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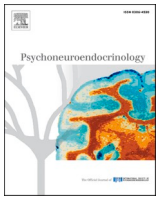

Diurnal cortisol cycle and cognitive performance in older people with Type 2 diabetes

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ABSTRACT

In older adults with Type 2 Diabetes (T2D), hypothalamic-pituitary-adrenal (HPA) axis dysregulation accompanied by cognitive impairment has been reported. While the impact of HPA function on declarative memory (DM), working memory (WM), and executive function (EF) has received increased attention in aging research, its role in T2D remains largely unexplored. This study compared diurnal cortisol patterns and cognitive performance between 51 patients with T2D treated with oral antidiabetic medications, injectable therapies, or a combination of both, and 51 healthy controls matched for age, sex, educational level and, body mass index. Participants completed a battery of neuropsychological tests and the Beck Depression Inventory (BDI-II). Additionally, they provided four saliva samples per day across two weekdays to assess the cortisol awakening response (CAR) and the diurnal cortisol slope (DCS). Group comparisons (T2D vs. controls) and moderation analyses were conducted to assess group differences and the associations between cortisol indices and cognitive performance, with group or depression included as moderators. T2D patients showed poorer performance than healthy controls, particularly on DM and WM, but no significant differences in CAR or DCS. In controls, a higher CAR was related to lower Stroop interference, although no significant relationships were found in T2D patients. Across the entire sample, CAR was negatively associated with Stroop interference at low and moderate depression levels, while DCS was positively associated with RAVLT delayed recall at low levels of depression. Our results indicate that medically treated T2D patients show poorer cognitive performance than healthy controls; however, cortisol does not seem to contribute to these cognitive deficits. These findings add to the limited literature on the impact of the HPA on cognitive function in T2D older adults, and they encourage future studies to delve into the mechanisms that could influence cognitive performance in this population, as well the relevance of depression in these cognitive deficits.

1. Introduction

Type two diabetes (T2D) has become one of the most important public health problems of the 21st century worldwide (Hu et al., 2018). Along with other noncommunicable diseases (NCDs), it represents an emerging global health threat that requires early detection and prevention (Jones and Gwenin, 2021). T2D is a chronic metabolic condition characterized by impaired glucose regulation and persistent hyperglycemia, leading to both micro and macrovascular complications (Biessels et al., 2017). In turn, hyperglycemia has been linked to diminished feedback regulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, and evidence suggests that T2D is associated with HPA axis hyperactivation and increased cortisol release (Sharma et al., 2020).

Cognitive consequences of T2D have been well documented. Although meta-analyses often report small effect sizes (Sola et al., 2024), declines across several domains—including verbal memory and executive function—have been observed among T2D participants compared to controls (aged 50–85 years) (Chung et al., 2015). T2D has been

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associated with cognitive deficits (Antal et al., 2022; Damanik and Yunir, 2021), mild cognitive impairment (MCI), and Alzheimer's disease (AD) (Kim, 2019). Structural brain changes (Bruehl et al., 2009; Den Heijer et al., 2003; Ho et al., 2013; Du et al., 2021) and reduced cognitive performance (Bruehl et al., 2009; Milne et al., 2018; Yau et al., 2014) have been reported in T2D, with meta-analyses showing small to moderate deficits in attention, memory, processing speed, and executive function (Palta et al., 2014; Pelimanni and Jehkonen, 2019; Sadanand et al., 2016; Vincent and Hall, 2015).

However, the underlying mechanisms of the relationship between T2D and cognition remain unclear (Marissal-Arvy and Moisan, 2022). Given the known relationship between stress, cognition, and metabolic dysfunction, HPA axis dysregulation has been proposed as a contributor to cognitive impairment in T2D (Johar et al., 2016; Joseph and Golden, 2017). In healthy individuals, altered HPA axis activity is associated with poorer cognition (Gardner et al., 2019; Lupien et al., 2005; Almela et al., 2012; Hidalgo, et al., 2016), raising interest in cortisol dynamics among T2D populations (Seal and Turner, 2021; Sunena and Mishra, 2022).

Normally, cortisol follows a circadian rhythm characterized by post-awakening cortisol rise, peaking within 30–45 min, known as the cortisol awakening response (CAR), and a gradual decline throughout the day to reach its lowest levels in the evening. The difference in cortisol levels from morning to evening allows for the calculation of the Diurnal Cortisol Slope (DCS) (Adam et al., 2017). In T2D, findings on HPA axis markers are inconsistent, some studies have reported a flattened CAR compared to healthy controls (Bruehl et al., 2009; Lederbogen et al., 2011; Panagiotou et al., 2021), whereas Johar et al. (2016) and Hackett et al. (2014) reported no differences. Similarly, results on DCS are mixed: some studies observed a blunted slope in T2D patients (Lederbogen et al. (2011); Hackett et al.,(2014), while Bruehl et al. (2009) found no differences between T2D individuals and healthy controls.

Therefore, despite evidence of cognitive impairment and HPA axis dysregulation in T2D, the relationship between diurnal cortisol indexes (CAR and DCS) and cognitive performance remains poorly understood. Findings across studies are inconsistent, and few have examined these associations specifically in older adults with T2D. To our knowledge, only one study reported significant associations between higher fasting cortisol levels and poorer WM and processing speed in older adults with T2D, although without healthy controls for comparison (Reynolds et al., 2010). Understanding how cortisol rhythms relate to cognitive performance in older adults with T2D is crucial for identifying mechanisms that contribute to dementia risk and for informing prevention strategies.

Older adults represent a particularly vulnerable population. They are at higher risk of both T2D and age-related cognitive decline, and the interaction between metabolic and neuroendocrine dysregulation may accelerate cognitive impairment in this group. Importantly, depression—a common comorbidity in T2D (Zanoveli et al., 2016)—may further influence cortisol–cognition associations, but its moderating role has not been systematically examined.

The present study aimed to test whether the diurnal cortisol cycle differs between older adults with T2D and matched healthy controls, and whether T2D participants show poorer cognitive performance. Specifically, we analyzed the associations between CAR and DCS and three cognitive domains—declarative memory (DM), working memory (WM), and executive function (EF). Based on prior evidence, we expected T2D participants to show a flatter CAR (Bruehl et al., 2009; Panagiotou et al., 2021; Lederbogen et al., 2011) and DCS (Hackett et al., 2014; Lederbogen et al., 2011), as well as poorer cognitive performance (Milne et al., 2018; Yau et al., 2014). In line with studies in healthy individuals, we hypothesized that a higher CAR would be associated with poorer DM (Hidalgo et al., 2016), but better WM and EF (Almela et al., 2012; Evans et al., 2012), and that a flatter DCS would be linked to poorer DM (O'Hara et al., 2007). No specific expectations were made regarding WM and EF associations with DCS, given the lack of prior research. Finally, we explored the role of depression, anticipating that higher depressive symptoms would strengthen the associations between cortisol indexes and cognitive performance (Potvin et al., 2013).

