Age-Related Loss of Brain Volume and T2 Relaxation Time in Youth With Type 1 Diabetes

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OBJECTIVE—Childhood-onset type 1 diabetes is associated with neurocognitive deficits, but there is limited evidence to date regarding associated neuroanatomical brain changes and their relationship to illness variables such as age at disease onset. This report examines age-related changes in volume and T2 relaxation time (a fundamental parameter of magnetic resonance imaging that reflects tissue health) across the whole brain.

RESEARCH DESIGN AND METHODS—Type 1 diabetes, $N = 79$ (mean age 20.32 ± 4.24 years), and healthy control participants, $N = 50$ (mean age 20.53 ± 3.60 years). There were no substantial group differences on socioeconomic status, sex ratio, or intelligence quotient.

RESULTS—Regression analyses revealed a negative correlation between age and brain changes, with decreasing gray matter volume and T2 relaxation time with age in multiple brain regions in the type 1 diabetes group. In comparison, the age-related decline in the control group was small. Examination of the interaction of group and age confirmed a group difference (type 1 diabetes vs. control) in the relationship between age and brain volume/T2 relaxation time.

CONCLUSIONS—We demonstrated an interaction between age and group in predicting brain volumes and T2 relaxation time such that there was a decline in these outcomes in type 1 diabetic participants that was much less evident in control subjects. Findings suggest the neurodevelopmental pathways of youth with type 1 diabetes have diverged from those of their healthy peers by late adolescence and early adulthood but the explanation for this phenomenon remains to be clarified.

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Diabetes is a disorder of glucose metabolism in which blood glucose levels often fall outside the normal range, even when the disease is well controlled. The brain requires a constant supply of glucose to function normally and is one of the body systems potentially affected in type 1 diabetes. Severe hypoglycemia leads to uncontrolled release of excitatory amino acids, such as glutamate and aspartate, triggering a cascade of events that may result in neuronal damage (1), whereas chronically elevated glucose levels induce a form of glucose neurotoxicity (2). Variations in insulin and counterregulatory hormone levels may also be neurotoxic (3,4).

There is a growing literature documenting central nervous system (CNS) changes in adults with type 1 diabetes, including lower density of cortical gray matter (GM) and white matter (WM) lesions (4). Neuroimaging studies in children with type 1 diabetes have been limited to date, and findings have implicated different brain regions and variable associations with illness-specific risk factors (5). These albeit inconsistent findings do suggest an adverse impact of type 1 diabetes on the developing brain, in line with evidence for neurocognitive deficits in childhood-onset type 1 diabetes (6). The exact nature, explanatory mechanisms, and timing of CNS damage, however, remain to be clarified.

Controlled studies that follow participants across childhood and into adulthood may be particularly informative in documenting the impact of type 1 diabetes on brain development. The Royal Children's Hospital, Melbourne (RCH) Cohort Study recruited consecutive admissions with newly diagnosed type 1 diabetes between 1990 and 1992, together with a healthy control group, into a longitudinal study. Twelve years after diagnosis, a subset of the cohort underwent neuroimaging with magnetic resonance imaging (MRI) to document structural changes in the CNS. Relative to control participants, a number of brain regions in participants with type 1 diabetes showed decreased GM and WM volumes and alterations in the T2 relaxation time, a fundamental MRI parameter that reflects the chemical environment of the brain and developmental changes such as myelination (7). In addition, we examined age-related volume loss and T2 relaxation time change in two brain regions, the thalamus and lentiform nuclei, that were the areas of most widespread change in the analyses of group (type 1 diabetes vs. control) differences. This report extends the initial analyses by examining the relationship between age with volume and T2 across the whole brain.

