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Regional Gray Matter Volumes as Related to Psychomotor Slowing in Adults with Type 1 Diabetes

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Abstract

OBJECTIVE—Psychomotor slowing is a common cognitive complication in type 1 diabetes (T1D), but its neuroanatomical correlates and risk factors are unclear. In non-diabetic adults, smaller gray matter volume (GMV) and presence of white matter hyperintensities (WMH) are associated with psychomotor slowing. We hypothesize that smaller GMV in prefronto-parietal regions explains T1D-related psychomotor slowing. We also inspect the contribution of microvascular disease and hyperglycemia.

METHODS—GMV, WMH, and glucose levels were measured concurrently with a test of psychomotor speed (Digit Symbol Substitution Test, DSST) in 95 adults with childhood-onset T1D (mean age/duration=49/41 years) and 135 similarly-aged non-T1D adults. Linear regression models tested associations between DSST and regional GMV, controlling for T1D, sex, and education; a bootstrapping method tested whether regional GMV explained between-group differences in DSST. For the T1D cohort, voxel-based and *a priori* regions-of-interest methods further tested associations between GMV and DSST, adjusting for WMH, hyperglycemia, and age.

RESULTS—Bilateral putamen, but not other regions, significantly attenuated DSST differences between the cohorts (bootstrapped unstandardized indirect effects: −3.49, −3.26; 95% confidence limits [−5.49, −1.80], [−5.29 −1.44], left and right putamen, respectively). Among T1D, DSST was positively associated with GMV of bilateral putamen and left thalamus. Neither WMH, hyperglycemia, age, nor other factors substantially modified these relationships.

CONCLUSIONS—For middle-aged adults with T1D and cerebral microvascular disease, GMV of basal ganglia may play a critical role in regulating psychomotor speed, as measured via DSST. Studies to quantify the impact of basal ganglia atrophy concurrent with WMH progression on psychomotor slowing are warranted.

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Keywords

Type 1 diabetes; brain imaging; gray matter volume; basal ganglia; psychomotor speed; Digit Symbol Substitution test

INTRODUCTION

Slow psychomotor speed is a common, serious neurocognitive complication in people with type 1 diabetes (T1D),(1–7) interfering with adherence to disease self-management.(8) In elderly non-diabetic populations, psychomotor slowing warns of future disability,(9, 10) dementia, (11) and death.(12) Characterizing psychomotor slowing in T1D is likely to become a public health priority in future years, considering the rising incidence of T1D (13) in conjunction with the increased life expectancy of people with T1D.(14) These aging individuals with T1D are simultaneously exposed to the detrimental effects of long-term T1D and of aging on the brain, potentially increasing their risk of future disability and/or dementia, with high personal and societal costs.(15)

Psychomotor slowing in T1D may develop in response to hyperglycemia-related degradation of the integrity of cerebral white and gray matter (see reviews (7, 16, 17)). However, the neural correlates and risk factors of this T1D complication remain poorly understood. Associations have been reported between smaller gray matter volume (GMV) of subcortical and fronto-parietal regions and the Digit Symbol Substitution Test (DSST, a measure of psychomotor speed) in elderly and in type 2 diabetes populations.(18–20) We know of two studies examining similar associations in T1D, with one finding an association in adults similar in age to our participants, mean age 45 years, (21) and another finding no association in older adults, mean age 61 years. (22)

We recently reported a strong association between cerebral white matter hyperintensities (WMH)(23) and lower DSST in middle-aged adults with childhood-onset T1D.(24) We also applied functional neuroimaging to explore the contribution of gray matter to DSST scores in this T1D cohort. We found that activation in select subcortical and parietal gray matter areas was related to lower DSST; these associations appeared to be influenced by hyperglycemia, but not WMH.(38)

We now propose to examine the role of gray matter volume (GMV) of the above-identified networks in relationship to DSST, and the effects of hyperglycemia and WMH on this association, in middle-aged adults with T1D. We also explore contributions of cardio-metabolic factors to these associations. We hypothesized that associations would be stronger for subcortical and fronto-parietal than for other regions (e.g. occipital), and that associations among T1D would be attenuated by WMH and hyperglycemia.