2. Methods

2.1. Participants

The final sample was composed of 51 T2D patients (26 men and 25 women) and 51 healthy participants (26 men and 25 women) between 52 and 80 years old. To recruit T2D subjects, informative advertisements were displayed in primary care clinics and hospitals. Additionally, patients received more information about the study and were invited to enroll during their medical follow-up visits. Healthy controls belonged to a study program at the University of Valencia for people over 55 years of age. They were matched to the T2D patients for sex, age, BMI, and educational level (see Table 1 for sample characteristics). Volunteers were excluded when they presented the following criteria: smoking more than 10 cigarettes per day, abuse of alcohol or other drugs of abuse, neurological or psychiatric disorders (e.g. depression), presence of a cardiovascular disorder, and visual or hearing impairment. None of the participants had a clinical diagnosis of major depression nor were they under treatment for depression. All individuals were non-smokers, except for 7 individuals (5 patients with T2D and 2 healthy controls) ranging from 1 to 5 cigarettes/day.

None of the participants reported a stressful life event or had had surgery under general anesthesia during the past year. Individuals who were being treated with drugs related to cognitive or emotional functions, medication that could influence hormonal levels (i.e., glucocorticoids, beta-blockers, antidepressants, asthma medication, or thyroid therapies), or psychotropic substances were also excluded. All participants with T2D had received a clinical diagnosis and were undergoing treatment with oral antidiabetic medications, injectable therapies, or a combination of both. All the participants scored more than 28 on the MMSE (Spanish version of the Mini-Mental Status Examination; Lobo et al., 1999).

2.2. Procedure and neuropsychological assessment

All the participants received verbal and written information about the study and signed an informed consent form. The study was carried out according to the Declaration of Helsinki, and the Ethics Research Committee of the University of Valencia approved the protocol (nº1034878).

This study consisted of one individual session that started between 10:00 and 12:00 h. Before the session, the experimenter first checked whether all the participants had followed the instructions before participation: refrain from heavy physical activity starting the evening before the session, maintain their usual sleep duration, and avoid alcohol consumption the night before the session. Additionally, they were instructed to drink only water and not eat, smoke, take any stimulants (e.g., coffee, cola, tea, chocolate), or brush their teeth at least 1 h prior to the session. Two capillary blood samples were taken at habituation (-20 min) and in the recovery period (+55 min) to measure glucose concentrations, using a glucose monitoring system (Onetouch ultraeasy life Scan Europe 6300 Zug. Switzerland. AW 0639870). All the participants followed the same time schedule for the sample collection and questionnaires administered.

During the session, a neuropsychological evaluation was carried out in which participants completed six tests that assessed different cognitive domains and one test that assessed depressive symptomatology. We assessed DM, WM, and EF through several neuropsychological tests chosen because they have been found to be more sensitive in assessing the largest performance differential between people with T2D and controls and with the largest effect sizes, specifically the RAVLT, Digit

Table 1
Descriptive statistics (mean ± SEM) for total sample and both the T2D and healthy groups.

	Total Sample (N = 102)	T2D Group (N = 51)	Healthy Group (N = 51)	t/ X^2	Sign. (*p*)	Cohen's d
Age (years)	65.81	65.92	65.71	.210	.834	0.04
	(.512)	(.758)	(.694)			
BMI (kg/m^2)	28.57	28.82	28.33	.545	.587	0.10
	(.451)	(.719)	(.558)			
SES	5.29	5.07	5.49	-1.713	.091	0.26
	(.122)	(.207)	(.135)			
Glucose I	126.020	149.700 (6.204)	101.857	5.426	< .001	1.07
	(5.008)		(6.267)			
Glucose II	112.313	128.48	95.816	5.144	< .001	1.02
	(3.563)	(4.468)	(4.513)			
ΔGlucose	13.707	21.220	6.041	3.529	< .001	1.01
	(2.287)	(3.939)	(1.729)			
Educational level (%)				6.734	.241	-
No studies	4.0	8.0	0			
Basic studies	35.6	36.0	35.3			
High school	31.7	32.0	31.4			
College or higher	13.9	21.6	23.3			
Marital status (%)				2.824	.420	-
Single	15.8	16.0	15.7			
Married	65.3	68.0	62.7			
Divorced	7.9	10.0	5.9			
Widowed	10.9	6.0	15.7			
Non-smokers (%)	93.1 %	90.2 %	96.1 %	1.374	0.240	-
CAR (AUCi)	2.194	1.478	2.851	-1.653	.102	0.53
	(.272)	(.362)	(.382)			
DCS	6.378	6.377	6.378	-.478	.633	0.00
	(.398)	(.607)	(.526)			
Awakening C	8.552	8.403	8.687	-.481	.316	0.06
Bedtime C	1.845	1.844	1.847	-.176	.430	0.00
Depression	7.461	10.92	4	6.292	< .001	1.25
	(.647)	(.994)	(.471)			
Waist	107.222	100.160	95.216	1.873	.064	0.35
	(1.208)	(2.020)	(1.705)			
Waist:Hip$_{ratio}$	.912	.928	.895	1.930	.056	0.06
	(.008)	(.085)	(.083)			

%=percentages; BMI=body mass index; SES=subjective socioeconomic status-scale (Adler et al., 2000; from 1: lowest to 10: highest level); CAR=Cortisol Awakening Response; DCS=Diurnal Cortisol Response

Span, TMT, and Stroop (Palta et al., 2014).

Declarative memory (DM) was assessed with the Spanish version (Miranda and Valencia, 1997) of the Rey Auditory Verbal Learning Test (RAVLT) and the Story Recall subtest from the Spanish version (Alonso and Prieto, 2004) of the Rivermead Behavioural Memory Test (RBMT) (Wilson et al., 1985). The RAVLT primarily evaluates verbal episodic memory and learning, requiring participants to encode, retain, and recall a list of unrelated words across multiple trials. In contrast, the RBMT Story Recall subtest measures everyday memory for narrative information, relying on contextual and semantic memory. Together, these tests provide complementary assessments of declarative memory, capturing both structured verbal learning and ecologically valid narrative recall.

Working memory (WM) was evaluated with the DS-Forward and DS-Backward subscales of the Digit Span (DS) and with Letter-Number Sequencing (LNS) from the Spanish version (Pereña et al., 2004) of the Wechsler Memory Scale III (Wechsler, 1997).

