer 2013; Junying Zhang 2014	Reijmer 2013; Bloemendaal 2016	Reijmer 2013; Junying Zhang 2014
	Inferior Longitudinal Fasciculus	Junying Zhang 2014; Kim 2016; Tan 2016; Yoon 2017	Reijmer 2013; Tan 2016	Reijmer 2013	Reijmer 2013
	Inferior fronto-occipital Fasciculus	Junying Zhang 2014; Jian-Hui Zhang 2016; Kim 2016; Nouwen 2017; Yoon 2017	-	Bloemendaal 2016	Nouwen 2017
	Corticospinal Tract	Xiong 2016; Nouwen 2017; Yoon 2017; Sun 2018	-	Bloemendaal 2016	Nouwen 2017
Subcortical Cluster	Thalamus/ Thalamic Radiations/ Fornix	Junying Zhang 2014; Rofey 2015; Kim 2016; Tan 2016; Xiong 2016; Fang 2017; Nouwen 2017; Yoon 2017; Sun 2018	Junying Zhang 2014; Tan 2016	Tan 2016; Xiong 2016; Sun 2018	Junying Zhang 2014; Xiong 2016; Nouwen 2017

Fig. 3. Proportion of studies reporting altered diffusion measures in lobar, cerebellar, white matter, and subcortical clusters.
Guide: blue: FA; yellow: MD; green: AD; red: RD. Direction: down: decrease; up: increase. Number of studies reporting altered diffusion measures (a) and number of studies which have assessed those measures (b) are shown as fraction a/b. Please note that because most of the studies have applied voxel-wise methods of analysis, we have only presented the clusters expressed in the articles' texts, tables, and figures footnotes, which are mostly the major clusters of significant between-group analyses. Therefore, the number (a) in the fraction maybe more than what is shown here.
Table above shows only studies that have found altered diffusion measures in represented clusters, regions or tracts.

decreased WM FA in the cerebellum (Yau et al., 2013; Yoon et al., 2017), and more specifically in its vermis (Tan et al., 2016) and peduncles (Xiong et al., 2016). Comparable to cerebellar WM, significant between-group differences were also found in the microstructural integrity of cerebellar GM (Hsu et al., 2012; Yau et al., 2014). Furthermore, fiber connectivity analysis (Fang et al., 2017) singled out 15 connections with reduced connectivity in patients with T2DM relative to controls. These connections were predominantly located in both cerebellar and cerebro-cerebellar circuits. The cerebellar circuit encompassed fibers connecting cerebellum IX (refer to the article's full text for detailed information regarding the selected ROIs) to vermis, and the cerebro-cerebellar circuit mostly included fibers connecting anterior crus to cortical areas, including the precentral gyrus, superior frontal gyrus, and superior parietal gyrus.