RESEARCH DESIGN AND METHODS

Participants and procedure

Consecutive admissions to RCH with newly diagnosed type 1 diabetes between 1990 and 1992 ($N = 133$), together with healthy control participants ($N = 126$), stratified for age and sex, formed the

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original cohort. A history of neurologic disease or trauma was an exclusion criterion. Twelve years after diabetes onset, 106 participants with type 1 diabetes and 75 control subjects were reassessed [see (7) for a full description of sample characteristics]. All participants had a neurocognitive assessment (7). The present report documents findings for the subset of participants (type 1 diabetes, $N = 79$; control subjects, $N = 50$) who were consecutively invited to undergo neuroimaging until available funding was exhausted. There were no differences between type 1 diabetic participants who underwent neuroimaging and those who did not on age at disease onset, history of hypoglycemia, or metabolic control. Blood glucose levels of diabetic participants were determined by capillary sample before neuroimaging to ensure a reading between 4 and 18 mmol/L. This study was approved by the Human Ethics Research Committee of the Victorian Government Department of Human Services.

Imaging

MRI was carried out on a 3 T scanner (GE Healthcare, Milwaukee, WI). Quantitative assessment of volume changes was carried out using voxel-based morphometry (VBM) (8). For VBM, a fast spoiled gradient recalled echo at steady-state sequence was used (repetition time [TR]/echo time [TE]/inversion time 13.8/2.7/500 ms; voxel size: 0.48 × 0.48 × 2 mm). For voxel-based relaxometry (VBR) (i.e., quantitative assessment of the T2 relaxation time) (9), a modified, optimized Carr-Purcell-Meiboom-Gill multiecho sequence was used (eight echoes; TE = 28.9–231 ms, TR = 6.24 s, 24 slices, 5-mm slice thickness; in-plane voxel size: 0.94 × 1.88 mm). The slice plane was perpendicular to the long axis of the hippocampus. T2 maps were generated by fitting to a monoexponential model with the inclusion of a baseline that minimizes the contribution of long T2 components (mainly cerebrospinal fluid) to the fit.

Images were warped to standard space in which they could be compared and smoothed. Smoothing kernels of 6 and 10 mm were applied to volumetric and T2 images, respectively. A larger smoothing kernel is necessary for the T2 analysis to eliminate the observation of artifactual signal changes at the boundaries between tissue and cerebrospinal fluid, where abrupt changes of the relaxation time are expected (10). All analyses were performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). GM volumetric analyses were performed using optimized VBM. Voxel-wise T2 relaxation time changes were assessed using the approach of VBR (9).

Analyses

1. SPM voxel-based age regression (separate groups): relationships between the volume and relaxometry data sets and age were examined using the regression model in SPM8. Spatial maps showing voxels with statistically significant regression coefficients were obtained separately for type 1 diabetic and control participants (threshold, $P < 5 \times 10^{-6}$ uncorrected).
2. Age regression including interaction term: the analysis described above can reveal potential differences in the magnitude of the regression coefficient between the participant groups (type 1 diabetes or control), but does not directly address the hypothesis that this difference is indeed group-dependent. To assess this, a model with an interaction term (group × age) was fitted. Both regional and whole-brain voxel-based analyses were performed and are described in turn.
3. Region of interest (ROI)-based interaction analysis: a general linear model was used to investigate the group by age interaction in prechosen, discrete brain regions, we previously identified (7) as differing between type 1 diabetic participants and control subjects.
4. SPM voxel-based interaction analysis: to extend the previous study (7) and depict the global picture of the interaction across the whole brain, voxel-based analysis was carried out in SPM8 using a linear model like that above with the addition of the interaction term. Spatial maps showing voxels with statistically significant interaction of group and age were obtained (threshold, $P < 0.001$ uncorrected; F test).

RESULTS

Sample characteristics

Sample characteristics are presented in Table 1. Type 1 diabetic participants and control subjects did not differ substantially on age, sex ratio, socioeconomic status, or full-scale intelligence quotient (IQ).