Executive Function (EF) was assessed by the Spanish version of the Trail Making Test (TMT; Reitan, 1992; Fernández et al., 2002) and the Stroop Color-Word Test (SCWT; Golden, 1978; Peña-Casanova et al., 2009). Regarding the SCWT, the interference index (calculated as indicated in Chafetz and Matthews, 2004) was used as a measure of the ability to inhibit automatic responses, as previously employed in our laboratory (Pulopulos et al., 2016; Montoliu et al., 2018).

Depressive Symptomatology was evaluated with the Spanish version of the Beck Depression Inventory (BDI-II; Beck et al., 1996). It measures somatic, behavioral, and cognitive symptoms of depression in the previous two months. The Cronbach's alpha for this study was.820. Low, moderate, and high levels were defined using the 16th, 50th (median), and 84th percentiles of the distribution, respectively.

2.3. Salivary cortisol

To measure the diurnal cortisol cycle, participants provided four saliva samples per day on two consecutive weekdays using salivettes (Sarstedt, Nümbrecht, Germany) at their home. The salivettes were stored in MEMS TrackCap containers (MEMS 6 TrackCap Monitor, Aardex Ltd. Switzerland) to record the time the participants opened the container to provide a sample. Moreover, the participants wrote the sampling times in a log. The saliva samples were provided immediately after awakening, 30- and 45-min post-awakening, and immediately before bedtime. Participants stored their samples in the refrigerator, and they brought them to the university within three days after completion. Adherence to the CAR protocol was evaluated by calculating the percentage of participants who exhibited a positive CAR. In the total sample, 79.4 % showed a positive CAR (76.47 % among participants with T2D and 82.35 % among healthy controls). There were no significant differences between the diabetic and control groups in adherence to the CAR ($\chi^2 = 0.58$, $p = 0.45$). Within-group analyses showed that both groups had significantly more adherent than non-adherent participants (T2D: $\chi^2 = 10.55$, $p = 0.001$; controls: $\chi^2 = 21.25$, $p < 0.001$).

Once in the laboratory, the samples were centrifuged at 4000 rpm for 15 min to obtain a clear supernatant that was stored at -80° C until the analyses were performed. Cortisol concentrations were determined by radioimmunoassay using the commercial kit Spectria Cortisol RIA from Orion Diagnostica (Espoo, Finland). Assay sensitivity was 0.8 nmol/L, and the within- and inter-assay variation coefficients were all below 8 %. Each participant's samples were analyzed in the same trial.

2.4. Statistical analyses and data management

Cortisol values did not show a normal distribution; therefore, they were log transformed. Because all the cortisol samples correlated across the two days (all $p < .001$), the average cortisol levels for both days was used to calculate the following indexes: i) CAR: calculated as the cortisol area under the curve with respect to the increase (AUCi, see Pruessner et al., 2003) from awakening, + 30, and + 45 min. Additionally, the CAR was calculated by subtracting the awakening cortisol from the + 30 min values ($CAR_{30'\text{-awakening}}$), following the procedure employed in the studies with T2D participants (Bruehl et al.,2009; Hackett et al., 2014; Lederbogen et al., 2011; Panagiotou et al., 2021), in order to facilitate comparison; ii) DCS: to reflect the decline in cortisol levels during the day, calculated as the awakening cortisol minus bedtime cortisol levels. ΔGlucose was calculated by subtracting glucose levels post session from the pre-stress levels. Higher ΔGlucose indicates higher glucose change during the session.

Student's *t* test and chi-square were used to test differences between groups (T2D vs healthy controls) in socio-demographic variables, glucose levels, depression, cortisol indexes, and neuropsychological tests. ANOVA for repeated measures was used to investigate group differences in cortisol levels during the day and DM (RAVLT and RBMT) performance, with Time (cortisol: Awakening, +30 min, +45 min, Bedtime; RAVLT: Trial 1, 2, 3, 4, 5, immediate and delay recall; RBMT: immediate and delayed recall) as the within-subject factor and Group (T2D and healthy) as a between-subject factor.

Moderation analyses were performed to test the associations between the cortisol indexes and cognitive performance, with Group or Depression as moderators. First, we conducted the analyses without including covariates (unadjusted analyses). Second, we performed new analyses controlling for possible confounders or covariates (adjusted analyses). The covariates were: for CAR, the time of awakening (Lederbogen et al., 2011; Hackett et al., 2014); and for the DCS, the time from awakening to bedtime (Hidalgo et al., 2021). According to previous studies (Hidalgo et al., 2016), delayed recall from the RAVLT and RBMT were adjusted for immediate recall from the RAVLT and RBMT, respectively. In addition, DS-Backward was controlled for DS-Forward, and TMT-B was controlled for TMT-A. The PROCESS macro in SPSS (Model 1) was used with 5000 bootstrapped samples. We included CAR or DCS as the independent variable, memory and EF outcomes as dependent variables, and Group (T2D and healthy) or Depression as moderators. We repeated the analyses (unadjusted and adjusted) using the $CAR_{30'\text{-awakening}}$.

For the cortisol indexes, one healthy man was eliminated due to being ±3 SD from the mean. Six outliers were also eliminated from the neuropsychological analyses, specifically, three women from the T2D group (one for RAVLT and TMT-A, one for TMT-A, and one for TMT-B), one healthy woman for DS-Backward, and two healthy men for LNS.

Greenhouse–Geisser was used when the requirement of sphericity in the analysis was violated. *Post hoc* planned comparisons were performed using Bonferroni adjustments for the *p* values. In contrast, no corrections for multiple comparisons were applied to the moderation analyses, as these were hypothesis-driven and specified a priori. Statistical analyses were carried out using SPSS 28.0. All *p* values reported are two-tailed. The level of significance was fixed at < 0.05. For easy interpretation, the values in the figures and tables represent raw values rather than logarithmic transformed values.

3. Results

3.1. Preliminary analyses

No significant differences were found between the T2D and healthy groups in age, SES, BMI, marital status, or education level (all $p > .091$). However, T2D patients had higher glucose levels pre and post session (both $p < .001$) than healthy participants, and higher ΔGlucose ($p < .001$) (Table 1).

There were significant group differences in depression ($p < .001$), and marginally in Waist ($p = .064$) and the $Waist{:}Hip_{ratio}$ ($p = .056$). The T2D group had higher values in both cases (see Table 1). In our sample, depression levels ranged from 0 to 33 (M=7.461, SD=0.674). Based on the clinical cut points for the BDI (Beck et al., 1996), only one participant with T2D showed severe depression, five T2D showed moderate levels, and the rest of the sample fell within the mild to minimal range.