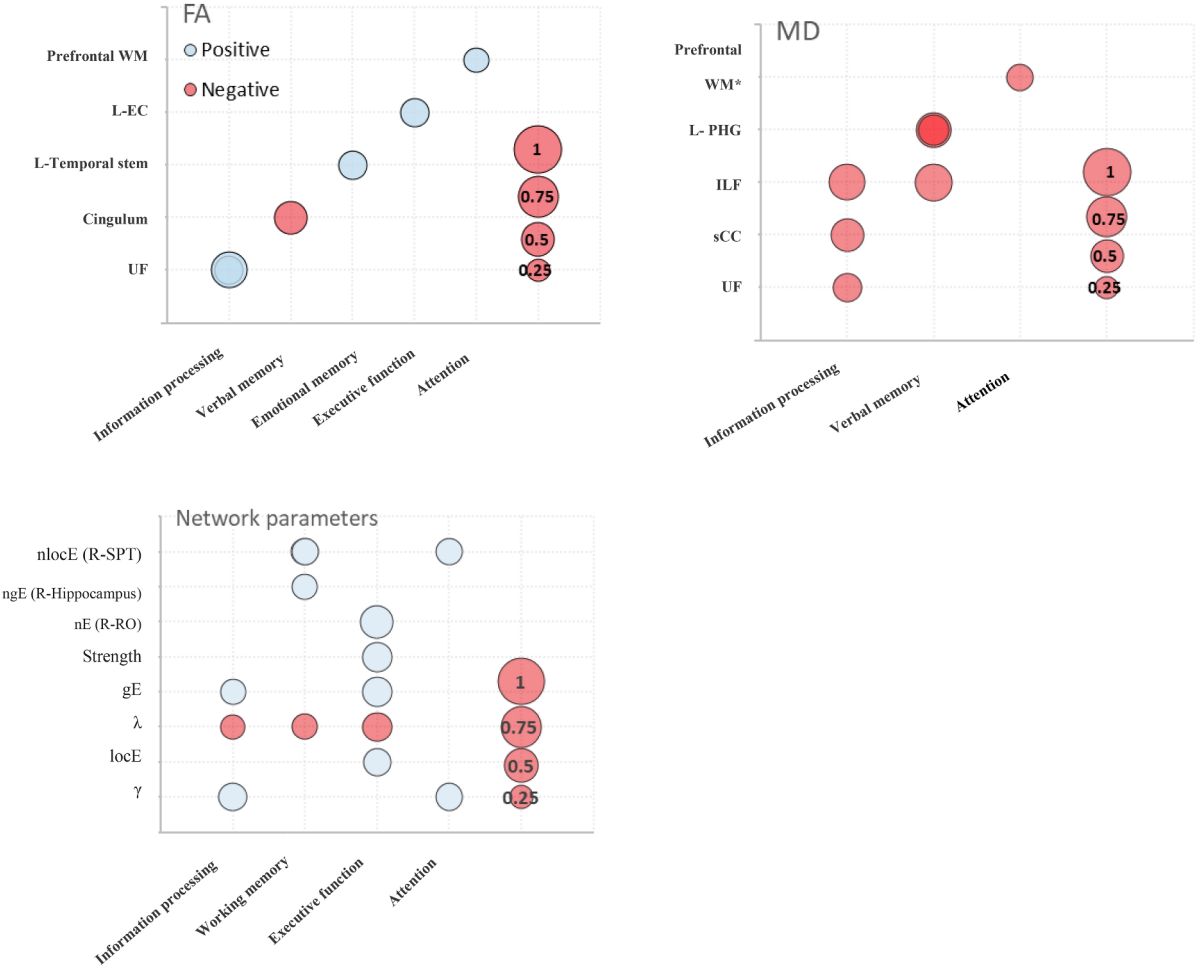


Fig. 4. Quantitative presentation of the reports of significant correlation between DTI metrics and cognitive performance in T2DM.
X axes represent scores for cognitive tests in each domain. Bubbles represent Pearson correlation coefficient except for: FA (UF, cingulum) in Hoogenboom et al. (2014) study, MD (PHG): Spearman correlation coefficient; FA (UF) in Reijmer et al. (2013) study, MD (UF, sCC, ILF): standardized β. Correlation coefficients/ standardized β are adjusted for age and gender, except for: FA (UF, cingulum) in Hoogenboom et al. (2014) study, and FA (temporal stem) only for age.
*Represents the radial diffusivity of prefrontal WM.
L: left; R: right; UF: uncinate fasiculus; EC: external capsule; sCC: splenium of corpus callosum; ILF: inferior longitudinal fasciculus; PHG: Para-hippocampal gyrus; RO: rolandic operculum; STP: superior pole of the temporal lobe; WM: white matter; (n)gE: (nodal) global efficiency; (n)locE: (nodal) local efficiency; λ: shortest path length; γ: clustering coefficient.

3.6. Microstructural abnormalities and cognitive dysfunction in T2DM

The results of the neuropsychological assessment in patients with T2DM delineate a pattern of cognitive dysfunction, to some extent similar to the pattern of Alzheimer's disease (Strachan et al., 2008; Domínguez et al., 2014). The overall findings suggest that T2DM is associated with deficits in the general cognitive status (Yau et al., 2010, 2014; Hoogenboom et al., 2014; Raffield et al., 2016; van Bussel et al., 2016; Zhang et al., 2016b; Xiong et al., 2018), as well as reduced performance on multiple domains of cognition, including verbal/emotional/working memory (Yau et al., 2009, 2010, 2014; Hoogenboom et al., 2014; Zhang et al., 2014, 2016a; Raffield et al., 2016; van Bussel et al., 2016; Yoon et al., 2017; Xiong et al., 2018), executive function (Yau et al., 2010; Hoogenboom et al., 2014; Zhang et al., 2014), attention and psychomotor speed (Yau et al., 2010; Hoogenboom et al., 2014; Zhang et al., 2014; Yoon et al., 2017), and information-processing speed (Raffield et al., 2016; Zhang et al., 2016a). This is in line with a meta-analysis of 24 studies with over 3500 patients with T2DM (Palta et al., 2014). Furthermore, the results show that cognitive deficits may occur even at very early stages of diabetes (Tables 1 and 3) or might not be detected even in elderly and after long disease duration (Zhang et al.; Reijmer et al., 2013a; Xie et al., 2017). This is while cognitive deficits are observed in prediabetic individuals (Yaffe et al., 2004). In fact, the timing and course of cognitive decline in T2DM are not clear yet. Longitudinal studies on T2DM have also failed to illustrate a consistent pattern of decline in cognitive function over time (Zilliox et al., 2016).

In order to determine the subtle neural differences between diabetic patients with mild cognitive impairment and patients with intact cognition, Xiong et al. have demonstrated that cognitive impairment is associated with more disruption in different neural structures involving the frontotemporal region, cingulum, corona radiata, internal and external capsules, corticospinal tract, and thalamic radiations (Xiong et al., 2016).

About one-third of studies have tried to determine the underlying neural structure of cognitive deficit in T2DM (Table 3). The relative size of correlation coefficients between DTI metrics and cognitive functions, only for significant reports, are depicted in Fig. 4. The findings from correlation analyses demonstrated that impaired immediate/delayed verbal memory is associated with disrupted microstructural integrity in

the cingulum (lower FA) (Hoogenboom et al., 2014), ILF (higher MD) (Reijmer et al., 2013a), and PHG (higher MD) (Yau et al., 2014). Besides, there were fewer WM connections between the hippocampus and temporal lobe in participants with impaired memory (van Bussel et al., 2016). A significant correlation was found between FA in the temporal stem and emotional paragraph-immediate recall (Yau et al., 2009). Working memory was also positively correlated with nodal network efficiency of the hippocampus and superior temporal lobe (Zhang et al.). However, two studies did not find any correlation between diffusivity measures of temporal stem or temporal WM with verbal memory in T2DM (Yau et al., 2014; van Bussel et al., 2016). In addition, some studies did not find any correlation between memory scores and specific brain structures (Zhang et al., 2014; van Bussel et al., 2016; Xie et al., 2017; Groeneveld et al., 2018; Xiong et al., 2018).

