White Matter Structural Differences in Young Children With Type 1 Diabetes: A Diffusion Tensor Imaging Study

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OBJECTIVE—To detect clinical correlates of cognitive abilities and white matter (WM) microstructural changes using diffusion tensor imaging (DTI) in young children with type 1 diabetes.

RESEARCH DESIGN AND METHODS—Children, ages 3 to <10 years, with type 1 diabetes (n = 22) and age- and sex-matched healthy control subjects (n = 14) completed neurocognitive testing and DTI scans.

RESULTS—Compared with healthy controls, children with type 1 diabetes had lower axial diffusivity (AD) values (P = 0.046) in the temporal and parietal lobe regions. There were no significant differences between groups in fractional anisotropy and radial diffusivity (RD). Within the diabetes group, there was a significant, positive correlation between time-weighted HbA_{1c} and RD (P = 0.028). A higher, time-weighted HbA_{1c} value was significantly correlated with lower overall intellectual functioning measured by the full-scale intelligence quotient (P = 0.03).

CONCLUSIONS—Children with type 1 diabetes had significantly different WM structure (as measured by AD) when compared with controls. In addition, WM structural differences (as measured by RD) were significantly correlated with their HbA_{1c} values. Additional studies are needed to determine if WM microstructural differences in young children with type 1 diabetes predict future neurocognitive outcome.

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Children diagnosed with the onset of type 1 diabetes before 5 years of age have impaired performance in memory, attention, visual-perceptual function, and fine motor speed/coordination (1,2). Young children with type 1 diabetes have the greatest excursions in blood glucose (BG) values (3) because of their irregular eating patterns and inability to recognize and report symptoms of hypoglycemia or hyperglycemia. Both hypoglycemia (4,5) and hyperglycemia (6,7) have been associated with neurocognitive effects and brain volume differences (8). Early childhood is a period of rapid and dynamic changes in the central nervous system, such as myelination, modification of synapses, and pruning. Therefore, during this time of potential increased vulnerability to central nervous system insults (9,10), increased occurrences of glycemic excursions may lead to neurocognitive deficits (11). Although there have been concerns regarding how type 1 diabetes and its treatment impact cognitive performance and brain structure, neither the extent of this impact nor the putative mechanisms have been elucidated.

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The white matter (WM) of the brain consists mostly of myelinated neuronal axons responsible for signal transfer between neuronal cells. We previously reported (12) no significant differences in *total* gray matter (GM) and WM volumes between children (3–10 years of age) with type 1 diabetes and healthy controls. However, *regional* differences in brain structure or function that could lead to undesirable behavioral and cognitive outcome have not been adequately evaluated in this young age group.

Diffusion tensor imaging (DTI) is a noninvasive magnetic resonance imaging (MRI)–based method that uses the diffusion of water molecules in the brain to investigate WM structure. To date, DTI has been used for the investigation of WM structure in adults with type 1 diabetes, but not in children. Kodl et al. (13) investigated adults with long-standing type 1 diabetes and found microstructural abnormalities in several WM tracts, including the posterior corona radiate and optic radiations. Further, WM structural variations observed with DTI in adult subjects with type 1 diabetes were correlated with poorer performance on the Rey-Osterreith Complex Figure Drawing and Grooved Peg Board tests (13). Using the same sample, Franc et al. showed a correlation between the WM tracts previously found to have reduced fractional anisotropy (FA) and regions with reduced cortical thickness (14). Together, these findings suggest that long-standing type 1 diabetes causes widespread microstructural WM alterations in the posterior cerebrum.

With no published DTI studies in children with type 1 diabetes, it is not known if and when putative insults to developing WM structure occur. We hypothesized that WM structure would be different in young children with type 1 diabetes when compared with matched healthy control subjects.

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS—Children between 3 and 10 years of age with type 1 diabetes for at least 6 months and healthy controls

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subjects were recruited. All procedures were approved by the institutional review board and all parents or guardians signed informed consents. Children over 7 years of age signed assents (ClinicalTrials.gov Study NCT #00449891). Diabetes history, time-weighted average HbA_{1c} (calculated using the trapezoid rule [15] for all HbA_{1c} values from the time of diagnosis), cognitive testing, and MRI training were completed as previously described (12). Subjects completed the Wechsler Preschool and Primary Scale of Intelligence III (WPPSI-III) or Wechsler Intelligence Scale for Children IV (WISC-IV) based on their age. All subjects were included in the full-scale intelligence quotient (FSIQ) scores analysis, but the younger subjects were excluded from the WISC-IV score analyses. The time-weighted HbA_{1c} value is used for all data analyses. BG values were between 80 and 250 mg/dL before the start of any neurocognitive testing or MRI scan. We specifically examined neurocognitive skills associated with WM function using tasks specifically designed for children, including subtests from the WISC-IV (block design digit span, picture concepts, vocabulary, letter-numbering sequencing, matrix reasoning, and comprehension) and the developmental neuropsychological assessment (NEPSY) (design copy, phonological processing, memory of faces, tower, auditory attention and response, speeded naming, arrows, delayed memory of faces, comprehension of instructions, imitating hand positions, and narrative memory).

