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SUBCORTICAL GRAY MATTER AND HIPPOCAMPAL SUBFIELD ALTERATIONS IN TYPE 2 DIABETES MELLITUS: A FREESURFER-BASED NEUROIMAGING STUDY WITH CORRELATION TO MOCA MEMORY INDEX SCORE

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ABSTRACT

Background: Cognitive decline in patients with type 2 diabetes mellitus is a growing clinical concern; however, it remains poorly recognized in routine diabetes care. The hippocampus and surrounding subcortical gray matter structures are particularly vulnerable to the metabolic and vascular damage that characterizes longstanding T2DM; however, most existing studies have relied on conventional MRI reporting rather than precise automated volumetric analysis. The Montreal Cognitive Assessment (MoCA) is widely used for cognitive screening in this population, but its standard Delayed Recall component has a limited scoring range that may miss early hippocampal-driven memory failure. Whether the Memory Index Score, a more comprehensive memory measure, better reflects hippocampal volume loss in patients with diabetes remains an open question.

Methods: A cross-sectional study was conducted at Saveetha Medical College and Hospital, Chennai, enrolling 100 participants with Type 2 diabetes mellitus. Brain MRI was performed for all participants, with subcortical gray matter and hippocampal volumes derived using FreeSurfer's automated segmentation. Cognitive function was assessed using the Montreal Cognitive Assessment, and both the Delayed Recall and memory index scores were recorded. Clinical variables, including HbA1c, diabetes duration, treatment type, lipid profile, and comorbidities, were documented. Group comparisons were performed using independent t-tests and chi-square tests, correlation analysis was performed using Pearson coefficients, and multivariate logistic regression was used to identify independent predictors of cognitive impairment.

Results: Cognitive impairment was observed in 62 of the 100 participants. It was more common in patients with diabetic complications (67.3%) than in those without (56.3%), although the difference was not significant (p=0.255). MoCA scores fell below the normal cutoff in both groups (23.46 and 22.67, respectively) and did not differ significantly between them (p=0.427). Hippocampal volumes were comparable among the groups (p=0.233). Age was the only variable that significantly predicted complication prevalence (p=0.027), with patients aged 50–69 years carrying the greatest burden. No significant correlations were found between MoCA scores, hippocampal volume, and the complication status.

Conclusion: Cognitive impairment in T2DM does not depend on the presence of diabetic complications; it runs across the board and starts earlier than most clinicians expect. Age is more important than glycemic control or complication status in determining who is at the highest risk. These findings make a straightforward case for routine cognitive screening in all patients with diabetes, not just those who have already developed complications, and for using more sensitive tools, such as the Memory Index Score and FreeSurfer-based volumetric analysis, to detect brain changes before they become irreversible.

KEYWORDS: Type 2 diabetes mellitus, hippocampal volume, subcortical gray matter, FreeSurfer, Montreal Cognitive Assessment, Memory Index Score, mild cognitive impairment, cognitive decline, neuroimaging, diabetic complications

INTRODUCTION

Diabetes mellitus has quietly become one of the most consequential chronic diseases of our time, and its reach extends far beyond the pancreas. Type 2 diabetes mellitus (T2DM) now affects hundreds of millions of people worldwide, and projections suggest the numbers will continue climbing well into the coming decades. What has become increasingly clear over the past two decades, however, is that diabetes does not limit its damage to the heart, kidneys, and peripheral nerves. The brain is equally vulnerable. Individuals living with T2DM carry a measurably higher risk of cognitive decline, ranging from subtle deficits in memory and attention to full-blown dementia, and this dimension of the disease has not received nearly the clinical attention it deserves [1].

Structural neuroimaging studies have done much to bring this issue into focus. MRI-based investigations have consistently identified changes in the brains of people with T2DM cortical thinning, subcortical atrophy, white matter hyperintensities, and reductions in total gray matter volume. These are not incidental findings. They correlate with real-world cognitive difficulties and appear to worsen with longer disease duration and poorer glycemic control [2]. Among the brain regions affected, the hippocampus has attracted the most attention, and for good reason. It sits at the centre of memory formation and spatial navigation, and it is particularly sensitive to the metabolic and vascular insults that characterize longstanding T2DM. Reductions in hippocampal volume have been documented across multiple studies and linked to measurable impairments in learning, recall, and executive function [3].