Methods

Participants

Adults with T1D (mean age and duration 49 and 40 years, respectively) were recruited from the Pittsburgh Epidemiology of Diabetes Complications Study, an on-going prospective

study of individuals diagnosed ≤ age 17 years. Baseline clinical assessment was 1986–1988 (N=658, mean age and duration 28 and 19 years, respectively). Biennial physical exams and questionnaires occurred through 1996–1998, with an additional exam in 2004–2006 [for details see (25)]. All locally-dwelling participants as of 01/01/2010 (N=263) were invited to this ancillary study. Of those, 81 refused, 26 never responded, and two were lost to follow-up. Of the 154 interested, 37 were MRI ineligible (e.g., metallic implants, claustrophobic) and five had scheduling conflicts, leaving 112 eligible and scheduled for testing. Of these, three failed to show for their scheduled visit. Another three refused MRI and nine refused cognitive testing at their scheduled exam, yielding an analytic sample of N=95.

Adults without T1D, participating in an observational study of the effects of pre-hypertension on cerebral structure and function, served as a comparison group. Inclusion criteria were: age 35–60 years, local to Pittsburgh, and blood pressure<140/90 mmHg. Full exclusion criteria are provided elsewhere.(24) Of 414 who responded to mailing/ advertisements, 110 were MRI ineligible, 60 changed their mind, and 14 withdrew, leaving 230 enrolled (mean age 46 years). To mirror the T1D cohort's racial distribution (99% white), only white non-T1D participants (N=135) were included in these analyses.

All study procedures received University of Pittsburgh Institutional Review Board approval. All participants provided informed consent prior to initiation of research procedures.

Measures

Demographics—For both cohorts, body mass index (BMI) and serum glucose were measured concurrent with cognitive testing, using standardized techniques. Any T1D participant with glucose ≤70 mg/dL was given a snack then retested after 15 minutes; no cognitive testing occurred until glucose was >70mg/dL.

Microvascular disease—WMH volume (% of total brain volume) and WMH severity (Fazekas 1 vs. 2–3) assessed cerebral microvascular disease (for details see (24)). The prevalence of microalbuminuria, distal symmetric polyneuropathy, cardiac autonomic neuropathy, and proliferative retinopathy was assessed periodically as part of the parent study protocol, using standardized methods [for details see (25)]; the most recent data for these complications prior to MRI was from 2004–2006.

Cardio-metabolic factors—For all participants, blood pressure was assessed concurrent with MRI, using standardized methods. For T1D participants, history of high blood pressure was based on ever self-reported use of anti-hypertensive medication and/or any blood pressure reading >140/90 mmHg, from 1986–1988 to 2010–2013; for non-T1D participants, this was based on self-reported prior high blood pressure, as current high blood pressure, treated or not, was cause for exclusion.

T1D-specific factors—The following were assessed concurrent with MRI: T1D duration (years); age at diagnosis (years); chronic hyperglycemia, per "HbA1c months", a calculated measure assessing degree and duration of hyperglycemia [for details see (26)]; insulin sensitivity, per estimated glucose disposal rate.(27) In addition, self-reported hypoglycemic

events requiring another's assistance to correct, or resulting in coma/hospitalization, was assessed biennially from 1986–88 to 2004–06.

Depression—T1D participants completed the Beck Depression Inventory concurrent with MRI; scores>=10 were classified as depressive symptoms.(28) Non-T1D participants completed the Center for Epidemiologic Studies – Depression Scale concurrent with MRI; scores>=16 were classified as depressive symptoms.(29)

Digit Symbol Substitution Test—Psychomotor speed was assessed via the DSST. This pencil and paper test provides a key grid of numbers and matching symbols, and a test section with numbers and empty boxes. Participants sequentially fill the empty boxes with the symbol matching each number, and the score is the correct number–symbol matches completed in 90 seconds.(30) DSST reflects multiple cognitive processes including visual scanning, associative learning, and hand-eye coordination [for details see (31)]. We chose this task because we and others have previously found DSST to be a strong predictor of future disability, dementia, and death, more so than psychomotor speed domain overall, or other measures of psychomotor speed (e.g., pegboard).(18–20)