Subjects underwent high-resolution structural MRI scans using a General Electric Signal 1.5 Tesla imaging system. Coronal three-dimensional volumetric spoiled grass gradient recalled series were acquired with the following scan parameters: repetition time (TR) 35 ms, echo time (TE) 6 ms, flip angle 45°, 1.5 mm thick, 0-mm gap, number of excitations 1, field of view (FOV) 24 cm, and a 256 × 192 matrix size for 124 contiguous slices (scan time: 14 min). Imaging parameters for the diffusion-weighted sequence were as follows: FOV, 24 cm; matrix size, 128 × 128; TR/TE 5,400/min; 43 axial-oblique slices; slice thickness, 3.2 mm/no skip. Diffusion gradient duration was δ = 32 ms and diffusion weighting was b = 850 s/mm^2, and b = 0 as reference images. Diffusion was measured along 22 noncollinear directions. This protocol was repeated six times.

Diffusion-weighted scans preprocessing

Diffusion-weighted images were corrected for eddy current distortions and head motion using an affine transformation of Automated Image Registration (16). All individual images were visually inspected to eliminate slices with motion artifacts. We excluded six subjects (four with diabetes, two control subjects) from further analysis because of significant artifacts. The remaining images were averaged and the pixel intensities of the multiple diffusion-weighted images were then fitted to obtain the six elements of the symmetric diffusion tensor. Scalars such as fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) were calculated using DTIStudio (https://www.mristudio.org/). FA is a measure that reflects the degree of diffusion anisotropy within a voxel. Anisotropy within a given WM voxel is determined by fiber diameter and density, degree of myelination, extracellular diffusion, interaxonal spacing, and intravoxel fiber -tract coherence. AD is the diffusivity of water molecules along the main axis of diffusion within a voxel (vector with the largest eigenvalue), and RD is the mean of the diffusivities perpendicular to the vector with the largest eigenvalue. AD is thought to reflect fiber coherence, whereas RD is thought to represent fiber integrity and myelination (17,18).

Tract-based spatial statistics (TBSS) analysis

First, FA images from each subject were aligned into a common space using nonlinear and linear registrations. Subsequently, FA images were averaged to produce a group mean FA image. A skeletonization algorithm was applied to the group mean FA image to define a group template of the lines of maximum FA, thought to correspond to centers of WM tracts. FA values for each subject were then projected onto the group template skeleton. The FA skeleton was thresholded to FA $\geq$0.3. The original registration parameters of the FA were then applied to the AD and RD images. FA, AD, and RD data projected onto the skeleton were fed into voxel-wise cross-subject statistics ($P < 0.05$) using "randomise" (v. 2.1 in FSL4.1), a permutation program used for inference (thresholding) on statistic maps when the null distribution is not known (19). All analyses were corrected for multiple comparisons (family-wise error) and used threshold-free cluster enhancement (20) with default parameters.

Statistical analysis

Statistical analyses of behavioral and cognitive data were performed using SPSS software version 13 (SPSS Inc., Chicago, IL). Index and specific subtest scores were compared between diabetes and HC subjects using *t* tests. Among those with diabetes, linear correlations were performed between WISC-IV and NEPSY subtest scores and HbA_{1c} and number of seizures All scores are reported as mean values and standard deviation. P values <0.05 were considered significant. We further analyzed correlations between cognitive data, time-weighted HbA_{1c}, age at diagnosis, duration of illness, history of seizures, and WM structure (FA, AD, and RD) using TBSS.

RESULTS—We approached 81 subjects with type 1 diabetes: 35 by e-mail or phone and 46 directly in the clinic. Likewise, 30 healthy control subjects, mostly siblings or friends of our subjects, were directly approached in person. Forty-five subjects (n = 27 diabetes, n = 18 healthy control subjects) completed the neurocognitive testing, and 42 (n = 26 diabetes, n = 16 healthy control subjects) of them completed DTI scans. Six subjects (n = 4 diabetes, n = 2 healthy control subjects) were excluded from further analysis because of significant image artifacts. The data presented in this manuscript are restricted to the subset of subjects who completed both the neurocognitive testing and the DTI scans (Table 1). One healthy control subject had an abnormal cisterna magna and was excluded.

