

Article

Cerebrospinal Fluid Biomarkers of Neuroinflammation and Neuroplasticity in Type 2 Diabetes Mellitus: Association with Cognitive Performance

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Abstract

Background: Type 2 Diabetes Mellitus (T2DM) is associated with cognitive decline, potentially mediated by neuroinflammatory processes and altered neuroplasticity. This study investigated cerebrospinal fluid (CSF) biomarkers of neuroinflammation and neuroplasticity in T2DM individuals versus controls, and their relationship with cognitive performance. **Methods:** This cross-sectional study included 56 T2DM individuals and 26 controls (aged 37–70 years; 48% male). CSF concentrations of leptin, IL-6, VEGF, BDNF, TNF- α , IGF-1, and IL-1 β were measured using ELISA. Cognitive function was assessed using MMSE, the Stroop test, SDMT, RCFT, and TAAV. Group comparisons used Mann–Whitney U or *t*-tests; Spearman correlations examined variable relationships. **Results:** No statistically significant differences in CSF biomarkers were observed between groups. However, T2DM patients showed lower word recall (4.66 ± 1.48 vs. 5.81 ± 1.52 ; $p = 0.002$), reduced Symbol–Digit performance (17.82 ± 12.16 vs. 24.92 ± 12.10 ; $p = 0.016$), and higher Complex Figure Test scores (19.94 ± 9.32 vs. 15.94 ± 5.02 ; $p = 0.009$). IL-6 was negatively correlated with MMSE ($r = -0.33$, $p = 0.005$). Significant correlations emerged between MMSE and Symbol–Digit scores ($r = 0.40$, $p < 0.001$) and among biomarkers. **Conclusions:** “No statistically significant differences in CSF biomarkers were observed between groups and unadjusted CSF biomarker concentrations did not differ significantly between groups; however, after adjustment for age and BMI, IL-6 was significantly elevated in T2DM patients, indicating that covariate-adjusted analyses may be more sensitive for detecting subtle neuroinflammatory differences in this population.



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1. Introduction

Type 2 Diabetes Mellitus (T2DM) affects over 589 million individuals worldwide in 2024 and is associated with numerous complications beyond glycemic dysregulation [1]. Emerging evidence indicates that T2DM significantly increases the risk of cognitive decline and dementia, with prevalence rates 1.5 to 2.5 times higher than those in non-diabetic populations [2,3]. The mechanisms underlying diabetes-associated cognitive performance

remain incompletely understood but likely involve multiple pathophysiological processes including chronic hyperglycemia, insulin resistance, vascular dysfunction, and neuroinflammation [4].

Neuroinflammation, characterized by activation of microglia and astrocytes with subsequent release of pro-inflammatory cytokines, has emerged as a critical mediator of neurodegeneration in metabolic disorders [5]. Key inflammatory mediators including interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- α), and interleukin-1 beta (IL-1 β) have been implicated in synaptic dysfunction and neuronal damage [6]. Concurrently, impaired neuroplasticity—the brain's capacity for structural and functional adaptation—may contribute to cognitive deficits in T2DM [7]. Brain-derived neurotrophic factor (BDNF), a crucial regulator of synaptic plasticity and neuronal survival, shows altered expression in diabetes [8].

Additional factors including leptin, an adipokine with neuroprotective properties [9], vascular endothelial growth factor (VEGF), which regulates angiogenesis and neurogenesis [10], and insulin-like growth factor-1 (IGF-1), essential for neuronal growth and survival [11], may also play roles in diabetes-related cognitive dysfunction. However, most studies have examined peripheral blood concentrations of these biomarkers, which may not accurately reflect central nervous system pathology.

Cerebrospinal fluid (CSF) analysis provides direct access to the brain's biochemical environment and offers superior sensitivity for detecting neuroinflammatory and neurodegenerative processes [12]. Despite this advantage, few studies have comprehensively examined CSF biomarkers of neuroinflammation and neuroplasticity in T2DM patients with cognitive performance. Understanding these relationships is critical for identifying potential therapeutic targets and developing biomarker-based diagnostic approaches.

The present study aimed to compare CSF concentrations of selected neuroinflammation markers (IL-6, TNF- α , IL-1 β , leptin) and neuroplasticity indicators (BDNF, VEGF, IGF-1) between individuals with T2DM and healthy controls, and to examine their associations with cognitive performance across multiple domains including global cognition, memory, attention, and executive function.

2. Materials and Methods

2.1. Study Design and Participants

This cross-sectional observational study included 82 participants: 56 individuals diagnosed with Type 2 Diabetes Mellitus (T2DM) and 26 control subjects without diabetes. Participants ranged in age from 37 to 70 years, with 48% male and 52% female representation. The T2DM group had a mean age of 58.39 ± 7.55 years, while controls averaged 54.88 ± 8.30 years. All participants provided informed consent, and the study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee.

Description of education level coding: 1 = primary education (≤ 5 years of formal schooling), 2 = secondary education (6–11 years of formal schooling), 3 = higher education (≥ 12 years of formal schooling, including technical, undergraduate and postgraduate education).

Sample size and statistical power:

- Acknowledgment that no formal a priori sample size calculation was performed;
- Retrospective justification based on the prior literature;
- Statement that the sample was recruited based on feasibility constraints (availability of participants willing to undergo lumbar puncture).

Clinical characteristics of T2DM participants:

- Medication use: All T2DM participants were receiving pharmacological treatment. Specifically, 82% (n = 46) were on metformin monotherapy or combination therapy, 25% (n = 14) were on sulfonylureas, 18% (n = 10) were on DPP-4 inhibitors, and 12% (n = 7) were on insulin therapy (some participants were on multiple agents).
- Microvascular complications: Diabetic retinopathy was present in 16% (n = 9), nephropathy (defined as albuminuria or reduced eGFR) in 14% (n = 8), and peripheral neuropathy in 21% (n = 12) of T2DM participants.
- Macrovascular complications: History of cardiovascular disease (myocardial infarction, stroke, or peripheral arterial disease) was present in 9% (n = 5) of T2DM participants.
- Glycemic control: Mean HbA1c was $7.8 \pm 1.4\%$ (62 ± 16 mmol/mol) range: 5.6–11.2% (38–99 mmol/mol).

Inclusion criteria for the T2DM group included the following: (1) confirmed diagnosis of Type 2 Diabetes Mellitus according to American Diabetes Association criteria; (2) age between 37 and 70 years; and (3) willingness to undergo lumbar puncture for CSF collection. Exclusion criteria included the following: (1) Type 1 Diabetes Mellitus; (2) acute diabetic complications; (3) severe psychiatric disorders; (4) neurological conditions other than diabetes-related complications; (5) recent head trauma; (6) active infections; and (7) contraindications to lumbar puncture.

Control subjects were individuals without diabetes, selected from the same geographic region, with no history of metabolic disorders, neurological diseases, or cognitive impairment.

Ethical considerations for lumbar puncture in controls are as follows: we believe our approach was ethically sound and scientifically necessary, but we acknowledge the inherent tension.

2.2. Biomarker Measurements

Cerebrospinal fluid samples were obtained via lumbar puncture performed by experienced anesthesiologists from the institutional research team using standard sterile technique under local anesthesia. CSF was collected in polypropylene tubes, immediately centrifuged at $2000 \times g$ for 10 min at 4°C , aliquoted, and stored at -80°C until analysis. All samples underwent a single freeze–thaw cycle to minimize degradation.

The following biomarkers were quantified using enzyme-linked immunosorbent assay (ELISA) kits from R&D Systems (Bio-Techne®, Minneapolis, MN, USA):

- Leptin: Adipokine involved in energy homeostasis and neuroprotection;
- Interleukin-6 (IL-6): Pro-inflammatory cytokine;
- Vascular Endothelial Growth Factor (VEGF): Angiogenic and neurotrophic factor;
- Brain-Derived Neurotrophic Factor (BDNF): Neurotrophin supporting neuronal survival and plasticity;
- Tumor Necrosis Factor alpha (TNF- α): Pro-inflammatory cytokine;
- Insulin-like Growth Factor-1 (IGF-1): Growth factor with neuroprotective properties;
- Interleukin-1 beta (IL-1 β): Pro-inflammatory cytokine.

All assays were performed according to manufacturer protocols. Samples were analyzed in duplicate, and mean values were used for statistical analysis. Intra-assay and inter-assay coefficients of variation were maintained below 10% and 15%, respectively.

