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Effects of glycaemic control on memory performance, hippocampal volumes and depressive symptomology

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Abstract

Background Diabetes and poor glycaemic control have been shown to negatively impact cognitive abilities, while also raising risk of both mood disorders and brain structural atrophy. Sites of atrophy include the hippocampus, which has been implicated in both memory performance and depression. The current study set out to better characterise the associations between poor glycaemic control, memory performance, and depression symptoms, and investigate whether loss of hippocampal volume could represent a neuropathological mechanism underlying these.

Methods 1331 participants (60.9% female, age range 18–88 (Mean = 44.02), 6.5% with likely diabetes) provided HbA1c data (as an index of glycaemic control), completed a word list learning task, and a validated depression scale. A subsample of 392 participants underwent structural MRI; hippocampal volumes were extracted using FreeSurfer.

Results Partial correlation analyses (controlling for age, gender, and education) showed that, in the full sample, poorer glycaemic control was related to lower word list memory performance. In the MRI sub-sample, poorer glycaemic control was related to higher depressive symptoms, and lower hippocampal volumes. Total hippocampus volume partially mediated the association between HbA1c levels and depressive symptoms.

Conclusions Results emphasise the impact of glycaemic control on memory, depression and hippocampal volume and suggest hippocampal volume loss could be a pathophysiological mechanism underlying the link between HbA1c and depression risk; inflammatory and stress-hormone related processes might have a role in this.

Keywords HbA1c, Memory, Diabetes, MRI, Depression, Hippocampus, Glycated haemoglobin, Mental health, Depressive symptoms, Hippocampal volume

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Background

Impaired glycaemic control has been linked to poorer cognitive function and increased risk of depressive symptomology. Haemoglobin A1c (HbA1c) in blood plasma is a commonly utilised biomarker of glycaemic control: it reflects mean blood glucose levels over the previous 2–3 months [1]. An HbA1c of 6.5% or above indicates a diabetes diagnosis according to World Health Organization (WHO) guidelines [2]. Diabetes is a pressing world health priority, with a global prevalence of 8.5% amongst adults [3]. Type 2 diabetes raises the risk of depression [4], cognitive impairment [5], and dementia [6].

Higher HbA1c levels have been linked to poorer cognitive performance in individuals with diabetes [7, 8] including delayed memory recall [9]. In individuals without diabetes, this is also the case. In healthy young adults (N=1200, aged 22 to 35), HbA1c negatively impacted working memory and fluid intelligence scores [10]. In a sample (N=600) including adults with normal glucose tolerance (34.6%), with pre-diabetes (34.5%), and with diabetes (30.8%) aged between 55 and 64, HbA1c correlated with word list recall performance (both immediate, and after a 15-minute delay) [11]. Further, in a longitudinal study of individuals aged 50+, higher HbA1c levels at baseline increased risk of subsequent memory decline regardless of diabetes status [12]; in participants with no diabetes aged over 75, higher baseline HbA1c levels has been linked to a greater decline in Mini-Mental State Exam scores at 32-month follow-up, even after excluding participants with suspected incipient diabetes [13]. Higher average blood glucose levels have also been shown to increase the risk of dementia in both individuals with diabetes and without diabetes, e.g. in adults over 65 followed up over 7 years [14].

However, the underlying mechanism behind the relationship between HbA1c levels and cognition is unclear. The hippocampus is a crucial structure supporting episodic encoding and retrieval [15, 16]. In participants with diabetes, studies have shown an inverse relationship between HbA1c levels and total hippocampal volume [17]. Garfield et al. [16] compared participants with diabetes/prediabetes, participants with normal HbA1c levels and participants with below-normal HbA1c levels (N=35,418). Participants with diabetes and prediabetes had smaller hippocampal volume than participants with normal HbA1c levels, and participants with below-normal HbA1c levels had larger hippocampal volume than participants with normal HbA1c levels [18]. Research based on continuous, rather than categorical, measures of HbA1c levels is lacking, but impaired glycaemic control likely impacts hippocampal volume through a variety of biological mechanisms including the action of advanced glycation end-products (AGEs) [19–21], glycoxidative damage [22], and elevated cortisol levels [23].

Given the well-established role of the hippocampus in memory, some (but not all) studies have found links between hippocampal volumes and memory performance, for example in relation to delayed recall in healthy young adults [24]. A recent meta-analysis in children/adolescents found a small, but significant, positive association between total hippocampal volume and memory performance across both immediate and delayed recall [25]. A neuroimaging study spanning the entire adult age range found links between volumes of the hippocampal cornus ammonis subregions in particular, with both immediate and delayed recall performance [26]. Hardcastle et al. [27] linked larger left hippocampal volume with better working and episodic memory performance in adults aged 65–89, and loss of hippocampal volume over 4 years in older adults has been correlated with memory decline [28]. Thus, the impact of HbA1c levels on hippocampal volume could undermine memory performance and at least partially explain the observed associations between HbA1c levels and memory.

A relationship between HbA1c and depressive symptomology has been shown but primarily using diabetes groups. Meta-analyses show patients with diabetes have higher levels of both incident clinical depression and self-reported depressive symptoms [29], health complications associated with diabetes such as micro/macrovascular disease, weight gain, and neuropathy, have been theorised to contribute [30] Longitudinal studies have shown an association between HbA1c levels and self-reported depressive symptoms in diabetes patients aged>50 [31]; depression also raises the risk of diabetes [32]. In one study including both healthy and individuals with diabetes aged>50, increased HbA1c levels were linked to higher self-reported depressive symptoms at follow-up (eight years) [33], similar results were observed in another community-based sample spanning ages 18–72 [34]. However, more research is needed to clarify the mechanisms involved.