Cognitive testing

WPPSI-III and WISC-IV results were very similar (P = 0.38) for FSIQ score for subjects with diabetes (WPPSI-III 109 ± 4.2; WISC-IV 108.4 ± 14.7) and healthy control subjects (WPPSI-III 107 ± 11.0; WISC-IV 112.7 ± 13.5). There were no statistically significant differences in general cognitive ability in regard to executive function, processing speed, memory/attention, and motor domains between subjects with diabetes and healthy controls (all P values > 0.05). However, calculations of the effect size are approximately 0.30 (Cohen's d), suggesting that there may be a modest difference between the two groups' WISC scores. There were no significant between-group differences on NEPSY scores (all P values > 0.05). Within the diabetes group, higher HbA_{1c} levels were correlated with lower overall intellectual functioning measured by FSIQ

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Table 1—*Demographics*

	Type 1 diabetes	Control subjects
Mean age (years ± SD)	7.8 ± 1.5 (5.4–9.9)	7.2 ± 1.6 (4.7–9.3)
Gender		
Male	11	5
Female	11	9
Handedness		
Right	21	13
Left	1	1
Mean time weighted HbA_{1c} % ± SD	8.0 ± 0.6	N/A
Mean age of onset (years ± SD)	3.4 ± 1.7	N/A
Mean duration of type 1 diabetes (years ± SD)	4.4 ± 2.1	N/A
Seizure occurrence		N/A
Yes	8	
1 seizure	4	
2 seizures	0	
>2 seizures	4	
No	14	

($R^2 = 0.215$, $P = 0.03$) (Fig. 1). There was a nearly statistically significant relationship between greater seizure occurrence and lower WISC-IV verbal comprehension index scores ($R^2 = 0.173$, $P = 0.054$), as well as with HbA_{1c} levels and WISC-IV digit span ($R^2 = 0.214$, $P = 0.053$). Lastly, greater seizure number was predictive of lower WISC-IV processing speed index scores ($R^2 = 0.402$, $P < 0.01$).

TBSS analysis

Compared with controls, children with diabetes had lower AD values ($P = 0.046$ covaried for age and gender) in the internal capsule, body of the corpus callosum (CC), right cingulate gyrus, right thalamus, right superior temporal gyrus, and posterior parietal lobe (Fig. 2). There were no significant differences between groups in FA and RD. Within the diabetes group, there was a statistically significant, positive correlation between time-weighted HbA_{1c} and RD ($P = 0.028$) (Fig. 3). Specifically, this correlation was seen in the inferior fronto-occipital fasciculi, uncinate fasciculi, subgenual WM, anterior forceps, right internal capsule, superior middle and inferior temporal gyri, splenium of the CC, superior longitudinal fasciculi, and occipital WM. A negative correlation between HbA_{1c} values and FA approached significance ($P = 0.057$) in the right internal capsule, the anterior forceps, inferior fronto-occipital fasciculi, and splenium of the CC.

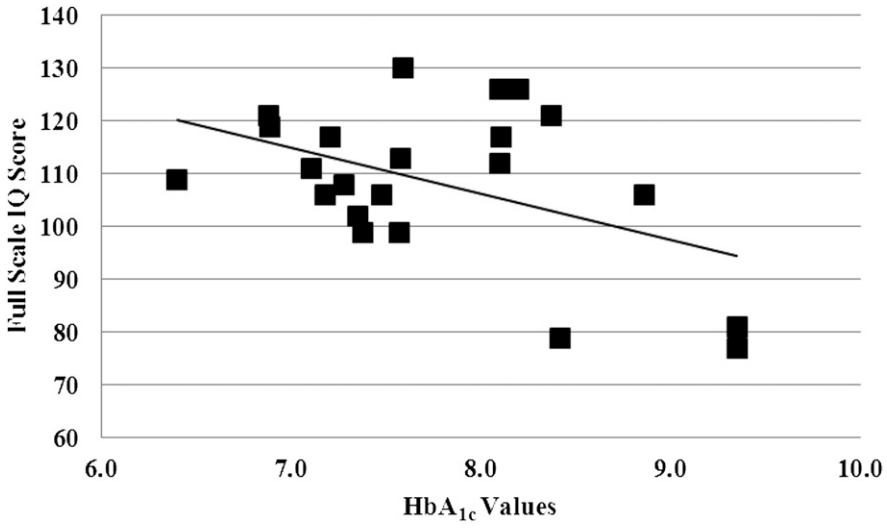

Figure 1—*Greater HbA_{1c} levels predicted lower overall intellectual functioning measured by FSIQ in children with type 1 diabetes* ($R^2 = 0.215$, $P = 0.03$). *Each box represents one subject.*

DTI and neurocognitive correlations

Within-group analysis of those with type 1 diabetes detected a positive correlation between FA and WISC coding ($P = 0.034$) and digit span ($P = 0.028$) subtests, and positive correlations between FA and WISC FSIQ ($P = 0.064$) and FA and WISC ($P = 0.058$) processing speed approached significance. Higher FA values correlated with the subjects' abilities to focus attention and quickly scan, discriminate between, and sequentially order visual information. There was a significant negative correlation between RD and WISC FSIQ ($P = 0.022$) and RD and NEPSY auditory attention score ($P = 0.02$). The negative correlation between RD and NEPSY attention/executive function approached statistical significance ($P = 0.067$). Lower RD values negatively correlated with overall IQ scores and attention-requiring tasks.