2.3. Cognitive Assessment

Cognitive function was evaluated using a comprehensive neuropsychological battery administered by trained psychologists:

- Mini-Mental State Examination (MMSE): Cognitive status was assessed using an adapted Spanish version validated for Colombian populations (scaled to a maximum of 36 points to enhance sensitivity for mild cognitive impairment across varying educa-

tional levels) [13]. This version has demonstrated psychometric properties comparable to the standard 30-point MMSE, with established normative data for age and education. Scores can be approximately converted to the 30-point scale by multiplying by 0.833. An independent evaluation of copying and memory was conducted.

- Word Recall Test (Recuerdo de Palabras): A verbal learning and memory test assessing immediate recall capacity. Participants were presented with a list of words and asked to recall them immediately [14].
- Digit Retention Test (Retención de Dígitos): Assessment of Working Memory and attention through forward and backward digit span tasks. Performance in the Digit Span Test is interpreted at several levels: raw score, standardized score, and qualitative analysis of the performance pattern [15].
- Symbol–Digit Modalities Test (SDMT, Part III—Símbolos y Dígitos): A measure of processing speed, visual scanning, and sustained attention. Participants match symbols to digits according to a key, with scores reflecting the number of correct substitutions within a time limit. The score corresponds to the number of correct answers in 90 s [16].
- Rey Complex Figure Test (Test de Figura Compleja de Rey): Assessment of visuospatial construction ability and visual memory through copying and delayed recall of a complex geometric figure [17].

All cognitive tests were administered in standardized conditions, and raw scores were used for statistical analysis.

2.4. Statistical Analysis

Statistical analyses were performed using Python (version 3.8 or higher) with SciPy, NumPy, and Pandas libraries. Descriptive statistics were calculated for all variables, including means, standard deviations, and sample sizes for each group.

2.4.1. Post Hoc Power Analysis

We conducted post hoc power analyses for key comparisons using G*Power 3.1:

Acknowledgment that no formal a priori sample size calculation was performed.

Retrospective justification based on the prior literature.

Statement that the sample was recruited based on feasibility constraints (availability of participants willing to undergo lumbar puncture).

Normality Assessment: The Shapiro–Wilk test was applied to assess the normality of distribution for all continuous variables in both T2DM and control groups separately. A significance level of $\alpha = 0.05$ was used, with $p < 0.05$ indicating significant deviation from normality.

Group Comparisons: Based on normality test results, appropriate statistical tests were selected:

- For variables showing normal distribution in both groups, independent sample *t*-tests were employed.
- For variables with non-normal distribution in either or both groups, Mann–Whitney U tests (non-parametric alternative) were used.

Effect sizes were calculated to quantify the magnitude of group differences: Cohen's *d* for *t*-tests (small: 0.2, medium: 0.5, large: 0.8) and rank–biserial correlation for Mann–Whitney U tests (small: 0.1, medium: 0.3, large: 0.5).

Statistical significance was set at $\alpha = 0.05$ (two-tailed).

Correlation Analysis: Spearman's rank correlation coefficients were calculated to examine relationships among all biomarkers and cognitive variables, given the predominantly non-normal distributions. Correlation strength was interpreted as: weak ($|r| = 0.10–0.29$), moderate ($|r| = 0.30–0.49$), or strong ($|r| \geq 0.50$). Significance was assessed at $\alpha = 0.05$,

with Bonferroni correction applied for multiple comparisons where appropriate; significance threshold: $\alpha = 0.05/66 = 0.00076$. We also applied the False Discovery Rate (FDR) method (Benjamini–Hochberg procedure) with $q = 0.05$ as a less conservative alternative.

Analysis of covariance (ANCOVA): Given that we found statistically significant differences in the variables age and BMI; biochemical differences were established between groups after adjusting for age and BMI; cognitive performance differences; and correlational patterns linking biochemical markers to cognitive outcomes across the full sample. All cytokine variables were log-transformed ($\log_{10}[x + 1]$) to address right skewness prior to analysis.

Multivariable regression models: The dataset comprised $n = 82$ participants (DM2 = 56; control = 26). Due to missing HbA1c data ($n = 35$ missing), complete-case analysis yielded: full sample models (M1, M2): $n = 46$ T2DM, subgroup models (M3, M4): $n = 35$. The following variables were defined as independent and dependent.

Independent Variables:

Interleukin-6 (pg/mL)	Log-transformed ($\log_{10}$)—right-skewed
Interleukin-1 β (pg/mL)	Log-transformed ($\log_{10}$)—right-skewed
Age in years	Continuous
Body Mass Index (kg/m ²)	Continuous
Education level	0–5 Ordinal, treated as continuous
Glycated hemoglobin (%)	Continuous
Biological sex (0 = Female, 1 = Male)	Binary

Dependent Variables

Mini-Mental State Examination (MEC)	0–36 (continuous)
Working Memory–Digit Span Scalar Score	Standardized scalar

Model Specifications

Four ordinary least squares (OLS) regression models were pre-specified:

Model 1 (M1)—Full sample, MMSE:

$$MMSE[M1.1][CB1.2] = \beta[M2.1]0 + \beta_1 \cdot \log [M3.1](IL-6) + \beta_2 \cdot \log (IL-1\beta) + \beta_3 \cdot Age + \beta_4 \cdot BMI + \beta_5 \cdot Education + \beta_6 \cdot HbA1c + \beta_7 \cdot Sex + \varepsilon$$

$$MMSE = \beta_0 + \beta_1 \cdot \log(IL-6) + \beta_2 \cdot \log(IL-1\beta) + \beta_3 \cdot Age + \beta_4 \cdot BMI + \beta_5 \cdot Education + \beta_6$$

Model 2 (M2)—Full sample, Working Memory:

$$WM = \beta_0 + \beta_1 \cdot \log (IL-6) + \beta_2 \cdot \log (IL-1\beta) + \beta_3 \cdot Age + \beta_4 \cdot BMI + \beta_5 \cdot Education + \beta_6 \cdot HbA1c + \beta_7 \cdot Sex + \varepsilon$$

$$WM = \beta_0 + \beta_1 \cdot \log(IL-6) + \beta_2 \cdot \log(IL-1\beta) + \beta_3 \cdot Age + \beta_4 \cdot BMI + \beta_5 \cdot Education + \beta_6$$

Model 3 (M3)—T2DM subgroup, MMSE: Same specification as M1, restricted to DM2 participants ($n = 35$).

Model 4 (M4)—T2DM subgroup, Working Memory: Same specification as M2, restricted to DM2 participants ($n = 35$)

All statistical tests were two-tailed, and results are reported with exact p -values. Figures were generated using Matplotlib and Seaborn libraries to visualize group differences and correlation patterns.

2.4.2. Analytic Hierarchy

Primary analyses: Unadjusted between-group comparisons of CSF biomarker concentrations and cognitive performance using Mann–Whitney U tests and independent-samples t -tests (Tables 3 and 4). These address the study's pre-specified aims and form the basis of all power calculations.

Secondary analyses: (1) ANCOVA adjusting for age and BMI to re-examine biomarker and cognitive group differences while controlling for confirmed between-group confounders. (2) Spearman correlations between CSF biomarkers and cognitive outcomes across the full sample (Tables 6 and 7), which address the secondary aim of characterizing biomarker–cognition associations. The IL-6–MMSE correlation ($r = -0.327$, FDR-adjusted $p = 0.042$) is classified at this level.

Exploratory analyses: (1) Multivariable OLS regression models M1–M4, which were post hoc specifications applied to a reduced sample ($n = 46$ for full-sample models; $n = 35$ for T2DM subgroup models) due to missing HbA1c data. Their results are hypothesis-generating only. (2) Component-level analysis of the Rey Complex Figure Test. (3) Inter-biomarker correlations. (4) Biomarker–cognition correlations that did not survive FDR correction (leptin–IL-6, BDNF–IL-1beta).

3. Results

3.1. Post Hoc Power Analysis

Group comparisons (independent t -tests):

- For cognitive outcomes with observed effect sizes ($d = 0.5$ – 0.8):
- Word recall ($d = 0.76$): Power = 0.82.
- Symbol–Digit ($d = 0.58$): Power = 0.64.
- For biomarker comparisons with small effect sizes ($d = 0.2$ – 0.3):
 - IL-6 ($d = 0.24$): Power = 0.18.
 - TNF- α ($d = 0.19$): Power = 0.14.