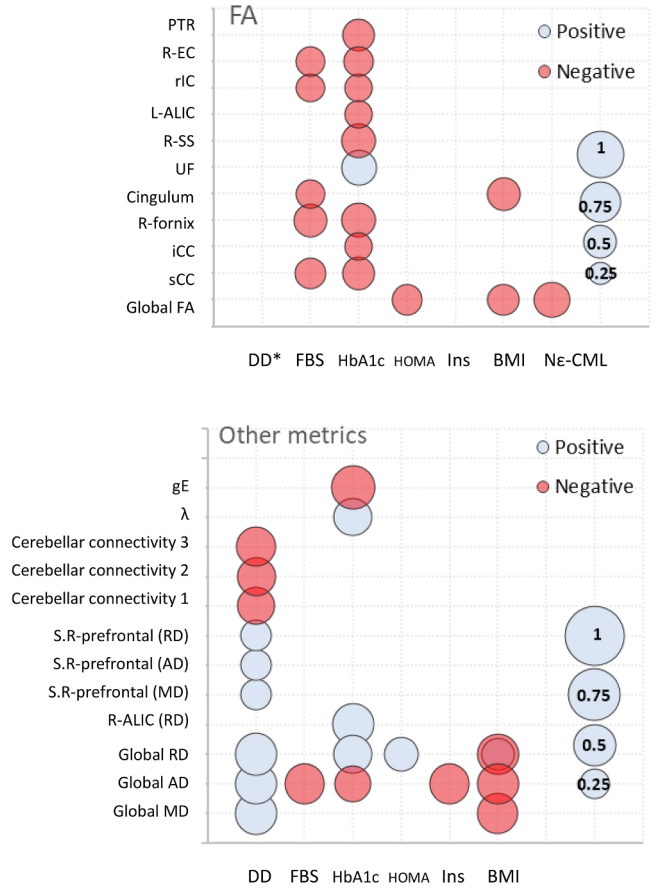


Fig. 5. Quantitative presentation of the reports of significant correlation between DTI metrics and endocrine profile in T2DM.
Bubble sizes represent the relative quantity of the correlation coefficient/standardized β. Most of the bubbles represent Pearson correlation coefficient. Most of the correlation coefficients/standardized β have been adjusted for age and gender. Correlation between BMI and global FA was not significant after adjustment for age.
*Yoon et al. (2017) have reported negative correlation between global, temporal and occipital FA, but quantitative results are not reported. Hsu et al. have reported t values for additional correlations between disease duration and FA/MD/AD/RD in posterior cerebellar lobes, middle frontal gyrus, brainstem, and lentiform nucleus (refer to Table 3).
DD: disease duration; FBS: fasting blood sugar; HOMA: HOMA-IR; Ins: fasting insulin; BMI: body mass index; Nε-CML: Nε-carboxymethyl-lysine; gE: global efficiency; λ: shortest path length; SS: sagittal striatum including inferior longitudinal and inferior fronto-occipital fasciculi; S.R-prefrontal: superior right prefrontal; Cerebellar connectivity 1, 2, 3 respectively: R-superior frontal gurys to R-cerebellar crus II, R-precuneus to R-cerebellar crus II, and L-cerebellar lobule IX to vermis lobule VIII. For other abbreviations refer to Table 2 footnote.

In order to detect the underlying neural substrates of executive dysfunction among patients with T2DM, only one study has attributed the performance in this cognitive domain with lesser integrity in the external capsule (Zhang et al., 2014). The external capsule is the connecting WM between medial and ventral prefrontal cortices and limbic system. Some fibers of IFOF and UF are located in the external capsule, which associates the hippocampus and amygdala with prefrontal and orbitofrontal cortices (Schmahmann et al., 2008; Shott et al., 2015). Other studies have not found such correlation with different neural structures such as UF, SLF, ILF, CC or cingulum (Reijmer et al., 2013a; Hoogenboom et al., 2014; Zhang et al., 2014; Xie et al., 2017). While Reijmer et al. did not report any correlation between cerebral network parameters and executive function in a group of well-controlled T2DM (Reijmer et al., 2013b), Zhang et al. found both disorganized segregation and integration parameters in association with worse executive function (Zhang et al., 2016a). In particular, lower nodal efficiency in the Rolandic operculum predicted deficits in this domain among diabetic patients.

It was found that decreased FA and increased RD of the prefrontal WM were correlated with a higher reaction time of the attention network test (Xie et al., 2017), which is an assessment of the attentional networks, specifically the alerting network (Adólfsdóttir et al., 2008). Moreover, there were significant associations between attentional networks and clustering coefficient and nodal local efficiency of the superior pole of the temporal lobe (Zhang et al.). Again, few other studies did not reveal any association between major WM major white matter tracts or network parameters with attention (Reijmer et al., 2013a; Zhang et al., 2014, 2016a; Xie et al., 2017).

Finally, the scores of digit symbol substitution test showed significant associations with MD of UF, ILF, and splenium of CC and FA of UF (Reijmer et al., 2013a; Hoogenboom et al., 2014), suggesting the possible role of microstructural abnormalities of these tracts in impaired information-processing speed in patients with T2DM. In addition, Groeneveld et al. have demonstrated a negative correlation between GM volume and only information-processing speed in a group of diabetic patients with poor cognitive performance in several domains (Groeneveld et al., 2018). Reijmer et al. have also related disturbed local and global network organization with worse scores in the information-processing speed task (Reijmer et al., 2013b).