SPM voxel-based age regression (separate groups)

The statistical parametric maps of the age-regression coefficients for type 1 diabetic and control participants are shown in Fig. 1 for the GM volumetric and T2 data, respectively. Areas of age correlation were minimal in the control subjects, whereas participants with type 1 diabetes showed stronger and statistically significant negative age correlations (volumetric reduction with increasing age) in the

Table 1—*Sample characteristics*

	Type 1 diabetes ($n = 79$)	Control ($n = 50$)	Student t score or χ^2	df	P value
Female sex, N (%)	32 (40.51)	24 (48.00)	0.70	1	0.4
Age (years), mean (SD)	20.32 (4.26)	20.54 (3.60)	−0.30	127	0.8
Socioeconomic status, mean (SD)	4.31 (1.10)	4.22 (1.07)	0.42	127	0.7
Full-scale IQ, mean (SD)	101.89 (12.56)	105.14 (13.07)	−1.41	127	0.2
Age of diabetes onset (years), mean (SD)	7.08 (3.64)				
Illness duration, mean (SD)	13.25 (1.05)				
Most recent HbA_{1c} (mmol/L), mean (SD)	9.06 (1.71)				
Percent of time HbA_{1c} >9% (mmol/L)*, mean (SD)	41.44 (26.48)				
Hypoglycemia†, N (%)	39 (49.37)				
BGL at imaging (mmol/L), mean (SD)	12.61 (5.36)				

Data are N (%) and mean (SD) unless otherwise indicated. BGL, blood glucose level at time of assessment; HbA_{1c}, glycosylated hemoglobin level. *Percentage of total time from diagnosis that HbA_{1c} was ≥9%. †More than or equal to one episode of hypoglycemia with associated seizure or coma.

