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Brain volume and white matter in youth with type 2 diabetes compared to obese and normal weight, non-diabetic peers: A pilot study☆

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) and obesity are linked to specific patterns of subcortical brain atrophy and decreased microstructural integrity of white matter. Fifteen adolescents (12–21-years-old, 80% Caucasian, 15% African American, mean BMI = 32)–five with T2DM confirmed by oral glucose tolerance test, five matched obese adolescent controls without diabetes (OBCN), and five matched (race, sex) normal-weight controls (NWCN)–underwent Magnetic Resonance Imaging (MRI) for the collection of gray matter volume and white matter integrity. Analyses of Variance (ANOVAs) of the neuroimaging data revealed significant differences in caudate nucleus volume [$F(2,12) = 7.79$, $p < 0.05$] such that the normal-weight group had significantly greater volume than the obese and T2DM groups (NWCN>OBCN, $p = 0.020$; OBCN > T2DM, $p = 0.042$; and NWCN > T2DM; $p = 0.003$) after controlling for participant Body Mass Index (BMI). Similarly, there was a main effect for the volume of the thalamus [$F(2,12) = 4.39$, $p < 0.05$] with greater volume for both the NWC and the OBC groups in comparison to the T2DM group (NWC > T2DM, $p = 0.020$; OBC > T2DM; $p = 0.040$). Finally, an examination of white matter integrity among the three groups illustrated a pattern of white matter integrity reduction between normal-weight participants and both obese controls and T2DM participants, with T2DM demonstrating the greatest deficit in functional anisotropy (FA) volume, but these results were not significant after further controlling for BMI. Results from the current pilot study illuminate a host of brain morphology differences between youth with T2DM, obese youth, and normal-weight controls; future research with a larger sample size is critical.

1. Introduction

In both childhood and adulthood, T2DM is consistently associated with differences in regional brain structure compared to non-diabetic controls (Biessels et al., 2008; Derakhshan and Toth, 2013; Yau et al., 2012). Adults with T2DM have reduced volume of the hippocampus and altered microstructural white matter parameters throughout the brain (Yau et al., 2012, 2013). These associations may place individuals with T2DM, as early as adolescence, at risk for decreased daily functioning and eventually significant cognitive impairment (Umegaki, 2014; Cukierman-Yaffe et al., 2009; Hugenschmidt et al., 2014).

While brain-based differences have been well-established in adults and somewhat in youth with diabetes, there is now compelling evidence that "less severe" metabolic dysfunction in adults (e.g., Metabolic Syndrome–elevations in fasting glucose levels or insulin resistance, lower high-density lipoprotein, hypertriglyceridemia, hypertension, and abdominal adiposity or obesity), is also adversely associated with brain volume and white matter microstructure (Yau et al., 2012). However, such comparisons using

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Table 1
Demographic and physiological characteristics for all participants, by group.

Average calculations for demographic and anthroprometric measures across the 3 groups			
Characteristic	Control	Obese	T2DM
Age, mean, (SD), mo	14.5 (2.5)	15.4 (2.2)	18 (1.4)
Female, No. (%)	2 (50%)	4 (80%)	4 (100%)
Weight, mean,(SD), kg	44.4 (12.9)	93.7 (18.7)	115.4 (31.5)
Race/ ethnicity, N0. (%)			
Black/ African American	2 (50%)	3 (60%)	2 (50%)
White	2 (50%)	2 (40%)	2 (50%)
Height, mean, (SD), cm	153.78 (6.97)	164.51 (8.41)	166.05 (4.56)
BMI, mean, (SD)	18.57 (4.18)	34.26 (3.48)	41.67 (11.07)
BMI Percentile, mean, (SD)	35.79 (29.80)	98.21 (0.58)	98.12 (2.10)
BMI Z-Scores, mean, (SD)	(−) 0.74 (1.39)	2.18 (0.24)	2.15 (0.38)