3.2. Cortisol pattern

Results showed a significant effect of Time ($F_{(2.018,\ 183.663)} = 543.283$, $p < .001$, $\eta^2_p = .857$) and, marginally, the Time x Group interaction ($F_{(2.018,\ 183.663)} = 2.657$, $p = .072$, $\eta^2_p = .028$). *Post hoc* analyses revealed that, overall, participants' cortisol levels significantly increased from awakening to + 30 min ($p < .001$), and then cortisol levels started to decrease until bedtime (+30 vs 45 min: $p = .019$, and +45 vs bedtime: $p < .001$). In addition, T2D patients showed, as a trend, lower cortisol levels than healthy participants in both the + 30 min ($p = .051$) and + 45 min ($p = .018$) samples. In T2D participants, cortisol levels significantly increased from awakening to + 30 min ($p < .001$), and then they started to decrease until bedtime (+30 vs 45 min: $p = .036$ and +45 vs bedtime: $p < .001$). In healthy participants, cortisol levels significantly increased from awakening to + 30 min ($p < .001$) and later remained stable (+30 vs 45 min: $p = .884$). After that, cortisol levels started to decrease until bedtime (+45 vs bedtime: $p < .001$) (Fig. 1).

No significant differences were found between the two groups in the CAR or DCS (both $p > .102$) (see Table 1). Additionally, T2D showed, as a trend, lower levels than the healthy group in $CAR_{30'\text{-awakening}}$ ($p = .061$).

3.3. Cognitive performance

Declarative memory Statistical analyses showed significant effects of Trial ($F_{(4.\ 079,\ 395.632)} = 117.338$, $p < .001$, $\eta^2_p = .547$), Group ($F_{(1,\ 97)} = 4.994$, $p = .028$, $\eta^2_p = .049$), and the Trial x Group interaction ($F_{(4.079,\ 395.632)} = 3.0545$, $p = .016$, $\eta^2_p = .031$) (Fig. 2). *Post hoc* analyses revealed a consistent learning pattern across both groups, with significant improvement from Trial 1 to Trial 3 (all $p < .001$). Performance plateaued between Trials 3 and 4 ($p > .99$), followed by a significant increase from Trial 4 to Trial 5 in the T2D group ($p < .001$), but not in healthy controls ($p = .727$). In both groups, immediate recall—conducted after the interference list—was significantly lower than Trial 5 ($p < .001$). Within-group analyses revealed that T2D participants recalled significantly more words in delayed recall than in immediate recall ($p = .004$), whereas healthy participants showed no such difference ($p > .99$). Group comparisons showed that participants with T2D recalled fewer words overall than healthy controls ($p = .028$), with significant differences in Trials 2 ($p = .049$), 3 ($p = .015$), 4 ($p = .002$), and immediate recall ($p = .017$). Trial 5 showed a trend toward significance ($p = .070$), while no differences were observed in Trial 1 or delayed recall (both $p > .285$) (Fig. 2A).

Regarding the RBMT, an effect of Group ($F_{(1,\ 99)} = 8.046$, $p = .006$, $\eta^2_p = .075$) was found. T2D participants had lower performance than healthy controls. No significant effects were observed for Time ($F_{(1,\ 99.000)} = 2.047$, $p = .156$, $\eta^2_p = .020$) or the Time x Group interaction ($F_{(1,\ 99)} = .003$, $p = .960$, $\eta^2_p = .001$).

Working memory Results revealed significant group differences on DS-Forward ($t_{(94)} = -2.958$, $p = .002$, $d = 0.61$, Fig. 2B) and, marginally, on DS-Backward ($t_{(96)} = 1.826$, $p = .071$, $d = 0.37$, Fig. 2C). Significant group differences were also observed in LNS ($t_{(96)} = -2.708$, $p = .008$, $d = 0.55$, Fig. 2D). In all cases, T2D patients showed poorer performance than healthy participants.

Executive function Group differences were found on TMT-A ($t_{(82)} = 3.757$, $p < .001$, $d = 0.83$) and TMT-B ($t_{(87)} = 2.974$, $p = .004$, $d = 0.64$) (Figs. 2E and 2F). T2D participants had a longer execution time on both

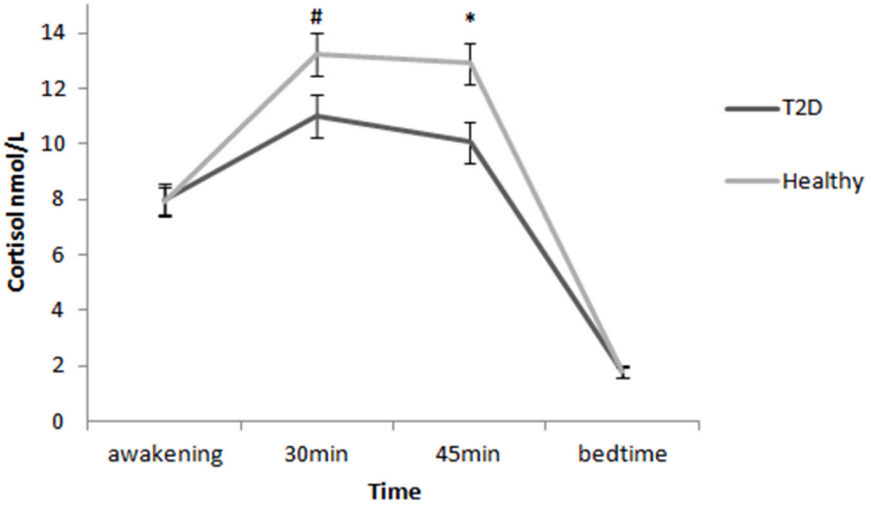

Fig. 1. Means and SEM of salivary cortisol concentrations. *p values ≤ 0.05; # trend towards significant differences.

tasks than healthy participants. However, no significant differences were found on Stroop interference ($t_{(92)}$= -.964, p = .338, d= 0.20) (Fig. 2G).

3.4. Cortisol indexes and cognitive performance

Adjusted moderation analyses between cortisol indexes and cognitive performance by group

Despite not showing any significant CAR X Group interactions (all p > .338), the analyses showed a significant negative relationship between the CAR and Stroop interference in the healthy group (p = .044) (Table 2; unadjusted analyses in Supplementary Material Table 1). We repeated the analyses (adjusted and unadjusted) using the $CAR_{30'\text{-awakening}}$ and also found a significant relationship between $CAR_{30'\text{-awakening}}$ and the Stroop Interference in the healthy group (p = .049). Although no significant effect was found for $CAR_{30'\text{-awakening}}$ X Group interaction on RAVLT delayed recall (p = .598), a negative marginal relationship was found on T2D group (p = .063) (Tables 2–3 in Supplementary Material).