MRI Protocol

In 2010–2013, participants underwent neuroimaging at the Pittsburgh Magnetic Resonance Research Center using a Siemens 12-channel head coil in a 3-T Siemens Tim Trio scanner. Details on acquisition protocols are described in detail elsewhere. (31, 32) Magnetization-prepared rapid gradient-echo T1-weighted images were acquired in the axial plane: repetition time=2300 milliseconds; echo time=3.43 milliseconds; inversion time=900 milliseconds: Flip angle=90°; slice thickness=1 mm; field of view=256 mm×224 mm; voxel size=1 mm×1 mm; matrix size 256×240; number of slices=176. The study radiologist examined images for unexpected findings.

The automated labeling technique delimitated 45 regions-of-interest defined by the Montreal Neurological Institute anatomical brain template.(33) Each individual's MRI was segmented into gray matter, white matter, and cerebrospinal fluid, using FMRIB Software Library (FSL). Whole-brain GMV was estimated in mm^3 by summing all the voxels classified as gray matter. To obtain GMV for the regions-of-interest, the Montreal Neurological Institute template was warped to the individual's MRI using a series of automated nonlinear registrations; this accounts for differences between the template and individual MRIs. These registrations were then applied to the template's region labels, and GMV of each region was estimated as the number of voxels of the warped region label that overlapped with the subject's native-space gray matter segmentation. Total brain volume (sum of total gray matter, total white matter, and total cerebrospinal fluid) was used to normalize regional GMV (regional volume/total brain volume * 100). WMH acquisition and grading details are described elsewhere.(24)

Regions-of-interest—Of 45 anatomically-defined regions obtained via the automated labeling pathway,(33) we selected seven, left and right, *a priori*: thalamus, putamen, anterior cingulate gyrus, hippocampus, precuneus, dorso-lateral prefrontal cortex, and superior

parietal lobe. These regions were selected based on prior work showing robust associations between GMV and lower DSST in non-T1D populations, with strong evidence for involvement of the basal ganglia and prefronto-parietal cortices.(19, 20, 34–37) These regions overlap with regions identified in our functional neuroimaging study.(38)

Voxel-based morphometry—Given reports of smaller GMV throughout the brain in children with than without T1D, (5, 39) we also employed a whole-brain approach to examine the spatial distribution of GMV in relationship to DSST. T1-weighted images were segmented and aligned to Montreal Neurological Institute 152-standard space using non-linear registration, and averaged to create a study-specific template. Native gray matter images were non-linearly registered to the study-specific template, modulated, and smoothed, with an isotropic Gaussian kernel, sigma=3mm. To assess the association with DSST, we used FMRIB Software Library voxel-based morphometry (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM) (40), pre-processing, (41) and Randomise (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise).(42) A threshold-free cluster enhancement controlled for multiple comparisons, (43) with a family-wise error correction of $p<0.050$.

Statistical Analyses

Cohorts were compared using t-test, Fisher exact, and Wilcoxon rank-sum test, as appropriate. Sex- and education-adjusted p-values were obtained from logistic regression models for dichotomous variables, and from ANCOVA for continuous variables, with statistical significance at $p<0.004$ per Bonferroni correction.

Spearman correlations tested associations between DSST and characteristics of the T1D and non-T1D cohorts, partialling out sex and education, with statistical significance at $p<0.002$ for the T1D and $p<0.004$ for the non-T1D cohorts, per Bonferroni correction. Both raw and age-, sex-, and education-adjusted DSST scores were compared, by T1D status. MANCOVA examined between-group differences in GMV of the *a priori* selected regions-of-interest, controlling for age, sex, and education, with $p<0.004$ significant per Bonferroni correction. Within each cohort, Spearman correlations partialling out age, sex, and education, tested associations between regional GMV and DSST, and between cohort characteristics, regional GMV and DSST.