Mean and standard deviations of Control, Obese, and Type 2 Diabetic patient groups. Patients aged between 11 and 19.
All patients with T2DM had the same age of onset (11 years) and duration (7 years); all are currently on Metformin and have been for $M = 10$ years.
All patients were Tanner stage V except for one female in each group which were Tanner stage IV on pubic hair and Tanner stage V on breasts.
All parents attained a college or graduate school degree.

neuroimaging studies in youth with differing degrees of metabolic dysfunction have not yet been conducted. In this pilot study, we evaluated reduced regional gray matter volume and white matter integrity in subcortical brain circuits involved in memory, reward, and motor control across 3 groups of youth (control, obese, diabetic). We postulated a parametric, stepwise association such that overweight adolescents with T2DM will show reduced volume and white matter integrity compared with overweight non-diabetic peers and normal-weight peers. More specifically, overweight non-diabetic youth would have smaller brain volumes and reduced white matter integrity compared to healthy-weight controls, and adolescents with T2DM would have smaller brain volumes and reduced white matter integrity compared to both overweight and normal-weight control groups.

2. Methods

This study was conducted at the Weight Management and Wellness Center at Children's Hospital of Pittsburgh and The Scientific Imaging and Brain Research Center at Carnegie Mellon University and approved by both Universities' Institutional Review Boards. Informed assent and consent were obtained from fifteen English-speaking participants (see Table 1 for demographics). Fifteen adolescents–five with T2DM confirmed by oral glucose tolerance test, five matched obese adolescent controls without diabetes (OBCN), and five matched normal-weight controls (NWCN)–were recruited from the Children's Hospital Diabetes Center, Weight Management and Wellness Center, and the community through newspaper advertisements, respectively. Adolescents with T2DM and obesity were matched on sociodemographic variables–race, sex, and BMI–with equal males and females, Tanner stage IV–V, and BMI ≥ 95th percentile. All patients with T2DM had the same age of onset (11 years) and duration (7 years); all were on Metformin and have been for $M = 6$ years. Youth with T2DM were antibody negative (Ia2 and GAD). Control, normal-weight participants had a BMI that was ≤ 85th percentile, matched for age, race, and sex, and had no known medical risk factors. Exclusion criteria were: (1) pregnancy, (2) history of bariatric surgery, (3) medical condition affecting body weight such as cancer, hypothyroidism, liver disease, eating disorder (4) known heart problems or cardiovascular disease, (5) psychiatric diagnosis, (6) metal in the body, (7) claustrophobia, or (8) traumatic brain injury. To ensure each participant benefited from the study, a brief lifestyle lesson focusing on the American Academy of Pediatrics recommendations for pediatric obesity was delivered by a masters-level trained clinician.

Following a thorough history and physical examination after consent was obtained, participants underwent Magnetic Resonance Imaging (MRI) for the collection of gray matter volume and white matter integrity. *Gray matter*: High-resolution anatomical MPRAGE (1 mm^3 voxels, 256 slices) images were used for volumetric analyses. For segmentation and volumetric analysis we employed FMRIB's Integrated Registration and Segmentation Tool (FIRST) in FMRIB's Software Library (FSL) version 5. FIRST is a semi-automated model-based subcortical segmentation tool utilizing a Bayesian framework from shape and appearance models obtained from manually segmented images from the Center for Morphometric Analysis, Massachusetts General Hospital, Boston. Structural and landmark information were obtained from 317 manually segmented and labeled T1 weighted images of the brain from normal children, and were modeled as a point distribution model in which the geometry and variation of the shape of the structure are submitted as priors. Volumetric labels are parameterized by a 3D deformation of a surface model based on multivariate Gaussian assumptions. FIRST then searches through linear combinations of shape modes of variation for the most probable shape given the intensity distribution in the T1 weighted image (Patenaude et al., 2007). This method first runs a two-stage affine registration to a standard space template (MNI space) with 1 mm resolution using 12-degrees of freedom and a subcortical mask to exclude voxels outside the subcortical regions. Second, the subcortical regions are segmented with 10–40 modes of variation. The modes of variation are optimized based on leave-one-out cross-validation on the training set and increases the robustness and reliability of the results (Patenaude et al., 2007). Finally, boundary correction takes place for each structure that classifies the boundary voxels as belonging to the structure or not based on a statistical probability (z-score > 3.00; $p < .001$). Segmentations from each participant were visibly checked for any significant error that could have occurred during the segmentation process. No errors were noted.

