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Microstructural abnormalities in white and gray matter in obese adolescents with and without type 2 diabetes

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ABSTRACT

Aims/hypotheses: In adults, type 2 diabetes and obesity have been associated with structural brain changes, even in the absence of dementia. Some evidence suggested similar changes in adolescents with type 2 diabetes but comparisons with a non-obese control group have been lacking. The aim of the current study was to examine differences in microstructure of gray and white matter between adolescents with type 2 diabetes, obese adolescents and healthy weight adolescents.

Methods: Magnetic resonance imaging data were collected from 15 adolescents with type 2 diabetes, 21 obese adolescents and 22 healthy weight controls. Volumetric differences in the gray matter between the three groups were examined using voxel based morphology, while tract based spatial statistics was used to examine differences in the microstructure of the white matter.

Results: Adolescents with type 2 diabetes and obese adolescents had reduced gray matter volume in the right hippocampus, left putamen and caudate, bilateral amygdala and left thalamus compared to healthy weight controls. Type 2 diabetes was also associated with significant regional changes in fractional anisotropy within the corpus callosum, fornix, left inferior fronto-occipital fasciculus, left uncinate, left internal and external capsule. Fractional anisotropy reductions within these tracts were explained by increased radial diffusivity, which may suggest demyelination of white matter tracts. Mean diffusivity and axial diffusivity did not differ between the groups.

Conclusion/interpretation: Our data shows that adolescent obesity alone results in reduced gray matter volume and that adolescent type 2 diabetes is associated with both white and gray matter abnormalities.

1. Introduction

There has been a marked world-wide increase in the prevalence of type 2 diabetes among young persons (Pinhas-Hamiel and Zeitler, 2005; Alberti et al., 2004). Although the cause is likely to be multi-factorial, childhood obesity is believed to be an important underlying factor (Pinhas-Hamiel and Zeitler, 2005; Haines et al., 2007).

Type 2 diabetes in adolescence is associated with structural brain abnormalities (Yau et al., 2010; Bruehl et al., 2011). Adolescents with type 2 diabetes are reported to have significantly reduced volume in hippocampus and prefrontal brain regions and higher rates of global cerebral atrophy compared to obese adolescents (Bruehl et al., 2011). These associations are similar to those reported for adults with type 2 diabetes (Moulton et al., 2015; Brundel et al., 2010; Anan et al., 2012; Hsu et al., 2012; Chen et al., 2012). For instance, gray matter reductions have been identified by Voxel Based Morphometry (VBM; a neuroimaging analysis technique using statistical parametric mapping), in adults with type 2 diabetes compared with healthy weight controls (Chen et al., 2012). Furthermore, differences in cortical white matter in adults with type 2 diabetes compared with healthy controls have also been found (Hsu et al., 2012; Chen et al., 2012).

In adults with type 2 diabetes, changes in gray matter volume have also been associated with levels of visceral fat (Anan et al., 2012) and several studies have found gray matter differences between obese patients and normal weight controls (Smucny et al., 2012; Pannacciulli et al., 2006). However, in adolescents, gray matter reduction was only

Abbreviations: HbA1c, Haemoglobin A1c

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observed in obese adolescents with type 2 diabetes and not those without diabetes, contrary to findings in adults, (Yau et al., 2010; Bruehl et al., 2011). Because cortical changes have been reported in obese adolescents without diabetes compared to healthy controls (Yokum et al., 2012) and in those with insulin resistance (Ursache et al., 2012), there is a need to compare between adolescents with type 2 diabetes, obesity and healthy weight.

A recent study comparing youth with type 2 diabetes to non-diabetic obese and healthy weight peers found that those with type 2 diabetes had reduced thalamic volume (Rofey et al., 2015). Although not statistically significant, the study also found microstructural white matter differences indexed by fractional anisotropy (FA) between the groups; those with type 2 diabetes showing the lowest FA levels (Hsu et al., 2012). However, the Rofey et al. (2015) study included only five participants per group and measured changes in a limited set of brain areas.

The exact extent and location of gray and white matter differences in adolescents with type 2 diabetes requires further examination using more accurate and impartial techniques, such as systematic voxel-wise mapping across the entire cortex and comparison across obese, type 2 diabetic and normal weight adolescents. The aim of this study was to examine whether type 2 diabetes and obesity are complementary or independent correlates of structural brain differences observed in adolescents with type 2 diabetes. Moreover, as FA is the combined measure of both radial and axial diffusion, which are often suggested to indicate demyelination and axonal degeneration respectively (Wozniak and Lim, 2006), we examined the composites of FA independently.