Again, the hippocampus might mediate the relationship between glycaemic control and depressive symptoms, as it is implicated in mood regulation [35], and hippocampal volume reduction is the most commonly reported structural imaging finding in major depressive disorder (MDD), with reductions of up to 10% (for meta-analyses see [36, 37]. Also, depressed patients with smaller hippocampal volume are less likely to respond to antidepressant treatment [38], and a longer duration of depression is associated with greater reductions in hippocampal volume [39]. Even in non-clinical samples, an inverse association between self-reported depressive symptomology and bilateral hippocampal volume has been shown [40, 41]; comparing the strength of the relationship within three different age ranges (those aged below 40, between 40 and 59, and 60 years and above)

indicated it might be stronger in later life [42]. This might result from increased vulnerability of the aged hippocampus to the effect of glucocorticoids [43]. The hippocampus has a role in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which produces stress-related glucocorticoids [44]. Reduced hippocampus volume has been linked to higher levels of circulating cortisol [45]. Animal studies suggest that this is because of impaired HPA regulation in response to stressors [46]. High levels of circulating glucocorticoids cause further dendritic shrinkage and loss of spines in hippocampus [47], setting up a feedback loop which could lead to further HPA impairment and further hippocampal damage. Reduced hippocampal volume predicts poorer outcomes in depressed patients, in terms of clinical response and relapse rate [48, 49], suggesting that lower hippocampal volume might be a vulnerability factor for MDD. Thus, hippocampal volume loss due to glucose dysregulation via the mechanisms discussed above, could represent a mediating pathway and mechanism, explaining the link between HbA1c and depressive symptoms, although this has not been explicitly studied.

In sum, research suggests that higher HbA1c levels are associated with both poorer memory and depression symptomology. However, previous work has tended to focus on older people with diabetes. The question of whether these associations are generalisable across the age range remains unanswered. Also, while higher HbA1c levels impact hippocampal volume, and its effects on this brain structure could be mediate its associations with cognition and depressive symptoms, this has not been explicitly investigated. Thus, the present study examined associations between HbA1c levels and both memory performance and depressive symptoms in a sizeable community-based sample spanning a wide adult age range. A subsample also provided magnetic resonance imaging (MRI) data. The data came from the Baependi Heart Study, a longitudinal cohort study that began in 2005 [50]. Hippocampal volume was extracted and associations with HbA1c levels, memory performance, and depressive symptoms were assessed. In contrast to most previous work, we took a dimensional rather than a categorical approach to quantifying depression and glycaemic control, with continuous measures of these employed in all analyses. We hypothesised that higher levels of HbA1c would be correlated with lower immediate memory recall performance, higher depressive symptoms, and smaller left, right, and total hippocampal volumes. In addition, given that some of the studies outlined above point to a possible effect of age, as a follow-up analysis, we examined whether the relationship between HbA1c levels and hippocampus volume, and depressive symptoms, might be stronger in those amongst the sample aged over 50. We used this age point as a cut-off so as to align with various previous relevant studies focusing on this age range, for example work exploring effects of diabetes and HbA1c level on depression symptoms [51], and impact of HbA1c on cognition and brain health [52], to specifically test the possibility that, in the ageing brain, the hippocampus might be more vulnerable to the toxic effects of HbA1c. Then, a series of mediation models were run to test the hypotheses that hippocampus volume mediates the association between HbA1c and depressive symptoms and memory performance.

Method

Participants

The data were obtained from the Baependi Heart Study, a longitudinal cohort study focused on cardiovascular risk factors amongst individuals living in a small town in Brazil [50]. See [53] for details regarding the population and sampling methods. We used cross-sectional data from a single wave of data collection since only this wave contained measures of HbA1c, memory, depression, and neuroimaging. All measures were collected from 2015 to 2017. Owing to limited resources, MRI scans were only obtained for a subset of the cohort; also, depression data was only available for this subset. Therefore, in the present study, analyses were conducted on two samples: the 'whole sample' and the 'MRI sample'. The MRI sample was comprised of a subset of participants from the full sample who were randomly invited for an MRI. Informed consent was obtained, consistent with the Helsinki Declaration. Ethical approval was granted by the ethics committee of the Hospital das Clinicas – Universidade de So Paulo, Brazil. All participants gave informed written consent before participation. Exclusion criteria for the whole sample: we excluded participants with a history of head trauma, stroke, or psychiatric diagnosis other than anxiety/depression. We also excluded 5 participants with unrealistically low values of HbA1c (below 4% [54]). We did not exclude participants with low cognitive performance as it could be confounded with low education [55]. Each analysis was conducted with the maximum N of available data.

Whole Sample

The whole sample consisted of 1331 (60.9% female) individuals. The participants' ages ranged between 18 and 88 ($M = 44.02$, $SD = 15.17$). According to the WHO (2011), an HbA1c level of 6.5% and above is recommended as a reliable cut-off value for the diagnosis of diabetes; 86 (6.5%) participants met this criterion. The whole sample was used to test the associations between HbA1c levels and memory. Mean education years was 8.66 (see Table 1), this aligns closely with the mean for Brazil (~8 years according to the World Bank's Human Capital Index 2020).

Whole Sample

MRI Sample. The MRI sample consisted of 392 individuals (63% female) aged between 18 and 85 (M=46.51, SD=15.08). 29 (7.4%) participants met the criterion for diabetes. The MRI sample was used to test the associations between HbA1c, depression, and hippocampal volume. Within the MRI sample, we also looked at effects amongst those participants aged 50 and over (the 'Age 50+ MRI sample'). The Age 50+ MRI sample comprised 180 participants (57.2% female, M_{age} = 59.97, SD=7.69).

