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Frontal Gray Matter Atrophy in Middle Aged Adults with Type 1 Diabetes is Independent of Cardiovascular Risk Factors and Diabetes Complications

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Abstract

Aims—To determine if regional gray matter volume (GMV) differences in middle-aged adults with and without type-1 diabetes (T1D) are localized in areas most vulnerable to aging, e.g. fronto-subcortical networks; and if these differences are explained by cardiovascular risk factors and diabetes complications.

Methods—Regional GMV was computed using 3 Tesla MRI of 104 adults with a childhood onset of T1D (mean age: 49±7 and duration: 41±6 years) and 151 adults without diabetes (mean age: 40±6). A Bonferroni threshold ($n=45$, $p=0.001$) was applied to account for multiple between-group comparisons and analyses were repeated in an age- and gender-matched subset of participants with T1D and controls ($n=44$ in each group, mean age [SD] and range: 44.0, [4.3], 17.4 and 44.6 [4.3], 17.0, respectively).

Results—Compared to controls, T1D patients had smaller GMV in the frontal lobe (6 to 19% smaller) and adjacent supramarginal and postcentral gyri (8 to 13% smaller). Between-group differences were independent of age, waist circumference, systolic blood pressure, fasting total

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Contribution statement

TMH was responsible for the analysis and interpretation of the data, production of tables and manuscript writing; HJA was responsible for the processing of MRI images using the ALP pipeline to obtain brain volumes as well as contributions to the intellectual content; PJG was responsible for the design and acquisition of the MRI data for the non-diabetic controls and revisions of manuscript; CMR, TC and TJO provided intellectual contributions the design of this study, interpretation of results, and revisions to the manuscript; RM, KN and ESS provided interpretation of results and revisions to the manuscript; and CR was responsible for the design and acquisition of the MRI data for the T1DM participants, as well as contributions to the design of this study, interpretation of results, and revisions to the manuscript. All authors approved of the final version of the manuscript.

Conflicts of interest

The authors have no conflicts of interest relative to this study to disclose.

cholesterol and smoking status and were similar in sensitivity analyses restricted to age- and gender-matched participants. Associations between GMV and diabetes complications were not significant.

Conclusions—These findings extend the notion of accelerated brain aging in T1D to middle-aged adults. The pathophysiology of frontal gray matter atrophy and its impact on future development of disability and dementia need further study, especially as middle-aged T1D patients progress to older age.

Keywords

Brain; Imaging (MRI); Complications; Retinopathy; Nephropathy; Hypertension

Background

Structural and functional changes to the brain are well-established sequelae of diabetes. Compared to individuals without diabetes, adults with a childhood-onset of Type 1 diabetes (T1D) show evidence of generalized brain atrophy and ventricle enlargement, reduced gray and white matter volumes, microstructural abnormalities in white matter tracts and cognitive changes like psychomotor slowing and poorer executive functioning that are not usually seen in adults without diabetes until they are substantially older [1, 2]. With better therapies and increased longevity in T1D, there is a marked increase in the number of adults with T1D who are aging [3, 4] and there is an urgent need to accurately estimate the contributions of age and disease to the evolution of brain changes observed with older age in T1D.

The potential role of T1D to accelerate brain aging has been mostly examined in studies of young patients with T1D [5]. However, such sequelae of accelerated or premature brain aging should also be detectable in older adults with T1D. Specifically, one would expect to see the greatest abnormalities, for example reduction in gray matter volume, in those regions that are most affected during the natural aging process. A large body of research has demonstrated that age-related reductions in gray matter thickness and surface area are most prominent in the frontal and parietal lobes, and less pronounced in temporal and occipital lobes [6, 7] although there is a very high degree of individual variability in both rate and degree of change over time [8]. Similar relationships between increasing age and decreasing gray matter volume have also been reported in several subcortical structures, including the putamen, thalamus, nucleus accumbens and hippocampus [9, 10].