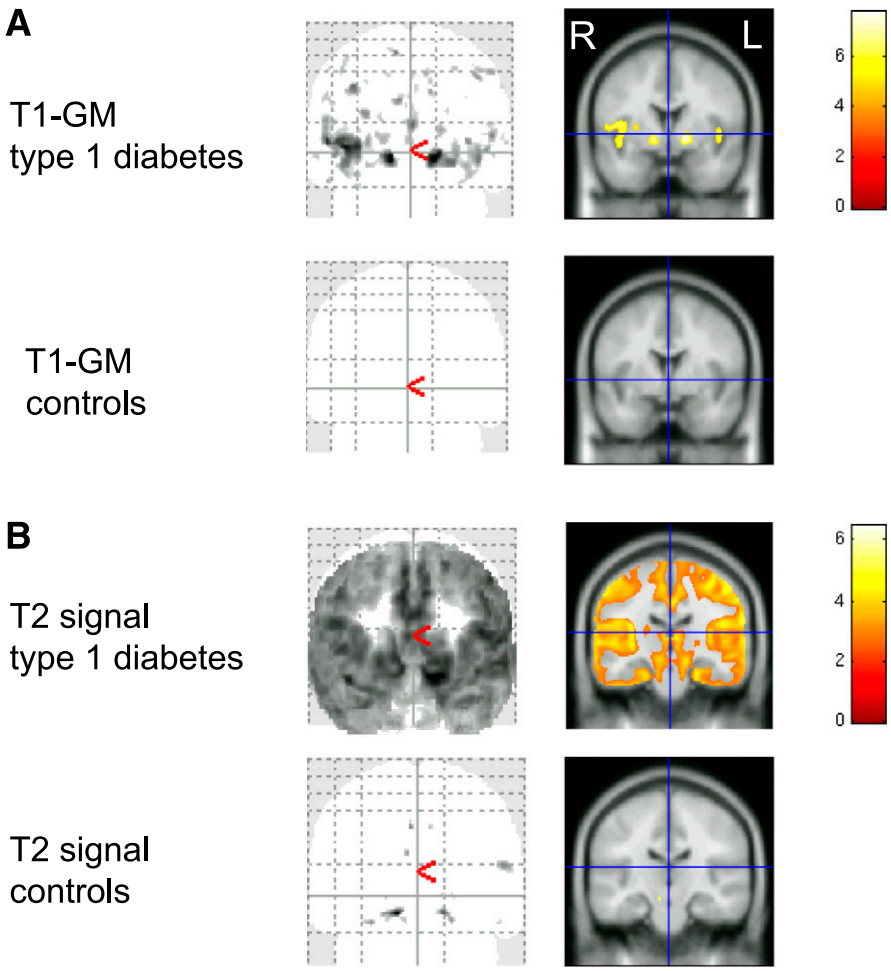

Figure 1—*Maps of significant age regression carried out separately in diabetes and control subject groups for T1-GM volumetry data* (A) *and T2 relaxometry* (B). *The statistical parametric maps indicate voxels in which the regression coefficient reaches significance* ($P < 5 \times 10^{-6}$ *uncorrected). Coronal glass brain images in the* left panels *display the total of significant voxels superimposed throughout the volume. The* right panels *are a representative coronal slice of the statistical parametric map overlaid on a canonical T1-weighted image. The T-statistic color scale is also shown. Smoothing kernels were 6 and 10 mm for volumetric and relaxometry data, respectively. (A high-quality digital representation of this figure is available in the online issue.)*

lentiform and thalamic nuclei and insular and cingulate cortices. Similarly, areas showing decreasing T2 relaxation time with increasing age were more widespread in participants with type 1 diabetes than in control participants and incorporated both cortical and subcortical brain regions, including frontal and temporal cortices.

Age regression including interaction term

ROI-based interaction analysis. Table 2 presents tests of the group by age interaction from the general linear models fitted for each ROI. It also shows the estimated age regression slopes (with 95% CI) separately for participants with type 1 diabetes and control participants. The results are ordered in terms of the size of the effect for the diabetes group (R^2). Volumetric analysis of GM showed group by age interactions in the left parietal insula, right precentral region, right superior frontal gyrus, and right thalamus. For T2, statistically significant group by age interactions were evident bilaterally in the caudate and lentiform nucleus; the slightly weaker statistical scores for the thalamus were consistent with the volumetric analysis. The estimates for the GM volume regression slopes in the separate groups showed a pattern consistent with the voxel-based age regression analysis. Slopes for the control group were small and close to zero, and slopes for the diabetes group were larger in absolute magnitude and negative. The slope estimates for T2 were generally negative for both groups, but stronger for the diabetes group than for the control subjects.

SPM voxel-based interaction analysis. The voxel-based analysis of the group by age interaction term indicated a pattern of similar, regionally specific areas to the ROI analyses (Fig. 2). The areas of statistically significant interaction in the T2 statistical parametric map were generally larger and more extensive than those for the GM volume. Regions in which the regression interaction term reached the statistical threshold (F test; $P < 0.001$ uncorrected) are listed as follows:

GM volume: bilateral insula, bilateral lentiform nuclei, bilateral precentral gyrus, right parahippocampal gyrus, left postcentral gyrus, inferior and superior frontal gyrus, bilateral thalami, left putamen, bilateral middle temporal GM, and left superior temporal GM.

T2 relaxation time: bilateral insula, bilateral lentiform nuclei, bilateral cingulate, bilateral inferior frontal gyrus, bilateral superior temporal gyrus, bilateral medial frontal gyrus, caudate nucleus, bilateral precentral gyrus, left putamen, bilateral parahippocampal gyrus, and inferior temporal gyrus.

CONCLUSIONS—This study examined age-related changes in brain volume and T2 relaxation times across the whole brain using both volumetric and relaxometry magnetic resonance data. We found a negative relationship between age and brain volume and T2 relaxation time loss across large areas of the brain in participants with type 1 diabetes, whereas only minimal changes were evident in the healthy control subjects. These findings were confirmed by regional and voxel-based analyses, which showed greater regional and global age-related reductions in brain volumes and T2 relaxation time in type 1 diabetic participants compared with control subjects. The brain regions most affected in type 1 diabetic participants include the thalamus, lentiform nuclei, insula, and areas in the frontal and temporal lobes. The findings of greater volume and T2 relaxation time decrease with age (and later diabetes onset) are somewhat counterintuitive given conventional wisdom about the greater vulnerability of the very immature CNS and the consistent association between very early onset disease (i.e., younger than 5 to 6 years) and neurocognitive deficits (6).

