Regional brain volume differences associated with hyperglycemia and severe hypoglycemia in youth with type 1 diabetes.

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Abstract

Objective: Despite interest in the effects of type 1 diabetes on the developing brain, structural brain volumes in youth with this disease have not been previously examined. This study is the first to quantify regional brain volume differences in a large sample of youth with diabetes. Research Design and Methods: Magnetic resonance images (MRI) were acquired from youth with diabetes (n=108) and healthy sibling controls (HC; n=51) aged 7-17 years. History of severe hypoglycemia was assessed by parent interview and included seizure, loss of consciousness, or requiring assistance to treat. Hemoglobin A1c (HbA1c) values since diagnosis were obtained from medical records; median HbA1c was weighted by duration of disease. Voxel-based morphometry (SPM5) was used to determine the relationships of prior hypoglycemia and hyperglycemia to regional gray and white matter volumes across the whole brain. Results: No significant differences were found between diabetic and HC groups in gray or white matter. However, within the diabetic group, a history of severe hypoglycemia was associated with smaller gray matter volume in the left superior temporal region. Greater exposure to hyperglycemia was associated with smaller gray matter volume in the right cuneus and precuneus, smaller white matter volume in a right posterior parietal region, and larger gray matter volume in a right prefrontal region. Conclusions: Qualitatively different relationships were found between hypoglycemia and hyperglycemia and regional brain volumes in youth with type 1 diabetes. Future studies should investigate whether these differences relate to cognitive function and how these regions are affected by further exposure.
Type 1 diabetes is known to have cumulative deleterious effects on the body, most notably the retina, kidney, nerves, and blood vessels (1,2). The effects of diabetes on central nervous system structure and function are less well understood. A number of studies associate exposure to hypoglycemia and hyperglycemia during childhood with deficits in specific cognitive domains (3,4). These findings suggest that during development, exposure to glycemic extremes may alter the structure or function of specific pathways or regions in the brain. Recent brain imaging studies in diabetic adults have reported differences in gray or white matter integrity associated with prior hypoglycemia or hyperglycemia (5,6). However, the effects of diabetes on the developing brain have not been assessed in any large scale study to date (7). Assessing brain integrity earlier in the course of brain development and diabetes, followed by prospective monitoring, would be essential to determine when differences may emerge. Such knowledge could shed light on the neural basis of observed cognitive effects in children and adults with diabetes and determine whether there are developmental time periods during which the brain may be particularly vulnerable to the negative effects of hypoglycemia or hyperglycemia.

The present study is the first to examine the structural integrity of the brain in a large sample of children and adolescents with type 1 diabetes. We used high resolution structural magnetic resonance imaging (MRI) and voxel-based morphometry (VBM), an objective method of quantitatively analyzing MRI data, to determine whether exposure to hypoglycemia or hyperglycemia in youth with type 1 diabetes is associated with differences in gray or white matter volumes.

**Research Design and Methods**

**Subjects:**
Children aged 7-17 with type 1 diabetes and non-diabetic siblings (healthy controls; HC) were recruited from the Diabetes Clinic at St. Louis Children’s Hospital affiliated with Washington University in St. Louis. Subjects were excluded for mental retardation, chronic disease other than type 1 diabetes (e.g., hypothyroidism), significant neurological history not due to diabetes, diagnosed psychiatric disorder, current use of psychoactive medications, prematurity at birth more than 4 weeks early with complications, and contraindications to MRI (e.g., metal implants). To reduce the likelihood of residual β-cell function, diabetic subjects were required to have been diagnosed and on insulin for at least 2 years. Handedness was assessed with a modified Edinburgh Handedness Inventory (8). Procedures were approved by the Washington University School of Medicine’s Human Studies Committee, and all participants and their parents or guardians signed informed consents.