To date, few neuroimaging studies of adults with T1D have examined the spatial distribution of brain structural changes, and in those that have, the focus has been on younger adults with regional effects being modest in size and highly inconsistent across studies. Using voxel-based morphometry techniques, Musen and colleagues [11] studied 82 young adults (mean age = 32 years) with a childhood-onset of diabetes and found ~ 5% less GMV in multiple cortical areas including the left temporal gyrus, left angular gyrus, left inferior parietal gyrus, left medial gyrus, left thalamus and right superior temporal gyrus. Other studies, using smaller samples of somewhat older subjects, found relatively few differences between participants with and without T1D, with regional differences either extremely circumscribed (e.g., limited to the inferior frontal gyrus and the occipital lobe [12]) or nonexistent [13]. The strongest evidence of an accelerated brain aging process related to T1D comes from a study of young adults with T1D (range: 16 to 26 years) and age-matched control adults without diabetes [5]. Analyses revealed statistically significant negative correlations of gray matter volume with age among T1D participants, mainly localized in fronto- temporal gyri and basal ganglia, but not among the controls.

To test the hypothesis that T1D is associated with accelerated brain aging in middle-aged adults, we used high resolution neuroimaging coupled with a detailed and reliable anatomical segmentation process, to compare regional gray matter volume between a large cohort of middle-aged adults with a childhood onset of T1D and adults of similar age without diabetes. We hypothesize that the gray matter volume differences between middle-aged adults with T1D and adults without diabetes should be most prominent in those cortical and subcortical brain regions known to change during the normal aging process. We also hypothesize that these differences would be explained by differences in cardiovascular risk factors and by diabetes-related complications.

Methods

Subjects

Participants with T1D were recruited from the Epidemiology of Diabetes Complications (EDC) study, a cohort of incident cases of childhood-onset (<17 years of age) diabetes diagnosed or seen within one year of diagnosis (1950–1980) at Children's Hospital of Pittsburgh. Following the first clinical assessment (1986–1988), when average participant age and diabetes duration were 28 and 19 years, respectively, biennial examinations were conducted for 10 years, with a further examination at 18 years and a 25 year examination currently ongoing [14, 15]. Among the 263 locally resident individuals who participated in the 24 year follow up and thus were invited for this neuroimaging study, 149 accepted the invitation, 112 did not have contraindication for brain MRI and 104 had usable MRI data to be included in this analysis.

Adults without diabetes (controls) participating in the Pittsburgh Imaging Project served as the comparison group for this study. A total of 151 individuals, 30 to 50 years of age, were recruited from the community if they were free from history of cardiovascular disease (cardiac surgery, chronic liver or kidney conditions, diabetes Type 1 or Type 2), of pulmonary or respiratory diseases, without prior diagnosis of substance abuse or mood disorders, prior surgery, head injury, or other neurological condition, any condition associated with loss of consciousness, or treatment with lipid-lowering or cardiovascular medications [16]. At time of MRI, sixteen (11%) of these participants had impaired fasting glucose levels (100–125 mg/dl) and 24 (15.8%) met criteria for metabolic syndrome as described in detail below in “Laboratory and Clinical measures”.

Each study protocol received local IRB approval prior to study initiation. All participants completed the informed consent process prior to any study procedures.

MRI acquisition

Participants of both groups completed the MRI study at the Pittsburgh Magnetic Resonance Research Center (MRRC) between 2010 and 2012 using a Siemens 12-channel head coil in a 3T Siemens Tim Trio MR scanner using identical protocols. Details on the protocol of acquisition are described in greater detail elsewhere [17]. Magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted images were acquired in the axial plane: TR = 2300 ms; TE = 3.43 ms; TI = 900 ms; Flip angle = 9°; slice thickness = 1 mm; FOV = 256 mm × 224 mm; voxel size = 1 mm × 1 mm; matrix size 256 × 240; number of slices = 176. The study radiologist examined the images to identify unexpected findings, including strokes, tumors or infarcts.

Automated Labeling Pathway (ALP) Technique

The automated labeling technique delimited forty-five regions of interest defined by the Montreal Neurological Institute (MNI) labeled single-subject high-resolution anatomical

brain template [18]. A series of automated nonlinear warpings of the brain template were applied to each individual's MRI to account for the nonlinear differences between the template and individual's MRI. After segmentation, GMV was estimated in cubic millimeters (mm^3) by summing all the voxels classified as this tissue type. Total intracranial volume (ICV) was computed as the volume contained within the “inner skull” [19] and was used to account for head size differences between subjects. Atrophy index was calculated as the ratio of GMV/ICV, with smaller values indicating more gray matter atrophy.