3.7. Microstructural abnormalities and clinical profile in T2DM

Possible correlation between the endocrine profile and microstructural alterations have been addressed by several studies (Table 3 and Fig. 5). The overall findings from the reviewed studies suggest that longer disease duration is correlated with more severe microstructural impairments in several regions of the brain. These regions include the frontal lobe and prefrontal region, temporal lobe, parietal lobe, cingulate, fusiform gyrus, precuneus, and cerebellum (Hsu et al., 2012; Xie et al., 2017), as well as disrupted connectivity in the frontocerebellar and parieto-cerebellar tracts (Fang et al., 2017). Nonetheless, it should be noted that some studies showed no relationship between disease duration and microstructural integrity in T2DM. While Yoon et al. discovered a negative association between global WM FA and disease duration (Yoon et al., 2017), diffusion parameters in the whole brain GM and WM did not show any relation with disease duration in other studies using global and TBSS analyses (Raffield et al., 2016; Nouwen et al., 2017). Specific WM tracts of interest, such as UF, SLF, ILF, cingulum, and CC did not confirm any association with duration of the disease (Reijmer et al., 2013a; Hoogenboom et al., 2014; Yu et al., 2018). Besides, network topological studies found no association between global or nodal network parameters and disease duration (Zhang et al.; Kim et al., 2016). Varieties among studies regarding age, onset and course of T2DM, and medical treatments pose a significant limitation in the interpretation of the relationship between disease duration and microstructural abnormalities.

Several studies have demonstrated a negative association between HbA1c and microstructural integrity globally (Nouwen et al., 2017) and more particularly in the ILF (Reijmer et al., 2013a), ALIC (Zhang et al., 2013), posterior thalamic radiation, retrolenticular part of the internal capsule, splenium of the CC, fornix, external capsule, and sagittal stratum (Kim et al., 2016). HbA1c was also correlated with network disorganization, reflected by increased λ and decreased network efficiency (Kim et al., 2016). However, there were several studies reporting positive or no association between HbA1c and microstructural integrity or network organization (Hoogenboom et al., 2014; Kim et al., 2016; Raffield et al., 2016; van Bloemendaal et al., 2016; Fang et al., 2017; Nouwen et al., 2017), which makes it difficult to suggest a reliable pattern of association between HbA1c and microstructural disruptions. Since HbA1c only reflects the most recent course of glycemic control, it may not reliably predict the damage of T2DM to the brain structure during a longer course of the disease. Interestingly, Hoogenboom et al. were the only authors to take into account the relevance of lifetime HbA1c with FA of cingulum and UF, although they did not find any significant relationship in this regard. In addition, overall findings showed no significant association between FBS and DTI metrics (Kim et al., 2016; Raffield et al., 2016; van Bloemendaal et al., 2016; Fang et al., 2017) or network topology parameters (Zhang et al.; Kim et al., 2016). However, there were few studies displaying a negative association between FBS and microstructural integrity in the cingulum (Hoogenboom et al., 2014), retrolenticular part of the internal capsule, splenium of the CC, fornix, external capsule (Kim et al., 2016), and in the tracts connecting hippocampus to the frontal lobe (van Bussel et al., 2016). Clearly, longitudinal follow-up of the patients will offer more reliable data regarding the effect of glucose balance on neural structures. Furthermore, glycation end products, the main culprits in chronic complications of T2DM, more directly replicate the neurotoxicity of glucose imbalance and have also been implicated in the pathogenesis of diverse group of disorders, such as aging and Alzheimer's disease, other than T2DM (Sasaki et al., 2001; Ramasamy et al., 2005). N-epsilon-(Carboxymethyl)-lysine (CML) is one of the main forms of advanced glycation end products, which deposits in the brain tissue, more rapidly in diabetic conditions, and advances brain aging (Jono et al., 2002). Remarkably, Zhang et al. verified that nonenzymatic glycation, measured by levels of peripheral CML contributes to the reduction in whole-brain WM FA and is related with the inferior general cognitive status among diabetic patients (Zhang et al., 2016b).

Under normal conditions, there is a delicate balance between the levels of reactive oxygen species (ROS) generation and antioxidant properties. However, in aging, Alzheimer's disease and T2DM, the activity of antioxidant enzymes diminishes, leading to redox disequilibrium and subsequent neural demise and cognitive decline (Bala et al., 2006; Sinha et al., 2008). In diabetes, hyperglycemia results in a concurrent increase of free radicals and decreased antioxidant properties (Bonnefont-Rousselot, 2002). The decline in the levels of antioxidant enzymes is repeatedly reported in T2DM (Kumar and Menon, 1993; Makar et al., 1995; Miranda et al., 2007; Alvarez-Nölting et al., 2012). Furthermore, oxidative-induced dysfunction in mitochondrial energy metabolism and electron transport exists in the diabetic brain and contributes to the neural apoptosis and suppression of neurogenesis (Merad-Boudia et al., 1998; Cui et al., 2006; Moreira et al., 2009; Cardoso et al., 2013). Despite this robust line of evidence regarding the key role of neuroinflammatory processes in diabetic neurodegeneration, none of the reviewed studies has tried to investigate the correlation between inflammatory markers and DTI parameters.

Another emerging view about the pathogenesis of cognitive decline in diabetes is insulin resistance and hyperinsulinemia. In addition to the role of insulin in glucose metabolism, insulin receptors are widely distributed in different brain regions, such as the cerebral cortices, hippocampus, amygdala, and hypothalamus. These receptors mediate synaptic function in several information processes in the nervous system, including memory and executive performance (Zhao and Alkon, 2001). Although neurons are not dependent on insulin for glucose intake, they respond to stimulation of insulin receptors. For instance, under the conditions of insulin resistance, peripheral neurons do not respond to growth factors, leading to peripheral degeneration and diabetic neuropathy (Belfiore et al., 2009). More significantly, insulin resistance is associated with impairments in mitochondrial bioenergetics (Lowell and Shulman, 2005; Anderson et al., 2009; Hoehn et al., 2009; Stiles, 2009; Cheng et al., 2010; Fisher-Wellman and Neufer, 2012). Thus, defective insulin signaling in T2DM might be a contributing factor in the neural damage and the consequent cognitive decline in patients with T2DM (Xu et al., 2004). MRI studies of patients with T2DM have demonstrated that regardless of vascular alterations, more severe atrophy in the hippocampus and amygdala is associated with insulin resistance and hyperinsulinemia (den Heijer et al., 2003; Convit, 2005). Positron emission tomography studies have also reported that reduced level of glucose metabolism manifests itself several years prior to the clinical symptoms of Alzheimer's disease (Reiman et al., 2004). Nevertheless, only few DTI studies have looked for the possible contribution of insulin resistance to neural microstructural damage in T2DM. Homeostasis model assessment-insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) are two valid indices which are commonly used to estimate the insulin sensitivity. Nouwen et al. showed that HOMA-IR is negatively correlated with FA values. However, other studies failed to demonstrate a significant association between microstructural features and fasting levels of plasma insulin, HOMA-IR or QUICKI scores (Yau et al., 2010; Hoogenboom et al., 2014; van Bloemendaal et al., 2016; Yoon et al., 2017).

