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Severity of clinical presentation in youth with type 1 diabetes is associated with differences in brain structure

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Abstract

Objective—Differences in cognition and brain structure have been found in youth with type 1 diabetes compared to controls, even after relatively short disease duration. To determine whether severity of clinical presentation contributes to these differences, we obtained structural MRI scans in youth ages 7–17 who were either newly diagnosed with type 1 diabetes (<3.5 months from diagnosis, n=46) or a sibling without diabetes (n=28).

Research Design and Methods—Severity of presentation was measured by the presence of diabetic ketoacidosis (DKA) and degree of hyperglycemia exposure (hemoglobin A1c (HbA1c)) at diagnosis. Magnetic resonance images were obtained using T1-weighted, T2-weighted, and Diffusion Weighted sequences.

Results—Within the group with type 1 diabetes, 12 subjects presented in DKA, and 34 did not. After controlling for age, sex and multiple comparisons, the type 1 diabetes group had lower volume in the left temporal-parietal-occipital cortex compared to controls. Within the type 1 diabetes group, DKA at presentation was associated with lower radial, axial and mean diffusivity

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throughout major white matter tracts and higher HbA1c was associated with lower hippocampal, thalamic, and cerebellar white matter volumes, lower right posterior parietal cortical thickness and greater right occipital cortical thickness.

Conclusion—These data suggest that severity of clinical presentation is an important factor in predicting brain structural differences in youth with type 1 diabetes approximately 3 months after diagnosis.

Keywords

Type 1 Diabetes; Diabetic Ketoacidosis; Brain structure

Introduction

Type 1 diabetes mellitus typically is diagnosed during childhood and over time can lead to complications affecting the retina, heart, kidneys, peripheral nerves, and more recently appreciated, the brain. During childhood, the brain undergoes significant structural and functional changes including a high and rapidly changing metabolic demand which may make the developing brain especially vulnerable to glycemic extremes (1–3). Accordingly, in youth with type 1 diabetes and varying duration of disease, studies find that early age of onset, accumulated exposure to hyperglycemia and repeated severe hypoglycemia during development are associated with lower cognitive performance and altered brain structure (2, 4–14). Our group and others have found intriguing relationships between structural brain differences and previous exposure to glycemic extremes in cross-sectional studies of youth with long duration type 1 diabetes (15). Across several studies, greater chronic exposure to hyperglycemia has been associated with lower gray and white matter volume in posterior cortical regions of the brain, most commonly the precuneus/cuneus cortex and history of significant glycemic excursions have been related to hippocampal and thalamic differences. However, variability in brain outcomes remains unexplained and may relate to the difficulty in disentangling often co-occurring factors of clinical presentation severity, subsequent exposure to chronic hyperglycemia or repeated hypoglycemia that can occur during a lifetime of diabetes (15).

Some studies have observed altered cognition and brain structure in children with a relatively short duration of illness (16, 17), suggesting that factors at clinical presentation may affect brain and cognitive function later on in the disease. Prior to diagnosis, children may have prolonged exposure to marked unrecognized hyperglycemia and as many as 30% present in a state of life-threatening metabolic derangement known as diabetic ketoacidosis (DKA) (18–20). Despite the high prevalence of these complications at diagnosis in childhood, few studies have investigated their longer-lasting impact on the brain. In a previous paper, we found an association between DKA and hyperglycemia at diagnosis and memory performance approximately 3 months post-diagnosis in children with type 1 diabetes (21). Moreover, a recent study found that DKA at diagnosis was associated with differences in white matter diffusivity and volume days afterwards, most of which resolved by 6 months. Interestingly, these initial differences were associated with poorer memory and attention 6 months later (22). However, this study did not have a control group without diabetes or an assessment of hyperglycemia at diagnosis, and our previous paper did not

address underlying brain structural effects. Thus, the goal of this study was to determine whether hyperglycemia and DKA at diagnosis contribute to brain structural differences several months post-diagnosis in youth with type 1 diabetes and to determine whether these effects are discrepant from normal brain development.