Beyond the hippocampus as a whole, there is growing interest in the individual subfields that make up this structure. The hippocampus is not a homogeneous region it comprises distinct subfields including the cornu ammonis sectors, the dentate gyrus, and the subiculum, each with somewhat different functional roles and potentially different vulnerabilities. Early work in Alzheimer's disease research showed that subfield-level analysis could detect atrophy that would be missed when looking at overall hippocampal volume alone. Whether a similar principle applies to diabetes-related neurodegeneration remains an open and clinically important question [4]. Alongside the hippocampus, the broader subcortical deep gray matter including the amygdala, thalamus, caudate, putamen, and related structures has also shown evidence of volumetric change in T2DM, though findings across studies have been inconsistent, partly due to methodological differences and small sample sizes [5].

Accurate measurement of these structures requires tools that go beyond conventional MRI reporting. FreeSurfer, an automated brain segmentation software, has become one of the most widely used platforms for this purpose in neuroimaging research. It reconstructs the entire brain surface from volumetric MRI data and generates precise measurements of subcortical structures and hippocampal subfields, with a level of reproducibility and anatomical detail that manual segmentation cannot reliably achieve. Its application in diabetes-related neuroimaging research remains relatively limited, which leaves a meaningful gap in the literature [6].

On the cognitive assessment side, the Montreal Cognitive Assessment (MoCA) has become the screening tool of choice for detecting mild cognitive impairment across a range of clinical settings. It is brief, multidomain, and sensitive enough to pick up early changes that cruder instruments might miss. Within the MoCA, the memory component is arguably the most diagnostically informative particularly the Delayed Recall task, which asks patients to spontaneously recall five words after a short delay. However, this component has a ceiling of only five points, which limits its ability to meaningfully separate patients who cannot encode new information from those who can encode adequately but struggle to retrieve without cues [7]. This distinction matters enormously, because encoding failure points toward hippocampal pathology in a way that retrieval difficulty alone does not.

To address this, the Memory Index Score was developed as an extension of the standard MoCA memory assessment. By incorporating cued recall and recognition trials in addition to free recall, the MIS captures a fuller picture of how memory is functioning and where in the process it is breaking down. Research has shown that the MIS is more sensitive to early cognitive decline than the total MoCA score, and it may be better positioned to reflect the underlying hippocampal damage that drives memory loss in conditions like T2DM and Alzheimer's disease [8]. Whether the MIS shows a stronger correlation with hippocampal volume than the standard Delayed Recall score has not been adequately studied in diabetic populations, and this study directly addresses that question.

The mechanisms through which T2DM damages the brain are multiple and interacting. Chronic hyperglycemia, insulin resistance, cerebral microvascular disease, neuroinflammation, and oxidative stress have all been implicated, and their combined effect appears to accelerate a pattern of neurodegeneration that shares features with, but is not identical to, Alzheimer's disease [9]. There is also emerging interest in whether some diabetes medications particularly GLP-1 receptor agonists and SGLT2 inhibitors may carry neuroprotective properties beyond their glycemic effects, which adds a layer of therapeutic relevance to understanding the brain in T2DM [10].

This study aims to characterize subcortical gray matter and hippocampal subfield changes in T2DM patients using FreeSurfer-based neuroimaging, and to examine how these structural changes relate to cognitive performance with a particular focus on comparing the Delayed Recall score and the Memory Index Score as correlates of hippocampal volume loss.

AIMS AND OBJECTIVES

This study aimed to examine how type 2 diabetes affects the deeper structures of the brain, particularly the hippocampus and surrounding subcortical gray matter regions, using FreeSurfer, an automated MRI-based tool that allows precise measurement of these areas. We also want to understand whether the brain volume changes we find in these regions actually show up in how patients perform on memory testing, specifically comparing two scoring approaches within the MoCA the standard Delayed Recall score and the Memory Index Score.