CONCLUSIONS—Neuroimaging techniques have been used to further our understanding of how medical diseases affect brain structure (21,22). In our study, we examined how type 1 diabetes affects WM microstructure in young children and the resultant effects on neurocognitive performance. Although there were no differences in cognitive test scores between the two groups, we did find that in those with diabetes, higher HbA_{1c} levels were correlated with lower FSIQ scores. Also, we describe differences in WM microstructure between those with diabetes and controls, especially in the frontal and temporal regions, and that these differences were more apparent among those with higher HbA_{1c} levels.

Neuroimaging studies in young children with type 1 diabetes have been limited to date (12,23,24), and understanding the impact of diabetes on neurodevelopment is still based largely on inferences drawn from adult neurocognitive and neuroimaging data (25). DTI provides a valuable tool to determine the relationship between WM connectivity and cognitive performance and allows additional, fine-grained investigation of WM microstructure. Based on adult studies, abnormal WM (lower FA) has been reported in four major brain regions and is thought to be responsible for neurocognitive

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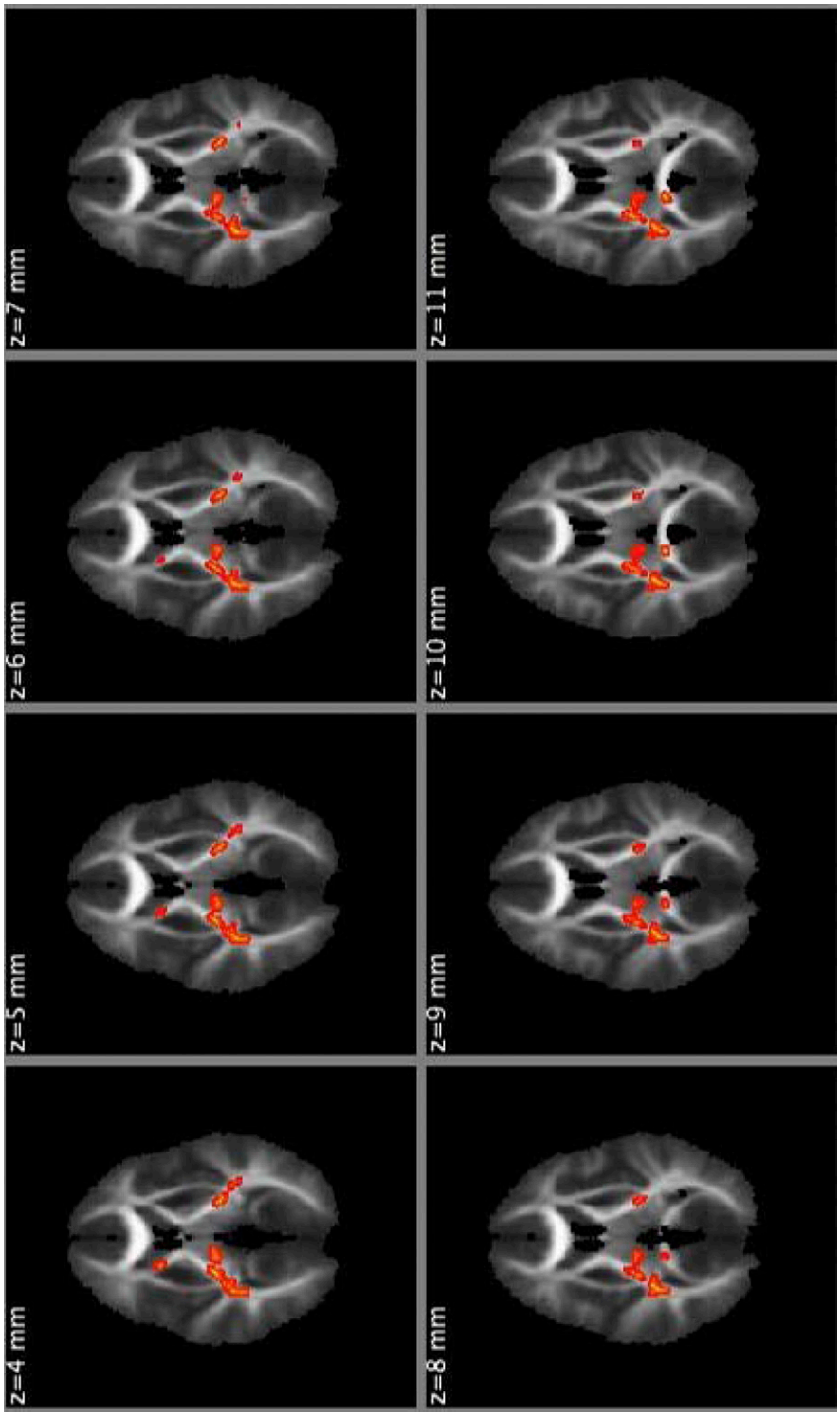