Regions of interest

Among the forty-five anatomically-defined brain regions of interest [18], 16 ‘age-related’ regions were identified: putamen, thalamus, hippocampus and 13 regions in the frontal lobe. The 13 regions in the frontal lobe included non-overlapping major and minor gyri, listed in Table 2: superior, middle, inferior operculum, inferior triangularis, superior medial, supplementary motor area, superior orbital, superior medial orbital, middle orbital, inferior orbital, gyrus rectus, precentral gyrus and the olfactory cortex. The remaining 29 regions in the MNI template were characterized as not strongly associated with aging, including gyri of temporal, parietal, occipital and limbic lobes as well as subcortical gray matter nuclei of the amygdala, caudate and pallidum.

Laboratory and clinical measures

Waist circumference in centimeters, height in centimeters, weight in kilograms, blood pressure, glucose, creatinine, albumin and lipids were measured time of MRI. Blood pressure was measured with a random zero sphygmomanometer after a five minute rest [20] and hypertension was defined as blood pressure $\geq 140/90$ mm Hg or use of antihypertensive medications. Lipids were measured in EDC participants using previously published protocols for high density lipoprotein cholesterol (HDLc) [21], cholesterol and triglycerides [22]. Non-HDL cholesterol was calculated as total minus HDLc. Lipids were measured in controls at time of MRI as part of the Pittsburgh Imaging Project; SYNCHRON CX® Systems were used to measure total cholesterol, HDLc and triglycerides at time of MRI. In both studies, low-density lipoprotein cholesterol (LDLc) was estimated by the Friedewald equation [23].

Metabolic syndrome was defined by the criteria of the National Cholesterol Education Program Adult Treatment Panel III. According to NCEP criteria, the MetS is defined as the presence of three or more of the following: (1) serum triglycerides > 150 mg/dL; (2) fasting serum glucose > 110 mg/dL; (3) waist circumference > 102 cm in men or > 88 cm in women; (4) SBP > 130 or DBP > 85 mm Hg; (5) serum HDL cholesterol < 40 mg/dL in men or < 50 mg/dL in women. A conservative guideline was applied to minimize confounding related to disease or medication use, and use of medication for hypertension or hyperglycemia was not factored into defining the presence of the metabolic syndrome in this cohort.

Diabetes-Associated Variables

Diabetes-associated variables and complications were measured at a time of MRI using previously published protocols. Duration of T1D was computed as the interval of time between initial diabetes diagnosis and age at MRI. Age of onset was reported in years. Fasting glucose was measured using the Cholestech LDX Analyzer; glycosylated hemoglobin (HbA_{1c}) was measured with the DCA 2000 analyzer (Bayer, Tarrytown, NY, USA); HbA_{1c} months was a measure of cumulative glycemic exposure [24]. Insulin dose was self-reported through questionnaires and expressed as units per kg of body weight. Other complications assessed at the 2006-2009 visit included: distal symmetrical polyneuropathy status, determined by medical history and clinical examination of symptoms, signs and reduced deep tendon reflexes using the DCCT protocol [25]; cardiac

autonomic neuropathy, assessed by heart variation during deep breathing and heart rate and blood pressure response to standing; retinopathy, determined by 3 standard field stereo fundus photographs at each examination and read by Madison Reading Center in Wisconsin and graded using the Early Treatment Diabetic Retinopathy Study Classifications; overt nephropathy, defined as the presence of renal failure (serum creatinine >5 mg/dl and/or end stage renal disease, i.e. dialysis and/or renal transplant) or an Albumin Excretion Rate >200 µg/min in at least 2 of 3 timed urine samples or (in the absence of any urine collections) a serum creatinine >2 mg/dl. The ratio of albumin to creatinine obtained at time of MRI was also used as a measure of renal function.

Statistical Analysis

Between-group differences of participant characteristics were tested using logistic regression, controlling for age and gender. Between-group differences in GMV and GM atrophy were first assessed in the total brain. To test for regional volumetric differences, GMV of all 45 anatomical regions was compared between participants with T1D and adults without diabetes. To account for multiple comparisons and minimize type-1 error, we applied a post-hoc Bonferroni threshold of $p = 0.001$. We used separate multivariable linear regression models to test between-group differences in regional GMV, adjusted first for age, gender and ICV (Model 1), using PROC GLM in SAS 9.2. We examined GMV differences in both hemispheres combined, then in the left and right hemispheres separately. For regions meeting the Bonferroni threshold, we explored the contribution of cardiovascular risk factors to GMV differences by adjusting each model for age, gender, ICV, race, waist circumference, years of education, sitting systolic blood pressure, fasting serum cholesterol and smoking status (Model 2). A 10% change in mean differences between Model 1 and Model 2 was considered a meaningful attenuation [26].