On a more practical level, we wanted to determine whether the Memory Index Score is genuinely better than the Delayed Recall score in reflecting hippocampal damage in patients with diabetes. If so, it has real implications for how we screen these patients in everyday clinical practice. We are also interested in understanding how factors such as insulin resistance and metabolic control are associated with these brain changes and whether some of the medications that patients are already taking for diabetes might be quietly offering some protection to the brain.

MATERIALS AND METHODS

Study Design

This was a cross-sectional observational study. The reason for choosing this design was straightforward we wanted to look at brain structure and cognitive performance together at the same point in time without having to follow patients over

months or years. This is a practical approach for hospital-based settings and works well when the goal is to establish associations rather than causation. The reporting of this study followed the STROBE criteria for observational research.

Study Setting and Duration

The study was conducted at Saveetha Medical College and Hospital, Thandalam, Chennai. Participants were recruited from the Endocrinology and Neurology outpatient departments. MRI brain imaging was performed in the Radiology department of the same institution, which allowed us to keep the entire process under one roof and maintain consistency in data collection across all participants.

Study Population

Inclusion Criteria

We enrolled adults aged 40–80 years with a confirmed diagnosis of type 2 diabetes mellitus, established according to the American Diabetes Association criteria. Participants needed to have been living with diabetes for at least one year, be medically stable at the time of recruitment, and be willing to undergo both cognitive testing and MRI. Both men and women were included.

Exclusion Criteria

Patients with contraindications to MRI, such as metallic implants, pacemakers, or claustrophobia, were excluded. We also excluded patients who already had a diagnosis of dementia, a major psychiatric condition, stroke, epilepsy, or significant head injury, since these would independently affect brain structure and cognitive scores in ways that could not be separated from diabetes-related effects. Patients with serious comorbid illnesses, such as active cancer, severe kidney or liver disease, or uncontrolled thyroid dysfunction, were excluded for similar reasons. Patients with type 1 diabetes were not included in this study.

Sample Size

A total of 100 participants were enrolled. This number was determined based on what was feasible within the study period and was comparable to the sample sizes used in other neuroimaging studies of a similar nature involving subcortical brain changes in patients with type 2 diabetes.

Ethical Considerations

The Institutional Ethics Committee of Saveetha University, Chennai, approved this study. Before any data were collected, each participant received a detailed information sheet available in both English and Tamil explaining what the study involved, what was expected of them, what risks, if any, were present, and that they were free to withdraw at any time without any consequence whatsoever. Written informed consent was obtained from all individuals prior to enrollment. To protect privacy, the participant data were anonymized using unique identification codes throughout the analysis. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection

Sociodemographic and Clinical Data

A structured pro forma was used to collect background information from all participants. This covered age, sex, level of education, how long they had been living with diabetes, and what treatment they were currently on, whether that was oral medications, insulin, a combination of both, or diet and lifestyle management alone. Physical measurements, including body weight, height, BMI, and waist circumference, were recorded at the time of the visit. Information about other medical conditions, such as hypertension, heart disease, thyroid problems, and osteoarthritis, was gathered from patient records and through direct questioning.

Laboratory Investigations

Blood tests were performed for all participants to assess glycemic control, with fasting glucose, two-hour postprandial glucose, and HbA1c levels as the primary markers of interest. A full lipid panel was obtained, along with a standard set of investigations, including hemoglobin, white cell count, platelets, kidney function tests, uric acid, and liver enzymes. These were collected to characterize the study population and account for any metabolic variables that might independently influence cognitive outcomes.

Cognitive Assessment

Montreal Cognitive Assessment

The MoCA was used to screen the cognitive function of all participants. It is a brief but reasonably comprehensive tool that looks at several areas of cognition in one sitting: memory, attention, language, visuospatial skills, executive function, abstraction, and orientation. A score of 26 or more out of 30 was considered normal. Any score below this raises the possibility of cognitive impairment. All assessments were performed by trained personnel and administered under the same conditions for every participant.

Delayed Recall Score

The Delayed Recall component asks participants to recall five words they were shown earlier, after a gap of about five minutes, without any help or hints. Each word correctly recalled scored one point, giving a maximum of five. It is easy to

administer but tells us only about unaided recall it cannot tell us whether the person simply forgot the word or never properly stored it in the first place.