Methods

Subjects

Subjects between 7–17 years of age with type 1 diabetes and their eligible siblings without type 1 diabetes were recruited from the Pediatric Diabetes Clinic at Washington University in St. Louis and St. Louis Children's Hospital (SLCH). Individuals with type 1 diabetes were recruited within three months of diagnosis and were excluded for chronic diseases other than type 1 diabetes, history of psychiatric or neurological disorder or use of psychoactive medications or premature birth (less than 36 weeks gestation) with complications. Individuals with contraindications to MRI such as claustrophobia, orthodontic braces or metal implants were also excluded. All procedures were approved by the Washington University School of Medicine Human Research Protection Office, and all participants and their parents or guardians signed informed consent forms.

Clinical Variables

SLCH medical records for each individual with type 1 diabetes were examined, and the following clinical variables from the time of diagnosis were collected: Tanner pubertal stage, blood glucose level (mg/dL), hemoglobin A1c (HbA1c; Afinion AS100 Analyzer), bicarbonate (HCO_3 in mmol/L; Radiometer Gas Machine model 837), blood urea nitrogen (BUN in mmol/L), sodium (Na in mEq/L), and osmolality (osmol/L). Osmolality was calculated using the formula $(2 \times \text{Na}) + (\text{blood glucose}/18) + (\text{BUN}/2.8)$. Puberty was defined as greater than or equal to Tanner stage 2 for breast or testicular development. DKA at diagnosis (DKA+ vs. DKA-) was determined using the Diabetes Control and Complications Trial (DCCT) criteria of ketonuria along with a venous pH <7.3, or bicarbonate <15mmol/L. Severity of DKA was classified as mild (venous pH between 7.20 and 7.29, or bicarbonate between 10 and 14mmol/L), moderate (venous pH between 7.10 and 7.19, or bicarbonate between 5 and 9mmol/L), or severe (venous pH <7.10, or bicarbonate <5mmol/L) (23). For individuals who did present in DKA, Glasgow Coma Score, anion gap, urine ketones, admission to the ICU, or use of an insulin drip were recorded. Finally, for all the patients with type 1 diabetes, the outpatient HbA1c level closest to the time of their MRI scan (within 3.5 months of diagnosis) was obtained (follow-up HbA1c).

Study visits were scheduled to occur within 3.5 months of the inpatient diagnosis. At these visits, participants underwent an MRI scan (details below), cognitive testing (21) and were asked to report any episode of severe hypoglycemia or DKA occurring between the time of diagnosis and the study date. Severe hypoglycemia was defined as in the DCCT as a low blood sugar event with neurologic dysfunction such as seizure or loss of consciousness in which the patient required the help of another person for treatment, and which improved following the administration of carbohydrate or glucagon (24). Due to the small number of

participants that had both valid cognitive and neuroimaging data, analyses here include only neuroimaging outcomes. Cognitive outcomes have previously been reported (21).

MRI Scans

All structural brain images were acquired on a Siemens 3T Tim Trio MRI scanner with a 12-channel head coil at the Center for Clinical Imaging Research (CCIR) at Washington University. Blood glucose levels were measured before and after scanning and had to be between 70–300 mg/dL prior to starting scanning in order to proceed. The following sequences were performed: *T1-weighted* using magnetization-prepared rapid gradient echo (MPRAGE) (sagittal acquisition TR=2400, TE=3.16, TI =1000, voxel resolution=1×1×1mm, Time=8:09 min); *T2-weighted* (TR=3200, TE=455, voxel resolution=1×1×1mm, Time=4:43 min) and *Diffusion Weighted Images (DWI)* sequences (echo planar sequence of 27 directions with b-values from 0 to 1400 s/mm², transverse acquisition, TR=12300, TE=108, voxel resolution=2×2×2 mm, time =5:44 min).