The regions correlated to DSST at $p<0.05$ were included in further analyses examining GMV contributions to between-group differences in DSST. Specifically, linear regression models using the combined cohorts tested associations of regional GMV (covariate of interest) and DSST (outcome), controlling for T1D status, sex, and education. We tested whether adding GMV regions produced a change>10% (44) and statistically significantly different from 0(45) in the regression coefficient of T1D predicting DSST, according to the Barron model and the Sobel test, and non-parametric bootstrapping, respectively. Further adjustment was done for age and factors that differed between cohorts at $p<0.004$ (Bonferroni correction).

In analyses restricted to T1D participants, we also applied a voxel-wise analysis to further test associations between GMV and DSST without restriction to *a priori* selected regions. Only regions related to DSST in both the *a priori* regions-of-interest and voxel-based

approaches were further examined. Models restricted to T1D participants tested contributions of chronic hyperglycemia, WMH severity, and age to the relationship between DSST and GMV of regions thus identified. Interactions between WMH severity and regional GMV were also tested. Other factors were examined in this model if they were associated with both DSST and GMV after Bonferroni correction.

Analyses were repeated after excluding those with history of high blood pressure (32 T1D, 5 non-T1D); stroke (5 T1D); or serum glucose >200 mg/dL (25 T1D). SPSS (version 22.0; SPSS Inc. Chicago, IL) was used for all analyses. All models report standardized beta coefficients.

Results

Characteristics of participants with and without T1D are similar to those previously reported.(24, 46–48) To summarize, raw mean DSST score was lower in T1D compared with non-T1D (Table 1; see (49) for previously published results on DSST and other cognitive tests for these cohorts).

Mean age-, sex, and education- adjusted DSST scores were similar to mean raw DSST scores and were significantly lower for the T1D cohort (Table 1). Cohorts did not differ in age, male:female distribution, systolic blood pressure, or BMI. Compared with non-T1D participants, T1D participants had significantly fewer years of education, higher glucose, higher prevalence of depressive symptoms, more severe WMH, and lower diastolic blood pressure (Table 1).

When examining associations between risk factors and DSST, the association with age was significant for both cohorts after Bonferroni correction; for T1D participants, associations were also significant for education, T1D duration, severe WMH, prevalent proliferative retinopathy, and prevalent distal symmetric polyneuropathy (Supplemental Digital Content, Table S1). Associations of DSST with depressive symptoms, cardiac autonomic neuropathy, and glucose disposal rate were significant at $p<0.050$ for T1D participants, but not after Bonferroni correction (Table S1). Associations between other factors and DSST were not significant among non-T1D participants (Table S1).

Normalized GMVs were smaller for T1D than non-T1D for all of the *a priori* selected regions-of-interest except left hippocampus (sex-, age-, education-adjusted $p<0.0001$, Supplemental Digital Content, Table S2).

Associations between GMV and DSST were significant for putamen and thalamus at $p<0.050$ for T1D, but not for non-T1D, participants; no other regions examined were significantly related to DSST for either cohort (Supplemental Digital Content, Table S3).

In linear regression models examining T1D and GMV predicting DSST in the combined cohorts, having T1D was related to almost 0.4SD lower DSST score, independent of education or sex (Table 2, Model 1). The association between DSST and bilateral putamen was independent of T1D status, sex, and education (Table 2, Model 2) and WMH (Table 2, Model 3). This relationship remained statistically significant for left, but not right, putamen,

after adjustment for age (Table 2, Model 4). Adding left or right putamen to the models changed the coefficient of T1D>10% (Table 2, Model 2); attenuation was statistically significant (95% bias-corrected confidence limits = [−5.49, −1.80], [−5.29 −1.44], left and right putamen, respectively). The association between DSST and thalamus was not significant (Table 2, Model 2). Results were overall similar when controlling for WMH severity (not shown).