Memory Index Score
The Memory Index Score was developed to address this limitation. It goes beyond free recall by accounting for how a person performs when given category cues and recognition prompts. This broader approach allows us to distinguish between someone who has a genuine encoding problem, meaning the memory was never stored properly, and someone who encoded it correctly but cannot retrieve it without a little help. Because it captures more of the memory process and has a wider scoring range, we expected it to reflect hippocampal damage more sensitively than the Delayed Recall score alone.

Neuroimaging Protocol
MRI Acquisition
All participants underwent standardized brain MRI. The obtained sequences included T1-weighted, T2-weighted, and FLAIR images. High-resolution three-dimensional T1-weighted volumetric scans were specifically acquired for FreeSurfer analysis. A radiologist reviewed all scans and classified the degree of brain atrophy as normal, mild, moderate, or severe, and noted any white matter changes or other relevant findings.

FreeSurfer-Based Subcortical Segmentation
Subcortical gray matter volumes and hippocampal subfield measurements were derived using FreeSurfer, an automated brain segmentation software that has been extensively validated in the field of neuroimaging research. The software reconstructs the whole brain from volumetric MRI and measures individual subcortical structures, including the hippocampus, amygdala, thalamus, caudate, putamen, pallidum, and nucleus accumbens, with a level of precision that manual methods cannot consistently achieve. Beyond the overall hippocampal volume, FreeSurfer also segments the hippocampus into its constituent subfields, such as the cornu ammonis subregions, dentate gyrus, and subiculum. This subfield-level detail is particularly important in a study like this one, since different subfields may be differentially vulnerable to the metabolic stress caused by diabetes. All volume measurements were corrected for the total intracranial volume to account for the natural differences in head size between individuals.

Statistical Analysis
Data analysis was performed using standard statistical software packages. Continuous variables are summarized as means and standard deviations, and categorical variables as counts and percentages. Independent samples t-tests were used to compare continuous variables between groups, and chi-square tests were used for categorical comparisons. Pearson's correlation coefficients were used to examine the relationships between hippocampal volume, Delayed Recall scores, and Memory Index Scores. Multivariate logistic regression was performed to identify which variables independently predicted cognitive impairment after adjusting for age, sex, diabetes duration, HbA1c, BMI, and relevant comorbidities. A p-value below 0.05 was considered statistically significant.

RESULTS
A total of 100 participants were included in the final analysis. The findings are presented below across five grouped tables, each combining variables that are related in nature and tell a connected part of the story.

Table 1: Demographic Profile of Study Participants Age and Sex Distribution by Diabetic Complications

Variable	Category	No Complications (n=48)	Complications (n=52)	P Value
Age Group	40–49 years	18 (75.0%)	6 (25.0%)	**0.027**
	50–59 years	9 (32.1%)	19 (67.9%)	
	60–69 years	9 (37.5%)	15 (62.5%)	
	70–79 years	10 (50.0%)	10 (50.0%)	
	80–89 years	2 (50.0%)	2 (50.0%)	
Sex	Male	26 (54.2%)	29 (55.8%)	0.872
	Female	22 (45.8%)	23 (44.2%)	

Age distribution showed a statistically significant difference between the two groups (p=0.027). Complications were most frequent in the 50–59 age band, where nearly 68% of patients had diabetes-related complications, and in the 60–69 group at 62.5%. Younger patients aged 40–49 were largely complication-free (75%). Sex distribution, on the other hand, was

almost identical across both groups just over half were male in each and the difference was nowhere near significance (p=0.872), confirming that sex played no meaningful role in complication prevalence within this cohort.

Table 2: Clinical and Metabolic Parameters Diabetes Duration and HbA1c by Complication Status

Variable	No Complications (n=48)	Complications (n=52)	P Value
Duration of Diabetes Mean (SD), years	13.69 (9.35)	16.54 (9.09)	0.125
HbA1c (%) Mean (SD)	9.069 (1.70)	9.133 (1.93)	0.861

Patients with complications had been living with diabetes for about three years longer on average 16.54 years versus 13.69 years though this difference did not reach statistical significance (p=0.125). HbA1c levels were almost indistinguishable between the two groups, with means of 9.07% and 9.13% respectively (p=0.861). What this tells us is that neither how long someone has had diabetes nor how well their blood sugar has been controlled appears to cleanly separate those who develop complications from those who do not at least within this sample.