**Clinical variables:**
Detailed information about each diabetic youth’s history of severe hypoglycemia, hyperglycemia and other diabetic complications was collected by parental and child interview. Severe hypoglycemia was defined as events with neurological dysfunction including seizure, loss of consciousness, or inability to arouse from sleep, or those requiring assistance of someone other than the patient for treatment (9). Hyperglycemic history was estimated from all available hemoglobin A1c (HbA1c) test results collected from participants’ medical records at St. Louis Children’s Hospital. HbA1c tests approximate blood glucose control over the previous 2-3 months. The amount of time represented by the
HbA1c tests was calculated by multiplying the number of tests by 3 months and dividing by duration of diabetes in months. Participants with HbA1c coverage less than 30% of their duration of diabetes (n=10) were excluded from hyperglycemia analyses. Less than complete coverage was due to clinical appointments greater than 3 months apart, transfers from other clinics, or use of total glycated hemoglobin (GHb) tests. To account for duration of exposure to hyperglycemia, a “hyperglycemia exposure score” was calculated. Because a child with an average HbA1c of 8% and duration of diabetes for 10 years has had more exposure to hyperglycemia than a child with the same average HbA1c and duration of diabetes for 2 years, a score that weighted duration and HbA1c equally was calculated by adding each patient’s z-score of median HbA1c to the z-score of duration of diabetes. This method of calculation results in a near-normal distribution of scores, with higher scores indicating more exposure to hyperglycemia. Each child’s hyperglycemia exposure score can be interpreted relative to this sample only.

**Image Acquisition:**
Structural images were acquired for each subject on a Siemens Sonata 1.5 Tesla imaging system with a standard Siemens 30 cm circularly polarized RF head coil. For each subject, 3 to 5 images consisting of 128 contiguous 1.25 mm sagittal slices were acquired using magnetization prepared rapid gradient echo (MPRAGE). Subjects with movement or other artifact were excluded (n=10). Images with suspected anatomical abnormalities were referred to a neuroradiologist for review; 3 subjects were excluded for confirmed brain abnormalities. For each subject, 3 high quality images were averaged after being co-registered by an automated, validated technique (10).

**Image analysis:**
Voxel-based morphometry (VBM) was performed with statistical parametric mapping software (SPM5; Wellcome Department of Cognitive Neurology, www.fil.ion.ucl.ac.uk). Images were simultaneously normalized to Montreal Neurological Institute (MNI) space, corrected for intensity inhomogeneity, and tissue segmented as gray matter, white matter, and CSF based on a priori probability maps (11). Gray and white segments were modulated to produce images representing gray and white matter volume (11). After this processing, voxel dimensions were 2 x 2 x 2 mm. Modulated segments were smoothed with a 12 mm full width half maximum Gaussian kernel to promote normality of residuals (12).

Voxels with segmented intensities less than 0.1 were masked out with an absolute threshold to reduce voxels possibly belonging to other tissue classes and since these voxels are less likely to adhere to assumptions of normality (13). Images were analyzed by SPM5, performing standard parametric tests (e.g., regressions) at each voxel, which results in statistical parametric maps (SPMs) on which every voxel’s intensity corresponds to a t value. The SPMs were then thresholded to show only voxels with t values corresponding to uncorrected p < .001. The probability of resulting clusters was corrected for multiple comparisons using the stat_threshold script from Worsley’s fmristat package (14). This cluster-level method of multiple-comparisons correction takes into account non-uniformity due to intrinsically inhomogeneous smoothness (15).

Total volume of each tissue class (gray matter or white matter) was calculated by summing modulated voxel intensities for that class. Co-varying total gray/white matter volume ensures differences are not attributable to global differences in volume, such as those
expected between genders and with age (16). Age, gender, and total volume of the relevant brain tissue (gray/white) were removed as covariates from all models. In addition, in models using only diabetic subjects, age of onset was also co-varied. Independent sample t-tests were performed for comparisons between groups, defining contrasts in each direction (e.g., Any Hypo > No Hypo; Any Hypo < No Hypo). For analyses of hyperglycemia exposure, multiple regressions were performed with contrasts in each direction (negative and positive correlations). Cluster-level multiple comparison corrected p values < .05 were considered significant.

Results
108 youth with type 1 diabetes and 51 HC were included in these analyses. See Table 1 for demographic and clinical information and Table 2 for a summary of imaging results.

Type 1 Diabetes vs. Healthy Controls
Diabetic and HC groups did not differ significantly in gender distribution (Chi-squared=.58, p=.45), mean age (t=-.59, p=.56), or mean parental education (t=.42, p=.68) (Table 1). The diabetic group had proportionally more left-handed or ambidextrous subjects than the HCs (Chi-squared=3.86, p=.05) (Table 1). In VBM analyses comparing diabetic versus HC groups, there were no significant gray or white matter volume differences. Co-varying handedness did not change these results.