There were no significant effects of the DCS X Group interaction (all p > .268), and no significant relationships between DCS and the cognitive indexes were found in any group (T2D group: all p > .301; healthy group: all p > .235) (Table 3; unadjusted analyses in Supplementary Material Table 4).

Adjusted moderation analyses between cortisol indexes and cognitive performance attending to depression

A significant marginal interaction was found between CAR X Depression on delayed recall from the RAVLT model (all p = .071), but this relationship was not significant at any of the depression levels (low: p = .229; middle: p = .549; high: p = .144). However, although the CAR X Depression interaction in the Stroop Interference model (p = .441) was not statistically significant, a negative significant relationship was found for low (p = .049) and middle levels of depression (p = .029) (Table 4; unadjusted analyses in Supplementary Material Table 5). We repeated the analyses (adjusted and unadjusted) using the $CAR_{30'\text{-awakening}}$ and found a marginal interaction between $CAR_{30'\text{-awakening}}$ X Depression on delayed recall from the RBMT model (p = .071). This relationship was significant at high depression level (high: p = .022). Although the $CAR_{30'\text{-awakening}}$ X Depression on RAVLT delayed model was not statistically significant (p = .273), a positive significant relationship was found for high levels of depression (p = .014) (see Tables 6–7 in Supplementary material).

Finally, a significant DCS X Depression interaction was found on delayed recall from the RAVLT model (p = .028). A marginal positive significant relationship was found between DCS and delayed recall from the RAVLT for low depression levels (p = .054) (Table 5, unadjusted in Supplementary Material Table 8).

4. Discussion

This study aimed to analyze differences between patients with T2D and healthy controls in their diurnal cortisol cycle and cognitive performance, as well the existing relationships. In the case of the HPA axis, whereas no differences were found in the indexes of the cortisol diurnal cycle, participants with T2D showed significantly lower cortisol levels at + 30 min and + 45 min after awakening than healthy controls. Regarding to cognition, patients with T2D showed lower DM, WM, and EF (except on Stroop interference) performance than healthy controls. Only in healthy controls, the moderation analyses showed a significant negative relationship between the CAR and Stroop interference. When depression was considered as a moderating factor, this latter association was found for participants with low and mid-level depression scores, and only in participants with low depression scores, DCS was positively related to delayed recall from the RAVLT.

4.1. Cortisol diurnal cycle

In our study, patients with T2D showed lower cortisol levels than healthy controls at + 30 min and + 45 min, which coincides with the lower cortisol levels at 30 min reported by Bruehl et al. (2009) when compared 18 patients with T2D with 12 non-diabetic controls. As mentioned above, we did not find significant differences in the CAR between T2D and healthy controls. We calculated the CAR as recommended (Stalder et al., 2022), with a minimum of three saliva samples on at least two days (waking, 30 min, and 45 min after waking). Regarding T2D group, a flatter CAR had been described in previous literature (Bruehl et al., 2009; Lederbogen et al., 2011; Panagiotou et al., 2021). In these studies, the CAR was calculated at two sampling points (on awakening and 30 min after awakening) and on only one day. When we additionally calculated the CAR as the difference between awakening and 30 min, we found that the T2D group showed, as a trend, smaller increases from awakening to 30 min compared to controls (see Supplementary material, Table 5-8). A similar result was found by Bruehl et al. (2009), who also employed the two estimations of the CAR, in that the largest difference between T2D and healthy controls occurred 30 min after awakening.

Regarding DCS, we did not observe group differences, similarly to Bruehl et al. (2009). In contrast, Lederbogen et al. (2011) reported a trend toward a smaller slope, whereas Hackett et al. (2014) observed a flattened DCS in participants with T2D that could be attributed more to higher bedtime levels than to lower awakening levels. Interestingly, we