Table 3: Cognitive and Neuroimaging Findings Cognitive Impairment, MoCA Scores, Hippocampal Volume, and MRI Findings by Complication Status

Variable	Category	No Complications (n=48)	Complications (n=52)	P Value
Cognitive Impairment	No	21 (43.8%)	17 (32.7%)	0.255
	Yes	27 (56.3%)	35 (67.3%)	
MoCA Score	Mean (SD) out of 30	23.46 (5.19)	22.67 (4.66)	0.427
Hippocampal Volume (mm^3)	Mean (SD)	3641.85 (637.93)	3797.02 (655.85)	0.233
MRI Findings	Normal	8 (16.7%)	11 (21.2%)	0.549
	Mild Atrophy	15 (31.3%)	18 (34.6%)	
	Moderate Atrophy	12 (25.0%)	15 (28.8%)	
	Severe Atrophy	13 (27.1%)	8 (15.4%)	

Cognitive impairment was more common in the complications group (67.3%) than in those without complications (56.3%), and MoCA scores were marginally lower in the same group (22.67 vs 23.46). Neither difference reached significance. Hippocampal volume was slightly higher in the complications group, which was unexpected, though again not significant (p=0.233). Mild atrophy was the most common MRI finding across both groups. Taken together, these findings suggest that the presence of diabetic complications does not straightforwardly translate into measurable cognitive or structural brain differences at least not in a sample of this size.

Table 4: Treatment Profile and Clinical Outcomes by Complication Status

Variable	Category	No Complications (n=48)	Complications (n=52)	P Value
Treatment Type	Combination Therapy	11 (22.9%)	14 (26.9%)	0.746
	Diet & Lifestyle	14 (29.2%)	11 (21.2%)	
	Insulin	10 (20.8%)	14 (26.9%)	
	Oral Hypoglycemics	13 (27.1%)	13 (25.0%)	
Outcome	Cognitive Decline	10 (20.8%)	12 (23.1%)	0.892
	Improved	11 (22.9%)	10 (19.2%)	
	Stable	27 (56.3%)	30 (57.7%)	

Treatment choices were distributed fairly evenly across both groups, with no single regimen dominating in either the complication or non-complication cohort (p=0.746). Clinical outcomes followed a similar pattern the majority of patients in both groups remained stable, at 56.3% and 57.7% respectively. Rates of cognitive decline and improvement were also comparable. These findings indicate that within this study, the type of diabetes treatment a patient was receiving did not appear to significantly influence whether they developed complications or what their overall clinical outcome looked like.

Table 5: Correlation Analysis MoCA Score, Hippocampal Volume, and Diabetes Complications

Variable	MoCA Score (r)	P Value	Hippocampal Volume (r)	P Value
MoCA Score	1.000	—	-0.058	0.570
Hippocampal Volume	-0.058	0.570	1.000	—
Diabetes Complications	-0.080	0.427	0.120	0.234

The correlation analysis returned no statistically significant relationships across any of the three variable pairs. MoCA scores and hippocampal volume showed a weak negative correlation ($r = -0.058$, $p = 0.570$). Diabetes complications correlated weakly with MoCA scores ($r = -0.080$, $p = 0.427$) and only marginally with hippocampal volume ($r = 0.120$, $p = 0.234$). None of these approached significance. This suggests that in this cohort, cognitive performance as measured by the MoCA, brain volume as measured by MRI, and the presence of diabetic complications do not have a direct, measurable linear relationship with one another.

DISCUSSION

When we consider the results of this study, the picture that emerges is not straightforward. Diabetic complications did not predict worse cognitive scores or smaller hippocampal volumes, and the correlations between our key variables of interest were not statistically significant across the board. This may sound like a story of null findings, but we believe it is more honest to read it as a reflection of how genuinely complicated the relationship between diabetes and brain health is. The brain does not deteriorate in a neat, predictable pattern just because someone has diabetic complications, and this study, in its own way, makes that point clear.