Measures

Sociodemographic variables

Participants provided their age, gender, and their education(years).

HbA1c

Participants fasted for 12 h prior to blood draw: time of collection ranged between 6.30am to 8am. Levels of HbA1c in blood were extracted via high-performance liquid chromatography (HPLC), using procedures that followed the National Glycohemoglobin Standardization Program (USA).

Word list recall task

Participants' immediate memory recall was assessed using the brief neuropsychological battery established by The Consortium to Establish a Registry for Alzheimer's disease (CERAD). Its applicability for use in Brazilian populations has been established [56]. Due to concerns around inaccurate/missing data, the delayed recall trials were not used. In this task, participants are asked to read aloud 10 unrelated items on printed cards presented one by one to them. After all of these items have been shown, the participants recall as many items as possible. This is repeated three times, and the presentation order of the 10 words is varied each time. Correct recalls are tallied and used to construct three measures of memory performance: "Word List: Total Immediate Recall" (the total number of items recalled (max=30)), "Word List: Trial 1" (recall on the first attempt only), "Word List: Learning" (memory improvement across trials: recall on trial 3 minus recall on trial 1).

Hospital anxiety and depression scale (HADS)

Depressive symptoms and anxiety were evaluated using a Portuguese translation of the HADS, validated in Brazilian populations [57]. The Portuguese translation has high sensitivity and specificity [58]. We only used summed scores from the depression subscale, which consists of 7 questions using a 4-point Likert scale (range from 0 to 3, with a maximum score of 21).

MRI acquisition

MRI scans were acquired at the Hospital Conego Monte Raso in Baependi on a 1.5 T MAGNETOM (Siemens, Munich, Germany). A high resolution T1-weighted structural images were obtained using a three-dimensional fast spoiled gradient echo T1-weighted sequence with the following parameters: Voxel size 1 mm^3, 160 slices, Matrix Size 256×256, TR 1700ms, TE 5.1 ms, flip angle 120, inversion time 850 ms, scan time 5m30s. A previous analysis using this dataset to examine associations with metabolic syndrome has been published [59]. The data collection period was from March 2015 to December 2017.

MRI Data Processing

All images were visually inspected, and then cortical reconstruction and volumetric segmentation were carried out using the Freesurfer 6.0 image analysis suite (https://surfer.nmr.mgh.harvard.edu). The reconstruction pipeline employed by Freesurfer includes intensity normalization, motion correction, and the exclusion of non-brain tissue was performed using a hybrid watershed/surface deformation procedure. Images are transformed into Talairach space, and the subcortical white matter and deep grey matter structures are segmented [60, 61]. Hippocampal volumes were calculated using Freesurfer's automated hippocampal and amygdala segmentation algorithm (included with the development version of Freesurfer 6.0) which uses a probabilistic atlas built with ultra-high resolution MRI data to segment the hippocampal substructures and nuclei of the amygdala [62]. The volumes of the whole hippocampus were extracted for each hemisphere. To account for differences in head size, we used Freesurfer's estimated total intracranial volume (ICV) as a covariate in our statistical analyses.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences, version 26.0 (SPSS, Chicago, IL). In this study, the whole sample was used to test the association between HbA1c and memory performance. Then, the MRI sample was used to examine the associations between HbA1c levels, depressive symptoms, and hippocampal volumes; the 50+sample was used to test these associations in participants aged 50 and over. Comparisons between the various samples in terms of participant characteristics were carried out with t-tests or ANOVA (where appropriate for continuous variables) and Pearson`s chi-squared test (for categorical variables). We first checked for extreme outliers in the data indicating unrealistic values, none were found. Normality was then checked by calculating skewness and kurtosis: values above 2 or below −2 were considered as indicating non-normality [63]. HbA1c levels were non-normally

distributed; therefore, HbA1c levels were log10 transformed to ensure more normally distributed data in all analyses, in line with the previous work [64]. The transformation was computed in SPSS.

Pearson's partial correlations were conducted to investigate the relationship between depressive symptoms, HbA1c, memory performance, and hippocampal volume (total, right, and left hippocampus volume). All partial correlations were adjusted for age, gender, and education. Due to non-normality in the Education (years) variable, we categorised participants into 3 education groups: Primary or less (<5 years education), Secondary (between 5 and 10 years education), and Higher (>10 years education), and this categorical variable was used as a covariate in the correlation and mediation analyses. The partial correlation analyses investigating the relationship between HbA1c levels and hippocampus volume also adjusted for depressive symptoms (HADS-D score) and ICV. As we had directional hypotheses, we report one-tailed results for all correlations.

In the MRI sample, we next sought to examine whether the effect of HbA1c on memory performance and depressive symptoms is mediated by total hippocampal volume. Model 1 tested whether the effect of an independent variable (IV: HbA1c) on the dependent variable (DV: Word List: Trial 1) is accounted for by the mediator (M: total hippocampus volume). Model 2 tested whether the effect of IV (HbA1c) on the DV (Word List: Total Immediate Recall) is accounted for by M (total hippocampal volume). Model 3 explored whether the effect of IV (HbA1c levels) on the DV (Depressive symptoms) is mediated by M (total hippocampal volume). We also tested these same three models in the 50+MRI sample as follow-up analyses. We first report the mediation results adjusted for age only. Then, we present mediation results with additional covariates added to the models (gender and education, and then with ICV also). All models were simple mediation models (Model 4) with 10,000 bootstrap samples using the PROCESS macro in SPSS [65].

Results

Demographic data

Table 1 presents the participant characteristics.