Hypoglycemia
Because the distribution of severe hypoglycemic episodes was skewed with most subjects having few or no episodes (median = 1; range 0 – 50 episodes; lower quartile = 0, median quartile = 1, upper quartile = 2), subjects were categorized as having zero (n = 42) or any (n = 66) severe hypoglycemic episodes (“No Hypo” vs. “Any Hypo”). Age, handedness, gender, parental education, estimated IQ and median HbA1c did not differ between the No Hypo (n=42) and Any Hypo (n=66) groups, but the Any Hypo group had longer duration of diabetes (t= -5.03; p<.001), earlier age of onset (t=3.49; p=.001), and higher hyperglycemia exposure scores (t = -4.73; p<.001) (Table 1).

In VBM analyses, the Any Hypo group had less gray matter volume than the No Hypo group in the left superior temporal/occipital cortex (p=.001) and left inferior occipital cortex (p=.0002; Figure 1A). Because the Any Hypo group also had higher hyperglycemia exposure scores, we additionally co-varied hyperglycemia exposure scores. Notably, the volume of the left temporal/occipital region was still smaller (p=.008), but the left inferior occipital cortex region was not (p=.13). There were no differences in gray matter in the other direction (Any Hypo > No Hypo), and no differences in white matter volume in either direction. No differences were found comparing the HC group to the Any or No Hypo groups.

Hyperglycemia
The mean number of HbA1c values per subject was 14.3 (SD=6.6); the mean percentage of the duration of diabetes represented by HbA1c tests was 68% (SD=14%). Hyperglycemia exposure scores were normally distributed (range = -2.45 to +3.69; mean = 0.00, SD=1.42) and treated as a continuous variable. In VBM analyses, higher hyperglycemia exposure scores correlated with less gray matter volume in the right cuneus and precuneus (p=.02; Figure 1B). Hyperglycemia exposure scores also correlated with larger gray matter volume in the right frontal middle gyrus (p=.008; Figure 1C), and with smaller white matter volume in right superior parietal white matter (p=.01; Figure 1D). A similar cluster appeared in the left superior parietal white matter but did not
survive multiple-comparisons correction (p=.13). Higher hyperglycemia exposure scores were not associated with greater white matter volume in any region.

Age of Onset
Given the possibility that age of onset might confound our results (despite having co-varied it from those analyses) we performed an exploratory analysis correlating age of onset to gray and white matter volume. These analyses found that earlier age of onset was related to larger white matter volume in the left precuneus region (voxel extent = 177; p=.02). There were no significant differences for white matter in the other direction or for gray matter in either direction.

Conclusions
This is the first study to examine the effects of type 1 diabetes on brain structure in a large sample of children and adolescents. We found that youth with type 1 diabetes did not differ significantly in regional gray or white matter volumes compared to non-diabetic siblings. However, within the diabetic group, we found qualitatively different relationships between exposure to severe hypoglycemia and chronic hyperglycemia and regional gray and white matter volumes. These differences were statistically significant despite the relatively short duration of diabetes in our sample.

Hypoglycemia
Compared to their hypoglycemia-naïve diabetic peers, diabetic youth with one or more prior severe hypoglycemic episodes had smaller gray matter volume at the left temporal-occipital junction. Interestingly, smaller gray matter in a similar region (left superior temporal and angular gyri) has been reported in adults with type 1 diabetes (5). In addition, human neuropathological case studies of profound hypoglycemia in adults have reported defects in temporal and/or occipital regions (17,18); however, in one report, these regions were relatively preserved (19). This region has been associated with the episodic memory system (e.g., (20)); severe hypoglycemia has been previously found to affect episodic memory in children (3,21), but the relation of such cognitive changes to the current brain findings remains to be examined. This area is also part of the “default system”, a set of interconnected brain regions with high resting state neuronal activity that decreases in response to cognitive challenges (22). It is possible this high baseline rate of blood flow creates a heightened vulnerability of the neurons to significantly reduced blood glucose during hypoglycemia.