Among T1D, voxel-based analyses identified positive associations between DSST and GMV in putamen and thalamus as well as areas in the fronto-parietal (orbitofrontal gyrus, pre-and post-central gyri, precuneus), temporal (amygdala, hippocampus, parahippocampus, posterior cingulate cortex, insula), and occipital lobes (cuneus, supracalcarine cortex) (Table 3). Negative associations between DSST and GMV were not significant. Further analyses restricted to T1D focused on putamen and thalamus because these regions were identified using both the *a priori* and the voxel-based approaches. For the non-T1D cohort, no further analyses were conducted since DSST was not significantly related to GMV of any selected region after controlling for age, sex, and education (Supplemental Digital Content, Table S3).

To identify explanatory factors of the association between GMV and DSST in the T1D cohort, in addition to hyperglycemia and WMH, we tested associations between risk factors related to both DSST and GMV; WMH severity, but no other factors, were significantly correlated to bilateral putamen and thalamus GMV (Supplemental Digital Content, Table S4). Associations of DSST with GMV of bilateral putamen and thalamus were each independent of sex and education (Table 4, Model 1), age (Table 4, Model 2), and hyperglycemia (Table 4, Model 3). Associations were also independent of WMH severity for bilateral putamen and left thalamus, but not right, thalamus (Table 4, Model 4). Interaction terms between WMH and GMV were not significant (all p>0.050, data not shown).

Sensitivity analyses excluding participants with high blood pressure, stroke, or glucose>200 mg/dL yielded similar results (data not shown).

Discussion

The application of high-resolution neuroimaging in this extensively phenotyped T1D cohort indicated a spatial distribution of smaller GMV underlying low DSST, primarily localized within the basal ganglia, and robust to adjustment for WMH severity and chronic hyperglycemia. This association appeared unique to T1D as it was not significant for the non-T1D cohort. The spatial distribution hereby observed is consistent with findings from studies of aging (19, 34, 37) and from other patient populations such as adults with type 2 diabetes,(36, 50) Huntington's Disease, (51) and multiple sclerosis.(35) The putamen and thalamus are involved in cognitive and motor control,(52) with the thalamus receiving sensory inputs and relaying these to the cerebral cortex, hence reduced GMV of these regions could impair aspects of DSST performance and possibly of psychomotor speed.

Our results add to the current knowledge of neural pathways potentially underlying psychomotor slowing, as assessed via DSST, in adults with T1D in several ways. First, we

have identified a selected group of regions within the basal ganglia in relationship to DSST in T1D. To date, T1D studies of GMV in relationship with psychomotor slowing are sparse, with conflicting results.(21, 22) In a small group of T1D similar in age to our participants, Franc et al. (2011) detected a relationship between worse performance on the grooved pegboard and reduced cortical thickness in parietal and occipital cortical regions.(21) In contrast, Brands et al. (2006) found no associations between psychomotor speed tests, including DSST, and any neuroimaging measures among an older T1D cohort, mean age 61 years.(22) The use of different tests of psychomotor speed across different studies makes interpretation of these results challenging. Moreover, these studies used lower-strength magnets (0.5–1.5T) that are less sensitive to smaller volumetric differences, and they included individuals with adult-onset T1D. Exposure to T1D during childhood, a period of critical brain development, combined with longer exposure to T1D, may contribute to more severe brain deficits in middle-age, as observed in our cohort. Indeed, Brands et al. report a smaller between-group difference (d=−0.34) in psychomotor speed (22) than we found in our cohort (d=−0.72) (24). Perhaps more pronounced psychomotor slowing is related to macrostructural changes, such as smaller GMV, while earlier/milder psychomotor slowing may be related to microstructural brain changes which require other neuroimaging modalities for study, e.g., diffusion tensor imaging.

Second, we found that larger bilateral putamen reduced, but did not completely eliminate, the between-group difference in DSST. This suggest that other neurological factors beyond GMV must be at play, warranting further studies of neural correlates underlying psychomotor slowing in T1D.