MRI Analyses

Gray and White Matter Volumes—To determine regional gray and white matter brain volumes from anatomically defined regions, MPRAGE images were analyzed with the semi-automatic segmentation program Freesurfer (v5.3)(25). This program reconstructs the brain from surface and volumetric registration to an atlas to quantify regional volumes. Left and right volumes were averaged and all were corrected for intracranial volume (ICV or volume within the skull, derived from Freesurfer) (26). *A priori* regions of interest were hippocampal and thalamic volumes, due to findings associating these regions with hyperglycemia and DKA in previous work (27–29). In addition, exploratory analyses were performed on a select number of other regions (n=11: brainstem, cerebellar gray matter, cerebellar white matter, pallidum, corpus callosum, amygdala, caudate, putamen, accumbens, total cortical gray, total cortical white matter).

Surface-based and Vertex-wise Cortical Metrics—To determine values for cortical thickness, surface area and volume independent of anatomical landmarks, we reconstructed and segmented individual subjects' cortical surfaces using Freesurfer (v5.3) (30–32). A triangular tessellation was applied across each subjects' cortical surface after identifying the pial surfaces and the gray/white matter border. From these maps, multiple surface-based measurements were calculated at the vertices of the triangular mesh. Cortical thickness is the distance between the white and pial surfaces, surface area is the sum of the areas of the triangles connected to a vertex, and gray matter volume is the product of cortical thickness and surface area. Using Freesurfer's group analysis tool, Qdec, vertex-by-vertex analyses were performed controlling for age and gender. Group effects were calculated by general linear model (GLM) at each vertex. Additional covariates for each GLM were selected by forward stepwise regressive fitting of a set of measures obtained from Freesurfer (intracranial volume, cortical white matter volume, cortical gray matter volume, subcortical gray matter volume, cortical surface area, thickness) and selection of the significant model with the largest F statistic. Based on those analyses, cortical volume and surface area were used as covariates for thickness; intracranial volume, cortical white matter volume, cortical volume, and thickness were used as covariates for surface area and surface area, and

thickness were covariates for cortical volume. Data were smoothed using a full width/half-maximum Gaussian kernel of 15mm for cortical thickness and of 10mm for surface area and volume, and corrected for multiple comparisons using Monte Carlo permutation cluster analyses with a significance threshold of $p < 0.05$. To confirm findings and to assess the data for the effects of possible interaction terms, values for thickness, surface area, or volume were extracted for significant clusters and analyzed post-hoc using IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corp).

White Matter Tract Structural Integrity—DWI images were atlas-transformed, and fractional anisotropy (33), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were calculated (34, 35) and analyzed with a voxel-wise tract-based spatial statistics (TBSS) approach (36) as previously published (4). Briefly, TBSS uses the calculated FA images to produce a mean FA skeleton to represent the center of the white matter tracts. FA images were projected onto the mean FA skeleton and thresholded at $FA = 0.2$. TBSS was used to compare group differences across the FA skeleton. We also calculated MD, AD, and RD images, and analyzed all images using Randomise (FSL, FMRIB, Oxford, UK), a permutation-based statistical approach that corrects for multiple comparisons (37). To ensure that motion artifacts were not responsible for any findings observed in DWI data, the number of rejected outlier data was collected from the image processing steps, and the number of bad encodes per subject was compared between groups (type 1 diabetes vs control) and type 1 diabetes subgroups (DKA+ vs DKA–).

Data Analysis—Comparisons of demographic and clinical characteristics between groups (type 1 diabetes vs control) and type 1 diabetes subgroups (DKA+ vs DKA–) were performed with t-tests and chi-square tests as appropriate (significance set at $p < .05$). For each neuroimaging metric, three primary analyses were performed, all of which controlled for age and sex: 1) univariate analyses to compare type 1 diabetes vs control groups, 2) univariate analyses to compare DKA+ vs DKA– subgroups and 3) hierarchical linear regression to determine if HbA1c at diagnosis was associated with the neuroimaging metric (significance set at $p < .05$). For the two *a priori* determined regions of interest (hippocampus and thalamus volumes), significance was set at $p < .05$. For the 11 exploratory volumes, Bonferroni correction was applied, yielding an adjusted alpha of 0.0045. For voxel-wise and vertex-wise whole brain analyses, the multiple comparison correction inherent in each software package was used. For any significant regions or clusters, the volume or mean value was extracted for each subject individually. These values were examined to confirm the original findings and to explore additional potential mediating variables such as time between diagnosis and study visit (disease duration), parental education, blood glucose at time of scan, and HbA1c at follow-up.