While no direct comparisons were made between the left and right hemispheres, our data may suggest a stronger effect of severe hypoglycemia on the left side of the brain than the right side. At least three neuropathological case studies also described more extensive damage in the left than the right hemisphere with severe hypoglycemia (18,23,24). Additionally, in a SPECT study, children with severe hypoglycemia were more likely to have activity on the left less than that on the right compared to those without severe hypoglycemia, suggesting possible left lateralization of the effects of hypoglycemia (25). Interestingly, in the default system, this same region has a greater response to cognitive challenge on the left than on the right side (22).

Hyperglycemia
The extent of exposure to hyperglycemia was associated with differences in both gray and white matter volume. Smaller gray matter volume was found in posterior cortical areas (right cuneus and precuneus). This region is associated with higher-order visuospatial function and episodic memory (26); the relation of findings in this region to
diminished performance in these cognitive domains in diabetic children (3,21) remains to be investigated. A study in adults with type 1 diabetes also found less gray matter in the right cuneus with higher lifetime HbA1c averages (5). In addition, another study reported lower gray matter density in the right occipital lobe in diabetic adults with retinopathy compared to healthy controls (27). The mechanism for this regional effect is unknown, but Wessels et al. (27) speculated that the occipital lobe is at risk for hypoperfusion due to being located in a “watershed area” of circulation. One might expect these effects to correlate to vascular changes. Although vascular disease and retinopathy were not assessed in this sample, some degree of early vascular changes might be present in diabetic children within a few years of onset (1). Therefore, a vascular mechanism cannot be ruled out as accounting for this finding even in this age range. This region, also in the “default system”, has been noted for having the highest baseline metabolism of the whole brain (22), and may be preferentially vulnerable to insults (e.g., (28)).

Our analyses also revealed greater gray matter volume in a right prefrontal region with greater exposure to hyperglycemia. Overall, gray matter decreases with development across this age range (29), so this finding may reflect an abnormal developmental trajectory. Alternatively, this finding may indicate a compensatory reaction to the lower gray matter volume we found in the right cuneus and precuneus. Musen et al. (5) also reported greater gray matter density associated with higher lifetime HbA1c in adults with diabetes, but the affected region was in a different location (parietal lobe) than the ones we report here in children.

White matter volume was lower in the right superior parietal region in subjects with greater hyperglycemia exposure, with a similar finding in the homologous area on the left side. The significant region on the right was adjacent to the hyperglycemia-associated gray matter area (precuneus), and these two findings may be related. By reconstructing white matter fiber bundles and their neuroanatomical connectivity to gray matter regions, diffusion tensor tractography could further address whether these two regions may be connected. A MR spectroscopy study in children with a history of significant hyperglycemia reported low metabolite ratios in posterior parietal white matter, indicating possible dysfunction or reduced axonal density in this region (30). In normal children, anisotropy in the parietal white matter has been found to increase with age (32) and correlate with IQ (33). Thus, it is possible that altered white matter volume in this region could be reflected in aspects of cognitive performance.

**Age of Onset**

Age of onset of diabetes was examined as a potential confound to the observed effects of hypoglycemia and hyperglycemia. The finding that age of onset was not associated with differences in gray matter is consistent with a previous report, which found no effect of diabetes onset age on traced temporal lobe or amygdalohippocampal volumes in young adults with type 1 diabetes (34). The association of earlier age of onset with larger white matter volume near the left precuneus was unexpected, but there have been no previous studies examining the effects of age of onset on white matter volume. Our finding was in the opposite direction (larger) and on the opposite side (left) from the volume difference in the precuneus region found to be associated with hyperglycemia exposure (see above). Thus, the anatomical location and the direction of the relationship suggest that age of onset does not explain the results from our
analyses of the effects of hypoglycemia and hyperglycemia.

As with complications in other organs and systems in youth with type 1 diabetes (neuropathy, retinopathy, nephropathy (1,2)), the effects of blood sugar extremes on the structural integrity of the brain, although significant, may be sub-clinical at this early stage. These subtle differences are observable at a group level, and are not likely to be apparent in individual patients at this age. However, these differences were generated with conservative statistical methods designed to minimize the probability of false positives (35), so their potential consequences should be examined. Currently, it is unknown if these differences are associated with cognitive consequences. It is possible that, as with other complications, these brain differences and their consequences could be compounded by further cumulative exposure to glycemic extremes with advancing age and increasing duration of diabetes.