Correlations between HbA1c and memory performance (whole sample)

As we had hypothesised an inverse relationship between HbA1c levels and memory performance, partial correlations were conducted between HbA1c levels and the Word List memory measures, controlling for age, gender, and education. HbA1c levels were related to Word List: Total Immediate Recall (r (1326) = −0.062, p = .012, 1-tailed) and Word List: Trial 1 (r (1326) = −0.053, p = .027, 1-tailed), see Fig. 1. There was no significant

Table 1 Participant characteristics

	Whole Sample (*N* = 1,331)	MRI Sample (*N* = 392)	Age 50+ MRI sample (*N* = 180)	Contrasts *p* value	Significant Contrasts
Age (*M, SD)*	44.02 (15.17)	46.51 (15.08)	59.97 (7.69)	< 0.001	Whole < MRI MRI < 50 + MRI
Female (N, %)	811 (60.9)	247 [63]	103 (57.2)	> 0.05	-
Education (Years)	8.66 (4.25)	7.89 (4.58)	6.35 (4.54)	< 0.001	Whole > MRI MRI > 50 + MRI
Education (Grouped)					
Primary or less	29.2%	36.5%	51.1%	< 0.05	
Secondary	23.1%	21.2%	22.8%		
Higher	47.8%	42.3%	26.1%		
HbA1c	5.50 (0.70) [a]	5.60 (0.70)[a]	5.80 (0.60)[a]	< 0.001	50 + MRI > MRI 50 + MRI > Whole
WL Total Immediate Recall	18.68 (4.01)	18.77(3.93)[b]	17.48(3.95)[c]	< 0.001	Whole < MRI Whole > 50 + MRI
WL Trial 1	4.5 (1.51)	4.56(1.45)[b]	4.12(1.43)[c]	0.007	Whole < MRI Whole > 50 + MRI
WL Learning	3.26 (1.47)	3.24(1.51)[b]	3.23(1.61)[c]	> 0.05	
HADS-D	NA	6.12 (3.54)	6.61 (4.01)	> 0.05	
HC Volume (mm^3)	NA	6,542.21 (654.99)	6,371.63 (699.60)	0.005	MRI > 50 + MRI
Left HC Volume (mm^3)	NA	3,253 (344.08)	3,146.44 (353.28)	< 0.001	MRI > 50 + MRI
Right HC Volume (mm^3)	NA	3,288 (344.35)	3,225.24 (363.58)	0.046	MRI > 50 + MRI

Abbreviations HADS-D = Hospital Anxiety and Depression Scale: Depression subscale, HbA1c = glycolated haemoglobin, HC = hippocampus, NA = Not available, WL: word list task

[a] Reported as Median (Interquartile range), *Mdn* (*IQR*)

[b] Word List data were available for 339 participants in the MRI sample

[c] Word List data were available for 140 participants in the 50 + MRI sample

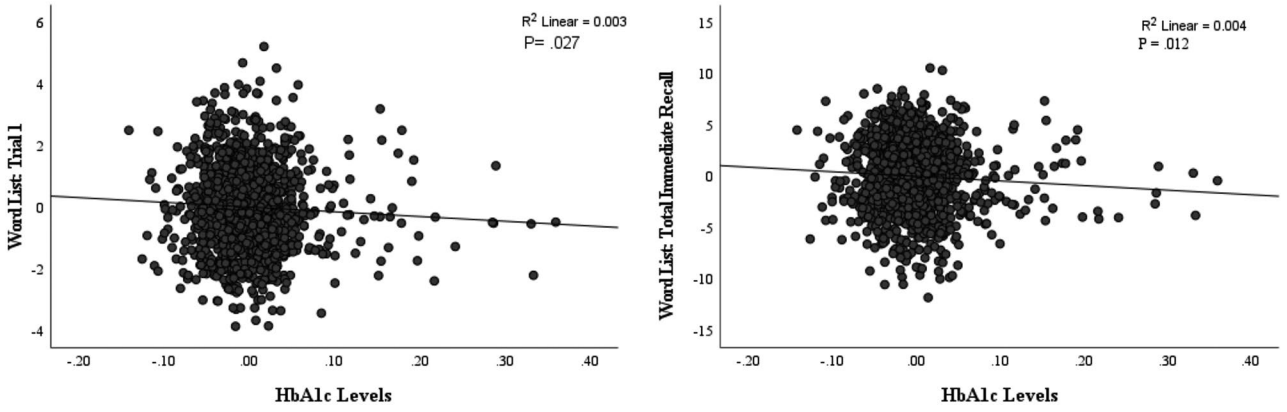

Fig. 1 Scatterplots of the associations between HbA1c levels, (**a**) Word List: Trial 1, and (**b**) Word List: Total Immediate Recall performance, in the Whole sample, after adjusting for age, gender, and education