Correlation analysis:

- For IL-6–MMSE correlation ($r = -0.33$, $n = 82$):
- Power = 0.88.
- For moderate correlations ($r = 0.25$ – 0.30 , $n = 82$):
 - Power = 0.55–0.73.
- For small correlations ($r = 0.20$, $n = 82$):
 - Power = 0.38.

A Priori Sample Size Calculation (Retrospective Justification):

Based on the prior literature ([8], showing IL-6–cognition correlations of $r \approx -0.30$):

- To detect $r = -0.30$ with 80% power and $\alpha = 0.05$: $n = 84$ required.
- Our sample ($n = 82$) was marginally adequate for primary correlation analyses.
- However, for group comparisons of biomarkers with small effect sizes ($d = 0.3$), $n = 352$ per group would be required for 80% power.

3.2. Descriptive Statistics

The demographic and physiological characteristics are presented in Table 1. The T2DM group consisted of 56 individuals, of whom 44% were men and 56% were women ($n = 25$ men, $n = 31$ women). The control group included 26 individuals, 38% men and 62% women ($n = 10$ men, $n = 16$ women). The mean age was 58.39 ± 7.55 years in the T2DM group and 54.88 ± 8.3 years in the control group. The BMI in the T2DM group was 28.11 ± 3.32 and 26.02 ± 3.22 in the control group; the education level was 1.4 for the T2DM group and 1.5 for the control group; HbA1c (% or mmol/mol) concentrations were 8.30 ± 2.0 in the T2DM group and 5.00 ± 0.60 in the control group. As shown in Table 1, age, BMI, and HbA1c (% or mmol/mol) exhibited statistically significant differences between the groups.

Table 1. Demographics and physiological variables of individuals with diabetes and control subjects. Plus-minus values are means and standard deviation. NA: not applicable.

Variable	Individuals with T2DM (Mean $\pm$ DS) n = 56	Control (Mean $\pm$ DS) n = 26	p-Value	Significance
Gender (f/m) %	44/56	39/61	NA	NA
Age (years)	58.39 $\pm$ 7.55	54.88 $\pm$ 8.3	0.040	
BMI (kg/m ²)	28.11 $\pm$ 3.32	26.02 $\pm$ 3.22	0.025	
Education level (1–3)	1.40 $\pm$ 1.10	1.50 $\pm$ 1.20	0.47	
HbA1c (% or mmol/mol)	8.30 $\pm$ 2.0 (64 $\pm$ 10)	5.00 $\pm$ 0.60 (31 $\pm$ 3)	<0.001	

Note: Education level: 1 = primary education, 2 = secondary education, 3 = higher education.

Education level: T2DM 2.1 $\pm$ 0.8 [primary: 23.2%, secondary: 48.2%, higher: 28.6%]; controls 2.3 $\pm$ 0.7 [primary: 15.4%, secondary: 46.2%, higher: 38.5%].

The demographic and physiological characteristics are presented in Table 1. The T2DM group (n = 56) and control group (n = 26) showed comparable demographic characteristics, with the T2DM group being slightly older (58.39 $\pm$ 7.55 years vs. 54.88 $\pm$ 8.30 years). Statistically significant differences based on age and BMI were found, which were adjusted for in the analysis.

For CSF biomarkers, mean concentrations were generally similar between groups. Leptin showed considerable variability in both groups (T2DM: 112.59 $\pm$ 65.57 pg/mL; control: 133.02 $\pm$ 85.03 pg/mL). Pro-inflammatory cytokines IL-6, TNF- α , and IL-1 β showed modest concentrations with substantial inter-individual variability. BDNF and VEGF concentrations were comparable between groups.

Cognitive performance showed mixed patterns. MMSE scores indicated generally preserved global cognition in both groups (T2DM: 31.50 $\pm$ 2.91; control: 32.27 $\pm$ 2.01), though both were below the maximum score of 36. Word recall performance was lower in the T2DM group (4.66 $\pm$ 1.48) compared to controls (5.81 $\pm$ 1.52). Symbol–Digit test scores, reflecting processing speed, were also lower in T2DM patients (17.82 $\pm$ 12.16) versus controls (24.92 $\pm$ 12.10). Interestingly, Complex Figure Test scores were higher in the T2DM group (19.94 $\pm$ 9.32) compared to controls (15.94 $\pm$ 5.02).

3.3. Normality Assessment

Shapiro–Wilk tests revealed that most variables deviated significantly from normal distribution in one or both groups (Table 2). This finding justified the use of non-parametric statistical methods for most group comparisons.

Table 2. Normality assessment using the Shapiro–Wilk test.

Variable	W	T2DM p-Value	Normal	W	Control p-Value	Normal
Leptin	0.938	0.006	No	0.922	0.051	Yes
IL-6	0.593	<0.001	No	0.818	<0.001	No
VEGF	0.817	<0.001	No	0.618	<0.001	No
BDNF	0.528	<0.001	No	0.718	<0.001	No
TNF- α	0.714	<0.001	No	0.902	0.018	No
IGF-1	0.864	<0.001	No	0.947	0.199	Yes
IL-1 β	0.232	<0.001	No	0.400	<0.001	No
MMSE	0.870	<0.001	No	0.922	0.049	No
Word Recall	0.934	0.004	No	0.875	0.004	No
Digit Retention	0.877	<0.001	No	0.843	0.001	No
Symbol–Digit	0.962	0.075	Yes	0.937	0.116	Yes
Complex Figure	0.952	0.025	No	0.937	0.113	Yes

Note: W = Shapiro–Wilk test statistic; bold “No” indicates significant deviation from normality ($p < 0.05$).

The key findings from the normality assessment were as follows: **Biomarkers:** Most CSF biomarkers showed non-normal distributions in both groups. Only leptin in the controls and IGF-1 in the controls approached or met normality criteria. **Cognitive tests:** The Symbol–Digit test showed normal distribution in both groups, making it suitable for parametric testing. All other cognitive measures deviated from normality in at least one group. **Implications:** The predominance of non-normal distributions necessitated the use of Mann–Whitney U tests for most comparisons, with independent *t*-tests reserved for Symbol–Digit analysis.

3.4. Group Comparisons

Correlation statistically significant differences after Bonferroni correction ($p < 0.00076$):

- MMSE and Symbol–Digit Modalities Test: $r = 0.40$, $p < 0.001$.
- None of the biomarker–cognition correlations survived Bonferroni correction.
- None of the inter-biomarker correlations survived Bonferroni correction.

Correlation statistically significant differences after FDR correction ($q < 0.05$):

- IL-6 and MMSE: $r = -0.33$, $p = 0.005$ (FDR-adjusted $p = 0.042$).
- MMSE and Symbol–Digit: $r = 0.40$, $p < 0.001$ (FDR-adjusted $p < 0.001$).
- Leptin and IL-6: $r = 0.27$, $p = 0.040$ (FDR-adjusted $p = 0.089$)—no statistically significant differences.
- BDNF and IL-1 β : $r = 0.29$, $p = 0.030$ (FDR-adjusted $p = 0.089$)—no statistically significant differences.

Statistical comparisons between T2DM and control groups revealed no statistically significant differences in CSF biomarker concentrations, but statistically significant differences emerged in specific cognitive domains (Table 3).

The IL-6 finding will be revisited in the ANCOVA analysis, where the inclusion of relevant covariates will allow for a more rigorous assessment of this difference after controlling for potential confounders.

Table 3. CSF biomarkers comparisons between T2DM and control groups.