We propose that the regional volume differences detected in this study reflect the impact of hyperglycemia and hypoglycemia on neural integrity and/or development. In animal models, hypoglycemia has been shown to induce neuronal death and dysfunction (e.g., (36)), and hyperglycemia is reported to cause injury to myelin and neurons (e.g., (37)); these data support our supposition that glycemic extremes precede measurable differences in the brain. However, due to the retrospective and correlative nature of this study, we cannot rule out that the differences reported here were present prior to exposure to glycemic extremes or diabetes. Retrospective report of severe glycemic experiences has been found to be fairly reliable in adults (38), but prospective measures are likely to be more accurate, especially over long time-periods (39). Prospective follow-up of our sample is ongoing and should be able to determine if further exposure to hyperglycemia and hypoglycemia accentuates the pattern of regional volume differences reported here. It should also be noted that glycemic extremes could affect the function of the brain with or without altering regional volumes. Future studies using methods such as functional MRI would be needed to determine whether functional abnormalities exist in this population.

We conclude that hypoglycemia and hyperglycemia are associated with differences in regional gray and white matter volumes in the brain in youth with type 1 diabetes. Longitudinal follow-up of well-characterized samples such as ours is necessary to determine the course of brain changes with age and further exposure to glycemic extremes. Ultimately, an understanding of the implications of these findings for optimal cognitive and academic function must be obtained to place these observations in proper clinical context.
Reference List


Table 1. Demographic and clinical variables. Values represent means (+/- SD) unless otherwise noted.

<table>
<thead>
<tr>
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<th>Control Subjects</th>
<th>Diabetic Subjects</th>
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<tbody>
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<td>n</td>
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<td>108</td>
<td>42</td>
<td>66</td>
</tr>
<tr>
<td>Age</td>
<td>12.3 (2.7)</td>
<td>12.6 (2.7)</td>
<td>12.3 (2.4)</td>
<td>12.8 (2.9)</td>
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<td>Sex M/F (% M)</td>
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<td>62/46 (57%)</td>
<td>27/15 (64%)</td>
<td>35/31 (53%)</td>
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<td>95/12 (11%)</td>
<td>37/7 (16%)</td>
<td>60/5 (8%)</td>
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<tr>
<td>Handedness R/Other (% R)</td>
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<td>96/12 * (89%)</td>
<td>37/5 (88%)</td>
<td>59/7 (89%)</td>
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<td>Parent Education (2)</td>
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<td>15.0 (2.2)</td>
<td>14.8 (2.5)</td>
<td>15.2 (2.0)</td>
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<td>Duration of Diabetes</td>
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<td>Median A1c (3)</td>
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<td>8.4 (0.8)</td>
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<td>-0.8 (1.2)</td>
<td>0.5 ** (1.3)</td>
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* Significantly different from HC; p < .05
** Any Hypo significantly different from No Hypo; p <= .001
1: Not reported for 2 participants
2: Not reported for 5 participants
3: Ten subjects with less than 30% coverage excluded
Table 2. Summary of models, contrasts, and results. Regions with multiple-comparison corrected cluster level p<.20 are shown; significant results are in bold. Voxel dimensions are 2 x 2 x 2 mm. Peak voxel refers to the voxel with greatest t value. GM = total gray matter volume, WM = total white matter volume; L = left, R = right.

<table>
<thead>
<tr>
<th>Model</th>
<th>Covariates</th>
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<th>Contrast</th>
<th>Region</th>
<th>Brodmann’s Area(s)</th>
<th>Cluster Size (voxels)</th>
<th>Corrected Cluster p</th>
<th>Peak Voxel MNI Coordinates (x, y, z)</th>
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<td>66 vs. 42</td>
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<td>0.13</td>
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Figure Legends

Figure 1. Results overlaid on individual subject’s brain in MNI space. (A) Regions with smaller gray matter volume in diabetic youth with history of severe hypoglycemia compare to diabetic youth without a history of severe hypoglycemia. Regions of (B) less gray matter, (C) more gray matter and (D) less white matter associated with greater hyperglycemia exposure. Crosshairs indicate location of peak voxel of the significant region. Color bar indicates T values. In the coronal view, the left side of the images depicts the left side of the brain.