White matter: White matter imaging was performed using a diffusor tensor imaging acquisition approach (DTI; 50 directions, 2.5 mm isotropic voxels, $b = 1000$ s/mm^2, TR = 1400 ms, TE = 135nms). Data were reconstructed using a q-space diffeomorphic reconstruction method (Yeh and Tseng, 2011) that reconstructs orientation distribution functions in each voxel in a normalized template space using a non-linear normalization routine in DSI Studio. Voxel-wise estimates of white matter integrity were taken using a generalized fractional anisotropy (gFA) approach. A region of interest approach was used to examine gFA values for a set of frontal corticostriatal pathways between the middle frontal gyrus and the striatal nuclei. To do this, deterministic tractography was performed on a 30-subject template brain (CMU-30 Template: http://www.psy.cmu.edu/~coaxlab/?page_id=305) to find 10,000 streamlines that connect the middle frontal gyrus to the striatal nuclei. These streamline maps were then converted into voxel masks and average gFA was estimated within these masks.

2.1. Statistical analyses

Chi-square and *t*-tests were conducted to compare demographic variables across groups. An Analysis of Variance (ANOVA) was used to assess differences across the three groups with age and body mass index (BMI) serving as covariates with post-hoc pairwise comparisons between each group. Given the pilot nature of this investigation, we had specific hypotheses about the hippocampus

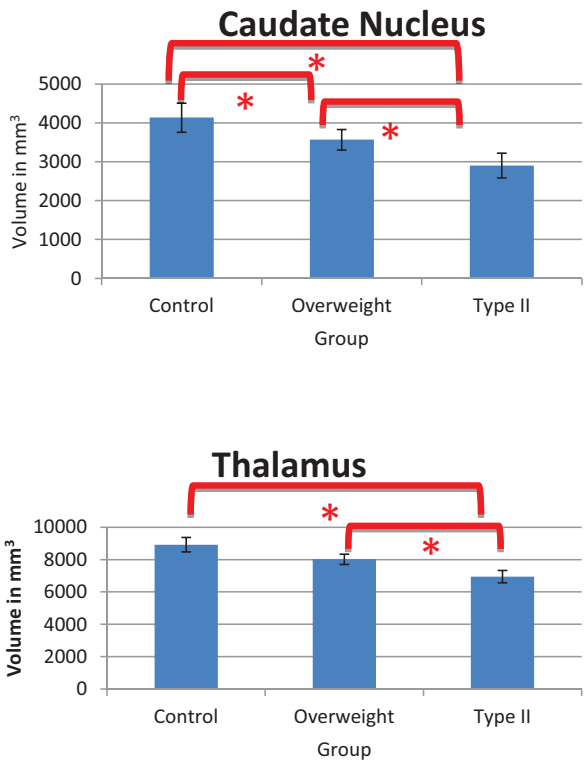

Fig. 1. Gray matter results: T2DM is associated with reduced brain volume across all brain regions. Above are graphs of regions (caudate nucleus and thalamus) that are statistically significant in this pilot study.

and basal ganglia; therefore, we performed exploratory analyses of other regions without multiple comparison correction.

3. Results

Neuroimaging revealed significant Analysis of Variance (ANOVA) differences in caudate nucleus volume [$F(2,12) = 7.79$, $p < 0.05$] such that the normal-weight group had significantly greater volume than either of the other groups (NWCN >OBCN, $p = 0.020$; OBCN > T2DM, $p = 0.042$; and NWCN>T2DM; $p = 0.003$) after controlling for participant Body Mass Index (BMI). Similarly, there was a main effect for the volume of the thalamus [$F(2,12) = 4.39$, $p < 0.05$] with greater volume for both the NWC and the OBC groups in comparison to the T2DM group (NWC > T2DM, $p = 0.020$; OBC > T2DM; $p = 0.040$). Despite a lack of statistical significance, there were clinically significant findings in all other regions tested (e.g., hippocampus, nucleus accumbens, amygdala, putamen, pallidum) with an overall downward trend among all 3 groups for most regions of the brain. See Fig. 1 for a summary of volumetric analyses.