Third, by examining the contribution of WMH to regional GMVs related to DSST, we uncovered a potential role of WMH as a risk factor for smaller GMV in this middle-aged T1D cohort. That WMH themselves are risk factors for reduced GMV in non-T1D populations has been previously suggested.(53) Whether this is true for our T1D population remains unknown, but our findings indicate that efforts to preserve psychomotor speed in T1D should concurrently target factors related to GMV and WMH.

Results of the voxel-based analysis complement results from the *a priori* selected regions-of-interest approach. In addition to thalamus and putamen, the voxel-based analyses found that lower DSST was related to smaller GMV in regions of primary and secondary somatosensory networks. Such findings are consistent with our knowledge of the functions associated with these regions. For example, the cuneus is important for basic visual processes, so smaller GMV here could negatively impact tasks requiring visual acuity, such as the DSST. Similarly, reduced GMV in the pre-central gyrus could negatively impact the motor component of the DSST. These regions were not identified using the regions-of interest approach, likely because the regions-of-interest approach has a higher threshold for detecting associations than voxel-based morphometry.(54) As this T1D cohort ages, associations between lower DSST and GMV may extend to other regions, highlighting the need for on-going neuroimaging and cognitive studies in aging T1D populations.

Why were associations with DSST stronger for basal ganglia than for other regions? Basal ganglia are generally considered more vulnerable to aging and disease-related processes

because of their non-anastomosing vascularization (55) and high density of insulin-like growth factor receptors.(56) Prior T1D neuroimaging studies indicate that the thalamus may be particularly vulnerable to hypoglycemia and other measures of metabolic dysregulation. (57, 58) However, we found no associations between hypo- or hyperglycemia and lower GMV in this study, nor in a prior report.(46) Others have shown that smaller GMV is detectable early in the course of T1D.(39, 59) It could be that, for our middle-aged cohort, T1D affected GMV development much earlier in life, making the influence of glycemic control no longer detectable after years of incubation; this possibility has been proposed by others.(17, 60) Study design does not allow us to determine whether exposure to T1D in childhood limited development in these regions at a young age or when GMV loss in the basal ganglia or other regions began. Future studies applying a longitudinal design, with repeated neuroimaging and assessment of factors related to psychomotor slowing, are needed to understand the determinants of GMV change over time in T1D.

Limitations of our study deserve mention. There may a selection bias related to MRI eligibility. We have previously shown that individuals from the T1D parent study who did not participate in this ancillary study were less healthy, with a higher prevalence of medical comorbidities and risk factors related to lower DSST and smaller GMV, than those who did participate.(24) This would bias our findings toward the null, underestimating the true association between DSST and GMV. Prevalence of T1D-related complications was assessed 5.8±0.6 years prior to MRI, likely underestimating their relationship with DSST and GMV. Although different instruments were used to assess depression, the cut points used to identify depressive symptoms have clinical relevance. While depression was not cause for exclusion, depressed individuals may self-exclude by refusing to respond/ participate. Results may not be generalizable to everyone with T1D, particularly not those diagnosed in adulthood.

In summary, our study has identified a distinct spatial distribution of smaller GMV within the basal ganglia that is important for DSST performance, and appears to be influenced by WMH. Strategies to preserve psychomotor speed as individuals with T1D age should address progression of both gray matter atrophy and cerebral small vessel disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

T1D	Type 1 diabetes
GMV	Gray Matter Volume

WMH	White matter hyperintensities
DSST	Digit Symbol Substitution Test
BMI	Body mass index
MRI	Magnetic Resonance Imaging
HbA1c	glycated hemoglobin

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Table 1

Comparison of middle-aged adults with and without childhood-onset type 1 diabetes (T1D).