Between-group differences were also tested using linear mixed models in a subset of participants with T1D matched for age and gender with control participants using a 1:1 matching scheme. This matching yield a subset of 44 participants with T1D and 44 controls (mean age [SD] and range: 44.0, [4.3], 17.4 and 44.6 [4.3], 17.0, respectively). None of the controls in this subset had impaired fasting glucose and 4/44 had metabolic syndrome. The association between diabetes-associated variables and GMV of the regions that differed between groups was estimated in this subset and also in the entire group of EDC participants.

Results

At the time of MRI, the T1D participants were between the ages of 32 and 69 years (mean $\pm$ SD: 49 ± 7 years), with a mean duration of diabetes of 41 ± 6 years (range: 32 - 59 years) and a median age at diagnosis of 9 years (range: 1 - 16 years). At clinic visit, 25% of T1D participants ($n = 25$) had overt nephropathy and approximately half had cardiac autonomic neuropathy ($n = 46$) or confirmed distal symmetric polyneuropathy ($n = 51$) (Table 1). Additionally, 90% had detectable retinopathy, with 28% having only detectable background changes and 62% having proliferative disease or history of laser therapy for proliferative retinopathy. Compared to the parent EDC cohort, participants in this MRI study were, on average, about two years younger ($p=0.05$), with a slightly shorter duration of diabetes ($p=0.05$) yet with similar rates of diabetes complications (data not shown). Note that these biomedical data were collected between 2004 and 2006, approximately 5 years prior to MRI acquisition.

Compared to T1D participants, participants without diabetes were younger (range: 30 - 50 years old), less likely to be white or former smokers, more likely to have higher sitting systolic and diastolic BP, as well as higher total and LDL cholesterol levels (Table 1). GM

atrophy was greater in the T1D group than in the control group, independent of age and gender differences (atrophy indices of 0.34 and 0.36, respectively, $p < 0.001$). Differences in GM atrophy between participants with T1D and controls were similar between males and females. Although gender differences in GM atrophy were not significant for T1D participants ($p = 0.13$), control males had significantly more atrophy compared to control females ($p < 0.01$).

Between-group differences in regional GMV were statistically significant, meeting the Bonferroni threshold of $p < 0.001$ after adjusting for age, gender and ICV, in 10 of the 13 subregions of the frontal lobe (ranging between 7 to 19% smaller in T1D compared to the control group). Between group differences also met the Bonferroni threshold in three adjacent areas that were not hypothesized to differ with age: the rolandic operculum (7% smaller for T1D) and the postcentral (8% smaller for T1D) and supramarginal gyri (13% smaller for T1D) (Table 2). Among the other regions of the frontal lobe, the gyrus rectus ($p = 0.002$), inferior orbital gyrus ($p = 0.08$) and olfactory cortex ($p = 0.19$) did not meet the Bonferroni threshold and between-group GMV differences ranged from 3 to 6% smaller for T1D.

Between-group GMV differences were detectable ($0.001 < p < 0.05$) but did not meet the Bonferroni threshold for significance in other brain regions, including the parietal, temporal, and limbic lobes and the insula. Interestingly, GMV was similar for T1D and control groups in the subcortical gray matter of the basal ganglia as well as in the occipital lobe. Separate models that assessed the laterality of GMV differences for all subregions indicated that the observed GMV differences meeting the Bonferroni threshold were similar for both the right and left hemispheres for each region – with the exception of the postcentral gyri and rolandic operculum of the central region. Between group GMV differences appeared to be stronger in the left versus the right hemispheres of the post central gyri (left, $p < 0.001$; right, $p = 0.12$) and weaker in the left versus the right hemisphere of the rolandic operculum (left, $p = 0.13$; right, $p < 0.001$).

The between-group differences in the ten regions of the frontal lobe and the three adjacent regions remained above the Bonferroni threshold and were only modestly modified after adjustment for education and cardiovascular risk factors such as waist circumference, systolic BP, fasting total cholesterol and smoking status (Table 2, Models 2). Analyses stratified by smoking status also yield similar results (not shown). Between-group differences also remained above the Bonferroni threshold in the age- and gender- matched subset of participants with T1D and controls ($n = 44$ in each group, mean age [SD] and range: 44.0, [4.3], 17.4 and 44.6 [4.3], 17.0, respectively), with the exception of the operculum of the inferior frontal gyrus and of the rolandic gyrus and the superior orbital gyrus ($p > 0.001$). Associations between diabetes-associated variables and GMV of the regions that differed between groups were all not significant in this subset of 44 participants with T1D ($p > 0.3$) nor in the entire group of 104 participants with T1D ($p > 0.2$). Associations of gray matter volume of these regions with number of drinks/week was also not significant ($p > 0.18$).