Volume loss and T2 reductions are characteristic of normal ageing, thus our

Table 2—*Group age regression slopes and the interaction term (Group × age) in brain regions*

		F	*P* value	R^2	β	95% CI for β	*P* value
T1 volume							
Left parietal insula	Group × age	11.01	0.001				
	Diabetes			0.323	−0.70	−0.94, −0.47	<0.001
	Controls			0.000	−0.02	−0.38, 0.34	>0.9
Right SFG	Group × age	3.24	0.07				
	Diabetes			0.144	−0.37	−0.57, −0.16	0.001
	Controls			0.002	−0.05	−0.35, 0.25	0.7
Left/right thalamus	Group × age	4.55	0.04				
	Diabetes			0.091	−0.27	−0.47, −0.08	0.007
	Controls			0.009	0.10	−0.20, 0.40	0.5
Left thalamus	Group × age	3.61	0.06				
	Diabetes			0.070	−0.26	−0.47, −0.04	0.02
	Controls			0.008	0.10	−0.22, 0.41	0.5
Right thalamus	Group × age	4.42	0.04				
	Diabetes			0.068	−0.25	−0.46, −0.04	0.02
	Controls			0.016	0.14	−0.18, 0.47	0.4
Right parahippocampal	Group × age	0.29	0.6				
	Diabetes			0.049	−0.25	−0.51, 0.00	0.05
	Controls			0.012	−0.14	−0.50, 0.23	0.5
Right precentral	Group × age	4.37	0.04				
	Diabetes			0.048	−0.20	−0.40, 0.00	0.05
	Controls			0.026	0.19	−0.15, 0.53	0.3
Right parietal postcentral	Group × age	0.55	0.5				
	Diabetes			0.047	−0.23	−0.46, 0.01	0.06
	Controls			0.004	−0.08	−0.42, 0.26	0.6
Left ITG WM	Group × age	2.59	0.1				
	Diabetes			0.046	0.18	−0.01, 0.37	0.06
	Controls			0.007	−0.07	−0.31, 0.17	0.6
Left temporal parahippocampal region WM/GM	Group × age	3.28	0.07				
	Diabetes			0.032	0.11	−0.03, 0.25	0.1
	Controls			0.022	−0.15	−0.44, 0.14	0.3
Left insula WM	Group × age	0.76	0.4				
	Diabetes			0.010	0.07	−0.09, 0.22	0.4
	Controls			0.004	−0.07	−0.36, 0.23	0.7
Left middle frontal gyrus WM	Group × age	0.43	0.5				
	Diabetes			0.008	−0.06	−0.19, 0.08	0.4
	Controls			0.027	−0.14	−0.39, 0.11	0.3
Right temporal parahippocampal region WM/GM	Group × age	1.67	0.2				
	Diabetes			0.001	0.03	−0.16, 0.21	0.8
	Controls			0.052	−0.17	−0.37, 0.04	0.1
Left MTG WM	Group × age	0.24	0.6				
	Diabetes			0.000	−0.01	−0.16, 0.14	0.9
	Controls			0.004	0.06	−0.25, 0.37	0.7
T2 volume							
	Group × age	10.44	0.002				
	Diabetes			0.536	−5.46	−6.62, −4.29	<0.001
Right caudate/right lentiform	Controls			0.286	−2.57	−3.75, −1.39	<0.001
Left lentiform	Group × age	11.40	0.001				
	Diabetes			0.518	−5.73	−7.00, −4.46	<0.001
	Controls			0.259	−2.49	−3.71, −1.27	<0.001
Left caudate	Group × age	12.62	0.001				
	Diabetes			0.505	−6.97	−8.56, −5.38	<0.001
	Controls			0.208	−2.70	−4.24, −1.17	0.001
Right lentiform	Group × age	4.79	0.03				
	Diabetes			0.473	−4.96	−6.16, −3.75	<0.001
	Controls			0.276	−2.88	−4.23, −1.53	<0.001