	Non-T1D (N=135)	T1D (N=95)	
	N (%), Mean ± SD, or Median (IQR)		p-value[1]
Digit Symbol Substitution Test score (DSST)	63.36 ± 12.14	54.74 ± 13.86	<0.001
Age-, sex-, education-adjusted DSST score	63.27 ± 5.78	54.63 ± 7.53	<0.001
Demographics			
Age (years)	48.69 ± 7.28	49.06 ± 6.70	0.63
Female	73 (54%)	48 (51%)	0.71
Education (years)	16 ± 3	15 ± 3	0.004
Serum glucose (mg/dL)	91.14 ± 16.33	176.13 ± 86.34	<0.001
Serum glucose >200 mg/dL		24 (26%)	
History of smoking 100+ cigarettes	57 (42%)	36 (38%)	0.27
Depressive symptoms [2]	4/134 (3%)	24/81 (30%)	<0.001
Beck Depression Inventory Score		7 (3–10)	
Center for Epidemiologic Studies –Depression Scale Score	4 (1–7)		
Microvascular Disease			
White matter hyperintensity (WMH; % total brain volume) [3]	0.145 (0.088–0.205)	0.185 (0.120–0.346)	0.001
WMH severity (Fazekas 2–3 vs 1)	6/81 (7%)	28/88 (32%)	<0.001
Cardiac autonomic neuropathy [4]		40 (46%)	
Distal symmetric polyneuropathy [4]		45 (51%)	
Estimated glomerular filtration rate [4]		83.32 ± 23.67	
Proliferative retinopathy [4]		44 (47%)	
Cardio-metabolic Factors			
Systolic blood pressure (mmHg)	119.68 ± 9.72	119.43 ± 15.48	0.81
Diastolic blood pressure (mmHg)	78.33 ± 7.06	65.85 ± 9.82	<0.001
BMI (m^2/kg)	28.46 ± 5.57	27.37 ± 4.77	0.096
Diabetes-Specific Factors			
T1D duration (years)		40.94 ± 6.19	
Age at diagnosis (years)		8.12 ± 4.17	
HbA1c months, 1986–2013 (AU)		1109.63 ± 432.09	
Number of severe hypoglycemic events [5]		3 (1–6)	
Glucose disposal rate (mg/kg/min)		7.22 ± 2.45	

All measures assessed in 2010–2013 unless otherwise indicated. P-values adjusted for sex and education.

[1] Statistical significance for non-T1D cohort at p<=0.004 and for T1D cohort at p<=0.002, per Bonferroni correction;

[2] Beck Depression Inventory Score>=10 for T1D; Center for Epidemiologic Studies–Depression Scale Score>=16 for non-T1D

[3] p-values based on log-transformed values

[4] Assessed in 2004–2006

[5] Assessed from 1986–88 (parent study baseline) through 2004–06

Table 2

Spatial distribution of positive associations between gray matter volume and Digit Symbol Substitution Test in adults with type 1 diabetes (N=95) using voxel-based morphometry.

Region	Cluster Size (mm^3)	Peak T-Score	Peak T-Score MNI Coordinates (X,Y,Z)
1: Left putamen	11096	4.224957	(−14,14,4)
2: Left posterior cingulate cortex	8344	5.318681	(−22, −66,20)
3: Left insula	9064	5.118507	(−42, −16, −6)
4: Left pre-central gyrus	6800	4.719274	(−48, −12,38)
5: Left middle-temporal gyrus	680	3.872096	(−50, −42, −2)
6: Left thalamus	288	5.101167	(0, −8, −2)
7: Right precuneus	1280	4.797203	(22, −62,26)
8: Parahippocampal gyrus	3744	3.684067	(22,4, −16)
9: Right pre-central gyrus	8104	5.248271	(46, −12,44)
10: Right middle temporal gyrus	408	4.280942	(54, −32, −10)
11: Left frontal pole	40	5.017745	(−32,44,8)

Peak T: maximum T-statistic of all the voxels within the cluster. Cluster size: total number of voxels in the cluster.