Results

Subjects

(Table 1). Seventy-three individuals were scanned (type 1 diabetes $n = 46$, control $n = 27$). Participants with type 1 diabetes were scanned between 3 weeks and 3.5 months after diagnosis. Twelve of these subjects had DKA at presentation (mild DKA $n = 7$, moderate

DKA $n=3$, severe DKA $n=2$). All patients with moderate and severe DKA were treated with insulin drips; one patient with severe DKA was admitted to the ICU and had altered mental status on arrival. After diagnosis, all subjects with type 1 diabetes were treated with an intensive basal-bolus insulin regimen with four injections per day. No subject experienced severe hypoglycemia or additional DKA events between diagnosis and scanning.

Five participants did not complete DTI images, and 6 participants did not have compatible MPAGE scans due to a change in scanning protocol. These issues left 67 subjects with usable MPAGE images (type 1 diabetes $n=42$, control $n=25$) and 68 subjects with usable DTI images (type 1 diabetes $n=44$, control $n=24$). One control was missing parental years of education, one participant with type 1 diabetes was missing blood glucose levels prior to scanning and another type 1 diabetes participant was missing a follow-up HbA1c value. Groups (type 1 diabetes vs control) and subgroups (DKA+ vs DKA-) did not differ in any demographic or clinical characteristics ($p>.05$) (Tables 1 and 2). Given the limited number of subjects with moderate or severe DKA, statistical analyses could not be performed across DKA severity categories.

Gray and White Matter Volumes

A priori regions—Groups (type 1 diabetes vs control) and subgroups (DKA+ vs DKA-) did not differ in hippocampal (type 1 diabetes vs control: $F(1,63)=0.52$, $p=0.47$; DKA+ vs DKA-: $F(1,38)=0.17$, $p=0.69$) or thalamic volumes (type 1 diabetes vs control: $F(1,63)=0.21$, $p=0.65$; DKA+ vs DKA-: $F(1,38)=0.46$, $p=0.50$) (Table 3). However, within the type 1 diabetes group, a higher HbA1c at diagnosis was associated with lower volume of the thalamus (Fig 1A; F Change $(1,38)=8.47$, $p=0.006$) and hippocampus (Fig 1B; F Change $(1,38)=4.95$, $p=0.03$) after controlling for age and sex. Additionally controlling for parental education, diabetes duration, HbA1c at follow-up, DKA status, and blood glucose at the time of scan did not alter results for the thalamus (F Change $(1,32)=5.33$, $p=0.028$) and only slightly muted the results for the hippocampus (F Change $(1,32)=3.55$, $p=0.064$). Finally, we repeated these last analyses after removing the 3 patients with < 1 month duration of T1DM and found somewhat similar results despite the reduced power (thalamus, $p=.058$, hippocampus, $p=.067$).

Exploratory Regions—Groups (type 1 diabetes vs control; DKA+ vs DKA-) did not differ in volumes in any of these regions (Table 3). However, higher HbA1c at diagnosis was associated with lower volume in cerebellar white matter (Fig 1C; F Change $(1,38)=10.36$, $p=.003$) after correcting for multiple comparisons. Additionally controlling for parental education, diabetes duration, HbA1c at follow-up, DKA status and blood glucose at the time of scan did not alter these results (F Change $(1,32)=9.83$, $p=0.004$). Finally, we repeated this last analysis after removing the 3 patients with < 1 month duration of T1DM and found similar results ($p=.003$).