Discussion

This study indicates that middle-aged adults with a childhood-onset of T1D have smaller GMV compared to adults without diabetes, with these differences apparent across virtually all subregions of the frontal lobes (6 to 19% smaller: $M_{\text{Lateral Surface}} = 13.9\%$; $M_{\text{Medial Surface}} = 13.1\%$; $M_{\text{Orbital Surface}} = 6.5\%$) as well as in areas of the insula and parietal cortex adjacent to the frontal lobe (8 to 13% smaller; $M = 8.7\%$) (Figure 1). The observed between-group differences in GMV appear in both hemispheres and remain statistically significant after the application of a conservative threshold to account for multiple comparisons and also after

age- and gender-matching. In contrast, between-group differences in subcortical GMV are far more modest and not significant (e.g., hippocampus, putamen, thalamus). Modest differences were found in the temporal lobe ($M = 3.9\%$) and the lateral surface of the occipital lobe ($M = 4.2\%$).

The observed GMV differences related to presence of T1D are much larger than the typical 1%/year decline in volume observed after age 50 for adults without diabetes [27]. Contrary to our predictions, the GMV differences related to the presence of T1D were not explained by cardiovascular risk factors and were not related to diabetes-associated variables. Of note, the participants with T1D had a more favorable cardiovascular risk factor profile compared to the adults without diabetes, despite their older age. This is likely a result of intensive cardiometabolic risk factor management among the T1D cohort and could also explain the lack of association between these factors and GMV. It is possible that the time and type of measurements of diabetes complications do not capture the aspects of T1D that contribute to gray matter atrophy. While long-term glycemic aberrations (hyper- or hypoglycemia), vascular disease and/or other diabetes-related factors (e.g., proinflammatory cytokines, advanced glycation end-products) may heavily contribute to the development of structural brain changes over an individual's lifetime, successful management of these factors may correct or decelerate these very same structural abnormalities. Longitudinal studies in older adults with T1D should explore the impact of the trajectories of diabetes care, including long-term management of complication risk factors on the evolution of brain abnormalities. Since age is a strong risk factor for brain abnormalities, the synergistic effect of T1D-specific factors and age-related brain degeneration may have dramatic debilitating effects in persons with T1D as they grow older. The potential neuroprotective effects of behavioral and lifestyle modification, including reduction in alcohol intake and smoking also deserve further study.

Our findings, and those of other investigators, indicate that both children and adults with T1D manifest structural changes within the brain, with the frontal and parietal regions being affected most often. The only other study to systematically examine multiple discrete brain regions [28] found that young adults ($M = 20.2$ years) with a childhood onset of diabetes ($M = 7.1$ years) showed reductions in brain volume in the frontal and parietal lobes. In addition, they found differences in multiple subcortical areas, including the basal ganglia and thalamus, areas that were unaffected in our middle-aged T1D cohort. The lack of a completely identical pattern of results across different pediatric or adult studies may reflect variations in neuroimaging procedures and analytic strategies, as well as differences in study cohorts. For example, only our group and Northam's group [28] used a 3 T scanner; others used less powerful 1.5 T scanners [11, 12, 29-31]. Our ability to identify more – and larger – regional differences in GMV may reflect our use of an anatomically-based method of segmentation that permits higher spatial resolution comparisons at the level of individual gyri. On the other hand, there are also significant differences between our subjects and those studied by others. Our cohort developed diabetes during childhood (median age at onset = 9 years) whereas other studies of adults with T1D included participants with a somewhat later age at onset, ranging from 12 years [11] to 27 years [13]. Indeed, we find it interesting that the one study that found no differences in brain morphology focused on older adults with T1D ($M = 61$ years of age) who had developed diabetes relatively late in life, with 65% being diagnosed after the age of 18 [13]. In contrast, those studies that evaluated either children or adults with an earlier age at onset were more likely to report marked reductions in gray or white matter volumes [5, 29].