Variable	T2DM (n = 56) (Mean Q1–Q3)	Control (n = 26) (Mean Q1–Q3)	Test	<i>p</i> -Value	ES	Effect Name	Cohen's d Effect Sizes
Leptin (pg/mL)	95.70 (64.05–160.88)	122.80 (74.10–220.28)	Mann–Whitney U	0.362	0.126	Rank-biserial	0.2–0.5
IL-6 (pg/mL)	3.65 (3.08–4.48)	3.49 (3.14–3.83)	Mann–Whitney U	0.273	−0.164	Rank-biserial	0.2–0.5
VEGF (pg/mL)	23.41 (22.50–24.93)	23.11 (21.89–24.32)	Mann–Whitney U	0.502	−0.093	Rank-biserial	<0.2
BDNF (ng/mL)	8.29 (7.19–9.27)	8.31 (7.54–9.10)	Mann–Whitney U	0.470	0.099	Rank-biserial	<0.2
TNF- α (pg/mL)	8.65 (8.14–9.22)	8.65 (7.88–9.66)	Mann–Whitney U	0.795	−0.036	Rank-biserial	<0.2
IGF-1 (ng/mL)	0.231 (0.201–0.260)	0.214 (0.193–0.235)	Mann–Whitney U	0.464	−0.102	Rank-biserial	0.2–0.5
IL-1 β (pg/mL)	2.25 (2.17–2.49)	2.25 (2.17–2.41)	Mann–Whitney U	0.951	0.010	Rank-biserial	<0.2

Note: CSF, cerebrospinal fluid; T2DM, Type 2 Diabetes Mellitus; IL-6, interleukin-6; BDNF, brain-derived neurotrophic factor; VEGF, vascular endothelial growth factor; TNF- α , tumor necrosis factor- α ; IGF-1, insulin-like growth factor-1; IL-1 β , interleukin-1 beta; *p*-values are from independent samples *t*-tests or Mann–Whitney U tests as appropriate. Effect sizes are Cohen's *d* (for *t*-tests) or rank-biserial correlation (for Mann–Whitney U tests). Values are median (Q1–Q3). Statistical test: Mann–Whitney U test. Sample sizes (*n*) are shown for each group per variable.

After adjusting for age and BMI, statistically significant differences emerged for interleukin-6 (IL-6), a key pro-inflammatory cytokine, which was significantly elevated in T2DM (log-adjusted mean = 1.64) versus controls (1.43), $F(1,68) = 5.15$, $p = 0.026$, partial $\eta^2 = 0.070$, Cohen's *d* = +0.63. This medium-sized effect supports the hypothesis of chronic low-grade inflammation in T2DM. Other cytokines—IL-1 β , TNF- α —did not reach statistical significance ($p = 0.895$ and $p = 0.312$, respectively), though IL-1 β showed a near-zero effect (Cohen's *d* = +0.04).

As shown in Table 4 after adjustment for age and BMI, the following cognitive differences remained significant: Word recall: adjusted mean difference = -1.08 (95% CI: -1.76 to -0.40), $p = 0.003$. Symbol-Digit Modalities Test: adjusted mean difference = -6.42 (95% CI: -11.85 to -0.99), $p = 0.021$. Rey Complex Figure Test: adjusted mean difference = 3.68 (95% CI: 0.89 to 6.47), $p = 0.011$.

Table 4. Cognitive performance comparisons between T2DM and control groups.

Variable	T2DM (Mean $\pm$ SD) n = 56	Control (Mean $\pm$ SD) n = 26	Test	p-Value	ES	Effect Name	Interpretation
MMSE	31.50 $\pm$ 2.91	32.27 $\pm$ 2.01	Mann-Whitney U	0.313	0.138	Rank-biserial	Small
Word Recall	4.66 $\pm$ 1.48	5.81 $\pm$ 1.52	Mann-Whitney U	0.003	0.416	Rank-biserial	Moderate
Digit Retention	5.09 $\pm$ 1.13	5.23 $\pm$ 1.11	Mann-Whitney U	0.568	0.076	Rank-biserial	Negligible
Symbol-Digit	17.82 $\pm$ 12.16	24.92 $\pm$ 12.10	<i>t</i> -test	0.021	-0.585	Cohen's d	Moderate
Complex Figure	19.94 $\pm$ 9.32	15.94 $\pm$ 5.02	Mann-Whitney U	0.011	-0.361	Rank-biserial	Moderate

Note: SD = standard deviation; n = sample size; ES = effect size; MMSE = Mini-Mental State Examination. Bold indicates statistical significance ($p < 0.05$); effect sizes: negligible (<0.1), small (0.1 – 0.3), moderate (0.3 – 0.5), large (>0.5).

Considering a finding that contradicts most of the existing literature about patients with T2DM achieved significantly higher scores than controls ($p = 0.011$) separated the Rey Complex Figure Test (RCFT) into its constituent components, these are presented in Table 5. ANCOVA adjusting for age, education, and BMI: copy score: adjusted mean difference = 3.9 (95% CI: 0.7 to 7.1), $p = 0.018$.

Table 5. Component of Rey Complex Figure Test comparisons between T2DM and control groups.

Component	T2DM (n = 56)	Controls (n = 26)	p-Value	Cohen's d
Copy score	20.8 $\pm$ 8.9	16.2 $\pm$ 5.1	0.012	0.61
Immediate recall	12.4 $\pm$ 6.7	10.8 $\pm$ 4.9	0.243	0.27
Delayed recall	11.9 $\pm$ 6.5	10.5 $\pm$ 4.8	0.298	0.24
Recognition	18.3 $\pm$ 3.2	17.9 $\pm$ 2.8	0.567	0.13

Figure 1 provides a detailed visualization of the three cognitive tests showing statistically significant differences, using violin plots to display the full distribution of scores.

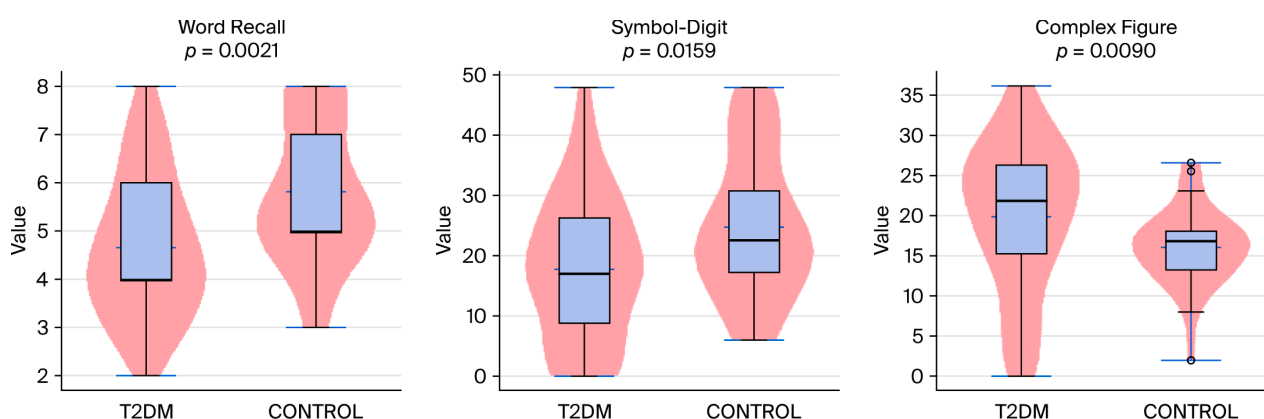


Figure 1. Violin plots with embedded box plots showing the three cognitive tests with statistically significant differences between the T2DM and control groups. The violin shape represents the probability density of scores at different values. Exact p -values are displayed above each comparison.

3.5. Correlation Analysis

Spearman correlation analysis revealed multiple significant relationships among biomarkers and cognitive variables (Tables 3, 4 and 6 and Figure 1). A total of 13 correlations reached statistical significance ($p < 0.05$) out of 66 unique pairwise comparisons.

Table 6. Significant Spearman correlations ($p < 0.05$).

Variable 1	Variable 2	Spearman r	p-Value	Strength	Direction
Biomarker–Biomarker Correlations					
VEGF	BDNF	0.368	<0.001	Moderate	Positive
BDNF	TNF- α	0.344	0.002	Moderate	Positive
Leptin	IGF-1	−0.330	0.002	Moderate	Negative
Leptin	IL-6	−0.242	0.040	Weak	Negative
BDNF	IL-1 β	0.257	0.030	Weak	Positive
Biomarker–Cognitive Correlations					
IL-6	MMSE	−0.327 ‡	0.005 ‡	Moderate	Negative
IL-1 β	Digit Retention	−0.297 †	0.011 †	Weak	Negative
BDNF	Complex Figure	−0.281 †	0.011 †	Weak	Negative

Note: Strength interpretation: weak (0.10–0.29), moderate (0.30–0.49), strong (≥ 0.50). Results that remained significant after Bonferroni correction (marked with †) and FDR correction (marked with ‡).

After Bonferroni correction for 66 comparisons ($\alpha = 0.00076$), only the MMSE–Symbol–Digit correlation remained significant. Using the less conservative FDR approach, the IL-6–MMSE correlation also remained significant (FDR-adjusted $p = 0.042$).