3.8. Microstructural abnormalities and common comorbidities in T2DM

As a key condition in the metabolic syndrome, T2DM is commonly associated with obesity, HTN, and dyslipidemia. These features have their independent influences on the brain neural structure (Alfaro et al., 2018). Therefore, some of the reviewed DTI studies on T2DM have tried to disclose the solid pattern of a diabetic brain by comparing the participants divided based on the presence of these related disorders.

Yau et al. (Yau et al., 2010) have compared brain complications of obese patients with T2DM with non-diabetic, but obese controls in a small sample of adolescents. Diabetic cases had poor glucose and lipid profile and cognitive performance relative to the controls and their imaging assessment revealed extensive voxels with impaired integrity in the prefrontal cortex, parietal cortex, temporal stem, and cingulum. Tractography of the fronto-striatal pathway also revealed higher disruption in the connectivity between prefrontal cortex to the striatal nuclei and thalamus in lean adolescents with T2DM compared to obese controls without diabetic condition (Rofey et al., 2015). Additional several major WM tracts were also shown to only distinguish lean diabetic adolescents from healthy and normal-weight controls, whereas obese but non-diabetic participants did not differ from healthy controls in a TBSS study of whole-brain WM (Nouwen et al., 2017). Moreover, Noewen et al. demonstrated that higher BMI is correlated with lower GM density, lower FA, and higher RD in T2DM. Additional comparison of diabetic middle-aged individuals split based on BMI demonstrated lower FA, specially in the prefronto-parietal WM in overweight/obese patients with T2DM. These patients also had slower psychomotor speed compared to normal-weight patients with T2DM (Yoon et al., 2017). Finally, van Bloemendaal et al. proposed that AD values are increased mainly in the corticospinal tract, IFOF, SLF, and forceps major of the right hemisphere in obese diabetic adults compared to healthy controls, while obese and non-diabetic participants did not show any significant alterations in microstructural integrity of their whole brain WM. The authors further claimed that BMI is the only independent predictor of AD changes in their participants (van Bloemendaal et al., 2016). A negative association between BMI and global MD/RD values (Hsu et al., 2012) or FA values in the cingulum (Hoogenboom et al., 2014) is also

reported in T2DM. More studies are needed to understand the direction of BMI correlation with WM integrity in T2DM, since both positive (Hsu et al., 2012; van Bloemendaal et al., 2016) and negative (Hoogenboom et al., 2014; Nouwen et al., 2017) associations have been suggested in this regard.

In an attempt to reveal the relative contribution of T2DM and HTN on cerebral WM, Yau et al. examined DTI data in hypertensive diabetic patients and hypertensive non-diabetic patients. They also found much more extensive microstructural damage throughout the diabetic brain (Yau et al., 2013).

Overall, these lines of evidence support the higher burden of T2DM on microstructural impairment relative to the comorbid metabolic features of obesity and HTN. Despite one report of lower triglyceride levels in association with higher global mean MD/AD/RD in a group of middle-aged patients with T2DM and high levels of triglyceride (Hsu et al., 2012), no other study has examined the interaction of lipid profile derangement with DTI parameters in T2DM.

4. Discussion

In summary, DTI studies have shown that patients with T2DM have several brain microstructural alterations compared to non-diabetic individuals. Although the affected regions and tracts in T2DM vary among studies, fronto-temporal region, thalamus, cerebellum and major WM tracts, such as CC, cingulum, UF, external capsule, corona radiata, and internal capsule are more consistently reported (Fig. 3). This pattern of brain involvement is compatible with observed dysfunction in different domains of cognition, including memory (verbal, emotional, and working), information-processing speed, executive function, and attention among diabetic patients. Some studies have revealed that uncontrolled glycemic control and cognitive dysfunction are correlated with more severe microstructural deficits. Besides, it seems that T2DM significantly adds to the burden of other common metabolic comorbidities, such as obesity and HTN on the brain. The findings further demonstrate that microstructural alteration due to T2DM can affect various cognitive functions of the brain, even when there are no identifiable macrostructural disturbances. More notably, review of the literature shows that diffusion and network metrics can be accounted as sensitive and quantitative markers of cognitive impairment in the early stages of T2DM, even when the neuropsychological tests do not show any decline in the cognitive performance.