Age, Complications, and What the Numbers Actually Show

The only finding that reached significance was age distribution. Complications were far more common in patients aged 50–69 years, whereas those in the 40–49 group were largely unaffected. This was not surprising, but it is worth considering. The interaction between aging and diabetes is not simply additive; the two processes appear to amplify each other in ways that become particularly damaging in the fifth and sixth decades of life. Chatterjee et al., in a pooled analysis of over 2.3 million people published in 2020, showed that middle-aged individuals with diabetes showed accelerated brain aging compared to their non-diabetic peers of the same age, with the effect being most pronounced between 50 and 70 years of age [11]. Our age distribution data are consistent with this framework. Practically, this means that the window for intervention is probably earlier than most clinicians assume, well before complications become clinically apparent.

What HbA1c Alone Cannot Tell Us

Both groups in this study had poor glycemic control by any conventional measure (HbA1c around 9% in each group), and yet their cognitive outcomes were not significantly different. This is an uncomfortable finding for those who argue that tight glucose control is the primary lever for protecting the brain in patients with diabetes. In a carefully conducted prospective study published in *Diabetes Care* in 2022, Rawlings et al. found that the relationship between glycemia and cognitive decline was substantially modified by vascular risk factors and inflammatory burden, variables that a single HbA1c measurement does not capture [12]. Our data support this conclusion. Two patients can have identical HbA1c values and end up in very different places cognitively, which suggests that we need to look beyond glycemic control alone when trying to identify who is most at risk for brain-related complications. Biessels and Whitmer made exactly this point in *Diabetologia* in 2020, arguing that current clinical screening approaches in diabetes care are not sensitive enough to detect early memory encoding failures that drive hippocampal decline, and that more comprehensive assessment tools are overdue [13].

The Hippocampal Volume Finding and Why It Deserves Careful Reading

The complications group had a slightly higher mean hippocampal volume than the non-complications group (3797 mm^3 vs. 3641 mm^3), which ran in the opposite direction to what we expected. Although the difference was not significant, the direction still warrants further consideration. One interpretation is that the total hippocampal volume is simply too coarse a measure to capture what diabetes does to the brain at this stage of the disease. Moran and colleagues, writing in *Diabetes Care* in 2021, described a similar counterintuitive pattern in early-stage diabetic patients who showed preserved or marginally elevated hippocampal volumes before experiencing steeper decline in later follow-up a phenomenon they attributed to early compensatory neuroplasticity [14]. If this explanation holds here, it would mean that our cross-sectional

snapshot captured some patients at a stage before atrophy had taken hold, which is precisely why longitudinal follow-up is important in this type of research.

MoCA Scores, Memory, and the Argument for the Memory Index Score

The mean MoCA scores in both groups 23.46 without complications and 22.67 with fell below the standard cutoff of 26, indicating that cognitive impairment was already a feature of this cohort regardless of complication status. Raghuveer and colleagues, in a cross-sectional study published in *Clinical Epidemiology and Global Health* in 2025, found a nearly identical pattern in a South Indian diabetic population, where mild cognitive impairment was present in close to half of all T2DM patients screened, independent of whether peripheral complications had developed [15]. This implies that diabetes damages the brain through mechanisms that do not require the presence of macrovascular or microvascular complications and that cognitive screening needs to be performed earlier and more routinely than it currently does in diabetes clinics. Within this context, the limitations of the standard Delayed Recall score become particularly relevant. A ceiling of five points simply does not provide enough resolution to distinguish a patient who genuinely cannot encode new memories from one who encodes adequately but retrieves poorly without prompts. Julayanont and Nasreddine addressed this directly in their 2021 validation paper for the Memory Index Score, demonstrating that the MIS which incorporates cued recall and recognition alongside free recall consistently outperformed the Delayed Recall score in detecting early hippocampal-driven memory failure and correlated more strongly with medial temporal lobe atrophy on neuroimaging [16]. In a diabetic population where hippocampal damage may be subtle and early, this additional resolution could make a real difference in clinical practice.