Cortical Volume, Thickness, and Surface Area—The type 1 diabetes group had lower cortical volume in the left hemisphere at the temporal-parietal-occipital cortical junction compared to controls (Fig 2A) after correcting for multiple comparisons. No other group or subgroups effects were identified in volume, thickness or surface area. Analyses of

the extracted region confirmed the main effect of group ($F(1,63) = 14.00$, $p < 0.001$), which did not change when parental education level was additionally covaried ($F(1,61) = 14.48$, $p < 0.001$). Interestingly, within this cluster we observed main effect of DKA group ($F(2,60) = 9.50$, $p < 0.001$), with the DKA+ group having thinner cortex than the DKA- group ($p = 0.05$) and controls ($p < 0.001$). The DKA- group was also different from controls ($p = 0.004$) (Fig 2B). We repeated this analysis after removing the 3 patients with < 1 month duration of T1DM and found similar results (main effect of DKA group, $p < 0.001$). No effect of HbA1c at diagnosis was observed in this region after controlling for age and sex (F Change (1,38) = 0.08, $p = 0.78$).

Higher HbA1c at diagnosis correlated with lower cortical thickness in the posterior parietal lobe and with greater cortical thickness in the occipital lobe (Fig 2C). Of note, prior to multiple comparisons correction, the left hemisphere had a cluster of lower cortical thickness in the posterior parietal lobe similar in location and shape to the cluster on the right hemisphere, but this did not remain significant after correction for multiple comparisons. Thicknesses within these clusters were extracted for each subject and examined, confirming the relationship for the parietal cluster (F Change (1,38) = 11.13, $p = 0.002$). This effect was still present after additionally covarying parental education, diabetes duration, HbA1c at follow-up, DKA status and blood glucose at the time of scan (F Change (1,32) = 8.69, $p = 0.006$). We repeated this last analysis after removing the 3 patients with < 1 month duration of T1DM and found similar results ($p = 0.016$).

In order to explore how those with type 1 diabetes and with higher HbA1c compared to controls, we divided the type 1 diabetes group by the median HbA1c value (11.5) and performed a univariate analysis on the 'lower' and 'higher' type 1 diabetes subgroups and controls, covarying for age, sex and parental education. The main effect of group was not significant ($F(2,60) = 2.22$, $p = 0.12$). The mean for the control group was intermediate between the 'lower' and 'higher' subgroups, but was not significantly different from either subgroup, but the 'higher' subgroup had lower thickness in this region than the 'lower' subgroup. The relationship between HbA1c and occipital region thickness could not be confirmed, after covarying age and sex (F Change (1,38) = 1.6, $p = 0.21$). Inspection of the subject level data suggests that outliers may have driven the original finding.

White Matter Tract Structural Integrity—There was no difference in number of excluded outlier measurements due to movement between type 1 diabetes and control subjects ($t = -0.40$, $df = 134$, $p = 0.69$) or between DKA+ and DKA- subjects within the type 1 diabetes group ($t = -0.44$, $df = 86$, $p = 0.66$). The type 1 diabetes group did not differ from controls in FA, RD, or AD after correcting for multiple comparisons. HbA1c at diagnosis did not relate to FA, RD or AD. However, the DKA+ group had lower RD and AD in multiple regions of the white matter skeleton, but did not differ in FA ($p < 0.05$; Figure 3A, 3B, 3C). Clusters of significant voxels for both RD and AD maps appeared in the corpus callosum, extending to the superior longitudinal fasciculi bilaterally and the anterior corona radiata bilaterally. Within the DKA+ group, there was no association between RD or AD in these clusters and osmolarity at diagnosis ($ps > 0.30$). Post-hoc analyses of mean values in significant clusters confirmed that the DKA+ cohort had lower RD and AD measures compared to the DKA- group (RD: F Change (1,40) = 28.53, $p < 0.001$; AD: F Change

(1,40)=38.43, $p<.001$) and that this effect remained after covarying for parental education, blood glucose at time of scan, diabetes duration, HbA1c at diagnosis and HbA1c at follow-up (RD: F Change(1,34)=26.01, $p<.001$; AD: F Change (1,34)=30.97, $p<.001$). We repeated these last analyses after removing the 3 patients with < 1 month duration of T1DM and found similar results (RD, $p<.001$; AD, $p<.001$). In addition, when the control group was added to the model, the main effect of group was still significant after covarying age, sex and parental education (RD: F (2,61)=14.22, $p<.001$; AD (F (2,61)=16.28, $p<.001$) and the DKA+ group also had lower RD and AD compared the DKA- group and to the control group ($p<.001$), but the DKA- and control groups were not different from each other (RD: $p=.17$, AD: $p=.09$).