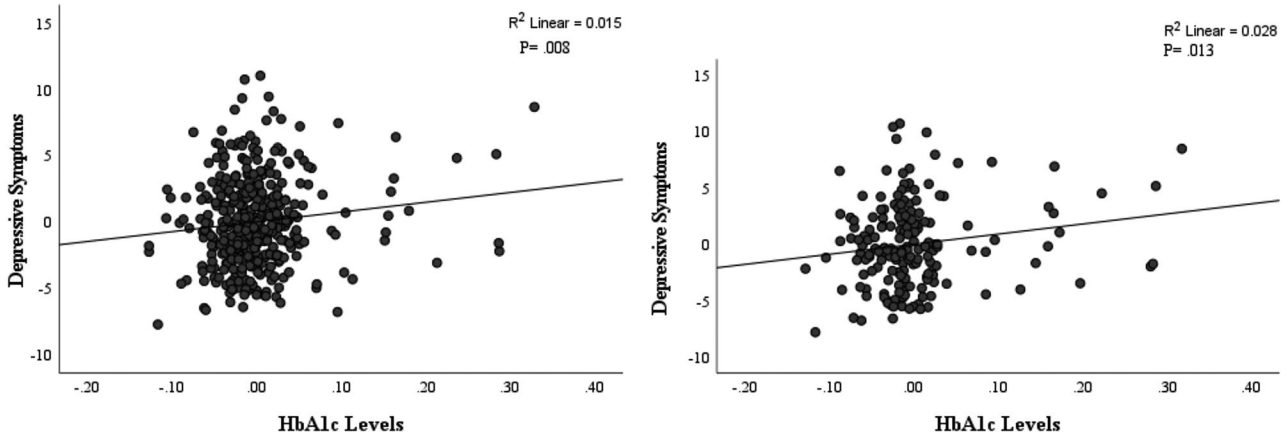

Fig. 2 Scatterplots of the positive associations between HbA1c levels and depressive symptoms in (**a**) the MRI sample and in (**b**) the Age 50+ MRI sample, after adjusting for age, gender, and education

correlation between HbA1c levels and Word List: Learning (p=.222, 1-tailed). Analyses in the MRI sample (and the age 50+MRI sub-sample) showed similar associations: significant correlations between HbA1c with Word List: Total Immediate Recall, and Trial 1, were found (see Supplementary Results 1, and Supplementary Figs. 1 and 2).

Relationship between HbA1c and depressive symptoms (MRI sample)

As we had hypothesised a positive relationship between HbA1c levels and depressive symptomology, a partial correlation (controlling for age, gender, and education) was conducted: the relationship was significant, (r (387)=0.121, p=.008, 1-tailed, see Fig. 2). In the Age 50+ MRI sample, the association was also significant (r (175)=0.168, p=.013, 1-tailed), see Fig. 2.

Correlations between HbA1c and hippocampal volumes (MRI sample)

To test whether higher HbA1c levels were associated with lower left, right, and total hippocampus volume, partial correlations were again performed (controlling for age, gender, education, ICV and depressive symptoms). Higher HbA1c levels were significantly associated with smaller left (r (385)=−0.108, p=.017, 1-tailed), and total hippocampal volume (r (385)=−0.101, p=024, 1-tailed), see Fig. 3. There was a trend-level association between HbA1c levels and right hippocampal volume (r (385) = -0.077, p=.065, 1-tailed). In the Age 50+ MRI sample, higher HbA1c levels were associated with smaller left (r (173)=−0.200, p=.004, 1-tailed), right (r [17]=−0.143, p=.0295, 1-tailed) and total hippocampus volume (r [17]=−0.180, p=.0054, 1-tailed), see Supplementary Fig. 3.

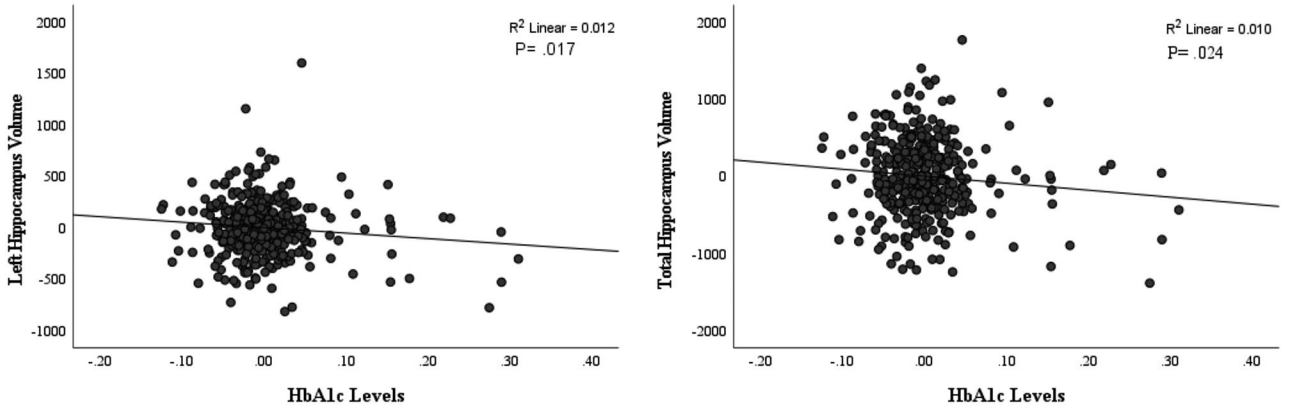

Fig. 3 Scatterplots showing the negative associations of HbA1c levels with (**a**) left hippocampus volume and (**b**) total hippocampus volume (in the MRI sample) after adjusting for age, gender, education, depressive symptoms, and ICV

Correlations between hippocampal volumes and memory performance (MRI sample)

To investigate whether Word List: Trial 1, Learning, and Total Immediate Recall were associated with hippocampus volumes, partial correlations were performed (controlling for age, gender, education, and ICV). Results showed that Word List: Trial 1 performance was not associated with left (p=.35), right (p=.31), or total (p=.48) hippocampus volume. Similarly, Word List: Total Immediate Recall performance was not associated with left (p=.35), right (p=.21), or total (p=.42) hippocampus volume. Again, Word List: Learning performance was not associated with left (p=.35), right (p=.49), or total (p=.42) hippocampus volume. In the Age 50+ MRI sample there was likewise no significant associations between any of the memory performance measures and left, right or total hippocampus volume (all p>.05).