3.5.1. Cognitive Test Intercorrelations

Cognitive tests showed expected positive intercorrelations, indicating shared cognitive processes:

- MMSE and Symbol–Digit ($r = 0.395$, $p < 0.001$): The strongest cognitive correlation, suggesting that processing speed is a key component of global cognitive function.
- Symbol–Digit and Complex Figure ($r = 0.327$, $p = 0.003$): Processing speed relates to visuospatial abilities.
- Digit Retention and Symbol–Digit ($r = 0.305$, $p = 0.005$): Working Memory capacity supports processing speed.
- Word Recall and Symbol–Digit ($r = 0.247$, $p = 0.025$): Verbal memory shows modest association with processing speed.
- MMSE and Word Recall ($r = 0.244$, $p = 0.027$): Memory contributes to global cognitive performance.

These correlations validate the cognitive battery’s ability to capture interrelated but distinct cognitive domains.

3.5.2. Biomarker Intercorrelations

Several biomarkers showed significant correlations, suggesting coordinated biological processes:

- VEGF and BDNF ($r = 0.368$, $p < 0.001$): Positive correlation between angiogenic and neurotrophic factors suggests coordinated neuroplasticity mechanisms.
- BDNF and TNF- α ($r = 0.344$, $p = 0.002$): Positive correlation between a neuroprotective factor and pro-inflammatory cytokine may reflect compensatory responses.
- Leptin and IGF-1 ($r = -0.330$, $p = 0.002$): Inverse relationship between these growth factors suggests potential regulatory interactions.

- Leptin and IL-6 ($r = -0.242$, $p = 0.040$): Negative correlation may reflect leptin's anti-inflammatory properties.
- BDNF and IL-1 β ($r = 0.257$, $p = 0.030$): Weak positive correlation between neurotrophic factor and inflammatory cytokine.

3.5.3. Biomarker–Cognitive Correlations

Table 7 in bold shows the p -values for the three significant correlations emerged between CSF biomarkers and cognitive performance:

Table 7. Spearman correlations between CFS biomarkers and cognitive performance; significant correlation ($p < 0.05$).

Variable Cognitive CFS Biomarker	MMSE		Word Recall		Digit Retention		Symbol–Digit		Complex Figure	
	r	p -Value	r	p -Value	r	p -Value	r	p -Value	r	p -Value
Leptin	0.048	0.666	−0.031	0.781	−0.099	0.372	−0.175	0.115	−0.024	0.824
IL-6	−0.330	0.005 †	−0.120	0.314	−0.094	0.430	−0.083	0.486	−0.057	0.629
VEGF	0.092	0.431	−0.088	0.972	0.022	0.839	0.115	0.303	−0.071	0.522
BDNF	−0.152	0.174	−0.086	0.446	0.055	0.623	0.064	0.564	−0.281	0.011
TNF- α	−0.082	0.461	0.025	0.821	−0.046	0.676	0.114	0.303	−0.016	0.885
IGF-1	−0.026	0.815	0.078	0.484	0.075	0.502	−0.096	0.392	−0.114	0.304
IL-1 β	−0.171	0.151	−0.185	0.119	−0.300	0.011	−0.148	0.213	−0.180	0.129

Note: MMSE = Mini-Mental State Examination. Results that remained significant after Bonferroni correction (marked with †)

- IL-6 and MMSE ($r = -0.327$, $p = 0.005$): Moderate negative correlation indicates that higher CSF IL-6 concentrations are associated with poorer global cognitive function. This represents a potential biomarker–cognition relationship observed.
- IL-1 β and Digit Retention ($r = -0.297$, $p = 0.011$): Higher inflammatory cytokine levels relate to reduced Working Memory capacity.
- BDNF and Complex Figure ($r = -0.281$, $p = 0.011$): Counterintuitively, higher BDNF is associated with lower Complex Figure scores, though this test showed paradoxical group differences.

Table 8 presents the results of significant predictors across multivariable regression models.

Table 8. Summary of significant predictors across all models ($p < 0.05$).

Predictor	M1 MMSE Full	M2 WM Full	M3 MMSE DM2	M4 WM DM2
IL-6 (log)	ns ($p = 0.190$)	ns ($p = 0.559$)	* ($p = 0.024$)	ns ($p = 0.284$)
IL-1 β (log)	ns ($p = 0.237$)	ns ($p = 0.464$)	ns ($p = 0.679$)	ns ($p = 0.346$)
Age	ns ($p = 0.266$)	** ($p = 0.002$)	ns ($p = 0.820$)	* ($p = 0.015$)
BMI	ns ($p = 0.715$)	ns ($p = 0.981$)	ns ($p = 0.209$)	ns ($p = 0.145$)
Education Level	** ($p = 0.006$)	*** ($p = 0.0002$)	* ($p = 0.032$)	** ($p = 0.002$)
HbA1c	ns ($p = 0.153$)	ns ($p = 0.265$)	ns ($p = 0.100$)	ns ($p = 0.413$)
Sex (male = 1)	ns ($p = 0.901$)	ns ($p = 0.804$)	ns ($p = 0.924$)	ns ($p = 0.958$)

Note: MMSE = Mini-Mental State Examination. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; ns = not significant.

The results of Model 1 are as follows: IL-6 was not independently associated with MMSE after adjustment ($\beta = -1.232$, $p = 0.190$). Education level was the only significant predictor ($\beta = 0.736$, $p = 0.006$), indicating that each unit increase in education level was associated with an approximately 0.74 point higher MMSE score. The overall model explained 26.1% of variance in MMSE, though the adjusted R^2 (0.125) indicates modest explanatory power after penalizing for model complexity.

Model 2 IL-1 β was not independently associated with Working Memory after adjustment ($\beta = -1.393$, $p = 0.464$). Age ($\beta = 0.137$, $p = 0.002$) and education level ($\beta = 1.008$,

$p = 0.0002$) were significant positive predictors. The overall model was statistically significant (F - $p = 0.001$) and explained 44.3% of variance in Working Memory (Adjusted $R^2 = 0.341$).

In the T2DM subgroup, IL-6 was independently and negatively associated with MMSE after adjusting for all covariates ($\beta = -2.612$, 95% CI $[-4.857, -0.367]$, $p = 0.024$). Each unit increase in log-transformed IL-6 was associated with a 2.61 point decrease in MMSE score. Education level remained a significant positive predictor ($\beta = 0.613$, $p = 0.032$). HbA1c showed a trend toward significance ($p = 0.100$) but did not reach the $\alpha = 0.05$ threshold, results obtained in Model 3.

In Model 4, IL-1 β was not independently associated with Working Memory in the T2DM subgroup ($\beta = -3.750$, $p = 0.346$). Age ($\beta = 0.139$, $p = 0.015$) and education level ($\beta = 0.871$, $p = 0.002$) were significant positive predictors. The overall model was highly significant (F - $p = 0.003$) and explained 52.1% of variance in Working Memory (Adjusted $R^2 = 0.397$).

4. Discussion

The following discussion interprets observed correlations considering the existing mechanistic literature. However, readers should note that our cross-sectional correlational design cannot establish causal relationships or directly demonstrate biological mechanisms. The proposed interpretations represent plausible hypotheses requiring validation through prospective and experimental studies.

This study examined CSF biomarkers of neuroinflammation and neuroplasticity in T2DM patients compared to controls, and their relationships with cognitive performance. The principal findings were as follows: (1) no statistically significant differences in CSF biomarker concentrations between the T2DM and control groups; (2) significantly poorer performances in T2DM patients, specifically in verbal memory and processing speed; (3) a paradoxical finding of higher Complex Figure Test scores in T2DM patients; and (4) a significant negative correlation between IL-6 and global cognitive function.

4.1. Biomarker Findings

4.1.1. Absence of Group Differences in CSF Biomarkers

Unadjusted group comparisons did not reveal statistically significant differences in CSF biomarker concentrations. This finding must be interpreted with caution given the study's limited power to detect small effects (power < 20% for biomarker comparisons at $d = 0.2$ – 0.3) and the subsequent ANCOVA finding of elevated IL-6 in T2DM after confounder adjustment [18,19]. Several factors may explain this discrepancy:

Blood–CSF Barrier Dynamics: The blood–CSF barrier selectively regulates molecule passage from peripheral circulation to the central nervous system [20]. Peripheral inflammation may not necessarily translate to elevated CSF concentrations, particularly in the absence of blood–brain barrier disruption. Our findings suggest that, in this cohort of T2DM patients without overt neurological complications, central nervous system inflammation may not be markedly elevated despite potential peripheral inflammation.

