Psychiatry Research: Neuroimaging 278 (2018) 1–6

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Higher fasting plasma glucose is associated with smaller striatal volume and poorer fine motor skills in a longitudinal cohort

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ARTICLE INFO

Keywords:
Type 2 diabetes
MRI
Striatum
Fine motor skills

ABSTRACT

Previous studies have demonstrated associations between higher blood glucose and brain atrophy and functional deficits, however, little is known about the association between blood glucose, striatal volume and striatal function despite sensori-motor deficits being reported in diabetes. This study investigated the relationship between blood glucose levels, striatal volume and fine motor skills in a longitudinal cohort of cognitively healthy individuals living in the community with normal or impaired fasting glucose or type 2 diabetes. Participants were 271 cognitively healthy individuals (mean age 63 years at inclusion) with normal fasting glucose levels (<5.6 mmol/L) (n=173), impaired fasting glucose (5.6–6.9 mmol/L) (n=57), or with type 2 diabetes (≥7.0 mmol/L) (n=41). Fasting glucose, Purdue Pegboard scores as measurement of fine motor skills, and brain scans were collected at wave 1, 2 and 4, over a total follow-up of twelve years. Striatal volumes were measured using FreeSurfer after controlling for age, sex and intracranial volume. Results showed that type 2 diabetes was associated with smaller right putamen volume and lower Purdue Pegboard scores after controlling for age, sex and intracranial volume. These findings add to the evidence suggesting that higher blood glucose levels, especially type 2 diabetes, may impair brain structure and function.

1. Introduction

Type 2 diabetes (T2D) is a common, chronic, and progressive metabolic disorder known to be associated with greater brain atrophy (Brundel et al., 2010; den Heijer et al., 2003) and an approximately two-fold increased risk of developing dementia (Cheng et al., 2012). Cognitive processes such as memory, processing speed, and executive function are likely to be affected by T2D (Kodl and Seaquist, 2008). A number of factors, including hyperglycemia, vascular disorders, hypoglycemia, and insulin resistance, have been hypothesized to mediate the risk between T2D and cognitive impairment (Kawamura et al., 2012). Previous studies have demonstrated associations between higher blood glucose levels and T2D-related atrophy of the whole brain and local brain areas such as the hippocampus (Moulton et al., 2015; Samaras et al., 2014; Tiehuis et al., 2008). In addition, while elevated blood glucose levels are characteristic of T2D, higher blood glucose levels in subclinical diabetes or even within the normal range may also adversely affect brain structure before the onset of T2D (Cherbuin et al., 2012; Mortby et al., 2013); in turn, brain volume differences in subclinical diabetes or within the normal range may be associated with cognitive decline (Mortby et al., 2013; Samaras et al., 2014). However, much of the current evidence is cross-sectional and longitudinal studies are required to confirm these associations, characterize their trajectories over time, and determine how they relate to cognitive function.

In this context a structure of particular interest is the corpus striatum (including caudate, putamen and globus pallidus) because it contributes to brain functions, such as fine motor movements, executive function and emotion regulation which have been found to be impaired in T2D. At least one study identified an association between T2D and lower Purdue pegboard score indicating impaired fine motor skills (Kumar et al., 2008). Our previous study found that higher fasting plasma glucose levels were associated with smaller regional volumes at striatal structures in cognitively healthy older people with and without T2D, using volumetric analysis and vertex-based shape analysis (Zhang et al., 2016). Also, some late stage diabetes patients may develop diabetic striatopathy with manifest motor symptoms similar to

Abbreviations: ICV, intracranial volume; IFG, impaired fasting glucose; NFG, normal fasting glucose; PP, Purdue Pegboard scores; PPd, Purdue Pegboard scores of dominant hand; PPn, Purdue Pegboard scores of non-dominant hand; PPb, Purdue Pegboard scores of both hands; T2D, type 2 diabetes mellitus

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https://doi.org/10.1016/j.pscychresns.2018.06.002
Received 1 December 2017; Received in revised form 4 June 2018; Accepted 5 June 2018
Available online 07 June 2018
0925-4927/

other brain diseases with striatal dysfunction (Abe et al., 2009; Lanciego et al., 2012). These studies have shown that striatal volumes differ between individuals with different glucose status, striatal structures are closely implicated in motor control, and other pathologies which affect the striatum can impact fine motor control. It is therefore theoretically important to determine whether there is a demonstrable link between blood glucose metabolism, striatal integrity, and fine motor function. However, functional implications of these morphological differences are unclear. In addition, it is not known whether variability in blood glucose affects striatal structure and function differently among individuals with normal blood glucose, with subclinical diabetes or with T2D.