Figure 2—*Regions of significant reductions in AD (shown in yellow) in children with type 1 diabetes as compared with healthy controls subjects, shown in serial images in the axial orientation. Group differences were "thickened" for visualization purposes (shown in red). (A high-quality digital representation of this figure is available in the online issue.)*

deficits involving mental processing speed, attention, and executive functioning skills such as mental flexibility (13,26). However, it is unknown when these WM differences developed or whether they are directly attributed to the course of the diabetes.

Although we did not find significant differences in FA between those with diabetes and controls, this may be due to the young age of our participants, resulting in lack of diabetes-related complications and shorter duration of the disease. Despite this, we did see a negative correlation between HbA_{1c} and FA; although this did not reach statistical significance, larger future studies may indicate a clearer connection. AD and RD are indices that complement FA in providing additional information and increased understanding about the underlying WM and neuronal integrity. In this study, children with type 1 diabetes had lower AD values, a measure associated with less axonal coherence (27,28). Within this group, there also was a significant, widespread positive correlation between HbA_{1c} and RD, suggesting that higher BG values may affect fiber myelination or the permeability of axonal membranes (14).

Parents and providers fear hypoglycemia in young children at the expense of hyperglycemia (29) and accept chronically elevated BG values as reflected by the American Diabetes Association guidelines where there is a higher HbA_{1c} target in young children (30). Hypoglycemia has been traditionally thought to be the cause of the neurocognitive deficits; however, two longitudinal pediatric studies show that history of severe hypoglycemia alone could not explain the neurocognitive differences from healthy controls (31,32). Although we found a near-significant relationship between history of seizure occurrence and selected neurocognitive measures, the parents' reaction to the hypoglycemia, resulting in a period of chronic hyperglycemia, may be a confounding factor. Therefore, the discrepancy between the between-group analysis (which revealed significant differences in AD) and the within-group correlation of WM structure (as reflected by RD and HbA_{1c} levels) could possibly be explained by other diabetes-related factors such as hyperglycemia, perhaps leading to increased nonenzymatic glycosylation.

Hyperglycemia has a number of proposed mechanisms to cause WM changes, including nonenzymatic glycosylation and activation of the sorbitol pathway. Myelin has lysine residues that are specifically susceptible to nonenzymatic glycosylation (33). In animal models of diabetes, advanced glycosylation end products and the receptor for advanced glycosylation end products are both increased in the hypothalamus (34) and associated with significant loss of WM (35). Activation of the sorbitol pathway has been seen in 1-month-old rats when subjected to