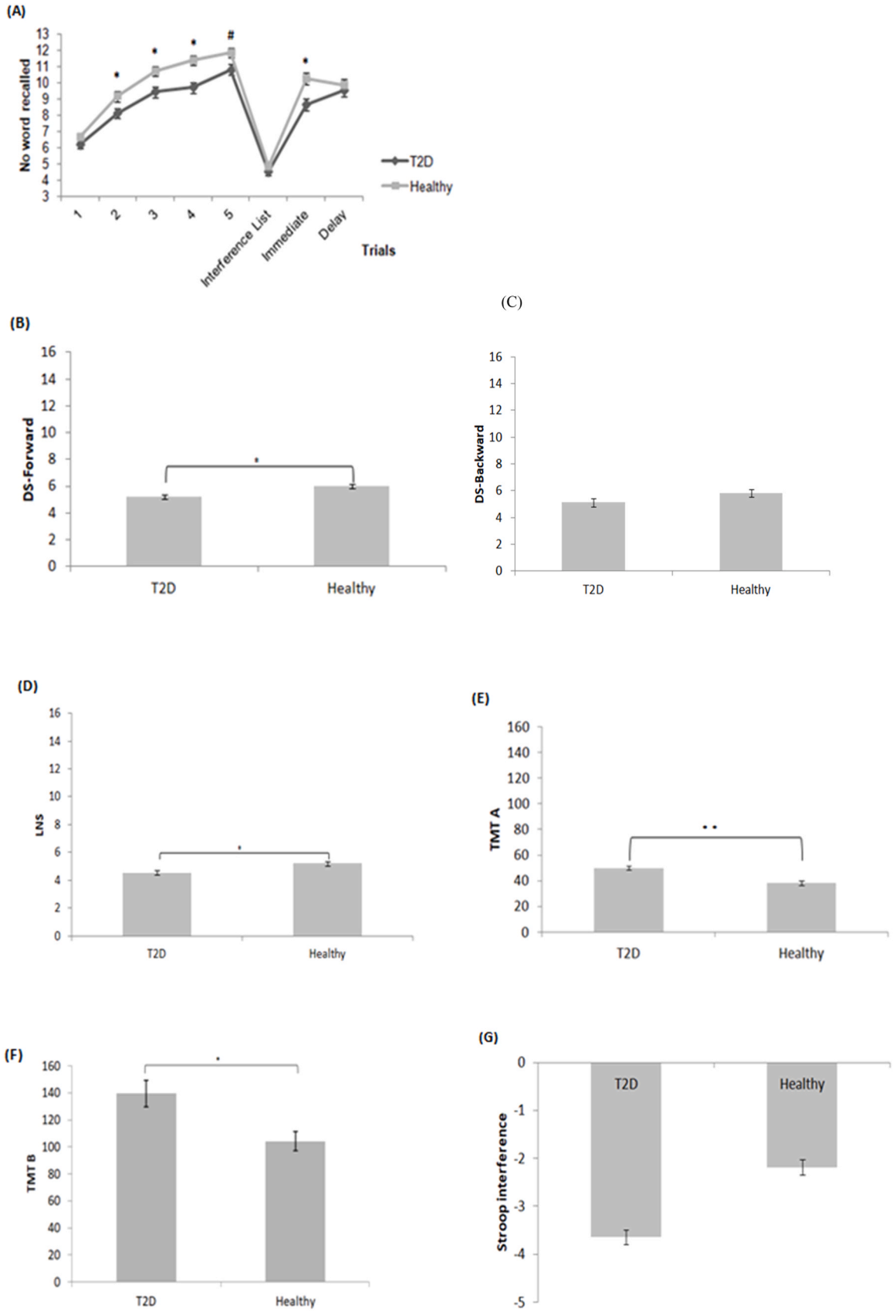

Fig. 2. Means and SEM of the neuropsychological tests. **Note:** *p values ≤ 0.05; ** p *values*≤ 0.001; # trend.

Table 2
Conditional effect of CAR on cognitive tests, with Group as moderator variable adjusted for covariates.

Moderator variable (W): Group						
Independent variable (X): CAR						
Dependent variable (Y): RAVLT delayed recall						
ΔR^2 interaction= .001 F = .252 p = . 617						
	Effect	SE	t	p	LLCI	ULCI
T2D	-.013	.088	-.145	.885	-.187	.162
Healthy	.048	.087	.551	.583	-.125	.221
Independent variable (X): CAR						
Dependent variable (Y): RBMT delayed recall						
ΔR^2 interaction = .001 F = .024 p = .876						
	Effect	SE	t	p	LLCI	ULCI
T2D	.098	.083	1.190	.237	-.066	.262
Healthy	.080	.083	.968	.335	-.085	.245
Independent variable (X): CAR						
Dependent variable (Y): DS-Backward						
ΔR^2 interaction = .003 F = .498 p = .482						
	Effect	SE	t	p	LLCI	ULCI
T2D	-.104	.115	-.905	.368	-.335	.125
Healthy	.011	.119	.091	.927	-.225	.247
Independent variable (X): AUCi						
Dependent variable (Y): LNS						
ΔR^2 interaction = .010 F = .928 p = .338						
	Effect	SE	t	p	LLCI	ULCI
T2D	-.132	.154	-.858	.393	-.437	.174
Healthy	.071	.149	.479	.633	-.224	.367
Independent variable (X): CAR						
Dependent variable (Y): TMT-B						
ΔR^2 interaction = .002 F = .188 p = . 666						
	Effect	SE	t	p	LLCI	ULCI
T2D	-.083	-126	-.659	.511	-.333	.167
Healthy	-.009	.119	-.073	.942	-.246	.229
Independent variable (X): CAR						
Dependent variable (Y): Stroop interference						
ΔR^2 interaction = .001 F = .808 p = .371						
	Effect	SE	t	p	LLCI	ULCI
T2D	-.126	.155	-.813	.418	-.435	.182
Healthy	-.323	.158	-2.043	.044	-.637	-.010

Note: CAR = Cortisol awakening response; T2D = Type 2 diabetes; RAVLT delayed recall= Rey auditory verbal Learning test; RBMT delayed recall = Rivermead Behavioural Memory test delayed recall; DS-Backward = Digit Span Backward; LNS= Letter-number sequencing; TMT-B= Trail Making Test B.

Table 3
Conditional effect of DCS on cognitive tests, with Group as moderator variable adjusted for covariates.

Moderator variable (W): Group						
Independent variable (X): DCS						
Dependent variable (Y): RAVLT delayed recall						
ΔR^2 interaction= . 003 F = .952 p = .332						
	Effect	SE	t	p	LLCI	ULCI
T2D	-.019	.092	-.202	.841	-.202	.165
Healthy	.105	.088	1.195	.235	-.070	.280
Independent variable (X): DCS						
Dependent variable (Y): RBMT delayed recall						
ΔR^2 interaction = .001 F = .070 p = .792						
	Effect	SE	t	p	LLCI	ULCI
T2D	.091	.088	1.040	.301	-.083	.265
Healthy	.059	.084	.707	.481	-.107	.226
Independent variable (X): DCS						
Dependent variable (Y): DS-Backward						
ΔR^2 interaction = .002 F = .322 p = .572						
	Effect	SE	t	p	LLCI	ULCI
T2D	.099	.119	.835	.406	-.137	.336
Healthy	.006	.116	.050	.961	-.225	.236
Independent variable (X): DCS						
Dependent variable (Y): LNS						
ΔR^2 interaction = .003 F = .236 p = .628						
	Effect	SE	t	p	LLCI	ULCI
T2D	.108	.153	.703	.484	-.197	.413
Healthy	.001	.158	.008	.993	-.312	.315
Independent variable (X): DCS						
Dependent variable (Y): TMT-B						
ΔR^2 interaction = .012 F = 1.243 p = .268						
	Effect	SE	t	p	LLCI	ULCI
T2D	-.113	.133	-.848	.399	-.377	.152
Healthy	.090	.123	.733	.466	-.154	.334
Independent variable (X): DCS						
Dependent variable (Y): Stroop interference						
ΔR^2 interaction = .006 F = .465 p = .497						
	Effect	SE	t	p	LLCI	ULCI
T2D	.061	.175	.349	.728	-.287	.409
Healthy	-.100	.160	-.623	.535	-.419	.219

Note: DCS = Diurnal Cortisol Slope; T2D = Type 2 diabetes; RAVLT delayed recall= Rey Auditory Verbal Learning Test; RBMT delayed recall = Rivermead Behavioural Memory Test delayed recall; DS-Backward = Digit Span Backward; LNS= Letter-number sequencing; TMT-B= Trail Making Test B.

did not find significant differences between groups in the awakening and bedtime cortisol values.