Therefore, this study aimed to investigate the relationship between fasting plasma glucose levels, striatal volumes and fine motor skills in cognitively healthy individuals living in the community with normal fasting glucose (NFG) levels, impaired fasting glucose (IFG), or with T2D over a 12-year follow-up using a longitudinal design. Specifically, it was hypothesized that higher fasting plasma glucose levels would be associated with smaller striatal volume, and that both higher fasting plasma glucose and smaller strial volume would be associated with lower Purdue pegboard scores, thus indicating poorer fine motor skill performance. This study also aimed to test the potential mediation by striatal volumes of the association between fasting glucose and motor skills.

2. Methods

2.1. Study population

Participants of the PATH Through Life study (Anstey et al., 2012) were randomly recruited from senior residents (60–64 years of age) of the cities of Canberra and Queanbeyan, Australia, through the electoral roll. This study focuses on 2551 participants from the cohort aged 60–64 years who agreed to participate in the PATH Through Life project at baseline (2001). Participants were included if they had MRI scan at baseline (wave 1) and they had follow-up scans at wave 2 (four years later) or wave 4 (twelve years later); wave 3 was not included because no fasting glucose was available at wave 3. Participants with unusable MRI scans, neurological disorders, or without fasting plasma glucose measures or Purdue Pegboard scores were excluded, leaving a total of 271 participants in analyses (see Supplemental Fig. 1 for details). This study was approved by the Australian National University Ethics Committee and all participants provided written informed consent.

2.2. T2D and fasting plasma glucose levels

Venous blood was collected following an overnight fast of at least 10 hours. Plasma and Serum aliquots were frozen at −80°C. Fasting plasma glucose levels (hereafter, fasting glucose) were measured on a Beckman LX20 Analyzer by an oxygen rate method (Fullerton, California, USA). Participants were considered to have T2D if they self-reported having T2D, were treated by T2D medication, or if their fasting glucose was greater than or equal to 7.0 mmol/L. Participants without T2D and a fasting glucose between 5.6 mmol/L and 6.9 mmol/L were classified as having impaired fasting glucose (IFG) (American Diabetes Association, 2014). Participants with a fasting glucose lower than 5.6 mmol/L were identified as normal fasting glucose (NFG). In addition, because the pathological processes leading to T2D are progressive and start developing before clinical T2D is diagnosed it is important to clearly separate those individuals who have a normal glucose metabolism throughout the period studied and those who come to develop IFG or T2D later in the study follow-up. Because the number of participants transitioning from one category to the other was too small to analyze transition states participants were categorized as T2D or IFG if they transitioned to this category in the course of the study.

2.3. Cognitive measures

Fine motor skills and complex upper limb movements were assessed with the Purdue Pegboard test (Tiffin and Asher, 1948). It involves placing as many pins as possible into holes in a board within 30 seconds over three trials, using the dominant hand (PPd), the non-dominant hand (PPn) and both hands (PPb) simultaneously.

2.4. MRI scan acquisition

Participants were scanned on a 1.5T Philips Gyroscan ACS-NT scanner at wave 1 and wave 2 and a Siemens 1.5T MPRAGE scanner at wave 4 for T1-weighted three-dimensional structural MRI. The T1-weighted MRI was acquired in sagittal orientation using the following parameters: Wave 1: repetition time = 28.05 ms, echo time = 2.64 ms, flip angle = 30°, matrix size = 256 × 256, field of view = 260 × 260 mm, slice thickness = 2.0 mm, and mid-slice to mid-slice distance = 1.0 mm, yielding over contiguous coronal slices. Wave 2: repetition time = 8.93 ms, echo time = 3.57 ms, flip angle = 8°, matrix size = 256 × 256, field of view = 256 × 256 mm and slice thickness = 1.5 mm. Wave 4: repetition time = 1160 ms, echo time = 3.57 ms, flip angle = 15°, matrix size = 512 × 512 and slice thickness = 1.0 mm.