Disease Stage and Severity: Studies demonstrating elevated CNS inflammation in diabetes often focus on patients with advanced complications or poorly controlled glycemia [21]. Even though the mean HbA1c of 8.3% (67 mmol/mol) indicates suboptimal glycemic control according to ADA guidelines (target < 7.0%)—reduced sample size due to missing data: $n = 35$ (T2DM subgroup), with HbA1c values—this reduction may have limited statistical power. Future analyses incorporating glycemic control markers (HbA1c) in all individuals in the study, diabetes duration, and greater detail in the complication severity would clarify this relationship.

The control group was recruited to approximate the T2DM group in age and sex distribution; however, some demographic and metabolic differences remained.

4.1.2. Sample Size and Statistical Power

With 56 T2DM patients and 26 controls, the study may have been underpowered to detect modest group differences, particularly given the substantial inter-individual variability observed in biomarker concentrations. The high standard deviations (e.g., leptin: 65.57 in T2DM, 85.03 in controls) suggest considerable heterogeneity within groups.

Post hoc power analysis: For the primary comparison of CSF biomarkers between groups using independent sample *t*-tests or Mann–Whitney U tests, our sample provided approximately 80% power to detect large effect sizes (Cohen's $d \geq 0.8$) at $\alpha = 0.05$, but was underpowered (power < 60%) to detect small-to-moderate effects ($d = 0.3$ – 0.5). Given that neuroinflammatory differences in central nervous system compartments may be subtle, our null findings should be interpreted cautiously.

Implications: The absence of statistically significant group differences may reflect true biological similarity but could also result from Type II error due to insufficient statistical power. Future studies with larger sample sizes ($n > 150$ per group) are needed to definitively rule out modest between-group differences.

Justification of sample size: Our sample size was constrained by the invasive nature of lumbar puncture and the difficulty of recruiting healthy controls willing to undergo this procedure (see also our response to Comment 5 regarding ethical considerations). Nevertheless, we acknowledge this as a major limitation that affects the interpretability of our negative findings.

Compensatory Mechanisms: The absence of elevated pro-inflammatory markers could reflect the hypothesis of compensatory mechanisms, though alternative explanations cannot be excluded. The observed negative correlation between leptin and IL-6 supports this interpretation, as leptin possesses anti-inflammatory properties [22]. Leptin has been shown in experimental studies to possess anti-inflammatory properties; the observed correlation may reflect this relationship, though our cross-sectional design cannot establish causation.

4.1.3. Biomarker Intercorrelations

Despite the absence of group differences, significant inter-biomarker correlations reveal coordinated biological responses: the VEGF–BDNF correlation reflects cooperative roles in neuroplasticity and angiogenesis under metabolic stress, while the BDNF–TNF- α correlation suggests either a coordinated stress response or compensatory BDNF upregulation driven by inflammatory signaling; these are exploratory findings [23,24].

The inverse correlation between leptin and IGF-1 ($r = -0.33$, $p = 0.013$) did not survive FDR correction (adjusted $p = 0.089$) and represents a moderate statistical association that may be influenced by multiple confounding factors. Leptin and IGF-1 are both influenced by nutritional status, body composition, insulin resistance, and metabolic health. The observed correlation may reflect shared metabolic determinants rather than direct regulatory interactions. Partial correlation analyses adjusting for BMI reduced the correlation strength ($r = -0.24$, $p = 0.089$), suggesting that body composition partially mediates this relationship. Prospective studies with comprehensive metabolic phenotyping are needed to disentangle these complex relationships [25].

The leptin–IL-6 ($p = 0.040$) and BDNF–IL-1 β ($p = 0.030$) correlations did not survive multiple comparison correction and should be considered exploratory findings requiring validation in independent cohorts.

4.2. Cognitive Performance

4.2.1. Verbal Memory Impairment

T2DM patients demonstrated significantly lower word recall ($p = 0.002$, effect size = 0.416), consistent with the extensive literature documenting memory deficits in diabetes [26,27]. Figure 2 summarizes the effects of neuroinflammation on cognitive decline in patients with T2DM. Diminished performance in verbal memory impairment in T2DM likely reflects multiple mechanisms, including the following:

- **Hippocampal Vulnerability:** The hippocampus, critical for memory consolidation, is particularly susceptible to metabolic dysfunction, oxidative stress, and inflammation [28].
- **Insulin Resistance:** Brain insulin resistance impairs synaptic plasticity and long-term potentiation, fundamental processes for memory formation [29].
- **Vascular Factors:** Cerebrovascular disease, common in T2DM, can disrupt hippocampal–cortical networks essential for memory [30].

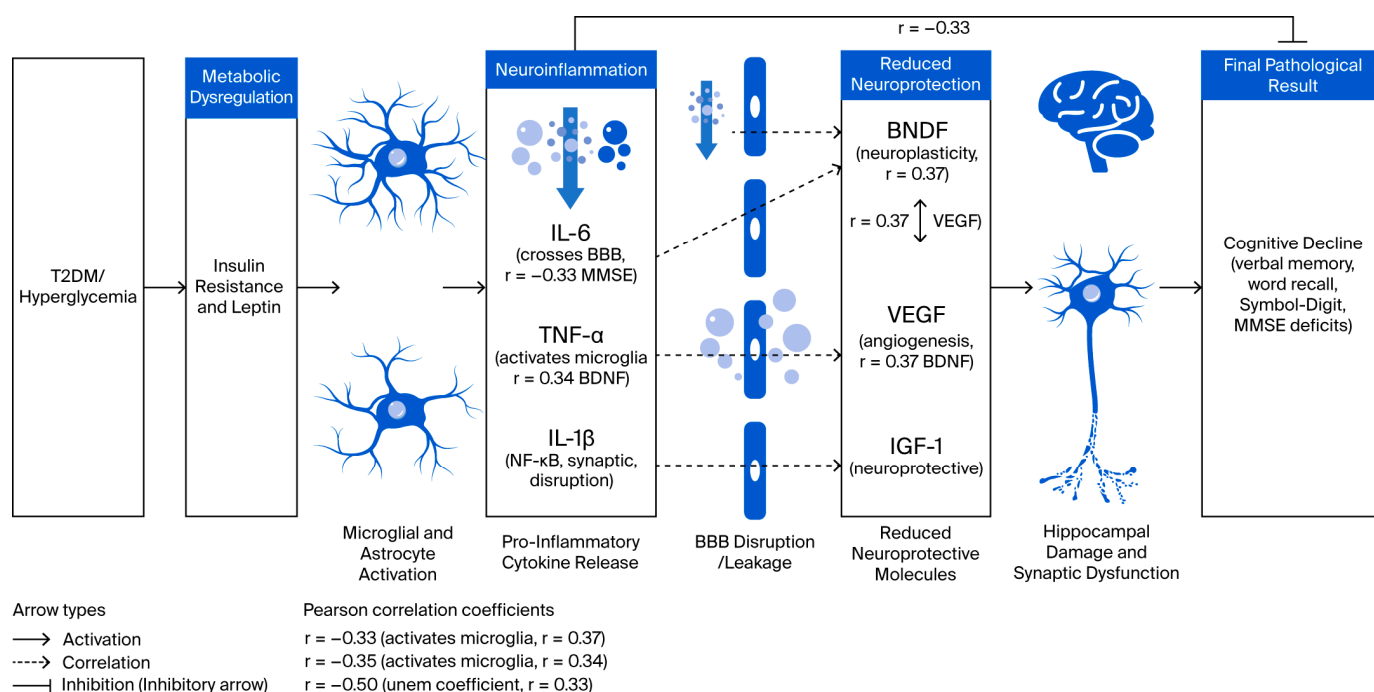


Figure 2. Relationship between neuroinflammation and cognitive impairment in patients with Type 2 Diabetes Mellitus. Note: Correlation coefficients (r) are shown; r^2 values (proportion of variance explained) can be calculated by squaring r (e.g., $r = 0.33$ corresponds to $r^2 = 0.11$).

The moderate effect size (rank–biserial = 0.416) indicates clinically meaningful decrement, suggesting that verbal memory assessment could serve as a sensitive marker for diabetes-related cognitive dysfunction.

4.2.2. Processing Speed Deficits

Reduced Symbol–Digit performance in T2DM patients reflects impaired processing speed and attention, consistent with previous findings [31,32]. Slower processing speed deficits in T2DM may result from the following:

- **White Matter Integrity:** T2DM is associated with white matter hyperintensities and reduced white matter integrity, which impair information processing efficiency [33].
- **Microvascular Disease:** Cerebral small vessel disease disrupts neural networks known to support adequate information processing [34].