Table 2—*Continued*

		F	*P* value	R^2	β	95% CI for β	*P* value
Right caudate	Group × age	13.63	<0.001				
	Diabetes			0.461	−6.32	−7.90, −4.75	<0.001
	Controls			0.157	−2.04	−3.40, −0.67	0.004
Right thalamus	Group × age	3.10	0.08				
	Diabetes			0.355	−4.57	−5.99, −3.15	<0.001
	Controls			0.301	−2.74	−3.95, −1.53	<0.001
Right insular	Group × age	3.62	0.06				
	Diabetes			0.351	−6.10	−8.00, −4.19	<0.001
	Controls			0.180	−3.28	−5.31, −1.25	0.002
Red nucleus	Group × age	2.26	0.1				
	Diabetes			0.317	−4.62	−6.18, −3.06	<0.001
	Controls			0.264	−2.88	−4.28, −1.49	<0.001
Left thalamus	Group × age	3.04	0.08				
	Diabetes			0.277	−3.57	−4.90, −2.24	<0.001
	Controls			0.221	−1.90	−2.93, −0.86	0.001
Right frontal WM	Group × age	0.182	0.7				
	Diabetes			0.169	−3.32	−5.01, −1.63	<0.001
	Controls			0.149	−2.76	−4.66, −0.84	0.006
Corpus callosum	Group × age	1.16	0.3				
	Diabetes			0.166	−3.66	−5.55, −1.77	<0.001
	Controls			0.094	−2.10	−4.00, −0.21	0.03
Right parietal GM	Group × age	0.28	0.6				
	Diabetes			0.024	−1.02	−2.50, 0.47	0.176
	Controls			0.071	−1.64	−3.36, 0.08	0.061

Results are ordered in terms of decreasing R^2 values for the Diabetes group. For T1, the *df* for the *F*-statistic 1,125. For T2, the *df* for the *F*-statistic is 1,123. The results for T1 have been rescaled (multiplied by 10). ITG, inferior temporal gyrus; MTG, medial temporal gyrus; SFG, superior frontal gyrus.

findings could be interpreted as accelerated brain ageing. MRI studies of healthy individuals have shown that brain volume increases during childhood, reaching a maximum in adolescence, thereafter declining in a fairly linear fashion, with acceleration in the rate of decline at ~55 years of age (11). T2 relaxation time also changes in an age-related manner across the life span. During early development, T2 relaxation time shortens, mainly reflecting the progression of myelination