2.5. Image processing

Participants' MRI scans were processed using the Freesurfer software (Fischl, 2012). Because the scans come from three different waves, the longitudinal Freesurfer processing pipeline was applied to extract reliable volume and thickness estimates by creating an unbiased within-person template from assessment points (Reuter et al., 2012). All segmentations were visually inspected for accuracy prior to inclusion in the analysis. Regional volumes of striatal structures (caudate, putamen, globus pallidus,) were automatically segmented with a validated method (Fischl et al., 2002). Globus pallidus was not included in analyses due to insufficient segmentation quality by visual inspection. Because the study applied different scanners and scanner parameters at different waves, we preprocessed the MRI data to correct for between-wave differences induced by scanners using a previously described method (Shaw et al., 2016).

2.6. Statistical analyses

Cross-sectional analyses at wave 1 using hierarchical linear regression models were first conducted to provide a baseline against which to compare similar estimates (fixed effects) that can also be obtained in longitudinal models, and to contrast the magnitude of findings obtained by simpler but methodologically more limited cross-sectional analyses against those of more robust longitudinal analyses. Covariates in these analyses included age (years), gender and intracranial volume (ICV) (mm^3).

Building on the cross-sectional models, more complex longitudinal analyses using multi-level models (linear mixed models) were applied to assess associations between fasting glucose and striatal volumes, between fasting glucose and PP scores and between striatal volumes and PP scores across the three waves. The association between glucose and each outcome measure was investigated in four multi-level models of increasing complexity. In these models, variability of blood glucose, striatal volumes and fine motor skills over time was measured by estimating the within-person slope over time (random effect of time) in fasting glucose in the follow-up measurements. The final mixed effect models included random intercept as the sole random effect, due to insignificant random linear effect of time which indicates that changes in blood glucose over time were not significantly different between persons (See Supplemental Methods for more details regarding model specification). In Model 0, covariates included age, sex and ICV. Model

1 tested the association between the main predictor variable (e.g. fasting glucose) and the outcome variable (e.g. striatal volume). The interaction between the predictor variable and age was entered in Model 2, while the sex interactions were tested in Model 3. Model fit between models is considered improved if the -2 log-likelihood value is significantly reduced between models ($p < 0.05$).

Sub-group analyses were conducted to contrast the effects of blood glucose levels (which in previous studies have been found to be already present within the normal range) from those more specifically linked to the clinical progression of T2D from normal range to subclinical diabetes and diabetes. As the rate of brain volume changes has been shown to vary by age or sex especially in elderly people (Fox and Schott, 2004; Hua et al., 2010), we tested their interactions to determine if the associations between glucose, striatal volumes and fine motor skills are modulated by age or sex. For all analyses, Bonferroni correction ($\alpha = 0.05$ adjusted to 0.025 for fasting glucose/striatal volume analyses, and 0.017 for fasting glucose/PP score analyses; see Supplemental Methods for details) was applied. All the statistical analyses were conducted using IBM SPSS 23.

3. Results

3.1. Sample characteristics

Table 1 shows the sample characteristics of included participants. Of these, 54 (20.0%) had no scans at wave 2 (17.5% with IFG, 22.0% with T2D), and 71 (26.2%) at wave 4 (17.5% with IFG, 22.0% with T2D). No PP score was available at wave 4 for 5 (1.8%) participants (3.5% with IFG, 2.4% with T2D). All the measures of variables included in this study followed normal distributions. Participants included in this study ($n = 271$) did not differ from participants of the larger cohort from which they were selected ($n = 2{,}551$) on age, sex and race, but had significantly more years of education compared to non-selected participants (14.4 vs 13.7 years). Changes in fasting glucose, striatal volumes and PP scores over time are shown in Supplemental Fig. 2.

Table 1
Participants' characteristics.