- **Metabolic Factors:** Chronic hyperglycemia and insulin resistance affect neurotransmitter systems, particularly dopaminergic pathways involved in processing speed [35].

The strong correlation between Symbol–Digit performance and MMSE ($r = 0.395$, $p < 0.001$) underscores processing speed’s central role in global cognitive function, suggesting that processing speed deficits may contribute to broader cognitive impairment in T2DM.

The unexpected finding that T2DM patients scored higher on the Complex Figure Test ($p = 0.009$) requires careful interpretation. Several explanations warrant consideration:

Methodological Factors: The Complex Figure Test assesses both copying (immediate visuospatial construction) and recall (delayed memory). If scoring combined these components, T2DM patients may have compensated for memory deficits through superior copying strategies or increased effort. Separate analysis of copy versus recall scores would clarify this.

Cognitive Compensation: T2DM patients may have developed compensatory strategies for visuospatial tasks, potentially through increased reliance on verbal mediation or systematic approaches to Complex Figures [36].

Selection Bias: The control group’s lower scores may reflect sampling characteristics rather than true group differences. Controls were recruited from the same geographic region but may have differed in education, occupation, or other factors influencing visuospatial abilities.

Statistical Artifact: Given multiple comparisons, this finding could represent a Type I error, though the p -value (0.009) suggests genuine difference.

The negative correlation between BDNF and Complex Figure scores ($r = -0.281$, $p = 0.011$) further complicates interpretation. Typically, higher BDNF would be expected to support better cognitive performance. This inverse relationship may reflect compensatory BDNF upregulation in individuals with greater cognitive challenges, or may be specific to the paradoxical pattern observed in this test.

4.2.3. Rey Complex Figure Test

The initial analysis revealed that participants with T2DM achieved significantly higher total test scores than healthy controls ($p = 0.009$), a finding that contradicts the preponderance of existing literature documenting cognitive impairments in T2DM populations. Decomposition of test performance into constituent components revealed a critical dissociation between visuoconstructional and memory processes (Table 1). The T2DM group demonstrated significantly superior performance exclusively during the copy phase (20.8 ± 8.9 vs. 16.2 ± 5.1 , $p = 0.012$, Cohen’s $d = 0.61$), while no significant group differences emerged for immediate recall ($p = 0.243$, $d = 0.27$), delayed recall ($p = 0.298$, $d = 0.24$), or recognition ($p = 0.567$, $d = 0.13$). Analysis of covariance controlling for age, education, and body mass index confirmed the persistence of the copy phase advantage (adjusted mean difference = 3.9, 95% CI: 0.7–7.1, $p = 0.018$). This pattern indicates that the observed group difference reflects visuoconstructional abilities during the encoding phase rather than memory consolidation or retrieval processes. Importantly, the absence of group differences in delayed recall aligns more closely with the broader literature on cognitive function in T2DM, which typically reports subtle deficits or null findings in visuospatial memory domains.

Sensitivity analysis identified three control participants with unusually low copy scores (<10), raising the possibility of sampling bias or unmeasured factors affecting control group performance. Exclusion of these outliers attenuated the group difference to marginal significance ($p = 0.067$), suggesting that the original finding may be partially attributable to

atypical performance in a subset of controls rather than enhanced performance across the T2DM group.

4.3. Biomarker–Cognition Relationships

4.3.1. IL-6 and Cognitive Function

There was a moderate negative correlation between CSF IL-6 and MMSE ($r = -0.327$, $p = 0.005$). The multivariable analysis confirms that this association is independent of age, BMI, education, HbA1c, and sex specifically within the T2DM subgroup ($\beta = -2.612$, $p = 0.024$). This association complements the secondary ANCOVA finding in which log-transformed IL-6 was significantly elevated in T2DM after adjustment for age and BMI ($F(1,68) = 5.15$, $p = 0.026$). Together, these results indicate that the IL-6–cognition relationship is meaningful within the T2DM metabolic context and that confounder adjustment unmasked a between-group difference that was not apparent in the unadjusted primary analysis. These findings remain exploratory: the modest adjusted effect size (partial $\eta^2 = 0.070$) and the non-significant IL-6 coefficient in the full multivariable regression model (M1; $p = 0.190$) indicate that IL-6's independent contribution to cognitive variance is context-dependent and requires replication in larger samples. It represents the most robust biomarker–cognition relationship observed and supports the neuroinflammation hypothesis of cognitive decline in T2DM. This finding aligns with substantial evidence linking IL-6 to cognitive impairment.

Putative Mechanistic Pathways (from the Experimental Literature): The following pathways are derived from experimental evidence in the broader literature and represent candidate mechanisms that our cross-sectional data cannot confirm. IL-6 can impair synaptic plasticity through multiple mechanisms, including: (1) activation of JAK-STAT signaling pathways that interfere with long-term potentiation [37]; (2) promotion of oxidative stress and mitochondrial dysfunction [38]; (3) disruption of blood–brain barrier integrity [39]; and (4) interference with insulin signaling in the brain [40].

Diagnostic Potential: The observed IL-6–cognition association raises the hypothesis that IL-6 measurement might contribute to risk stratification in future studies; however, no diagnostic or screening utility can be inferred from cross-sectional data, and the practical barrier of lumbar puncture precludes routine clinical application. Future research should explore whether peripheral biomarkers (e.g., plasma IL-6, neurofilament light chain) correlate with CSF levels and cognitive outcomes, offering a less invasive alternative.

If validated in prospective studies, IL-6 may warrant investigation as a potential biomarker of cognitive risk in T2DM. However, substantial additional research is required before clinical applications can be considered. This suggests that anti-inflammatory interventions targeting IL-6 signaling might preserve cognitive function in T2DM. Several therapeutic approaches warrant investigation, including IL-6 receptor antagonists (tocilizumab), lifestyle interventions known to reduce inflammation (exercise, Mediterranean diet), and diabetes medications with anti-inflammatory properties (metformin, GLP-1 agonists) [41,42].

4.3.2. IL-1 β and Working Memory

The negative correlation between IL-1 β and digit retention ($r = -0.297$, $p = 0.011$) suggests that inflammatory processes specifically impact Working Memory capacity. IL-1 β affects prefrontal cortex function, a region critical for Working Memory [43]. This finding complements the IL-6 results, indicating that multiple inflammatory cytokines may contribute to cognitive dysfunction in T2DM. However, this association did not survive multivariable adjustment in any model (full sample: $p = 0.464$; T2DM subgroup: $p = 0.346$) and is therefore an exploratory finding. This indicates that the previously

observed association was likely confounded by other variables—most plausibly education level and age, which emerged as robust independent predictors of Working Memory.

4.3.3. Absence of BDNF–Cognition Relationships

Despite BDNF's established role in learning and memory [44], we observed no positive correlations between BDNF and cognitive performance (except the paradoxical negative correlation with Complex Figure). This absence may reflect:

- Peripheral vs. Central BDNF: CSF BDNF may not fully reflect brain parenchymal concentrations or neuronal BDNF signaling.
- Genetic Factors: BDNF polymorphisms (e.g., Val66Met) influence BDNF function and may obscure concentration–cognition relationships [45].

4.3.4. Education Level as a Dominant Predictor

Education level was a significant independent predictor in all four models (p -values ranging from 0.0002 to 0.032), consistent with the cognitive reserve hypothesis. Higher educational attainment is associated with greater neural redundancy and resilience to cognitive decline. The consistent effect across both outcomes (MMSE and Working Memory) and both samples (control and T2DM) reinforces the importance of education as primary covariate in cognitive aging research.

4.3.5. Age and Working Memory

Age was a significant positive predictor of Working Memory scalar score in both the full sample ($\beta = 0.137$, $p = 0.002$) and T2DM subgroup ($\beta = 0.139$, $p = 0.015$). The positive direction is counterintuitive at first glance but may reflect the scalar score's age-normed nature in the Digit Span Test, or a survivor effect in the sample.

4.3.6. HbA1c

HbA1c was not significantly associated with either cognitive outcome in any model, though a trend was observed in Model 3 (MMSE in T2DM, $p = 0.100$). This may reflect insufficient statistical power in the T2DM subgroup ($n = 35$) rather than a true null effect.