Mediation Analyses (MRI sample)

Mediation analyses were carried out to explore whether total hippocampus volume mediates the observed relationships between HbA1c levels and two of the memory performance measures (Model 1 - Word List: Trial 1; Model 2 - Word List: Total Immediate Recall), and the observed relationship between HbA1c levels and depressive symptoms (Model 3). We first conducted partially-adjusted mediation models (adjusted only for age), then again further adjusting for gender, and education, and finally additionally adjusting for total intracranial volume (ICV).

Model 1

(IV: HbA1c levels, DV: Word List: Trial 1, M: total hippocampal volume) showed no significant mediation effect of total hippocampal volume. In the age-adjusted mediation model, results showed that higher HbA1c levels were associated with lower total hippocampal volume (p<.05), however, hippocampal volume did not predict Word List: Trial 1 performance (p>.05); the indirect effect of total hippocampal volume was not significant in either the MRI (est=0.005, 95% CI [-0.018, 0.029]) nor the Age 50+ MRI sample (est=0.026, 95% CI [-0.016, 0.079]). Similar results were found with gender and education as additional covariates: the indirect effect was non-significant in both the MRI (est=0.009, 95% CI [-0.010, 0.037]) and Age 50+ MRI sample (est=0.030, 95% CI [-0.015, 0.094]) samples. Adding ICV as a further covariate, the mediation analysis showed that the indirect effect of HbA1c levels on Word List: Trial 1 was again non-significant in both the MRI (est=0.002, 95% CI [-0.019, 0.025]) and the Age 50+ MRI samples (est=0.017, 95% CI [-0.026, 0.070]).

Model 2

(IV: HbA1c levels, DV: Word List: Total Immediate Recall, M: total hippocampal volume) also revealed no significant mediation effect of total hippocampal volume in the age-adjusted model. The path from HbA1c to hippocampal volume was significant, but the association between hippocampal volume and Word List: Total Immediate Recall was not (p>.05); the indirect effect was also not significant in either the MRI (est=−0.010, 95% CI [−0.051, 0.076]) nor the50+MRI (est=0.095, 95% CI [−0.022, 0.246]) samples. Again, adding gender and education yielded similar results, the indirect effect was not significant in either the MRI (est=0.029, 95% CI [-0.022, 0.098]) nor the 50+MRI (est=1.989, 95% CI [-0.149, 5.053]) samples. Adding ICV as a further covariate showed that the indirect effect of HbA1c levels on Word List: Total Immediate Recall remained non-significant in both the MRI (est=0.001, 95% CI [-0.054, 0.056]) and the Age 50+ MRI sample (est=0.048, 95% CI [0.071, 0.184]) samples.

Thus, there was no evidence of a mediating effect of hippocampal volume for either of the memory measures (see Supplementary Tables 1, 2 and 3).

Model 3

(IV: HbA1c levels, DV: depressive symptoms, M: total hippocampal volume) showed a significant mediation effect of total hippocampal volume in the age-adjusted model, see Fig. 4. Higher HbA1c levels were associated with lower total hippocampus volume (a = -90.905, p=.011) and lower total hippocampus volume was subsequently associated with higher depressive symptoms (b=−.001, p<.001). A 95% confidence interval based on 10,000 bootstrap samples indicated that the indirect effect (est=.085, 95% CI [0.014, 0.174]) was significant. However, the direct effect was also still significant (c' = 0.444, p=.025). Thus, total hippocampus volume partially mediated the association between HbA1c levels and depressive symptoms in the MRI sample. However, after adding gender and education as additional covariates, the indirect effect was weakened and the CIs were seen to marginally overlap with zero (est=0.030, 95% CI [-0.010, 0.089]). After adding ICV as a further covariate, no indirect effect through the mediator was observed (est=−0.010, 95% CI [-0.060, 0.033]).

In the Age 50+ MRI sample, total hippocampal volume fully mediated the association between HbA1c and depressive symptoms in the age-adjusted model, as the indirect effect was significant (est=.146, 95% CI [0.032, 0.289]), while the direct effect was not (c' = 0.450, p=.063) (see Supplementary Results 2, and Supplementary Fig. 4). However, when adding gender and education as additional covariates, the indirect effect was again seen to be weakened, with the CIs marginally overlapping with zero (est=0.069, 95% CI [-0.010, 0.176]) and the direct effect almost reached statistical significance (c' = 0.069, p=.057) (see supplementary Results 2). After adding ICV as a further covariate, no indirect effect through the mediator was observed (est=−0.001, 95% CI [-0.086, 0.095]); however, the direct effect of HbA1c was significant (c' = 0.482, p=.040).

Discussion

The current cross-sectional study examined the association between HbA1c levels and memory, as well as associations amongst HbA1c levels, depressive symptoms, and hippocampal volumes. We made use of a large community sample spanning the whole adult age range, of which a subset underwent MRI. In the entire sample, higher HbA1c levels were related to lower trial 1 and total immediate recall performance word list recall; these effects were also present in the MRI subset. Also, higher HbA1c levels were associated with higher depressive symptoms, and smaller left and total hippocampal volume (an association with right hippocampal volume was additionally present in those aged 50+). We then explored whether total hippocampal volume acted as a mediator in these relationships between HbA1c and memory, and HbA1c and depression. No mediation effect was seen for immediate memory recall, but total hippocampus volume partially mediated the association between HbA1c levels and depressive symptoms, although it should be noted that this was only evident when models were adjusted for age only; adding further covariates (gender, education, ICV) undermined the mediation effect.

