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

Tianqi Zhang[a], Marnie E. Shaw[a], Erin I. Walsh[a], Perminder S. Sachdev[b], Kaarin J. Anstey[a], Nicolas Cherbuin[a,*]

[a] Centre for Research on Ageing, Health and Wellbeing, Australian National University, Canberra, Australia
[b] School of Psychiatry, University of New South Wales, Sydney, Australia

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

* Corresponding author.
E-mail address: nicolas.cherbuin@anu.edu.au (N. Cherbuin).

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