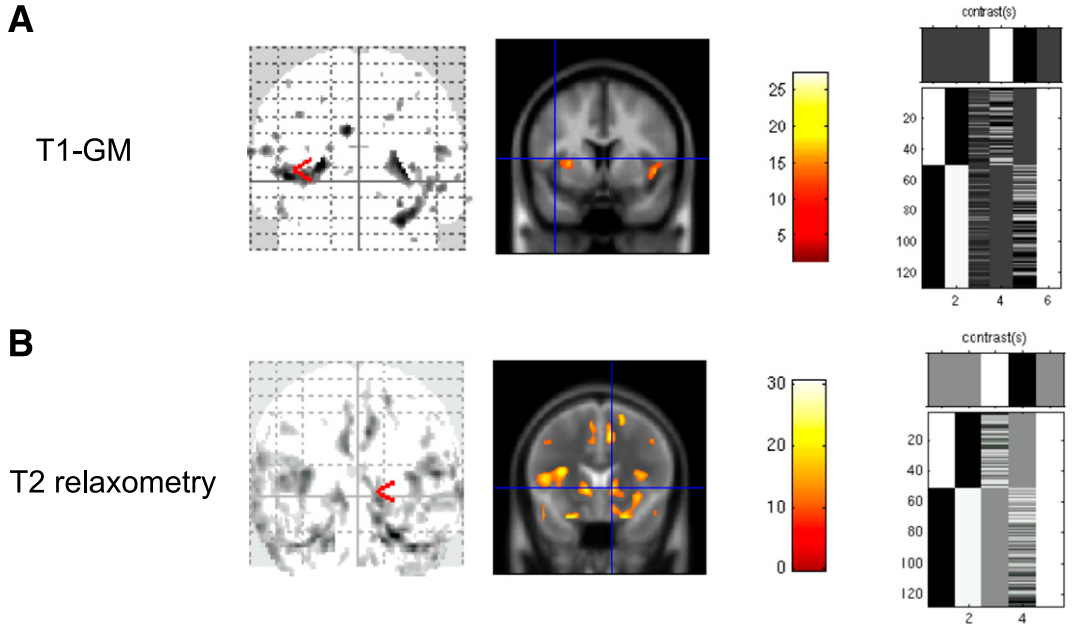

Figure 2—*Group × age interaction term for T1-GM volumetry data* (A) *and T2 relaxometry data* (B). *The statistical parametric maps indicate voxels in which the regression interaction term reaches significance* (F *test;* P < *0.001 uncorrected). Coronal glass brain images are shown next to a representative coronal slice of the statistical parametric map overlaid on a canonical T1-weighted image. Smoothing kernels were 6 and 10 mm for volumetric and relaxometry data, respectively. (A high-quality digital representation of this figure is available in the online issue.)*

in WM. In addition, a decrease in T2 relaxation time in extrapyramidal structures such as the putamen and caudate nucleus, clearly evident from ~20 years of age, reflects age-dependent accumulation of iron (12). It is interesting to note that the accelerated T2 reduction observed in the type 1 diabetic participants in this study includes several of these extrapyramidal brain regions, which therefore may indicate a modified rate of iron deposition in these subjects. Indeed, elevated levels of iron have been found in blood plasma in both type 1 and type 2 diabetes (13), which may be due to modified turnover of erythrocytes (14). The phenomenon of accelerated brain ageing in diabetes has previously been described by Biessels et al. (15), but only in older adults, and particularly, but not exclusively, in reference to type 2 diabetes. To our knowledge, this is the first study to raise the possibility of such an effect in a population of youth with type 1 diabetes and a mean age of just 20 years.

Alternatively to a process of premature senescence, our findings might indicate some disruption to the final stages of neurodevelopment, in a process qualitatively different from the neurodegenerative changes postulated by Biessels et al. (15). Type 1 diabetes, or an aspect of the disease, may affect neurodevelopment such that youth with the disease show less normative age-related increase in brain volume. This is consistent with the findings in a recent study in which the expected rate of increase in total WM volume during early development was not observed in a group of younger (3–10 years old) children with type 1 diabetes (16). Diabetes-related effects on GM may occur later in neurodevelopment (i.e., during adolescence). Perantie et al. (5) imaged a sample (mean age of ~12 years) and found no overall differences in GM volume between those with type 1 diabetes and healthy control subjects. In contrast, Musen et al. (17) conducted voxel-based analyses of a sample of young adults with a mean age ~32 years and reported volume loss in frontal and temporal regions and left thalamus, brain regions that overlap considerably with our own findings (7). Taken together, these findings suggest that late adolescence-early adulthood may be a critical period in which the GM volumes of youth with type 1 diabetes diverge from those of their healthy peers. This interpretation is consistent with Ryan's diathesis hypothesis (18), which posits that early exposure to hyperglycemia increases the vulnerability of the brain to subsequent CNS disruption.