There is little previous work that directly explored these questions. In one longitudinal study, higher HbA1c values were associated with lower episodic memory (composite scores of immediate and delayed word recall) at baseline, and a steeper decline over six years, in a community sample aged 60 and over [66]. However, in another cross-sectional study in healthy participants aged between 50 and 75, HbA1c was not associated with performance on the California Verbal Learning Test (CVLT) or story recall (Logical Memory of the Weschler Memory Scale- III) [67], although this study excluded those whose HbA1c levels met the diagnostic criterion for diabetes, and it was severely underpowered (N=34). Thus, the current study is novel in that we used a large sample that spanned most of the adult age range (18 to 85); in which

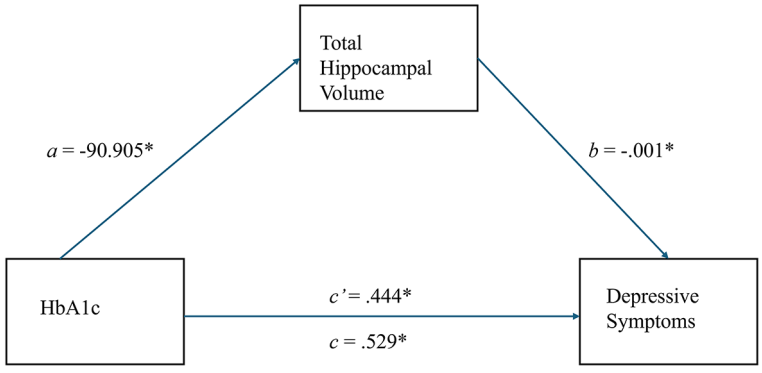

Fig. 4 Mediation Model 3 (MRI sample, adjusted for age only). Notes: *p < .05; statistics are unstandardized; a is effect of HbA1c on total hippocampal volume; b is effect of total hippocampal volume on depressive symptoms; c' is direct effect of HbA1c on depressive symptoms; c is total effect of HbA1c on depressive symptoms. See Supplementary Fig. 4 for the results in the Age 50+ MRI sample

only a small minority (~7%) met diabetes criteria: findings indicate that even within the normal range, poorer glycaemic control is related to reduced immediate memory recall performance, throughout adulthood, while controlling for age, gender and education.

While we cannot infer the direction of causality from this cross-sectional study, this finding suggests neural systems subserving memory are impacted by poorer glycaemic control, and this effect is not just limited to older adulthood. We also found a significant positive relationship between HbA1c levels and depressive symptoms. Again, there is a paucity of research examining the association between HbA1c levels and depressive symptoms in community samples, as most studies have investigated this in patients with diabetes: the association between diabetes and depression is well established [33, 68]. One previous longitudinal study linked higher HbA1c levels with an increase in depressive symptoms, in a mixed community sample of healthy adults and diabetes patients aged 50+ [33]. Our results provide evidence that even in healthy adults, a higher HbA1c level is associated with elevated depressive symptoms. Further, this seems to be the case throughout adulthood, and not just in later life.

The MRI data showed that higher HbA1c levels were associated with smaller left and total hippocampal volumes; an association with right hippocampal volume was additionally present in those aged 50+. Prior studies have shown similar results, but mostly by comparing diabetes patients and healthy participants [69]. One previous study used UK Biobank to test for an effect of low-to-normal HbA1c values, as compared to individuals with normal glycaemic control, prediabetes, undiagnosed and known diabetes (age range 40–69) [16]. A stepwise reduction in hippocampal volume was observed according to the diagnostic group. The current study builds on that finding by showing that this relationship holds, in a sample of a wider age range, and when HbA1c was considered as a continuous variable, rather than grouping participants by category. There are various mechanisms that could link HbA1c levels to hippocampal volume reductions. Elevated cortisol has been associated with poor glycaemic control, and the hippocampus is highly sensitive to the neurotoxic effects of cortisol [23]; glucotoxicity due to hyperglycaemia may also contribute, through the build-up of AGEs [19, 20]. These factors can induce oxidative stress, triggering neuronal apoptosis in hippocampus [70]. In previous work, hippocampal volume has been found to partially mediate the effect of HbA1c on delayed recall and learning ability (measured by the REY Auditory Verbal Learning Test) in healthy participants aged 50–80 [64]; hippocampal microstructural metrics were also found to partially mediate the relationship, thus representing an additional possible mechanism. Here, we did not find any significant mediation effect of hippocampal volume in the association between HbA1c and immediate memory performance. We included age and other covariates in our mediation models but Kerti et al. [64] did not, which could explain the differences in findings. Alternatively, it might have been due to the specific memory measure used here: the current work is limited by the fact that only immediate but not delayed recall was tested, and used word list learning only: future work should utilise a broader range of memory tasks, to clarify the role of hippocampal volume as a possible mediating factor. Indeed, we did not identify a link between hippocampal volume and memory performance in our sample: previous work on this point is conflicting, with mixed reports in both developmental and adult samples [25]; some studies have reported a significant association between total hippocampal volume and memory (e.g., 23) while others have reported no association (e.g., [71]).

We also explored whether impaired glycaemic control may impact depressive symptomology via hippocampal volume reductions. Research has indicated the detrimental effect of depression on hippocampal volume due to cortisol-related neurotoxicity [23]; studies also suggest that smaller hippocampi might also be a risk factor for depression [48, 49]. For example, in middle-aged and older people, smaller hippocampal volume at baseline was associated with higher depressive symptoms over an eight-year follow-up [72].