4.2. Cognitive assessment

We found significantly poorer performance in participants with T2D compared to controls on overall performance and immediate recall of the RAVLT, but not on delayed recall. This aligns with meta-analyses by Palta et al. (2014) and Sadanand et al. (2016), which suggest that immediate recall is more sensitive to T2D-related deficits than delayed recall. The RAVLT is an unstructured verbal memory list-learning task that places high demands on learning, retention, interference management, encoding, and retrieval, relying heavily on prefrontal functioning (Palta et al., 2014; Lezak et al., 2004). In contrast, the RBMT, which uses paragraph recall, has high ecological validity and is more dependent on hippocampal functioning, providing a measure of declarative memory in a real-world context. In our study, patients with T2D showed poorer overall performance on the RBMT, although differences in immediate and delayed recall were not statistically significant. These findings are consistent with Sadanand et al. (2016), who reported small differences between T2D and controls on paragraph-based memory tests, and differ from Shimada et al. (2010), who found no significant RBMT differences. Taken together, the pattern of results may suggest that T2D preferentially affects cognitive processes involving the prefrontal cortex (as taxed by the RAVLT), whereas hippocampal-dependent declarative memory (assessed by paragraph recall) is relatively preserved in our sample.

With regard to WM, our results showed poorer performance in patients with T2D compared to healthy controls on DS-Forward and LNS tasks, with marginal differences on DS-Backward. The absence of significant differences on DS-Backward aligns with findings by Bruehl et al. (2007). However, Mollon et al. (2020) reported poorer performance on both DS-Backward and LNS in a T2D subsample from the San Antonio Family Heart Study compared to unaffected participants, whereas Mallorquí-Bagué et al. (2018) found no differences between T2D and controls groups on either Digit Span subtest in the PREDIMED-Plus study. In our study, the significant differences on the LNS test may reflect its greater cognitive demands relative to DS-Backward, as it requires manipulating more information within a limited time frame. Overall, WM deficits in T2D are generally recognized, although findings across studies remain heterogeneous. Notably, Pelimanni and Jehkonen (2019) identified WM as one of the most affected cognitive domains in middle-aged individuals under 65, and Palta et al. (2014) emphasized the moderating role of age in T2D-related cognitive effects. More recently, Antal et al. (2022) suggested that T2D may accelerate normal brain aging, implying that the presence and severity of cognitive deficits could vary depending on the age of the sample studied. Regarding the EF, we found poorer performance on both the TMT A and TMT B, consistent with previous findings (Palta et al., 2014; Vincent and Hall, 2015; Mansur et al., 2018). However, we did not observe differences in Stroop interference between the groups, which aligns with Saczynski et al. (2008), but contrasts with the meta-analyses by Palta et al. (2014)

Table 4
Conditional effect of CAR on cognitive tests, with Depression as moderator variable adjusted for covariates.

Moderator variable (W): Depression						
Independent variable (X): CAR						
Dependent variable (Y): RAVLT delayed recall						
ΔR^2 interaction= .012 F = 3.348 p = .071						
BDI	Effect	SE	t	p	LLCI	ULCI
-.836	-.112	.093	-1.212	.229	-.297	.072
-.377	-.042	.070	-.601	.549	-.182	.098
.848	.144	.098	1.475	.144	-.050	.339
Independent variable (X): CAR						
Dependent variable (Y): RBMT delayed recall						
ΔR^2 interaction = . 001 F = .052 p = .820						
	Effect	SE	t	p	LLCI	ULCI
-.836	.102	.086	1.181	.241	-.070	.274
-.377	.094	.065	1.446	.152	-.035	.222
.848	.071	.092	.773	.441	-.112	.255
Independent variable (X): CAR						
Dependent variable (Y): DS-Backward						
ΔR^2 interaction = .007 F = 1.042 p = .310						
	Effect	SE	t	p	LLCI	ULCI
-.836	-.147	.121	-1.218	.227	-.388	.093
-.377	-.096	.091	-1.052	.296	-.277	.085
.848	.041	.127	.323	.747	-.212	.295
Independent variable (X): CAR						
Dependent variable (Y): LNS						
ΔR^2 interaction = .018 F = 1.750 p = . 188						
	Effect	SE	t	p	LLCI	ULCI
-.836	.073	.144	.505	.615	-.214	.359
-.377	-.006	.109	-.058	.954	-.224	.211
.848	-.217	.153	-1.424	.158	-.521	.086
Independent variable (X): CAR						
Dependent variable (Y): TMT-B						
ΔR^2 interaction = .005 F = .542 p = .463						
	Effect	SE	t	p	LLCI	ULCI
-.836	-.103	.124	-.833	.407	-.350	.143
-.377	-.065	.094	-.692	.491	-.252	.122
.848	.036	.133	.274	.784	-.228	.301
Independent variable (X): CAR						
Dependent variable (Y): Stroop interference						
ΔR^2 interaction = .006 F = .598 p = .441						
	Effect	SE	t	p	LLCI	ULCI
-.836	-.325	.162	-2.002	.049	-.647	-.002
-.377	-.274	.123	-2.224	.029	-.519	-.029
.848	-.139	.165	-.845	.400	-.468	.189

Note:: CAR = Cortisol awakening response; T2D = Type 2 diabetes; RAVLT delayed recall= Rey auditory verbal Learning test; RBMT delayed recall = Rivermead Behavioural Memory test delayed recall; DS-Backward = Digit Span Backward; LNS= Letter-number sequencing; TMT-B= Trail Making Test B; BDI = Beck Depression Inventory; values for quantitative moderators are the 16th, 50th and 84th percentiles.

Table 5
Conditional effect of DCS on cognitive tests, with Depression as moderator variable adjusted for covariates.

Moderator variable (W): Depression						
Independent variable (X): DCS						
Dependent variable (Y): RAVLT delayed recall						
ΔR^2 interaction= . 018 F = 4.984 p = .028						
BDI	Effect	SE	t	p	LLCI	ULCI
-.836	.156	.080	1.947	.054	-.003	.316
-.377	.062	.065	.951	.344	-.068	.193
.848	-.188	.126	-1.490	.140	-.439	.063
Independent variable (X): DCS						
Dependent variable (Y): RBMT delayed recall						
ΔR^2 interaction = .001 F = .021 p = .886						
	Effect	SE	t	p	LLCI	ULCI
-.836	.066	.075	.876	.383	-.084	.215
-.377	.071	.061	1.163	.248	-.051	.193
.848	.086	.118	.734	.465	-.148	.321
Independent variable (X): DCS						
Dependent variable (Y): DS-Backward						
ΔR^2 interaction = .011 F = 1.583 p = .212						
	Effect	SE	T	p	LLCI	ULCI
-.836	.115	.101	1.129	.262	-.087	.316
-.377	.048	.084	.572	.569	-.119	.215
.848	-.130	.160	-.808	.421	-.448	.189
Independent variable (X): DCS						
Dependent variable (Y): LNS						
ΔR^2 interaction = .009 F = .920 p = .340						
	Effect	SE	T	p	LLCI	ULCI
-.836	.108	.144	.753	.453	-.178	.395
-.377	.040	.113	.357	.7222	-.184	.264
.848	-.142	.202	-.704	.483	-.543	.259
Independent variable (X): DCS						
Dependent variable (Y): TMT-B						
ΔR^2 interaction = .014 F = 1.594 p = .210						
	Effect	SE	t	p	LLCI	ULCI
-.836	.089	.108	.827	.410	-.125	.304
-.377	.017	.089	.194	.847	-.160	.195
.848	-.175	.173	-1.010	.315	-.518	.169
Independent variable (X): DCS						
Dependent variable (Y): Stroop interference						
ΔR^2 interaction = .104 F = 1.206 p = .275						
	Effect	SE	t	p	LLCI	ULCI
-.836	-.131	.145	-.903	.369	-.419	.157
-.377	-.049	.118	-.409	.684	-.284	.187
.848	.171	.225	.761	.449	-.276	.618