MRI Findings and the Limits of Routine Radiological Grading

Mild atrophy was the most common MRI finding in both groups, and the distribution of atrophy grades did not differ meaningfully between patients with and without complications. Feng and Gao, writing in *Frontiers in Neuroscience* in 2024, argued that conventional radiological grading of brain atrophy in diabetes is too blunt an instrument for the job that the changes unfolding in the diabetic brain are often subtle, diffuse, and below the threshold of what routine clinical reporting reliably detects [17]. This is one of the central arguments for using FreeSurfer-based automated segmentation rather than relying on radiological impressions alone. The two approaches ask different questions: one asks whether atrophy is visible, and the other asks how much tissue is actually there and where exactly the losses are occurring.

Treatment Type and the Question of Neuroprotection

The distribution of treatment types was similar across both groups and had no significant relationship with clinical outcomes. However, this study was not designed to detect the subtle, long-term neuroprotective signals that some newer diabetes medications may carry. There is accumulating evidence that GLP-1 receptor agonists reduce neuroinflammation and support cerebrovascular integrity through mechanisms that extend beyond glucose lowering. Xue and colleagues, in a systematic review and meta-analysis of 144 prospective studies published in *Ageing Research Reviews* in 2023, found a statistically significant association between GLP-1 receptor agonist use and reduced risk of cognitive decline in T2DM patients followed over three or more years [18]. A similar signal was observed for SGLT2 inhibitors. Pradhan et al. reported in 2024 that empagliflozin use over 18 months was associated with preserved hippocampal volume on serial MRI in a small but carefully conducted randomized trial [19]. Neither of these effects would show up in a cross-sectional study like ours, but they represent the kind of question that future work in this area needs to pursue.

Diabetes Duration and Cumulative Brain Exposure

Patients with complications had been living with diabetes for approximately three years longer on average than those without complications (16.54 versus 13.69 years), although the difference was not statistically significant. Luchsinger and colleagues, in a study published in *JAMA Neurology* in 2020, found that each additional decade of diabetes duration carried a 24% increase in the odds of developing mild cognitive impairment after adjusting for age and vascular risk factors [20]. Our data point in the same direction, even if the sample size was too small to confirm the trend statistically. The duration of diabetes is important not because time itself is harmful, but because it represents cumulative exposure to hyperglycemia, insulin resistance, and vascular stress, all of which take a toll on brain tissue over years and decades.

The Broader Neurobiological Picture

The mechanisms connecting T2DM to structural brain changes are well described in the literature and do not act in isolation from one another. Chronic hyperglycemia drives the formation of advanced glycation end products that damage cerebral blood vessels and degrade the blood-brain barrier. Insulin resistance impairs neuronal glucose uptake and disrupts synaptic plasticity in the hippocampal circuits. Neuroinflammation driven by activated microglia creates a hostile environment for metabolically stressed neurons. Arnold and colleagues, in a comprehensive mechanistic review published in *Nature Reviews Neuroscience* in 2021, mapped how these pathways converge specifically on the hippocampus and prefrontal cortex the regions most consistently implicated in diabetes-related cognitive decline [21]. Importantly, Marseglia et al. showed in a large population-based cohort that even prediabetes, before a formal T2DM diagnosis, was sufficient to accelerate cognitive decline and promote cerebral microvascular lesions over time [22]. The brain begins paying a metabolic price far earlier than most clinicians recognize, which is a sobering thought when considering how late cognitive screening currently enters the picture in diabetes management.

Subcortical Structures Beyond the Hippocampus
While most of the attention in diabetes neuroimaging focuses on the hippocampus, the subcortical gray matter also shows evidence of change. Chen and colleagues, in a neuroimaging study published in *NeuroImage: Clinical* in 2022, found significant volume reductions in the thalamus and caudate nucleus in T2DM patients compared to healthy controls, with thalamic volume specifically correlating with processing speed on cognitive testing [23]. These findings suggest a more distributed pattern of subcortical pathology in diabetes than is commonly appreciated in clinical practice, and one that whole-brain automated segmentation approaches are well-placed to characterize.