2. Methods

2.1. Participants

Fifteen adolescents with type 2 diabetes, 21 obese and 22 control adolescents participated (see Tables 1a and 1b). All adolescents with type 2 diabetes were referred to the study by collaborating paediatric endocrinologists in the Midlands and North-West of England. Obese adolescents were either referred by dieticians or responded to study advertisements; control participants were recruited from local schools. Recruitment took place from November 2010–October 2012.

Selection criteria included: (Alberti et al., 2004) aged between 12 and 18 years, (Alexander et al., 2007) being able to understand and read English and (Allen et al., 2016) being diagnosed for at least 6 months (for the type 2 diabetes group). Each adolescent's BMI was converted to a Z score (SD-BMI) based on the British 1990 growth reference for height, weight, and body mass index (Cole et al., 1995). Obese adolescents were defined as having a SD-BMI exceeding 1.96 standard deviations from the mean (> 95th percentile). We excluded adolescents if they had (Alberti et al., 2004) major medical conditions (other than type 2 diabetes, polycystic ovarian syndrome, hirsutism, which were included) or learning disabilities, (Alexander et al., 2007) any contraindication to being in a MRI scanner or (Allen et al., 2016) major changes in diabetes related medication in the past 6 months. None of the adolescents in our study had diabetes complications.

Two participants were excluded due to movement artefacts, one due to signal loss and one due to a brain abnormality. T1 weighted scans (see below) were obtained from 14 participants with type 2 diabetes, 20 obese participants and 19 control group participants. Due to discomfort during scanning not all participants underwent a diffusion weighted scan. Hence, whole brain diffusion weighted scans (see below) were obtained from 12 adolescents with type 2 diabetes, 13 obese and 20 control participants. Fully informed consent was taken from all participants and their respective parent/guardian prior to participation. The study was carried out in accordance with Declaration of Helsinki for experiments involving humans and approved by the National Research Ethics Service and the Birmingham University Imaging Centre.

Table 1a
Demographic and clinical characteristics of the VBM groups. Participants with type 2 diabetes (T2DM) were referred to the study by Paediatric Endocrinologists and obese adolescents were either referred by dieticians or responded to study advertisements. Where possible data for insulin and diabetes related measures were also collected by the study team.

Characteristic	T2DM *N* = 14	Obese *N* = 20	Controls *N* = 19	F or Fisher's exact test	p
Age	16.1 ± 1.5	14.9 ± 2.00	16.4 ± 1.7	3.93	0.026
Sex (female, *n*, %)	14 (100%)	15 (75%)	14 (74%)		
Ethnicity (*n*)					
White	6	9	9	8.0	0.36
Asian	8	7	7		
Black	0	3	0		
Other	0	1	3		
SD-BMI (sd)	2.22 ± 1.55	3.25 ± 0.78	0.23 ± 0.96	38.08	< 0.0001
Fasting blood glucose (mmol/l) ± sd	9.54 ± 3.88 *n* = 11	4.9 ± 0.53 *n* = 20	4.77 ± 0.51 *n* = 17	26.32	< 0.0001
Fasting insulin (pmol/l) ± sd	257.7 ± 171.7 *n* = 6	172.8 ± 141.8 *n* = 19	77.2 ± 72.6 *n* = 16	5.30	0.009
HbA_{1c} (%) ± sd (mmol/mol)	8.10 ± 2.26 (65.0) *n* = 13	5.56 ± 0.39 (37.3) *n* = 19	5.35 ± 0.32 (35.0) *n* = 14	21.29	< 0.0001
HOMA-IR ± sd	102.2 ± 120.2 *n* = 5	40.0 ± 37.6 *n* = 19	16.5 ± 15.8 *n* = 16	5.97	0.006
c-Peptide (pmol/l) ± sd	1386.8 ± 905.6 *n* = 6	1226.7 ± 572.6 *n* = 18	762.7 ± 274.4 *n* = 16	4.37	0.020
2 h-OGTT (mmol/l) ± sd	NA	6.84 ± 1.49 *n* = 20	5.31 ± 0.97 *n* = 18	13.58	< 0.001
Duration of diabetes (months) ± sd Range	32.6 ± 30.0 7–106 (IQR = 36)	NA	NA		
Diabetes treatment (*n*)					
Metformin	6	4	NA		
Metformin + gliclazide	1	0			
Metformin + insulin	2	NA	NA		
Insulin	2	NA	NA		
GLP-1 agonist	1	0	NA		

Values are means ± SD; T2DM = type 2 diabetes; IQR = interquartile range; NA = not applicable.