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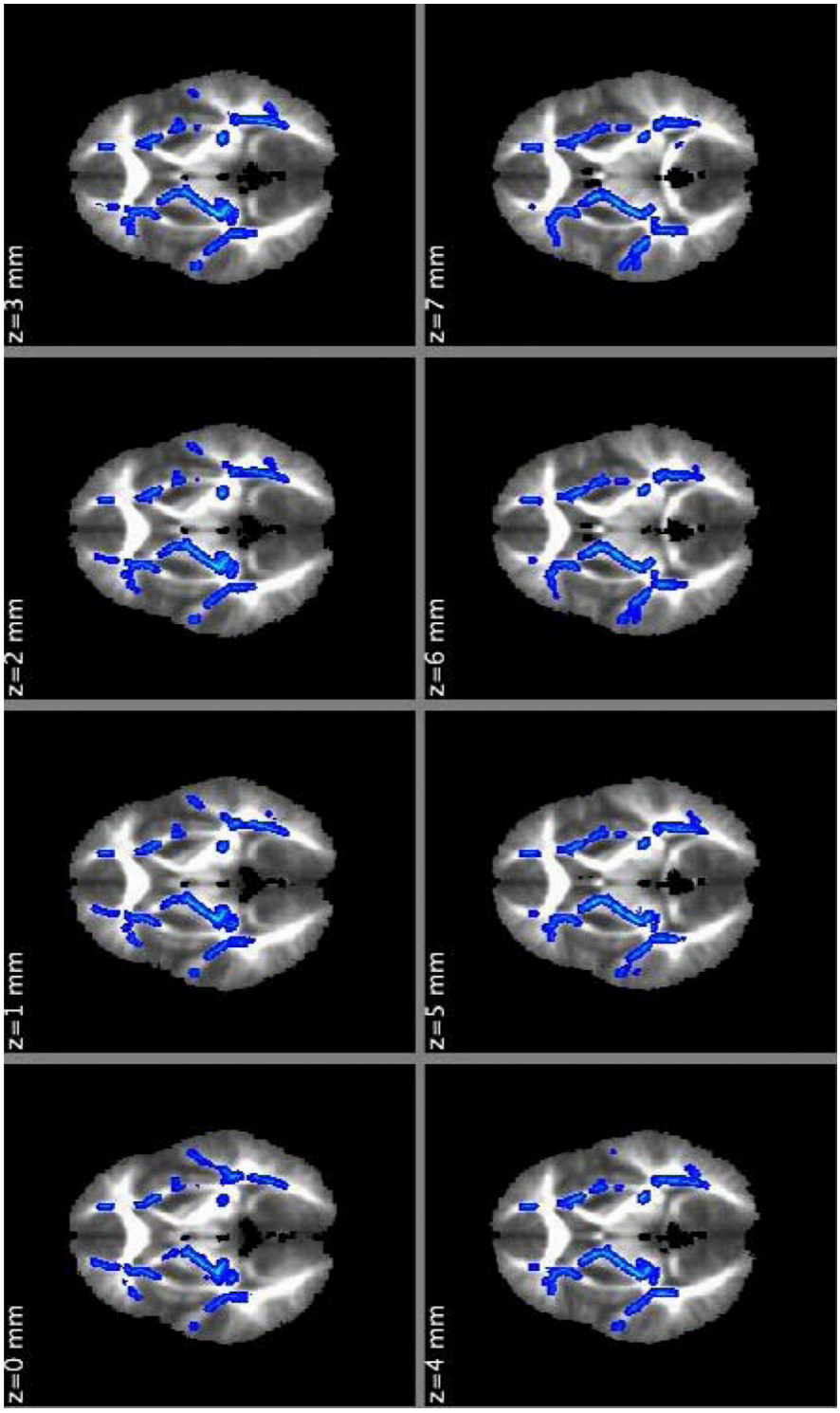

Figure 3—*Regions of significant positive correlation between HbA_{1c} values and RD (shown in light blue) within the type 1 diabetes group, shown in serial images in the axial orientation. Group differences were "thickened" for visualization purposes (shown in dark blue). (A high-quality digital representation of this figure is available in the online issue.)*

chronic hyperglycemia, leading to reductions in dendritic branching and spine density, and subsequent significant increases in brain sorbitol and inositol, when compared with rats with hypoglycemia (36). Therefore, the effect of hyperglycemia in young children may be particularly relevant to WM microstructure and in the resulting neurocognitive implications.

A history of diabetic ketoacidosis (DKA) may be another cause of axonal injury and be reflected in changes in AD. The study from Ghetti et al. (37) of children between ages 7 and 16 years found that children with a history of type 1 diabetes and DKA perform poorly on tests of memory function compared with children with a history of type 1 diabetes but not DKA. The memory deficits seem to be specifically related to the hippocampus, a region of the brain that is particularly sensitive to episodes of hypoxia or ischemia. In our study, seven of the children with diabetes had presented with DKA at onset and no one experienced DKA after diagnosis. We did not observe a significant correlation between those who experienced DKA and FA or AD or RD, although our small number of subjects do not allow for valid inferences.

Between-group differences in AD and RD occurred most prominently in the temporal and parietal regions of the brain in our study. Positron emission tomography studies in healthy adults show that the temporal and frontal regions are most vulnerable to hypoglycemia and hyperglycemia (5,28). Young children with diabetes frequently experience glycemic variability (3), resulting in more fluctuations in brain glucose levels and impacting brain glucose metabolism. Therefore, it is not surprising to find that the most prominent areas of WM microstructural changes in children with type 1 diabetes also occur in these regions. Although the study did not find any particular neurocognitive variation that correlated with either the temporal or frontal lobe function at this time, it will be intriguing to see if the microstructural changes on DTI predict temporal and frontal lobe–related neurocognitive changes over time. Perhaps decreased episodes of glycemic variability in these regions prevent memory loss, improve attention span, or decrease the comorbidity of depression in children with diabetes as they age. It will also be important to elucidate if WM microstructural patterns predict adverse neurocognitive changes over time, and to develop clinical interventions to prevent such changes.