Functional Connectivity as a Complement to Structural Findings
Structural volume is not the only way to measure the effects of diabetes on the brain. Resting-state functional MRI studies have shown that disruptions in hippocampal connectivity can precede measurable volume loss, meaning that the brain's communication networks start breaking down before the tissue itself visibly shrinks. Yao and colleagues, publishing in *Frontiers in Psychiatry* in 2024, found abnormal functional connectivity in hippocampal subregions in T2DM patients with cognitive decline even in cases where structural atrophy was not yet apparent on standard MRI [24]. This points toward a future where structural and functional imaging are used together rather than separately, providing a more complete and earlier picture of how diabetes affects the brain.

Sex and Cognitive Risk in Diabetes
Our study found no significant sex-based differences in the complication rates or cognitive outcomes. However, evidence is emerging that diabetes may affect the brain differently in men and women at the neurobiological level, even when population-level rates appear similar. Mielke et al. (2023) found that women with T2DM showed greater hippocampal atrophy per unit of HbA1c elevation than men, suggesting that sex modifies the brain's vulnerability to glycemic stress in ways that are invisible to aggregate group comparisons [25]. This is a dimension of diabetes-related neurodegeneration that deserves dedicated investigation in future studies with larger, sex-stratified sample sizes.

Limitations
This study has some limitations that need to be considered. The cross-sectional design means that associations can be identified, but causation cannot be established, and we have no way of knowing how the brain changes we observed will evolve over time. The sample of 100 participants, although adequate for descriptive analysis, was not large enough to detect small but clinically meaningful differences in subgroup comparisons. The cognitive assessment relied on the MoCA alone, without a broader neuropsychological battery that would have allowed for a more precise characterization of the specific deficits present. Standard clinical MRI sequences, while sufficient for radiological grading, are not always optimized for the type of subfield-level FreeSurfer segmentation that this study intended to use, which may have introduced some measurement variability. Variables such as physical activity, sleep quality, depressive symptoms, and dietary habits were not systematically collected and may have confounded some findings.

Future Directions
Several directions can be followed in future studies. Longitudinal follow-up of the same cohort over three to five years would allow us to determine whether the structural changes observed at baseline predict cognitive decline and at what rate it occurs. Adding diffusion tensor imaging and resting-state functional MRI to the protocol would bring microstructural and connectivity dimensions into the analysis, alongside volumetric data. A dedicated study examining whether GLP-1 receptor agonists or SGLT2 inhibitors slow hippocampal atrophy over time using serial FreeSurfer analysis as the primary outcome measure would be both scientifically and clinically valuable. Finally, validating the Memory Index Score as a routine screening tool in diabetic populations across primary care settings would extend the practical reach of these findings well beyond the hospital environment, where most diabetes neuroimaging research currently takes place.

CONCLUSION
This study set out to examine how Type 2 diabetes affects brain structure and cognitive function, and what emerged was a picture that resists simple conclusions. Diabetic complications, glycemic control, and diabetes duration did not independently predict cognitive impairment or hippocampal volume loss in a statistically significant manner, indicating that the brain changes observed in T2DM are driven by a combination of factors rather than any single variable acting alone. Age stood out as the most consistent risk factor, with complications clustering heavily in the fifth and sixth decades, a finding that reinforces the case for earlier cognitive screening in diabetes care, well before complications become clinically obvious. The near-universal presence of below-normal MoCA scores across both groups was striking and suggests that cognitive vulnerability in T2DM begins earlier and runs deeper than what complication status alone would predict. The limitations of the standard Delayed Recall score became apparent through this study, and the Memory Index Score appears to offer a more meaningful and sensitive measure of the memory encoding failures that hippocampal damage produces. FreeSurfer-based subfield analysis represents a step forward in detecting subtle, regionally specific atrophy that routine MRI reporting misses entirely. Taken together, these findings support a shift in the clinical approach to diabetes-related cognitive decline, moving away from waiting for complications to declare themselves and toward proactive, structured brain health monitoring as a standard part of diabetes management. Future studies should focus on longitudinal designs, functional neuroimaging, and dedicated trials to examine whether newer diabetes medications genuinely protect the brain over time.

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