Demographic variables	All (n = 271)	NFG (n = 173)	IFG (n = 57)	T2D (n = 41)
Female, n (%)	135 (49.8)	94 (54.3)	21 (36.8)	20 (48.8)
Age[a], years (SD)	63.1 (1.4)	63.2 (1.5)	62.8 (1.4)	63.0 (1.3)
Education[a], years (SD)	14.3 (2.5)**	14.6 (2.3)	14.2 (2.7)	13.4 (2.8)†
Caucasian, n (%)	260 (95.9)	168 (97.1)	53 (93.0)	39 (95.1)
Fasting glucose, mmol/L				
Wave 1	5.6 (0.9)	5.2 (0.5)	6.0 (0.4)‡	6.8 (1.4)‡
Wave 2	5.6 (1.1)	5.1 (0.4)	5.8 (0.4)‡	7.2 (2.0)‡
Wave 4	5.5 (1.4)	5.0 (0.4)	5.9 (0.6)‡	7.7 (2.7)‡
PP scores of dominant hand, score (SD)				
Wave 1	13.7 (1.8)	13.9 (1.8)	13.6 (1.8)	12.9 (2.0)‡
Wave 2	13.9 (1.9)	14.1 (1.9)	13.5 (1.8)	13.1 (1.9)‡
Wave 4	12.0 (2.0)	12.2 (1.9)	12.1 (1.8)	11.2 (2.3)‡
PP scores of non-dominant hand, score (SD)				
Wave 1	13.1 (1.9)	13.4 (1.8)	12.9 (1.7)	12.4 (2.0)‡
Wave 2	13.0 (1.9)	13.3 (1.9)	12.9 (1.8)	12.0 (1.8)‡
Wave 4	11.4 (1.9)	11.6 (1.8)	11.5 (1.7)	10.5 (2.2)‡
PP scores of both hands, score (SD)				
Wave 1	10.7 (1.5)	10.9 (1.5)	10.5 (1.5)	9.9 (1.6)‡
Wave 2	10.8 (1.8)	11.0 (1.7)	10.6 (1.5)	10.0 (2.0)‡
Wave 4	9.3 (1.8)	9.5 (1.8)	9.4 (1.3)	8.4 (1.8)‡

[a] at wave 1.
** $p < 0.01$ compared with non-selected.
† $p < 0.05$ compared with normal.
‡ $p < 0.01$ compared with normal.

3.2. Cross-sectional association between fasting glucose, striatal volumes and PP scores at wave 1

3.2.1. Cross-sectional association between fasting glucose and striatal volumes

No significant cross-sectional associations were detected at wave 1 between fasting glucose and striatal volumes in the whole sample or when stratifying by fasting glucose status (Supplemental Table 1).

3.2.2. Cross-sectional association between fasting glucose and PP scores

A significant negative association between higher fasting glucose and lower PPb was detected at wave 1 among all participants ($\Delta R^2 = 0.033$, $\beta = -0.184$, $p = 0.002$) indicating that for every additional 1 mmol/L in fasting glucose above 3 mmol/L there was a 0.184 decrease in PP score accounting for 3.3 % of variance in PP score; a similar negative association was found between fasting glucose and lower PPn ($\Delta R^2 = 0.037$, $\beta = -0.193$, $p = 0.001$). No associations were detected in sub-group analyses (see Supplemental Table 2).

3.2.3. Cross-sectional association between striatal volumes and PP scores

No cross-sectional associations were detected between striatal volumes and PP scores at wave 1 in the whole sample or when stratifying by fasting glucose status (Supplemental Table 3).

3.3 Association between fasting glucose, striatal volumes and PP scores across multiple assessments

3.3.1. Association between fasting glucose and striatal volumes

Results demonstrated a significant negative association between fasting glucose and right putamen volume (estimate: -41.14; SD 257.9; $p = 0.023$) among all participants, indicating that those with a higher fasting glucose level had lower right putamen volume (Fig. 1) and that for each additional 1 mmol/l of fasting glucose above 3.0 mmol/L right putamen volume was smaller by -38.46 mm^3 (0.9 %/mmol/L). Among T2D participants, a trend towards significant negative association between fasting glucose and left putamen volume (estimate: -42.33; SD 122.3; $p = 0.030$) and right putamen volume was observed (estimate: -38.64; SD 111.0; $p = 0.029$). No other significant associations between fasting glucose and striatal volumes, nor fasting glucose by Age or fasting glucose by Sex interactions, were found in the full sample or in sub-group analyses (Fig. 1, Supplemental Table 4).