Next, an examination of white matter integrity differences measured in functional anisotropy between the three groups illustrate a pattern of white matter integrity reduction between normal-weight participants and both obese controls and T2DM participants, with T2DM demonstrating the greatest deficit in FA volume. Prior to controlling for BMI, there were significant differences among all three groups. In all pathways, we identified significant group effects on the white matter regions of interest. In the left hemisphere, the corticostriatal projections from the middle frontal gyrus were marginally, but not significantly, lower in the obese and T2 groups than in the controls ($B(10) = -0.24$, $p = 0.10$). This group effect was significant in the right hemisphere ($B(10) = -0.33$, $p = 0.0023$). In the thalamic pathways, both the left and right white matter was significantly lower in the obese and T2 groups than controls (Right: $B(10) = -0.15$, $p = 0.016$; Left: $B(10) = -0.18$, $p = 0.019$). See Fig. 2 for microstructural analyses. After controlling for BMI, differences were no longer statistically significant.

4. Discussion

To the best of our knowledge, this is the first report demonstrating differences in brain morphology among youth with T2DM vs. obese peers vs. normal weight peers. Our preliminary results suggest that T2DM is associated with reduced volume and white matter integrity in the caudate nucleus and thalamus regions. These findings should be interpreted cautiously in light of study limitations noted below. However, despite the non-significant results for other brain regions in this pilot feasibility study, the results shown in Fig. 1 are noteworthy and suggest that a more sufficiently powered study may be able to detect differences in many different brain regions. Moreover, as seen in Fig. 2, white matter integrity differences among the three groups seem to be driven by BMI and not hyperinsulinemia. Further investigation controlling for these factors in a larger sample is warranted.

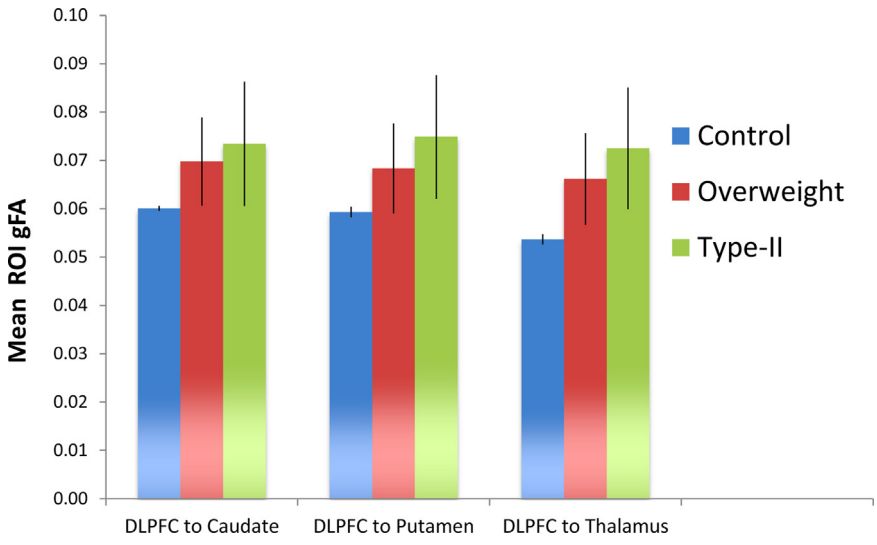

Fig. 2. White matter results: Differences in functional anisotropy in white matter for control, overweight, and diabetic youth.

Nonetheless, limiting our interpretations to the caudate nucleus and thalamus, our results suggest that youth with T2DM may experience reduction in areas of the brain responsible for learning and memory, reward sensitivity, and executive control (caudate functions), as well as decreased perception and attention (thalamus functions). Furthermore, our results also showed that participants with T2DM had diminished hippocampal volume in comparison to normal-weight controls, suggesting that these youth may also experience reduced ability to consolidate memory.