Discussion

This study shows that two markers of severity of clinical presentation at diagnosis of type 1 diabetes in youth, DKA and HbA1c levels, have independent associations with cortical thickness, cortical and subcortical volume, and white matter integrity approximately 3 months after diagnosis. These associations were present in groups and individuals, regardless of degree of glycemic exposure between diagnosis and imaging, parental education level, blood glucose at the time of scan and duration of diabetes. The neuroanatomical patterns observed share similarities with findings from studies of individuals with longer duration of type 1 diabetes (38, 39), suggesting that events surrounding diagnosis could contribute to these patterns. Our results will require replication and extension in larger and more diverse samples of newly diagnosed youth with T1DM.

We have previously noted that brain regions within the default mode network appear to show some preferential vulnerability to extreme glycemic states experienced over time (15). The default mode network is a set of cortical regions that have high levels of glucose metabolism and glycolysis at rest (40, 41), which we speculate may make it vulnerable to glycemic extremes. In this study, we find that two regions within the default mode network also show an association with events around the time of clinical presentation. Specifically, we found lower volume in the left temporal-parietal-occipital cortical junction in youth with type 1 diabetes (particularly those who experienced DKA at diagnosis) compared to controls. In addition, we found that higher HbA1c at diagnosis was associated with lower cortical thickness in the right posterior parietal cortex. These regions have been noted to be altered in studies of adults with longer-duration of type 1 diabetes (38, 39, 42), and reduced volume and white matter structure in this region has been linked to greater exposure to hyperglycemia in children with longer duration type 1 diabetes (14, 43). While intriguing, this potential mechanism for vulnerability does not explain all of our results, suggesting that a unifying theory of regional brain vulnerability to glycemic extremes during development remains to be proposed.

Greater hyperglycemia in the months prior to diagnosis was associated with a lower volumes in our *a priori* regions (hippocampus and thalamus), and in one exploratory region after correction for multiple comparisons (cerebellar white matter). Animal studies have shown that hyperglycemia and DKA can lead to varying degrees of dysfunction in the hippocampus (44–46) and human studies have linked severity of clinical presentation in youth with type 1

diabetes to decreased delayed memory performance, a critical function of the hippocampus (5, 21, 22). Unfortunately, in our dataset, we had few subjects with both valid imaging and cognitive data to perform correlations between these two outcomes with adequate power. Lower thalamic T2 signal has been associated with previous hyperglycemia in type 1 diabetes (29) and the thalamus is thought to play an important role in the autonomic response to recurrent hypoglycemia (47). These data further support the hypothesis that these two regions have some susceptibility to the extreme glycemic states, even when experienced at diagnosis. The association between lower cerebellar white matter and greater hyperglycemia exposure at diagnosis is novel and will require replication.

Previous studies investigating the impact of DKA on brain structure and function have found differences in white matter microstructural integrity, regional volumes, and markers of diffusion in white matter tracts, in patients that had experienced DKA at any time in the course of type 1 diabetes (22, 48, 49). However, DKA at time of diagnosis is rarely accounted for and most studies lack control groups without diabetes or without DKA exposure. We found that DKA at diagnosis (independent of HbA1c at diagnosis), was associated with lower diffusivity measures (RD and AD) within multiple white matter tracts, compared to both type 1 diabetes without DKA and normal controls. A similar study of newly-diagnosed youth with type 1 diabetes found higher mean diffusivity (MD) in cortical white matter within 48 hours of experiencing DKA, compared to those without DKA at diagnosis (22). This difference resolved 5 days later following initiation of IV insulin therapy and remained stable at a 6-month follow-up. In other studies, MD was lower during acute DKA compared to 72 hours after treatment (49), with one of the studies also observing a higher FA (48). It is unclear why diffusivity measures appear to be affected in opposite directions in these two acute DKA studies. However, since these studies did not include controls without type 1 diabetes and the second study did not assess a group of patients without DKA, it is difficult to know whether these values fully normalized with time or if there were continued abnormalities even after treatment.