3.3.2. Association between fasting glucose and PP scores

Results demonstrated a significant association between fasting glucose and PPb (estimate: -0.182; SD 0.955; $p = 0.002$) among all participants, indicating that those with a higher fasting glucose level had lower PPb and that for each additional 1 mmol/L of fasting glucose above 3.0 mmol/L PPb scores were lower by 0.114 (1.1%/mmol/L). Significant association between higher fasting glucose and lower PPn (estimate: -0.178; SD 1.103; $p = 0.008$) (1.3%/mmol/L) and a trend towards significant association between fasting glucose and PPd (estimate: -0.151; SD 1.119; $p = 0.027$) (1.6%/mmol/L) were also detected (Fig. 2). However, none of these associations were found in sub-group analyses (Fig. 2). None of the fasting glucose by Age or fasting glucose by Sex interactions reached significance (Supplemental Table 5).

3.3.3. Association between striatal volumes and PP scores

No significant associations between striatal volumes and PP, nor fasting glucose by Age or fasting glucose by Sex interactions, were found in the full sample or in sub-group analyses (Supplemental Table 6).

3.3.4. Sensitivity analysis

To investigate whether associations between fasting glucose and striatal volumes or PP scores were affected by having diabetes, we repeated previous analyses while controlling for T2D. After controlling

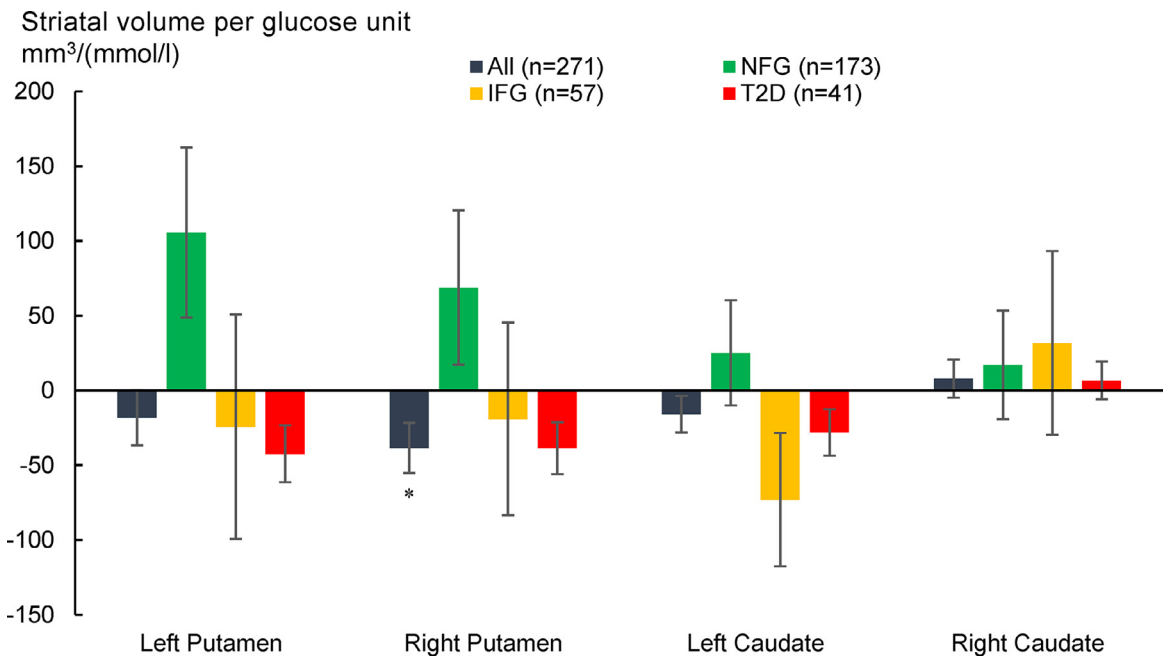

Fig. 1. Results from longitudinal analyses showing association between fasting plasma glucose levels and striatal volumes, among all participants, participants with NFG, with IFG or with T2D, controlling for Age, Sex, ICV and scanners. Bars show Estimate ± SE. *: $p < 0.017$ **:$p < 0.001$.