In addition to reduced volume, adolescents with T2DM had reduced integrity of the white matter projections into the caudate from the lateral frontal regions compared to the obese and normal-weight groups. These differences may suggest slower processing for functions dependent on the caudate nucleus, especially for youth with T2DM. Similar differences were evidenced by a comparison of overweight and healthy-weight participants, although not as consistently across brain regions. A more adequately powered study is needed to make more causal interpretations.

Overall, results from the current pilot study support our hypotheses by illuminating a host of volumetric and white matter integrity differences between youth with T2DM, obese youth, and normal-weight youth. Given the preliminary nature of this study, cautionary implications should be made. Future directions should expand the sample size and collect assessments of cognitive functioning, together with metabolic parameters including insulin sensitivity. Moreover, baseline variables should be matched on age and BMI (for the obese and T2DM groups). Withstanding these limitations, our study results extend the work of researchers uncovering brain-based differences between overweight and normal weight youth (Maayan et al., 2011; Yau et al., 2014) and corroborate the work of researchers who are beginning to examine these differences in youth with insulin resistance (Yau et al., 2012). Moreover, broader studies should also investigate the effects of socioeconomic status and the impact that this may have on cognitive functioning impairments. This sample was homogenous on SES (see Table 1) and generalizability may be limited (Hackmanet al., 2010). Attaining earlier scans may also begin to unravel the direction of impairment (i.e., do brain-based deficits affect eating behaviors or vice versa). Findings that obese and T2DM youth demonstrate compromised brain structures are especially salient during adolescence–a critical period of brain maturation and plasticity. The translation of these structural changes to alterations in brain function is crucial, and future research should investigate whether or not the observed changes are reversible and what approaches are most successful.

References

Biessels, G.J., Deary, I.J., Ryan, C.M., 2008. Cognition and diabetes: a lifespan perspective. Lancet Neurol. 7 (2), 184–190.

Cukierman-Yaffe, T., Gerstein, H.C., Williamson, J.D., 2009. Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) investigators. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial. Diabetes Care 32 (2), 221–226.

Derakhshan, F., Toth, C., 2013. Insulin and the Brain. Curr. Diabetes Rev. 9 (2), 102–116.

Hackman, D.A., Farah, M.J., Meaney, M.J., 2010. Socioeconomic status and the brain: mechanistic insights from human and animal research. Nat. Rev. Neurosci. 11 (9), 651–659.

Hugenschmidt, C.E., Lovato, J.F., Ambrosius, W.T., Bryan, R.N., Gerstein, H.C., Horowitz, K.R., et al., 2014. Cross-section and longitudinal associations of diabetic retinopathy with cognitive function and brain MRI findings: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care.

Maayan, L., Hoogendoorn, C., Sweat, V., Convit, A., 2011. Disinhibited eating in obese adolescents is associated with orbitofrontal volume reductions and executive dysfunction. Obesity 19, 1382–1387.

Patenaude, B., Smith, S.M., Kennedy, D.N., Jenkinson, M., 2007. A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage 56 (3), 907–922.

Umegaki, H., 2014. Type 2 diabetes as a risk factor for cognitive impairment: current insights. Clin. Interv. Aging 28 (June (9)), 1011–1019.

Yeh, F.C., Tseng, W.Y., 2011. NTU-90: a high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. Neuroimage 58, 91–99.

Yau, P.L., Castro, M.G., Tagani, A., Tsui, W.H., Convit, A., 2012. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. Pediatrics 130 (4), 856–864.

Yau, P.L., Hempel, R., Tirsi, A., Convit, A., 2013. Cerebral white matter and retinal arterial health in and type 2 diabetes mellitus. Int. J. Hypertens., 1–9.

Yau, P.L., Kang, E.H., Javier, D.C., Convit, A., 2014. Preliminary evidence of cognitive and brain abnormalities in uncomplicated adolescent obesity. Obesity 22 (8), 1865–1871, http://dx.doi.org/10.2337/dc14-0.