This study has several limitations, the main one being the small sample size. Both the small sample size and the high heterogeneity in performance on neurocognitive testing in this age group may have not allowed for detection of the cognitive differences. The study was not adequately powered to detect subtle or

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even moderate WM neurocognitive measures between those with type 1 diabetes and controls. Also, subjects in this study completed different Wechsler Intelligence Scales because of their ages. Although not ideal, there is still a strong correlation between the two Wechsler Intelligence Scales. The correlation between the two FSIQ scores ($r = 0.89$) (38) is nearly as high as the WISC-IV FSIQ test-retest correlation and WPPSI-III FSIQ test-retest correlations ($r = 0.93$ and $r = 0.92$, respectively [38,39]), suggesting they measure similar constructs. Finally, because of the age range of our sample, the subjects in the study are undergoing brain development at varying rates. However, the examination of WM microstructure variations in this age range is important and makes this study novel.

WM changes and neurocognitive differences reported in adults with long-term type 1 diabetes likely begin in childhood. An association between early age of onset of disease (generally before the age of 6 years) and neurocognitive deficits has been the most consistent finding in the pediatric literature (1,25). As Northam et al. (25) recently summarized, chronic hyperglycemia, occurrence of diabetic ketoacidosis, BG fluctuations, and hyper- or hypoinsulinism all may impact the neurodevelopment of young children with type 1 diabetes. We suggest that there are WM microstructure differences between young children with type 1 diabetes and healthy controls after a short duration of diabetes, and support larger, longitudinal studies to confirm these changes. Knowledge of when these changes begin will impact our understanding of diabetes and the brain, identify the mechanisms of neuronal injury, and modify management of diabetes to minimize the chances of injury. Traditionally, the management of type 1 diabetes in young children has been to avoid hypoglycemia; however, we may need to tolerate less hyperglycemia during childhood as well.

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T.A. designed the study, collected and analyzed data, and wrote, reviewed, and edited the manuscript. N.B.-G. analyzed data and wrote, reviewed, and edited the manuscript. C.A. and D.M.W. reviewed and edited the manuscript. S.H., K.S., Y.P., and J.D. collected and assisted in the analysis of data. A.L.R. helped design the study, analyzed data, and reviewed and edited the manuscript. B.A.B. helped design the study and reviewed and edited the manuscript. T.A. is the guarantor of this work and as such had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Gaudieri PA, Chen R, Greer TF, Holmes CS. Cognitive function in children with type 1 diabetes: a meta-analysis. Diabetes Care 2008;31:1892–1897
2. Naguib JM, Kulinskaya E, Lomax CL, Garralda ME. Neuro-cognitive performance in children with type 1 diabetes—a meta-analysis. J Pediatr Psychol 2009;34:271–282
3. Gandrud LM, Xing D, Kollman C, et al. The Medtronic Minimed Gold continuous glucose monitoring system: an effective means to discover hypo- and hyperglycemia in children under 7 years of age. Diabetes Technol Ther 2007;9:307–316
4. Hershey T, Perantie DC, Warren SL, Zimmerman EC, Sadler M, White NH. Frequency and timing of severe hypoglycemia affects spatial memory in children with type 1 diabetes. Diabetes Care 2005;28:2372–2377
5. Bolo NR, Musen G, Jacobson AM, et al. Brain activation during working memory is altered in patients with type 1 diabetes during hypoglycemia. Diabetes 2011;60:3256–3264
6. Jacobson AM, Ryan CM, Cleary PA, et al.; Diabetes Control and Complications Trial/EDIC Research Group. Biomedical risk factors for decreased cognitive functioning in type 1 diabetes: an 18 year follow-up of the Diabetes Control and Complications Trial (DCCT) cohort. Diabetologia 2011;54:245–255
7. Tan ZS, Beiser AS, Fox CS, et al. Association of metabolic dysregulation with volumetric brain magnetic resonance imaging and cognitive markers of subclinical brain aging in middle-aged adults: the Framingham Offspring Study. Diabetes Care 2011;34:1766–1770
8. Perantie DC, Koller JM, Weaver PM, et al. Prospectively determined impact of type 1 diabetes on brain volume during development. Diabetes 2011;60:3006–3014
9. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioural plasticity after early brain insult. Brain 2011;134:2197–2221
10. Anderson V, Catroppa C, Morse S, Haritou F, Rosenfeld J. Functional plasticity or vulnerability after early brain injury? Pediatrics 2005;116:1374–1382
11. Reiss AL, Abrams MT, Singer HS, Ross JL, Denckla MB. Brain development, gender and IQ in children. A volumetric imaging study. Brain 1996;119:1763–1774
12. Aye T, Reiss AL, Kesler S, et al. The feasibility of detecting neuropsychologic and neuroanatomic effects of type 1 diabetes in young children. Diabetes Care 2011;34:1458–1462
13. Kodl CT, Franc DT, Rao JP, et al. Diffusion tensor imaging identifies deficits in white matter microstructure in subjects with type 1 diabetes that correlate with reduced neurocognitive function. Diabetes 2008;57:3083–3089
14. Franc DT, Kodl CT, Mueller BA, Muetzel RL, Lim KO, Seaquist ER. High connectivity between reduced cortical thickness and disrupted white matter tracts in long-standing type 1 diabetes. Diabetes 2011;60:315–319
15. Whittaker ETR, Robinson G. The trapezoidal and parabolic rules. In *The Calculus of Observations: A Treatise on Numerical Mathematics*. 4th ed. New York, Dover, 1967, 156–158
16. Woods RP, Grafton ST, Holmes CJ, Cherry SR, Mazziotta JC. Automated image registration: I. General methods and intrasubject, intramodality validation. J Comput Assist Tomogr 1998;22:139–152
17. Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage 2002;17:1429–1436
18. Chen CI, Mar S, Brown S, Song SK, Benzinger TL. Neuropathologic correlates for diffusion tensor imaging in post-infectious encephalopathy. Pediatr Neurol 2011;44:389–393
19. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 2002;15:1–25
20. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 2009;44:83–98
21. Wilde EA, Newsome MR, Bigler ED, et al. Brain imaging correlates of verbal working memory in children following traumatic brain injury. Int J Psychophysiol 2011;82:86–96
22. Peters SU, Kaufmann WE, Bacino CA, et al. Alterations in white matter pathways in Angelman syndrome. Dev Med Child Neurol 2011;53:361–367
23. Perantie DC, Wu J, Koller JM, et al. Regional brain volume differences associated with hyperglycemia and severe