While this study presents novel findings regarding the unique effects of DKA and hyperglycemia at the time of clinical diagnosis on brain structure months later, there are several limitations to our design. 1) The cross-sectional nature of this study limits causal inferences between severity of clinical presentation and neuroimaging measures. However, our use of sibling controls and lack of any demographic differences between groups and subgroups strengthens the inference that brain differences in those with type 1 diabetes and DKA do not predate diagnosis. The only way to establish a true baseline would be to scan individuals before they show any sign of type 1 diabetes. 2) Although there was some variability in disease duration (3 weeks to 3.5 months), this variable was skewed (mean=2.14 months) and also did not explain our findings in post-hoc analyses. 3) A minority of patients (26%) presented in DKA, most events were mild and our overall sample size was relatively small. Our results represent an initial exploration of the risk factors for subsequent brain changes in newly diagnosed youth with T1DM. A larger sample with more variability in DKA severity would allow us to explore relationships that are more specific between DKA severity measures and brain structure. 4) A longitudinal design is needed to ascertain that the brain differences observed here persist beyond 3.5 months post-diagnosis.

Overall, our study suggests that DKA and hyperglycemia exposure at diagnosis independently may influence brain structure in childhood and adolescence and highlights the regional vulnerability of the developing brain to glycemic extremes. These results support the importance of avoiding DKA and limiting exposure to hyperglycemia prior to diagnosis and further motivate the development of screening strategies for earlier detection of type 1 diabetes in childhood. Longitudinal studies with larger, more diverse samples are necessary to determine whether the severity of clinical presentation interacts with subsequent glycemic control to influence developmental brain trajectories.

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Figure 1. Relationship between HbA1c at diagnosis and volume of the (A) thalamus, (B) hippocampus and (C) cerebellar white matter in the type 1 diabetes group after controlling for intracranial volume, age and sex.

Figure 2.

A) Region of lower volume in the left temporal-parietal-occipital junction (in blue) in the type 1 diabetes group compared to controls, controlling for age and sex. B) Thickness of left temporal-parietal-occipital region in diabetic ketoacidosis (DKA) subgroups. Asterisk = different from those without DKA (DKA-) ($p=.05$) and control ($p<.001$) groups. C) Region of lower cortical thickness in the posterior parietal cortex (in blue) and higher cortical thickness in occipital cortex (in red) associated with higher HbA1c at diagnosis. The occipital region was not reliable in post-hoc analyses.

Figure 3. Diffusivity differences in diabetic ketoacidosis (DKA) subgroups. Mean white matter skeleton shown in green, with red-yellow heat maps showing areas where radial diffusivity (RD) (A) or axial diffusivity (AD) (B) were significantly lower ($p < 0.05$) in youth with type 1 diabetes who presented in DKA at diagnosis compared to those without DKA. All results shown are the result of voxel-wise independent samples t-tests, covarying age and sex and corrected for multiple comparison.

Table 1

Means (23) or % for demographic and clinical variables for subjects with diffusion weighted imaging (DWI) and with magnetization-prepared rapid gradient echo (MPRAGE) data. Groups were not different on any of the demographic variables ($p > .05$).