We found evidence that the association between HbA1c and depressive symptom severity is partly mediated by total hippocampal volume in the mediation models that adjusted for age, although this did not survive in the fully-adjusted models. To our knowledge, the present study is the first to investigate the mediating role of hippocampal volume in the association between HbA1c levels and depressive symptoms in a community sample, and this finding is important in that it points to a potentially important role for hippocampal volume loss as an explanatory variable in this association. The mediation effect was stronger in the 50+subsample in that a full mediation occurred, but again only in the age-adjusted model. Adding gender and education weakened the mediation effects to borderline significance, while adding ICV abolished it. This could be due to the complex interactions between HbA1c, gender and global brain volumes indicated by recent work: a large study in UK Biobank participants found an association between higher HbA1c levels and lower whole brain volume [52], while a study in older adults linked HbA1c to lower whole brain volumes exclusively in females [73]. Given this preliminary evidence, it is possible that impaired glycaemic control has widespread impact on brain volumes, with females at higher risk – thus confounding and undermining the mediation effect when gender and ICV were added to the

models. Further work is needed to more fully characterise the complex effects of HbA1c on hippocampal as well as whole brain volumes.

The impact of impaired glycaemic control on the hippocampus has been clearly shown in diabetes, which has been linked to neurodegeneration and abnormal signalling in human hippocampi [74]. In animals, improving glycaemic control by insulin treatment reverses the effect of induced diabetes on hippocampal volume and affective behaviour [75]. The current findings, indicating hippocampus volume as a potential mediator in the glycaemic control - depression relationship, is noteworthy as the sample largely had HbA1c levels in the normal range, suggesting that this might be a generalisable mechanism and not restricted to diabetes. The damaging effects of cortisol on the hippocampus could contribute, and should be investigated by future work since (as discussed above), increased circulating cortisol has been linked to higher HbA1c levels, as well as the risk of depressive symptoms [23, 76–78]. The neurotoxic effects of cortisol on the hippocampus are well established [23]; elevated cortisol levels cause both hippocampal volume loss and the inhibition of neurogenesis [79]. In the 50+age group, the mediation effect appeared to be stronger, in line with evidence showing that the hippocampus is particularly vulnerable to the effects of ageing. However, it should be noted that our 50+group had lower levels of education compared to the MRI sample as a whole, which could have influenced findings, for example due to lower cognitive reserve capacity.

The robust associations between HbA1c and hippocampal volumes found here are also of importance; again, these were most apparent in the 50+age group, with associations found with both left and right hippocampal volumes in this age range. The hippocampus is one of the first brain regions to be affected by Alzheimer's disease (AD) pathology [80]. Moreover, higher HbA1c levels and depressive symptoms have been shown to increase the risk of AD [81, 82] and memory decline [12, 83]. Therefore, our findings point to HbA1c as a modifiable risk factor that should be targeted, to minimise hippocampal atrophy and the risk of cognitive decline in later life. This is further supported by the full mediation effect identified in those aged 50+: since HbA1c appears to link to depression symptoms via hippocampal volume, and depression itself raises the risk of AD, cognitive decline, and hippocampal atrophy, maintaining healthy HbA1c levels might be of prime importance to prevent a negative feedback loop from occurring, particularly in mid-age and older individuals. However, future studies should investigate the associations longitudinally, and also characterise and account for effects on whole brain volume and potential gender interactions, since the mediation effect observed here was only present in the partially-adjusted models, as discussed above. The cross-sectional research design is a limitation of the current study and prevents us making any casual inferences: it should be emphasised that we cannot discount the possibility of reverse causation i.e., depression levels could exert influences on hippocampal volume and HbA1c levels, perhaps due to dysregulated sleep, cortisol, or poorer dietary choices. Longitudinal work should seek to clarify causal relationships and mechanisms linking impaired glycaemic control to reduced hippocampal volume, increased risk of depression, and cognitive decline. Also, it is important to note that there are various potential confounding variables (such as body mass index) which future studies should attempt to control for: missing information in the present dataset meant we could not control for these here, and this might have impacted the findings. Body mass index and blood markers associated with obesity have been shown to impact on cognitive performance [84] and cortical volumes [85], and although findings are not consistent, it would be valuable to include such measures in future work, to rule out possible confounding effects and confirm the relationships reported here. Future work should also aim to replicate the current findings in other populations, the current findings are valuable in that they were derived from an understudied, non-Western population, but need to be confirmed in other samples.

Conclusions

The current study addresses knowledge gaps around the associations between HbA1c levels, cognition, depressive symptomology, and brain volumes, and revealed the impact of poor glycaemic control on immediate memory recall, depression levels and hippocampal volumes, in a large non-clinical sample covering the whole adult age range. Also, this is the first study to investigate hippocampal volumes as a possible mediator in the association between HbA1c levels and depressive symptoms, and shows that hippocampal structural integrity might be an important mechanistic pathway in the relationship between HbA1c and depressive symptoms, particularly in older adults. Given the powerful negative consequences of poor glycaemic control for mental health, cognitive function and brain structure demonstrated by the current findings, results underline the importance of implementing policies and interventions focused on optimising HbA1c levels, to avoid the negative outcomes identified here.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-024-01429-2.

Supplementary Material 1

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Author contributions
G.Y.S. Formal analysis, Writing – original draft; S.E. Formal analysis, Writing – original draft, E.A. Data preparation, Writing - review & editing; T.P.T. Data collection, Data preparation, Writing - review & editing; J.E.K Study Design, Data collection; A.C.P Study Design, Writing - review & editing.

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Data availability
Data will be made available on reasonable requests.

Declarations

Ethical approval
Informed consent was obtained, consistent with the Helsinki Declaration. Ethical approval was granted by the ethics committee of the Hospital das Clinicas – Universidade de So Paulo, Brazil. Participation in this study was voluntary and all participants gave informed written consent before participation.

Competing interests
The authors declare no competing interests.

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