Several diffusion and network studies of diabetic brain on a whole scale demonstrated that T2DM is associated with a lower level of global microstructural integrity and network organization. Previous studies have reported that diabetic brain is significantly smaller than the healthy brain (Wu et al., 2017), and brain atrophy is associated with cognitive impairment in T2DM (Roberts et al., 2014). Temporal lobe and in particular the hippocampus seem to be susceptible to T2DM-induced structural disruptions. Our findings are in agreement with previous literature showing considerable atrophy (den Heijer et al., 2003; Korf et al., 2006; Gold et al., 2007) and abnormal pattern of functional connectivity (Xia et al., 2017) in the temporal lobe and hippocampus in T2DM. In this regard, DTI studies have found that T2DM is associated with microstructural and network impairment in different regions of the temporal lobe and hippocampus and also in their corresponding association fibers. These structures have been numerously implicated in memory formation and learning (McCrimmon et al., 2012). Results from DTI studies showed that deficits in microstructural and topological properties of the hippocampus and temporal GM and WM are associated with impairments in different aspects of memory, including verbal, emotional, and working memory. Interestingly, in a human brain autopsy study (Heitner and Dickson, 1997), increased amyloid-beta (Aβ) plaques and neurofibrillary tangles were found in the diabetic hippocampus, which is the hallmark pathology of the Alzheimer's disease. It is postulated that excessively advanced glycation end products and insulin resistance might lead to Aβ and neurofibrillary aggregations in T2DM, leading to macro- and microstructural defects and thus, cognitive impairment in these patients (Ledesma et al., 1994; Kuusisto et al., 1997; Munch et al., 1998).

In addition to the temporal lobe, overall diffusion findings exhibited microstructural abnormalities in both frontal GM and WM in T2DM. Decreased volume (Bruehl et al., 2011), blood flow (Last et al., 2007), and resting-state function (Wang et al., 2014) in the prefrontal region are also consistently reported in T2DM. Previous studies have demonstrated that prefrontal atrophy is correlated with higher levels of HbA1c (Bruehl et al., 2011). Furthermore, deficits in either prefrontal cortex or WM may be the underlying reasons for executive dysfunction (Duan et al., 2015) and memory loss (Preston and Eichenbaum, 2013) in patients with T2DM. In addition, prefrontal WM impairment is consistently shown by DTI studies to be associated with both attentional network and disease duration in T2DM. This relationship signifies that attentional deficits in patients with T2DM might be partly due to diabetes-induced prefrontal WM microstructural abnormalities over time.

WM tracts are the essential backbone of information transition between different parts of the brain. Generally, the evidence from diffusion imaging showed that widespread WM tracts are microstructurally damaged in T2DM. Other imaging modalities have shown that hyperglycemia and insulin resistance lead to increased WM lesions (Alexandrou et al., 2010; Katsumata et al., 2010; Ryu et al., 2014; Ogama et al., 2018) and impaired WM functional connectivity (Liu et al., 2018). Accordingly, altered diffusion properties of WM tracts were demonstrated by DTI studies to be associated with both glucose metabolism impairment (e.g. higher BMI, FBS, and HbA1c) and cognitive deficits (particularly information-processing speed, memory, executive function, and attention) (Figs. 4 and 5). It should be noted that brain connections and functions are not as simple as a one-to-one relationship between a WM tract and a cognitive ability. Due to the complex nature of brain networks, it seems difficult to attribute local WM microstructural disruptions to specific cognitive functions. However, the preliminary reports of significant correlations between DTI parameters of specific WM fibers and cognitive functions in patients with T2DM suggest that detrimental effects of glucose metabolism derangement on higher-level brain functioning might be partly through structural disruptions in the major WM tracts. As shown in Fig. 4, the regions or tracts which diffusivity or nodal efficiency are found to be significantly correlated with different domains of cognitive function, are the key limbic structures in the temporal lobe and prefrontal region and their interconnecting tracts, i.e., cingulum, UF, and external capsule (Fig. 4).

Thalamus is the primary gateway which receives sensory information and relays them to specific cortical regions. Within the circuit of Papez, it is connected with the medial temporal lobe and plays a major role in processing the information related to memory and learning. It is shown that defects in the thalamus in vascular dementia and Alzheimer's disease lead to cognitive dysfunction in various domains, including attention, memory, and motivation (Szirmai et al., 2002; Aggleton et al., 2016). Findings from DTI studies of T2DM displayed less organized network and impaired microstructure of the thalamus and its connections, including fibers to the frontal cortex. Accordingly, the resting-state functional analysis in T2DM has shown decreased thalamic functional connectivity to the cortical and cerebellar regions (Chen et al., 2015). Using magnetization transfer imaging, Yang et al. showed that impaired integrity of macromolecular protein pools in fronto-striato-thalamic circuits in T2DM is correlated with levels of HbA1c and vascular risk factors, as well as cognitive deficits in the domains of memory, executive function, information-processing speed, and attention (Yang et al., 2015). Collectively, thalamus appears to be an important candidate structure underlying T2DM-associated cognitive decline.

Eventually, cerebellum is a crucial structure in cognitive performance (Fine et al., 2002; Strick et al., 2009; Stoodley and Schmahmann, 2010) and plays an important role in executive functions (Albus, 1971;

Schmahmann and Caplan, 2006; Schmahmann et al., 2008; Stoodley and Schmahmann, 2010; Stoodley, 2012). Review of DTI studies demonstrated that both GM and WM of cerebellum along with its connections to the frontal and parietal cortices are microstructurally disrupted in T2DM. Of note, patients with longer disease duration had more deficits in cerebellar connections. Despite the significant role of the cerebellum in both motor coordination and executive functions, which are both prevalently disturbed in patients with T2DM, this structure is mostly overlooked in the neuroimaging investigations (Rosenberg et al., 2018).