Potential weaknesses of our study include those related to our subject samples. T1D participants were somewhat older, with a broader age range, than those in the control group; however, sensitivity analyses restricted to age- and gender-matched participants yield

similar results. Data on some of the diabetes-associated variables (distal symmetrical polyneuropathy status, retinopathy, nephropathy, cardiac autonomic neuropathy) were obtained in T1D participants several years prior to the date of MRI and hence may misrepresent their health status at the time of brain imaging. The extent to which other metabolic and vascular factors contribute to the development of diabetes-associated brain anomalies – particularly in older adults with T1D – remains poorly understood and deserves additional study.

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Figure 1.

Regions showing between-group differences in gray matter volume after correction for multiple comparisons ($p < 0.001$) in middle-aged type 1 diabetic participants compared to control participants.

Table 1

Characteristics of middle aged participants with type 1 diabetes (T1D) and without diabetes (Controls).

	T1D Participants (32 - 69 years) N=104		Control Participants (30 - 50 years) N=151		age and gender- adjusted p- value
Age, mean±std	48.7	±7.0	40.4	±6.2	<0.001
Women, n, %	53	51%	72	48%	0.885
White, n, %	102	98%	108	73%	<0.001
Height (cm), mean±std	167.9	±8.6	171.5	±9.8	0.029
Weight (kg), mean±std	77.1	±14.8	80.6	±15.7	0.339
Body Mass Index	27.3	±4.7	27.4	±5.0	0.941
Waist circ. (cm), mean, std	90.3	±13.2	91.2	±13.6	0.545
Smoking status, n, % *					<0.001
Current	6	6%	30	20%	
Former	29	28%	24	16%	
Education (years), mean, std *	16.5	±1.3	17.1	±3.3	0.619
Heart rate (beats / min), mean, std	73.7	±10.2	73.9	±9.6	0.190
Sitting systolic (mmHg), mean, std	119.5	±15.3	121.6	±9.4	<0.001
Sitting diastolic (mmHg), mean, std	65.6	±11.2	73.6	±8.9	0.044
Total cholesterol (mg/dL), mean, std *	172.6	±33.3	186.6	±30.6	0.008
HDL (mg/dL), mean, std *	60.3	±16.4	49.5	±16.3	<0.001
LDL (mg/dL), mean, std *	96.9	±28.6	118.7	±28.2	<0.001
Triglycerides (mg/dL), mean, std *	82.4	±41.8	94.3	±59.4	0.271
ADA diabetes status, n, %					--
Normal	--		135	89%	
IFG	--		16	11%	
DM	104	100%	0	0%	
Intracranial volume (mm ³), mean, std	1867490	±199466	1833230	±165288	0.016
Atrophy index (GMV/ICV), mean, std	0.34	±0.02	0.36	±0.02	<0.001
Duration of diabetes (years), mean, std	41	±6	--	--	
Hemoglobin A1c (%), mean, std	7.7	±1.4	--	--	
Age of onset (years), median [IQR]	8	[1, 16]	--	--	
Cardiac autonomic neuropathy status, n, % *	46	44%	--	--	
Confirmed DSPS, n, % *	51	49%	--	--	
Overt nephropathy, n, % *	25	24%	--	--	
Retinopathy level, n, % *			--	--	
None	10	10%	--	--	
Background	28	27%	--	--	
Proliferative or Laser Therapy	62	59%	--	--	

IQR = interquartile range

DSPS - distal symmetric polyneuropathy status

** For age comparisons, p-values are adjusted only for gender; for gender comparisons, p-values are only adjusted for age

* indicates measures taken from most recent clinic visit 2004-2006.

Table 2

Gray matter volume of middle-aged participants with type 1 diabetes (T1D) and without diabetes (Controls). All differences are adjusted for age, gender and intracranial volume.