The mechanisms underlying neural changes in our cohort with type 1 diabetes are unclear. Hyperglycemia is linked to excessive activation of the polyol pathway with resulting formation of advanced glycation end products and atrophy, as well as increased oxidative stress associated with cell death (4). Alternatively, as a consequence of elevated blood glucose levels, the cells may become desensitized to glucose due to saturation of their metabolic activity, endoplasmic reticulum stress, or mitochondrial dysfunction. Glucose has been shown to act as a mitogen in some contexts such as human β-cells (19). In a different context, hyperglycemia was shown to lead to myocyte cell death (20) and to reduced cell differentiation in endothelial progenitor cells that is indicative of advanced cell senescence (21). The effects observed in this study may suggest the existence of a cell-survival failsafe mechanism following sustained hyperglycemia in which glucotoxicity and apoptosis are avoided by desensitization to raised glucose levels such that the propensity for cell division is reduced. In addition, the interaction of age with diabetes demonstrated in this study may reflect diabetes-induced modulation of synaptic plasticity. In groups of young and aged rats exposed to streptozotocin-induced diabetes, the impairment in plasticity was shown to be greater in the older group, implying an interaction between ageing and plasticity-related dysfunction in a model of type 1 diabetes (22).

It is important to note that the CNS changes that we demonstrated are subtle and of uncertain functional significance, although we have previously reported lower school completion rates in our cohort (7). Scans were scrutinized by a neuroradiologist (A.M.), and three participants only had abnormalities that required clinical investigation, two of whom were control participants. Although meta-analyses of both children (6) and adults (23) with type 1 diabetes confirm subtle neurocognitive deficits, and there is increasing evidence of structural brain changes [see (24) for review], the literature is difficult to interpret because of inconsistency across individual reports. Different methodologies and samples heterogeneous for age, age of disease onset, illness duration, and metabolic control history almost certainly contribute to inconsistent findings. We have previously reported that neurocognitive deficits were greater in those with early onset (<5 years) diabetes (7,25), yet brain volume and T2 reduction was most evident in our older and later-onset participants. It is difficult to explain the lack of correspondence between structural CNS changes and functional neurocognitive deficits, but this disassociation has been reported before (3,11). Lenroot and Giedd (26) caution that relationships between brain structures and cognition are rarely straightforward even in healthy youth. In our cohort, constant exposure to abnormal glycemic variation may disrupt skill acquisition in the very young child even in the absence of structural CNS change, whereas subtle changes in brain structure may precede global cognitive difficulties in the participants who were older at disease onset.

It is possible that some, or all, of the pathophysiological processes described above have contributed to our findings of age-related brain volume loss and T2 reduction in type 1 diabetic participants. The selectively greater impact on our older participants suggests an interaction between disease effects and neurodevelopmental stage, but serial imaging of a diabetic cohort through childhood to CNS maturity in a controlled design would be necessary to confirm this. Further exploration to clarify age-related changes and the mechanisms underlying brain changes in type 1 diabetes in general are important though, as animal studies have indicated that adjunctive neuroprotective strategies may be possible using either systemic IGF-I (27) or glucocorticoid receptor antagonists such as mifepristone (28). These strategies, though promising, are either untried or nascent in the human context.

In the last 15–20 years, standards of care have improved vastly for young people with type 1 diabetes to the point that we rarely see evidence of traditional diabetes complications in pediatric diabetes clinics. The new frontier in diabetes research and care is to facilitate the preeminent developmental task of childhood and adolescence: optimal brain development and function.

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G.S.P. researched the data and wrote the manuscript. A.L. researched the data, conducted the data analyses, contributed to the discussion, and reviewed the final manuscript. R.M.W. researched the data, contributed to the discussion, and reviewed the final manuscript. G.A.W. contributed to the discussion and reviewed the final manuscript. F.J.C. contributed to the discussion and reviewed the final manuscript. S.J.F. conducted data analyses and reviewed the final manuscript. J.P. contributed to the data analyses and reviewed the final manuscript. E.A.N. contributed to the discussion and wrote the final manuscript. E.A.N. 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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