for diabetes, there remained a trend towards significant negative association between fasting glucose and right putamen volume (estimate: −31.01; SD 294.0; $p = 0.083$) and left caudate volume (estimate: −23.56; SD 207.6; $p = 0.062$) among all participants; no significant association was observed between fasting glucose and PP scores or between striatal volumes and PPb. To examine whether blood glucose was associated with volumes beyond the impact of diabetic status, we obtained the residuals of fasting glucose in a linear regression with glucose status (NFG/IFG/T2D) as predictor of fasting glucose levels. We repeated previous analyses with this variable in the place of fasting glucose. No significant association was observed between fasting glucose and striatal volumes or between fasting glucose and PP scores.

To further investigate possible differences in effects in the different sub-groups, analyses testing group differences in striatal volumes or PP scores between those with NFG, IFG or T2D were conducted. There was a trend towards significant association between T2D and right putamen (estimate: −185.94; SD 1305.5; $p = 0.038$) and left caudate volume (estimate: 159.22; SD 1122.2; $p = 0.039$). Significant negative associations between T2D and PPb (estimate: −1.096; SD 3.482; $p < 0.001$), PPd (estimate: −1.055; SD 3.628; $p < 0.001$) and PPn (estimate: −1.242; SD 3.818; $p < 0.001$) were observed when comparing NFG participants with T2D participants indicating that those with T2D had PP scores about 1 point (approx. 7–10%) lower than those with NFG. Similar associations were found when comparing IFG participants with

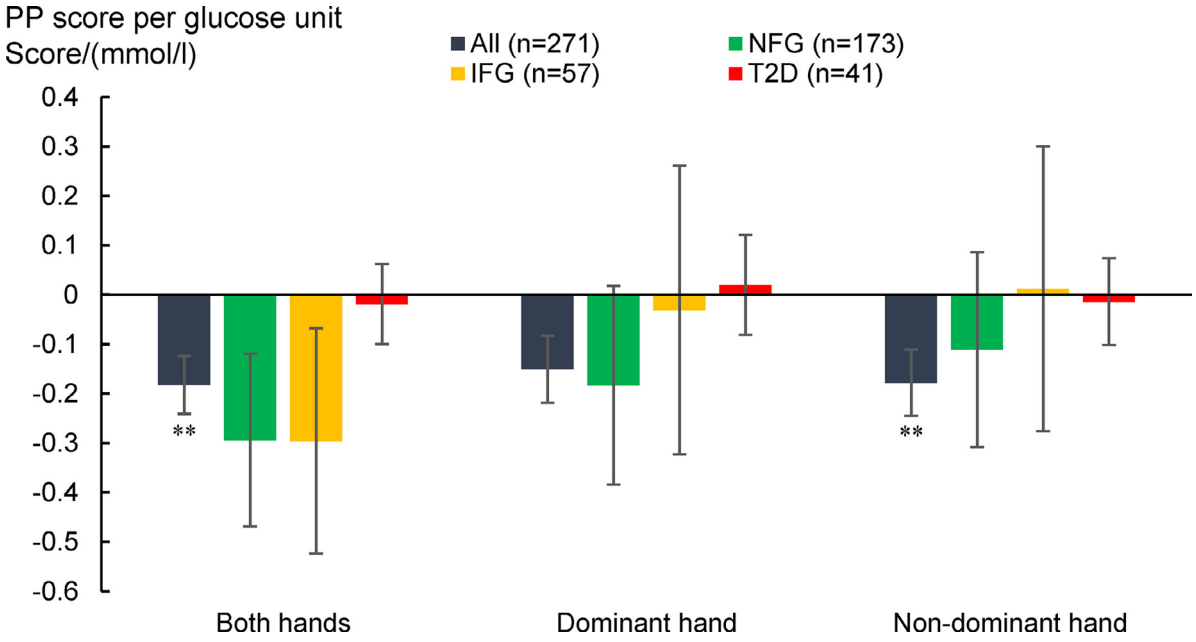

Fig. 2. Results from longitudinal analyses showing association between fasting plasma glucose levels and Purdue Pegboard (PP) scores of both hands, dominant hand and non-dominant hand among all participants, participants with NFG, with IFG or with T2D, controlling for Age, Sex and ICV. Bars show Estimate ± SE. *: $p < 0.025$ **: $p < 0.001$.