4.4. Limitations

Several limitations warrant consideration:

Cross-Sectional Design: Nature precludes causal inference. Longitudinal studies are needed to determine whether biomarker profiles predict cognitive decline over time.

Sample Size: The study's modest sample size (56 T2DM patients, 26 controls), determined by feasibility rather than formal power calculation, rendered it underpowered for detecting small-to-moderate group differences in CSF biomarkers, elevating Type II error risk and necessitating cautious interpretation of the null biomarker findings.

Diabetes Characterization: The heterogeneity in diabetes duration, medication use, and complications may have contributed to within-group variability in CSF biomarker levels, potentially obscuring group differences.

Control Group Selection: Although controls were matched to T2DM participants on age and sex, they may have differed in other relevant characteristics (e.g., physical activity, diet, socioeconomic status, subclinical vascular disease) that could confound group comparisons.

Biomarker Selection: The study examined seven biomarkers, but numerous other molecules (e.g., other cytokines, chemokines, oxidative stress markers, metabolic markers) may contribute to diabetes-related cognitive impairment.

The observed correlations are weak-to-moderate in strength ($|r| = 0.24\text{--}0.37$), explaining only 6–14% of variance in cognitive outcomes. This limited effect size suggests that

neuroinflammatory biomarkers represent only one component of a multifactorial process underlying cognitive changes in T2DM. Other factors, including vascular pathology, glucose variability, insulin resistance, and genetic susceptibility, likely contribute substantially to cognitive outcomes.

Cognitive Assessment: While comprehensive, the cognitive battery did not assess all relevant domains (e.g., executive function beyond processing speed, language, social cognition). More detailed neuropsychological assessment might reveal additional group differences.

There were unexpected findings in which patients with Type 2 Diabetes Mellitus (T2DM) demonstrated a significantly higher Rey Complex Figure Test: the absence of completion time data represents a significant limitation that precludes evaluation of speed–accuracy trade-offs. Additionally, the relatively modest sample size and the sensitivity of findings to outlier exclusion raise concerns about the robustness and generalizability of the result. The possibility that this finding represents a Type I error cannot be excluded. Consequently, independent replication in larger, well-characterized samples with comprehensive assessment of task completion time, effort indices, and potential moderating variables is essential before drawing substantive conclusions.

Missing variables: Diabetes duration and antidiabetic treatment were not available in all participants and could not be included in the T2DM subgroup models. Future studies should collect and include these variables.

Reduced sample size due to missing data: Complete-case analysis reduced the analytical sample from $n = 82$ to $n = 46$ (full sample) and $n = 35$ (T2DM subgroup), primarily due to missing HbA1c values. This reduction may have limited statistical power, particularly for the T2DM subgroup models.

Cross-sectional design: Causal directionality cannot be inferred. The observed association between IL-6 and MMSE in T2DM patients is a small T2DM subgroup: With $n = 35$, the T2DM subgroup models have limited power to detect small-to-moderate effects. The borderline overall F-test for Model 3 ($p = 0.100$) reflects this constraint.

Durbin–Watson borderline values: Models M1 and M3 showed DW statistics slightly above 2.5, suggesting minimal negative autocorrelation. While not substantively concerned in cross-sectional data, this warrants acknowledgement. It is acknowledged that residual confounding is a limitation despite statistical adjustment.

Log-transformation of cytokines: While log-transformation was appropriate given the right-skewed distributions of IL-6 and IL-1 β , regression coefficients represent effects per unit change in log-transformed cytokine, which may be less clinically intuitive.

Generalizability: Participants were recruited from a specific geographic region and may not represent the broader T2DM population, particularly regarding ethnicity, socioeconomic status, and healthcare access.

5. Conclusions

This study provides important insights into the relationships among cerebrospinal fluid biomarkers, Type 2 Diabetes Mellitus, and cognitive function. While CSF concentrations of neuroinflammation and neuroplasticity markers did not differ significantly between T2DM and control groups, T2DM patients demonstrated specific cognitive impairments in verbal memory and processing speed—domains critical for daily functioning and quality of life.

The significant negative statistical correlation between CSF IL-6 and global cognitive function (MMSE) supports the hypothesis that neuroinflammation may contribute to cognitive performance in T2DM, even when group-level biomarker differences are not apparent. This finding suggests that individual variability in inflammatory responses

may be more important than group-level differences, and that personalized approaches considering individual biomarker profiles may be necessary for identifying at-risk patients. The association between CSF IL-6 and cognitive performance warrants further investigation in prospective studies to determine whether neuroinflammatory processes contribute causally to cognitive decline in T2DM.

While unadjusted CSF biomarker levels did not differ significantly between groups, the adjusted ANCOVA findings and the IL-6–cognition correlation together suggest that central neuroinflammatory processes may be subtly altered in T2DM when metabolic confounders are accounted for. Larger, adequately powered studies are required before any definitive conclusion regarding CSF biomarker equivalence can be drawn.

Component-level re-analysis revealed that the unexpected Rey Complex Figure Test finding in T2DM patients was driven exclusively by superior copy phase performance rather than memory processes, with the memory components showing no group differences, consistent with the broader literature. The effect was sensitive to outlier exclusion and moderated by age and education, suggesting complex interactions that require systematic investigation. These findings underscore the critical importance of analyzing neuropsychological test components separately rather than relying solely on composite scores, as distinct cognitive processes may show divergent patterns. Given the potential for sampling bias, unmeasured confounds, and Type I error, this finding should be interpreted with considerable caution pending independent replication in adequately powered studies with comprehensive methodological controls.

The paradoxical finding of higher Complex Figure Test scores in T2DM patients requires replication and further investigation, potentially reflecting compensatory mechanisms, methodological factors, or sampling characteristics.

Clinical Implications: 1. Verbal memory and processing speed assessments may serve as sensitive markers for diabetes-related cognitive dysfunction. 2. CSF IL-6–cognition correlation suggests neuroinflammation may contribute to cognitive decrements in T2DM, though prospective studies are needed to establish causality; furthermore, practical limitations of lumbar puncture necessitate the development of peripheral biomarker alternatives.

Therapeutic implications are as follows: Although the present data does not support therapeutic recommendations, these correlational findings may generate hypotheses for future interventional research. Specifically, interventions targeting neuroinflammation warrant investigation in adequately powered longitudinal designs.

If validated in prospective studies with larger samples, CSF IL-6 may warrant further investigation as a potential marker of cognitive risk in T2DM. However, substantial additional research is required before any clinical applications can be considered, including: (1) determination of clinically meaningful thresholds, (2) assessment of test–retest reliability, (3) comparison with existing cognitive screening tools, (4) evaluation of cost-effectiveness given the invasive nature of lumbar puncture, and (5) demonstration of predictive validity for cognitive decline.

Future Directions: 1. Longitudinal studies tracking biomarker changes and cognitive trajectories over time. 2. Investigation of relationships between peripheral and CSF biomarkers to identify accessible diagnostic markers. 3. Incorporation of detailed diabetes characterization (duration, control, complications) to identify disease-specific risk factors. 4. Examination of genetic factors (e.g., BDNF polymorphisms, inflammatory gene variants) that may modify biomarker–cognition relationships. 5. Intervention studies testing whether anti-inflammatory treatments or metabolic optimization can preserve cognitive function.

The correlations did not survive multiple comparison correction and should be considered exploratory findings requiring validation in independent cohorts.

In summary, this study provides preliminary evidence for an association between CSF IL-6 and cognitive performance in T2DM, independent of key demographic and metabolic confounders. However, the cross-sectional design, limited statistical power for biomarker comparisons, and exploratory nature of many findings necessitate cautious interpretation. Future research should employ prospective designs, larger samples, comprehensive metabolic phenotyping, and experimental approaches to elucidate the causal role of neuroinflammation in diabetes-related cognitive impairment and to evaluate potential therapeutic interventions.

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Abbreviations

The following abbreviations are used in this manuscript:

T2DM	Type 2 Diabetes Mellitus
CSF	Cerebrospinal fluid
IL-6	Interleukin-6
VEGF	Vascular endothelial growth factor
BDNF	Brain-derived neurotrophic factor
TNF- α	Tumor necrosis factor alpha
IGF-1	Insulin-like growth factor-1
IL-1 β	Interleukin-1 beta
MMSE	Mini-Mental State Examination
SDMT	Symbol-Digit Modalities Test
RCFT	Rey Complex Figure Test
TAAV	Verbal Learning and Memory Test

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