	DWI		MPRAGE	
	Type 1 diabetes	Control	Type 1 diabetes	Control
N	44	24	42	25
Age in years	11.98 (2.58)	12.51 (2.60)	11.88 (2.56)	12.25 (2.79)
% Female	43.2	54.2	45.2	56.0
% Caucasian	88.6	91.7	88.1	92.0
Mean parental years of education	14.48 (2.37)	15.21 (2.33)	14.67 (2.22)	15.32 (2.13)
Disease duration in months	2.13 (0.63)	--	2.10 (0.66)	--
HbA1c at diagnosis	11.51% (1.94) (102.3 mmol/mol)	--	11.46% (1.96) (101.7 mmol/mol)	--
HbA1c at follow-up	6.71% (0.86) (49.8 mmol/mol)	--	6.74% (0.87) (50.2 mmol/mol)	--
Osmolarity in osm/L	298.77 (9.53)	--	298.38 (9.28)	--
Blood glucose at time of scan in mg/dL	152.09 (55.64)	--	156.58 (58.1)	--

Table 2

Means (23) or % for demographic and clinical variables for subjects with type 1 diabetes with and without diabetic ketoacidosis (DKA), for those with diffusion weighted imaging (DWI) and with magnetization-prepared rapid gradient echo (MPRAGE) data. Groups were not different on any of these demographic or clinical variables ($p>.05$).

	DWI		MPRAGE	
	DKA+	DKA–	DKA+	DKA–
N	10	34	12	30
Age in years	11.48 (2.95)	12.13 (2.49)	11.15 (2.77)	12.17 (2.45)
% Female	60.0	38.2	58.3	40.0
% Caucasian	90.0	88.2	91.7	86.7
Mean parental years of education	14.15 (1.97)	14.57 (2.49)	13.96 (1.84)	14.95 (2.32)
Disease duration in months	1.93 (0.67)	2.19 (0.62)	1.86 (0.68)	2.19 (0.64)
HbA1c at diagnosis	11.87% (1.55) (106.2 mmol/mol)	11.41% (2.04) (101.2 mmol/mol)	11.79% (1.47) (105.4 mmol/mol)	11.33% (2.13) (100.3 mmol/mol)
HbA1c at follow-up	6.95% (0.77) (52.5 mmol/mol)	6.64% (0.89) (49.1 mmol/mol)	6.95% (0.69) (52.5 mmol/mol)	6.66% (0.93) (49.3 mmol/mol)
Osmolarity in osm/L	299.70 (11.91)	298.50 (8.90)	298.92 (11.14)	298.17 (8.64)
Blood glucose at time of scan in mg/dL	168.30 (58.15)	147.32 (54.85)	170.67 (65.47)	147.87 (54.38)

Table 3

Regional volume means (SEM) by group and subgroup for the two primary regions of interest (ROIs) and the 11 exploratory regions of interest (ROI). Volumes (mm³) were corrected for intracranial volume, age and sex. No significant differences were seen in either group analysis (type 1 diabetes vs control or those with diabetic ketoacidosis (DKA+) or without (DKA-) ($p>.05$).

ROI (*a priori)	Control	Type 1 diabetes	DKA-	DKA+
n	25	42	30	12
Hippocampus*	3968 (60)	3914 (46)	3897 (50)	3936 (80)
Thalamus*	7201 (78)	7247 (60)	7269 (71)	7177 (113)
Accumbens	688 (14)	690 (11)	672 (12)	741 (20)
Amygdala	1642 (32)	1646 (25)	1634 (29)	1682 (46)
Brainstem	18861 (253)	18958 (195)	18808 (233)	19239 (372)
Caudate	3937 (75)	4030 (58)	4045 (73)	4006 (117)
Cerebellar Gray Matter	53070 (706)	52499 (544)	52243 (650)	53163 (1039)
Cerebellar White Matter	14912 (236)	14900 (181)	14901 (241)	14702 (385)
Corpus Callosum	2867 (71)	2920 (55)	2946 (60)	2827 (96)
Cortical Gray Matter	537857 (4382)	537452 (3374)	540500 (3753)	534448 (6002)
Cortical White Matter	398693 (3213)	398840 (2473)	398005 (2951)	401389 (4719)
Pallidum	1711 (41)	1737 (32)	1702 (36)	1841 (58)
Putamen	6204 (126)	6118 (97)	6002 (118)	6413 (188)