Note: DCS = Diurnal cortisol slope; T2D = Type 2 diabetes; RAVLT delayed recall= Rey auditory verbal Learning test; RBMT delayed recall = Rivermead Behavioural Memory test delayed recall; DS-Backward = Digit Span Backward; LNS= Letter-number sequencing; TMT-B= Trail Making Test B; BDI = Beck Depression Inventory; values for quantitative moderators are the 16th, 50th, and 84th percentiles.

and Vincent and Hall (2015). Variability in how Stroop interference is calculated may contribute to these mixed results.

As mentioned above, only a few studies have investigated how the CAR and DCS are associated with cognitive performance in people with T2D compared to healthy controls. In our study, no significant associations were found within the T2D group. However, among healthy controls, a significant negative relationship between the CAR and Stroop interference was found. This finding aligns with evidence suggesting that a larger CAR is associated with better cognitive performance in older adults (Gardner et al., 2019).

Despite the cognitive deficits associated with T2D and evidence of HPA axis dysregulation, this study did not confirm a relationship between these two dimensions in a small, but strictly matched mixed-sex sample of patients with T2D and healthy controls. In the literature, most positive findings on these associations come from epidemiological studies with a larger sample sizes, though often with less rigorous control of confounding factors. It is also worth noting that deficits in DM and EF are more commonly observed in patients with T2D who also present with renal or cardiovascular comorbidities (for instance, Murray et al., 2011).

Because diabetes is a chronic metabolic stressor, it has been suggested that the neurochemical and anatomical basis for cognitive impairment in diabetes may resemble those observed in chronic stress and stress-related psychiatric disorders (Reagan, 2012). Individuals with T2D are clearly at greater risk of depression compared with non-diabetic individuals (Anderson et al., 2001), with prevalence rates approximately twice as high as those in the general population (Holt, 2014). Depression has been linked to increased risk of progressive insulin resistance and the onset of T2D, although the nature of this relationship is not completely understood (Liu et al., 2024). On one hand, depression may arise from the psychological burden of coping with a chronic illness; on the other hand, metabolic consequences of T2D may predispose individuals to depression or result from cerebral vascular damage. Furthermore, the relationship may be bidirectional, as depression itself may increase vulnerability to developing T2D (Reijmer et al., 2010). Given the significant differences in depressive symptoms between T2D and healthy controls groups found in our study, symptoms that can affect cognitive performance, a second block of moderation analyses was conducted considering depression scores as moderator. Results revealed a negative relationship between CAR and Stroop interference at low and

middle levels of depression, and a positive relationship between DCS and RAVLT delayed recall at low depression levels. These findings suggest that depression moderates the relationships between cortisol indices and specific cognitive processes. Although initially counterintuitive, the pattern observed in our moderation analyses may reflect the nonlinear effects of depression on HPA axis–cognition link. Mild to moderate depressive symptoms have been associated with heightened HPA axis sensitivity, which may amplify cortisol–cognition associations. In contrast, more severe depression is often linked to HPA axis dysregulation—such as flattened diurnal cortisol rhythms or glucocorticoid receptor resistance—which may obscure or dampen these associations (Pariante and Lightman, 2008; Burke et al., 2005). Lupien et al. (2009) further suggest that cortisol–cognition relationships are most detectable under conditions of moderate physiological or psychological stress, where HPA axis responsiveness is preserved. Our findings are also consistent with prior research suggesting that adaptive cortisol patterns—such as a greater CAR and a steeper DCS—are associated with enhanced cognitive performance. A robust CAR may facilitate executive functioning by mobilizing energy and attention resources at the start of the day (Stalder et al., 2025), while a steeper DCS reflects healthy HPA axis regulation and has been linked to better memory and cognitive control (Lupien et al., 2009; Evans et al., 2011). Our results extend this literature by showing that these associations are most evident at lower levels of depressive symptoms, suggesting that preserved HPA axis responsiveness may be a key factor in maintaining cognition in older adults

Our study is limited by its cross-sectional design and relatively modest sample size, which may reduce statistical power and limit the detection of small-to-moderate effects. Some null findings, particularly those concerning cortisol–cognition relationships, should be interpreted with caution. Our findings underscore the need for standardized measures to investigate mechanisms underlying potential associations. Further studies with larger and more diverse samples are needed to specifically examine differences related to sex/gender and age, even in older population. Finally, findings related to depressive symptomatology should be explored in larger samples that include individuals with clinical levels of depression, not only subclinical levels as in our case. This limitation may explain why significant results were found only for low to moderate levels of depression.

In this study, we aimed to explore cognitive function across three key domains, along with two indices of the diurnal cortisol cycle, in a mixed-sex sample of older adults with T2D. To clarify the relationships between cognitive performance and cortisol, we included a control group of healthy individuals matched on relevant characteristics. Our findings revealed only small differences in the CAR and significantly poorer memory performance in the T2D group, but no significant associations between cortisol measures and cognitive outcomes. To advance research in this area, it is essential to use well-matched control groups and to address the limitations outlined above. Finally, given that cognitive deficits are associated with poorer adherence to medical treatment, suboptimal dietary control, reduced functional independence, and ultimately a lower quality of life, there is a clear need for further studies aimed at screening for these impairments. Such efforts could support patients in engaging more effectively in self-care and help mitigate the broader challenges associated with T2D.

CRediT authorship contribution statement

Vanesa Hidalgo: Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Alicia Salvador:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Mariola Zapater-Fajarí:** Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization. **Teresa Montoliu:** Methodology, Investigation, Data curation. **Lorena Vallejo:** Writing – original draft, Formal analysis, Data curation, Conceptualization.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2025.107718.

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