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hypoglycemia in youth with type 1 diabetes. Diabetes Care 2007;30:2331–2337
24. Sarac K, Akinci A, Alkan A, Aslan M, Baysal T, Ozcan C. Brain metabolite changes on proton magnetic resonance spectroscopy in children with poorly controlled type 1 diabetes mellitus. Neuroradiology 2005;47:562–565
25. Northam EA, Lin A. Hypoglycaemia in childhood onset type 1 diabetes—part villain, but not the only one. Pediatr Diabetes 2010;11:134–141
26. Ryan CM, Geckle MO, Orchard TJ. Cognitive efficiency declines over time in adults with type 1 diabetes: effects of micro- and macrovascular complications. Diabetologia 2003;46:940–948
27. Budde MD, Xie M, Cross AH, Song SK. Axial diffusivity is the primary correlate of axonal injury in the experimental autoimmune encephalomyelitis spinal cord: a quantitative pixelwise analysis. J Neurosci 2009;29:2805–2813
28. Alavi A, Reivich M, Greenberg J, et al. Mapping of functional activity in brain with ^{18}F-fluoro-deoxyglucose. Semin Nucl Med 1981;11:24–31
29. Haugstvedt A, Wentzel-Larsen T, Graue M, Søvik O, Rokne B. Fear of hypoglycaemia in mothers and fathers of children with type 1 diabetes is associated with poor glycaemic control and parental emotional distress: a population-based study. Diabet Med 2010;27:72–78
30. American Diabetes Association. Standards of medical care in diabetes—2012. Diabetes Care 2012;35(Suppl 1):S11–S63
31. Northam EA, Anderson PJ, Jacobs R, Hughes M, Warne GL, Werther GA. Neuropsychological profiles of children with type 1 diabetes 6 years after disease onset. Diabetes Care 2001;24:1541–1546
32. Rovet JF, Ehrlich RM, Czuchta D, Akler M. Psychoeducational characteristics of children and adolescents with insulin-dependent diabetes mellitus. J Learn Disabil 1993;26:7–22
33. Weimbs T, Stoffel W. Topology of CNS myelin proteolipid protein: evidence for the nonenzymatic glycosylation of extracytoplasmic domains in normal and diabetic animals. Biochemistry 1994;33:10408–10415
34. Aragno M, Mastrocola R, Medana C, et al. Up-regulation of advanced glycated products receptors in the brain of diabetic rats is prevented by antioxidant treatment. Endocrinology 2005;146:5561–5567
35. Yang C, DeVisser A, Martinez JA, et al. Differential impact of diabetes and hypertension in the brain: adverse effects in white matter. Neurobiol Dis 2011;42:446–458
36. Malone JI, Hanna SK, Saporta S. Hyperglycemic brain injury in the rat. Brain Res 2006;1076:9–15
37. Ghetti S, DeMaster DM, Yonelinas AP, Bunge SA. Developmental differences in medial temporal lobe function during memory encoding. J Neurosci 2010;30:9548–9556.
38. Wechsler D. *WISC-IV Administration and Scoring Manual*. San Antonio, The Psychological Corportation, 2003
39. Wechsler D. *WPPSI-III Administration and Scoring Manual*. San Antonio, The Psychological Corporation, 2002

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