Cluster 1 peaked in the left putamen; it included the adjacent structures of the head of the caudate, amygdale, and parahippocampus, and extended rostrally toward the orbitofrontal cortex, laterally to the insular cortex and left temporal pole, and inferiorly to the nucleus accumbens. Cluster 2 peaked in the left posterior cingulate, extending laterally to include the precuneus and the lingual gyrus, and caudally toward the cuneus and supracalcarine cortex. Cluster 3 peaked in the left insular cortex; it included the left middle and superior temporal gyri, extending subcortically to include putamen, thalamus, amygdale, and hippocampus. Cluster 4 peaked in the left pre-central gyrus, extending posteriorly to the post-central gyrus. Cluster 5 was constrained to the left middle temporal gyrus. Cluster 6 was constrained to the left thalamus. Cluster 7 peaked in the right precuneus, extending caudally to include the right cuneus and supracalcarine cortex. Cluster 8 peaked in the right parahippocampus, extending to the putamen, caudate head, and amygdale, and inferiorly toward the nucleus accumbens. Cluster 9 peaked in the right pre-central gyrus, extending posteriorly to the post-central gyrus. Cluster 10 was constrained to the right middle temporal gyrus. Cluster 11 was constrained to the left frontal pole.

Table 3

Linear regression models testing contributions of *a priori* selected regional gray matter volumes (GMV) to Digit Symbol Substitution Test score in adults with and without type 1 diabetes (N=169).

Factor(s) in Model	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
	Standardized β (p-value)			
Type 1 diabetes	−0.358 (<0.001)	−0.202 (0.012)	−0.171 (0.033)	−0.195 (0.009)
Left putamen *		0.285 (<0.001)	0.241 (0.003)	0.196 (0.010)
WMH severity			−0.184 (0.010)	−0.095 (0.16)
Age				−0.332 (<0.001)
Type 1 diabetes	−0.358 (<0.01)	−0.231 (0.005)	−0.193 (0.018)	−0.219 (0.004)
Right putamen *		0.231 (0.005)	0.192 (0.018)	0.145 (0.057)
WMH severity			−0.199 (0.005)	−0.107 (0.12)
Age				−0.337 (<0.001)
Type 1 diabetes	−0.358 (<0.001)	−0.295 (<0.001)		
Left thalamus		0.121 (0.14)		
Type 1 diabetes	−0.358 (<0.001)	−0.315 (0.001)		
Right thalamus		0.074 (0.39)		

*Indicates normalized GMV for this region significantly attenuated the relationship between type 1 diabetes and DSST;

Regional GMV normalized to total brain volume.

White matter hyperintensity (WMH) severity: Fazekas score 2–3 vs. 1

Factors in model:

[a]T1D status, education, sex

[b]Model 1 plus regional GMV

[c]Model 2 further adjusted for WMH severity

[d]Model 3 further adjusted for age

Table 4

Linear regression models showing relationships between *a priori* selected regional gray matter volumes (GMV) and Digit Symbol Substitution Test in adults with type 1 diabetes (N=88).

	Factor(s) in Model	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
		Standardized β (p-value)			
Left Putamen	GMV	0.293 (0.003)	0.246 (0.006)	0.284 (0.004)	0.238 (0.015)
	Age		−0.406 (<0.001)		
	Hyperglycemia			−0.118 (0.22)	
	WMH severity				−0.247 (0.011)
Right Putamen	GMV	0.242 (0.015)	0.207 (0.021)	0.236 (0.017)	−0.207 (0.031)
	Age		−0.417 (<0.001)		
	Hyperglycemia			−0.129 (0.19)	
	WMH severity				−0.273 (0.005)
Left Thalamus	GMV	0.269 (0.006)	0.288 (0.001)	0.261 (0.008)	0.204 (0.037)
	Age		−0.449 (<0.001)		
	Hyperglycemia			−0.122 (0.21)	
	WMH severity				−0.245 (0.013)
Right Thalamus	GMV	0.198 (0.046)	0.223 (0.012)	0.191 (0.054)	0.121 (0.22)
	Age		−0.449 (<0.001)		
	Hyperglycemia			−0.129 (0.19)	
	WMH severity				−0.264 (0.009)

Regional GMV normalized to total brain volume.

White matter hyperintensity (WMH) severity: Fazekas score 2–3 vs. 1

Factors in model:

Model 1: Regional GMV, education, sex

Model 2: Model 1 plus age

Model 3: Model 1 plus HbA1c months (see (23) for details)

Model 4: Model 1 plus WMH severity