T2D participants between T2D and PPb (estimate: −0.8452; SD 2.455; $p=0.001$), PPd (estimate: −0.9043; SD 2.722; $p=0.001$) and PPn (estimate: −0.9074; SD 2.999; $p=0.004$).

To investigate whether extreme values (values beyond three times the interquartile range) in the data had an impact on the results from the main analyses, sensitivity analyses that repeated all the main analyses while excluding extreme values in explanatory variables were conducted. Across all analyses, fewer than 2.5% of the original sample were excluded as extreme values. The direction and significance of associations in sensitivity analyses were consistent with the main analyses.

No mediation analysis could be conducted to investigate whether striatal volumes mediated the association between blood glucose and PP scores, due to lack of significant association between striatal volumes and PP scores.

4. Discussion

The main findings of this study were that higher fasting glucose was associated with lower striatal volume but only significantly so in the putamen. Moreover, higher fasting glucose and T2D were also associated with poorer fine motor skills as assessed with the Purdue Pegboard task. However, no association between striatal volumes and fine motor skills was observed. Results were similar in cross-sectional analyses at wave 1 and longitudinal analyses across the three waves.

Building on our previous cross-sectional study demonstrating the presence of local striatal shape deformation associated with higher fasting glucose (Zhang et al., 2016), we aimed in this study to determine whether such effects could be demonstrated for volumetric measures using a more robust longitudinal methodology. In the present study, higher fasting glucose was significantly associated with lower putamen volume among all participants, with a trend towards significance among T2D participants, but not in the NFG and IFG subgroups. This association was not significant at baseline, possibly because of smaller sample size of baseline data compared with data from three waves. Moreover, when comparing striatal volumes between fasting glucose subgroups, no significant difference in striatal volume was found between NFG, IFG, and T2D. This contrasts with our previous study which found significant morphological differences in T2D, albeit at older ages. However, sensitivity analyses while controlling for T2D or using residual of fasting glucose predicted by glucose status, showed that there was limited associations between fasting glucose and striatal volumes when trying to remove effects of T2D on striatal volumes. Thus, these results support the conclusion that T2D is associated with lower putamen volume.

The fact that significant effects were only detected in the putamen among all participants is noteworthy. It may be because of the putamen's larger size compared to the caudate allowed for greater variability in volume that could be detected. Also, we only observed significant effects when looking at all participants but not in sub-group analyses. If the effect of higher fasting glucose occurs across all fasting glucose levels, sub-group analyses which divide participants by glucose levels may weaken our ability to detect such effect. This ability is further limited by the smaller sample size of sub-group analyses.

Despite using a longitudinal analyses, we did not observe a random effect of time on individual changes of striatal volume and fine motor skill performance associated with higher fasting glucose levels. As participants are over sixty years of age at first assessment, it is possible that such effects may largely occur before participants reach their sixties, because participants may have been exposed to higher blood glucose levels for some time. In this study, most participants with T2D already had the disease at baseline (26/41), which is consistent with statistics showing that most of T2D patients over 65 years of age had suffered from the disease for a long time (Kirkman et al., 2012; Ma and Chan, 2013). These T2D participants may also have had well-controlled glucose levels at baseline. Moreover, this study includes far fewer T2D and subclinical diabetes participants than normal participants, leaving fewer people with higher glucose levels. The participants were well-educated and generally financially comfortable, therefore they may have had better controlled blood glucose levels and this might have led to less on-going neurodegeneration. These factors likely limited our ability to detect associations between higher blood glucose and striatal volumes and fine motor skill performance. Further longitudinal studies that include middle aged participants may clarify whether associations between higher fasting glucose and striatal structure may lead to functional change over time.