Of significant importance, the overall findings of included studies should be explicated prudently, as we have reviewed a heterogeneous constellation of studies with different acquisition parameters and analysis methods. Different acquisition parameters are associated with dissimilar rates of imaging artifacts and divergent accuracy of DTI results. Besides, the results might be confounded by type 1 and 2 errors associated with different methods of analysis. For instance, the voxel-wise analysis may result in false-positive results because of highly localized perspective (type 1 error), while ROI analysis might take no notice of the regions outside of the defined ROIs (type 2 error). Other DTI-based methods of analysis including tractography, TBSS, and graph-theoretical approach, which have been used as the main analytical models in most of the included studies, are escorted with notable limitations; The presumed assumption of all diffusion-metric models is that the principal diffusion direction is aligned with the axon orientation, leading to missing of kissing or crossing axon structures (Jbabdi and Johansen-Berg, 2011). Besides, tractography is not able to distinguish the exact originating/ending points of WM tracts in the cortex or subcortical nuclei, known as the radial and transverse accuracies, and cannot determine the polarity of tracts, afferent vs efferent. In the TBSS approach, it is assumed that areas with the highest FA are the anatomical centers of the tracts. This assumption might be violated in FA-reducing lesions, which are frequently seen in T2DM (Bach et al., 2014). Finally, graph results can vary from study to study, since most of the topological measures could be affected by the size of the network, including the number of nodes and connections (van Wijk et al., 2010).

5. Beyond DTI

A bulk of evidence suggests that DTI is a very sensitive modality in the identification of early microstructural alterations in T2DM. Nevertheless, several methodological (subject motion and image resolution), physiological (arrangement and density of axons and complex fiber structures), and pathological events might lead to changes in DTI metrics (Basser and Jones, 2002; Tournier et al., 2011). Besides, DTI is not as sensitive to GM abnormalities as it is for WM disruptions. More importantly, the efforts for associating the alterations in FA/MD/AD/RD to a specific abnormality, such as axonal damage or demyelination have failed (O'Donnell and Pasternak, 2015; Chen et al., 2016). These deficits in specificity and precision of DTI metrics have incited the development of more advanced imaging methodologies. These techniques generate metrics with higher sensitivity to subtle alterations and increased specificity to the underlying pathologies, especially of the GM impairments. Diffusion kurtosis imaging (DKI) and diffusion spectrum imaging (DSI) have been recently applied to study the microstructural abnormalities in T2DM. Briefly, DKI, unlike DTI, does not adhere to the assumption of Gaussian distribution of water molecules. In a hindered area, as in WM tracts, DKI measures the level of deviation from Gaussian distribution (Jensen et al., 2005). In addition to DTI measurements, DKI provides three main kurtosis metrics including mean kurtosis (MK), axial kurtosis (AK), and radial kurtosis (RK), reflecting the structural restriction and complexity. Two recent studies have used DKI for the assessment of brain microstructural integrity in age-, gender-, and education-matched T2DM and control subjects. Albeit, the settings of these studies are relatively different. While Xie et al. (2017) have investigated a larger sample size (58 T2DMs and 58 controls) using VBA and ROI analyses with lower b-values (0, 1000, and 2000 s/mm^2), Xiong et al. (2018) have conducted TBSS and ROI analyses on a smaller population (30 T2DMs and 28 controls) with higher b-values (0, 1250, and 2500 s/mm^2). DKI was more sensitive to T2DM-induced microstructural abnormalities than conventional DTI, as subtle impairments in some structures such as decreased FA in the prefrontal WM and increased MD in the temporal WM were detected only by DKI (Xie et al., 2017). Additionally, MK/AK/RK could uncover a higher percentage of voxels in the whole brain WM with altered diffusivity compared to conventional DTI metrics (Xie et al., 2017). Investigating the relationship between kurtosis metrics and clinical or cognitive characteristics, Xie et al. (2017) found no significant association in T2DM or healthy controls. However, Xiong et al. (2018) reported a negative association between MK of the genu of CC and disease duration and a positive association between MK of the cingulum and general cognitive tests scores. MK, the main kurtosis metric, is calculated as the average level of kurtosis in all possible diffusion directions and indicates the diffusion restriction imposed by microstructural density and complexity (Wu and Cheung, 2010; Steven et al., 2014). Previous kurtosis studies on Alzheimer's disease and Parkinson's disease have reported higher levels of MK in the thalamus (Gong et al., 2017) and substantia nigra (Wang et al., 2011), respectively, which are attributed to amyloid β or iron accumulation. On the other hand, studies on traumatic brain injury, epilepsy, and depression have demonstrated lower values of MK, possibly due to disarranged cellular order and membrane permeability (Jensen and Helpern, 2010; Lee et al., 2013). The superiority of DKI over DTI metrics may be due to the assumption of Gaussian diffusion by conventional DTI, where non-Gaussian diffusion of water molecules are reported to be robust (Le Bihan, 1995). In contrast to conventional DTI, the ability of kurtosis metrics to identify microstructural abnormalities is not affected by crossing/kissing fibers, as they are not restricted to anisotropic environments (American Diabetes, 2010). Furthermore, GM microstructural impairments are better detected by DKI, because it is not reliant on the spatial orientation. Although the findings recommend that DKI is more sensitive to microstructural impairments compared to conventional DTI, it should be kept in mind that this increased sensitivity might be associated with augmented false-positive results.

DSI approach provides a 3D estimation of displacement function by acquiring a dense sampling of q-space (Wedeen et al., 2005). In most studies, DSI has been used to generate the gFA based on an estimation of the orientation distribution function (ODF) of a fiber. gFA is the normalized standard deviation of ODF and thus, is less affected by complex WM structures, such as crossing fibers (Fritzsche et al., 2010). Application of DSI in patients with T2DM is carried only by one recent study. Using DSI tractography, Zhang et al. (2018) demonstrated that compared to age-, gender-, and education-matched controls, patients with T2DM have worse scores in cognitive assessments and lower gFA in the left UF and right superior cingulum bundle. They reported that gFA of the right superior cingulum bundle is negatively associated with verbal fluency test scores in T2DM. Although DSI requires long acquisition time and high b-values, it can provide valuable information about the orientation of intra-voxel fibers, especially in the areas with a high density of crossing fibers. Herein, the results from DSI are in agreement with previous DTI findings. Zhang et al. (2018) suggested the DSI tractography as a sensitive and reliable tool for the evaluation of brain microstructural pattern. However, additional studies are required to investigate the applicability of DSI in T2DM further.