The most significant finding in this study is that higher fasting glucose was associated with lower PP scores across all participants at baseline and across the three waves, which was more strongly driven by those with T2D as suggested by our sensitivity analyses. It provides converging evidence that glucose-related brain differences detected in our population may be linked to functional differences in the same individuals. Importantly, T2D participants were more strongly affected and presented with significantly lower PP scores (~7–10%) than those with NFG or IFG. While these results are consistent with previous findings (Kumar et al., 2008) the mechanisms linking blood glucose metabolism in the normal range and in T2D, striatal structure, and brain function is not well understood.

Previous studies found that striatum is susceptible to vascular lesion, with a higher percentage of lacunar infarct happening in this area (Feekes and Cassell, 2006). Because sensorimotor zone of the corticostriatal input (mostly consisting of putamen and caudate) correspond to blood supply from lenticulostriate arteries (Feekes and Cassell, 2006), lesions in this area may affect motor functions. For instance, a study found that patients with subcortical infarction involving the striatum have a higher risk of developing early motor deterioration (Kim et al., 2008). T2D is associated with macrovascular changes in the brain as a result of combined mechanisms such as hyperglycemia, inflammation and abnormal coagulation, and is a known risk factor of stroke (Biessels et al., 2006). For instance, T2D patients with an uncommon late stage T2D complication termed “diabetic striatopathy” exhibit vascular pathology and motor symptoms such as hemichorea-hemiballism similar to those with striatal lesion (Abe et al., 2009). Mechanisms such as inflammation and coagulation may develop with increasing level of blood glucose and before onset of T2D (Dentali et al., 2009; Esposito et al., 2002). Possibly vascular changes at the striatum can result in changes in striatal function with increasing blood glucose levels which may not be reflected by striatal volume. It is also possible that T2D complication such as peripheral neuropathy contributes to lower fine motor skill performance. For those with T2D, lower fine motor skill performance associated with higher fasting glucose may be a combination of mechanisms from the central and peripheral nervous systems.

This study has some limitations. Participants were over 60 years of age due to unavailable MRI data for 40s participants at all corresponding waves investigated. They were mainly Caucasian, who may have different prevalence of diabetes than other age groups or races. Also, the classification of NFG, IFG and T2D participants are based on fasting glucose and self-report of diagnosis. Self-reported T2D may be susceptible to under-reporting by participants (Dunstan et al., 2002); however, this under-reporting would be counteracted by our use of objective fasting blood glucose measures in assigning people to the T2D category. Due to lack of data for complications of T2D, we could not investigate the possible contribution of peripheral neuropathy on motor skills, which deserve further attention in future studies on central and peripheral caused for glucose-related fine motor skill deficit. In addition, T2D participants may have received medication, resulting in fasting glucose levels lower than actual glucose status. While the sample studied was randomly selected from a larger cohort randomly selected from the community, participants had a high level of education and the present findings may not be completely representative of the population at large. However, its large size and the fact that the selection process

was less biased than many neuroimaging studies brings some confidence that the current results are not restricted to this sample.

5. Conclusion

In conclusion, these results provide evidence that higher blood glucose levels, particularly in T2D, may affect both fine motor skill performance and related brain structures. The results further our understanding of how blood glucose may affect cerebral health, highlighting the need to identify the early risk factors and predictors of higher blood glucose levels before old age and develop preventative and risk reduction strategies at the population level. Further, future studies should investigate how higher blood glucose levels are related to morphological changes at the striatum and its associated fibre projections and cortical regions, as well as how these changes are associated with functional changes in the related brain regions.

Funding

The study was supported by NHMRC of Australia grant No. 973302, 1002160 and 1063907. Nicolas Cherbuin and Kaarin Anstey are funded by ARC Fellowship no. 12010227 and NHMRC Fellowship no.1002560.

Conflict of Interest

None.

Ethical approval and informed consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

Acknowledgements

The authors are grateful to Anthony Jorm, Peter Butterworth, Simon Easteal, Chantal Meslin, Patricia Jacomb, Karen Maxwell, and the PATH project interviewers. This research was partly undertaken on the National Computational Infrastructure (NCI) facility in Canberra, Australia, which is supported by the Australian Commonwealth Government.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2018.06.002.

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