6. Limitations and future directions

Despite the growing number of DTI assessments in patients with T2DM, most of the studies have examined fewer than 50 patients with various ranges of diabetes duration and clinical outcomes. Information regarding important confounding features, such as hypertension, dyslipidemia and medical treatment of metabolic and cardiovascular

disorders are not well described or addressed by most of the reviewed studies. The heterogeneity of clinical features in the diabetic patients, coupled with small sample sizes lead to inconsistent results, which make it difficult to come to a conclusion. In addition, a limited number of previous DTI studies have included neuropsychological assessments. These assessments provide valuable information for extending the results form DTI measures to clinical and perceptible findings. Moreover, investigating the overlap between functional and structural connectivity in the same sample of participants will provide more reliable data than a preliminary correlation analysis regarding the brain-behavior relationship. Among the reviewed articles, only three studies have applied simultaneous DTI and resting-state functional MRI on a group of patients with T2DM. Hoogenboom et al. have discovered reduced functional connectivity in the default mode network between posterior cingulate gyrus and both left fusiform and left medial frontal gyrus in middle-aged patients with T2DM. As expected, reduced FA in the cingulum was correlated with lower functional connectivity between cingulate and medial frontal gyri (Hoogenboom et al., 2014). In another study, reduced hippocampal functional connectivity to the cingulate, frontal gyrus, and caudate were interrelated with altered diffusivity in the PTA and splenium of the CC in a group of diabetic patients with intact cognition (Sun et al., 2018). More recently, Yu et al. have shown that callosal disruption due to T2DM causes sensorimotor functional dysconnectivity and therefore, worsens the clinical outcome after stroke (Yu et al., 2018). Despite introducing promising results of the functional disruptions following microstructural impairments in the neural structures, none of these studies has examined the brain-behaviour relationship. Such multimodal imaging studies are obviously needed to investigate the structural and functional dysconnectivity in a diabetic brain in association with cognitive deficits.

Neurodegenerative processes, such as aging are accompanied by compensatory neural changes, such as recruiting secondary or bilateral circuits in performing cognitive tasks, in an attempt to alleviate the reduction in cognitive reserve (Reuter-Lorenz et al., 2000; Sullivan and Pfefferbaum, 2006; Reuter-Lorenz and Cappell, 2008). However, bilateral involvement of neural structures in T2DM, even in patients who are recently diagnosed, may emphasize the severity of diabetic damage on the central nervous system. Among the reviewed DTI studies, compensative alterations in terms of better diffusion or network characteristics in between-group comparisons or correlated with the cognitive function were negligible. Whether the damage is that much rapid and severe that does not allow the development of adaptive and compensatory mechanisms, is an important question that should be addressed in future research. Well-designed longitudinal studies, starting from the prediabetic condition, will bring new insights on the course of neural changes, disruption, and compensation under the influence of T2DM.

T2DM shows a bimodal sex-specific pattern regarding the pathophysiological processes and behavioral outcomes (Kautzky-Willer et al., 2016). Despite medical complications, even hippocampal atrophy is more prominent among females (Hempel et al., 2012). Although most of the studies have controlled for the effect of gender in analyzing the imaging parameters, research on the gender differences of microstructural alteration may help explain the diversity of findings to some extent. Examining the role of advanced glycation end products, inflammatory markers, hormone profile, and lipid homeostasis, as presumptive contributors to the microstructural damage in T2DM, is also lacking in the existing literature focused on DTI.

Finally, imaging methodology and precision have considerable effects on the results. Future imaging methods should control acquisition parameters, image resolution and distortion, and motion artifact in order to enhance the preciseness of the results. More importantly, several new advanced imaging methods with much more sensitivity and specificity have been recently developed, such as connectometry, constrained spherical deconvolution, neurite orientation dispersion and density imaging (NODDI), and fixel-based analysis. These methods provide insights beyond the access of conventional DTI, such as information regarding complex fiber structures and intra-voxel fiber orientation.

7. Conclusion

Mounting evidence by DTI studies approves that patients with T2DM undergo insidious microstructural changes throughout their central nervous system, leading to interruption in a wide range of cognitive functions. Different diffusion and graph analytical methods have reported decreased integrity and network disorganization in cortical regions, more consistently in the temporal, frontal, and parietal cortices, subcortical area including thalamus and hippocampus, WM pathways, such as commissural (corpus callosum), association (uncinate fasciculus, cingulum, and external capsule), and projection (corona radiata and internal capsule) fibers, as well as cerebellum and its connections. The fact that T2DM-associated microstructural abnormalities are more concentrated in components, such as temporal lobe, prefrontal cortex, thalamus and hippocampus may explain the higher risk of Alzheimer's disease in patients with T2DM, and suggests that T2DM and Alzheimer might be related disorders of the neurodegeneration. The findings also demonstrate that microstructural disruptions in certain limbic structures, namely the prefronto-temporal regions and their interconnecting WM pathways, i.e., cingulum, UF, and external capsule are associated with impairments in cognitive functions including memory, information-processing speed, executive function, and attention. There is still controversy in the relevance of chief metabolic derangement in T2DM, i.e. glycemic homeostasis and insulin resistance with the neural microstructural impairment. Longitudinal DTI studies from the pre-diabetic status to more advanced stages of T2DM, while taking into account the influence of medical treatments, would develop a body of knowledge about underlying mechanisms of neural damage in the microstructural scale.

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Appendix A. Supplementary material

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