		T1D Participants (n=104)		Control Participants (n=151)		Mean difference	95% Confidence Limits		Percent mean difference
		L Smeans	SE	L Smeans	SE		Lower	Upper	
Total GMV		628141	4103	660167	3303	-32026	-43232	-20819	<0.001
	Model 2	609287	5913	656077	3673	-46789	-60154	-33425	<0.001
Frontal lobe*									
<i>Lateral and medial surfaces</i>									
Superior gyrus		21158	250	25319	201	-4161	-4843	-3479	<0.001
	Model 2	20357	377	25235	234	-4878	-5731	-4025	<0.001
Middle gyrus		30134	343	35161	277	-5027	-5965	-4089	<0.001
	Model 2	29608	525	35094	326	-5486	-6672	-4299	<0.001
Inferior gyrus, operculum		8964	121	9632	98	-668	-1000	-336	<0.001
	Model 2	8580	183	9542	113	-963	-1376	-550	<0.001
Inferior gyrus, triangularis		14374	180	16340	145	-1966	-2456	-1476	<0.001
	Model 2	13750	265	16066	165	-2315	-2915	-1715	<0.001
Precentral gyrus		22410	232	24616	186	-2206	-2838	-1573	<0.001
	Model 2	21796	348	24558	216	-2761	-3548	-1975	<0.001
Supplementary motor area		14310	173	16423	139	-2113	-2585	-1640	<0.001
	Model 2	13644	258	16434	160	-2791	-3374	-2207	<0.001
Superior medial gyrus		16306	227	19009	183	-2702	-3323	-2081	<0.001
	Model 2	15327	337	18767	210	-3440	-4203	-2677	<0.001
Orbital surface									
Superior gyrus		8977	100	9504	81	-527	-802	-253	<0.001
	Model 2	8818	153	9496	95	-677	-1023	-332	<0.001
Superior medial gyrus		8475	110	9212	89	-737	-1038	-436	<0.001
	Model 2	8220	166	9136	103	-915	-1291	-540	<0.001
Middle gyrus		7101	111	7999	89	-898	-1201	-595	<0.001
	Model 2	6856	168	7911	105	-1056	-1436	-675	<0.001
Inferior gyrus		14484	165	14948	133	-465	-915	-15	0.043

	T1D Participants (n=104)		Control Participants (n=151)		Mean difference		95% Confidence Limits		Percent mean difference
	LSmeans	SE	LSmeans	SE			Lower	Upper	p-value
Gyrus rectus	8300	111	8695	89	-395		-698	-91	0.011
Olfactory cortex	3186	46	3266	37	-80		-206	46	0.211
Sub cortical gray nuclei									
Putamen *	6352	140	6297	113	55		-328	439	0.776
Thalamus *	4826	83	4713	67	112		-116	340	0.333
Caudate nucleus	8937	109	8923	88	14		-285	313	0.926
Pallidum	778	25	679	20	99		32	166	0.004
Limbic lobe									
Hippocampus *	11097	90	10960	72	137		-109	383	0.273
Anterior cingulate	10891	182	11505	146	-614		-1111	-117	0.016
Dorsal cingulate gyrus	15000	166	15572	134	-572		-1025	-118	0.014
Posterior cingulate gyrus	3147	55	3149	44	-3		-152	147	0.972
Parahippocampal gyrus	12629	115	12184	93	445		130	759	0.006
Insular cortex									
Rolandic operculum	10019	118	10603	95	-584		-906	-262	<0.001
Model 2	9894	181	10578	112	-683		-1092	-274	0.001
Insula	17746	175	18067	141	-322		-799	156	0.186
Parietal lobe									
<i>Lateral surface</i>									
Supramarginal gyrus	11552	160	12756	129	-1205		-1643	-766	<0.001
Model 2	10994	238	12568	148	-1575		-2112	-1037	<0.001
Postcentral gyrus	25859	274	27423	220	-1563		-2311	-815	<0.001
Model 2	25143	412	27380	256	-2238		-3169	-1306	<0.001
Superior gyrus	14238	199	13842	160	396		-148	940	0.153
Inferior gyrus	13786	165	14301	132	-515		-965	-66	0.025
Angular gyrus	11015	148	11697	119	-682		-1087	-277	0.001
<i>Medial surface</i>									
Precuneus	25189	280	25762	226	-572		-1337	193	0.142
Temporal lobe									
Gyrus rectus									-4.5%
Olfactory cortex									-2.5%
Putamen *									0.9%
Thalamus *									2.4%
Caudate nucleus									0.2%
Pallidum									14.6%
Hippocampus *									1.3%
Anterior cingulate									-5.3%
Dorsal cingulate gyrus									-3.7%
Posterior cingulate gyrus									-0.1%
Parahippocampal gyrus									3.7%
Rolandic operculum									-5.5%
Model 2									-6.5%
Insula									-1.8%
Supramarginal gyrus									-9.4%
Model 2									-12.5%
Postcentral gyrus									-5.7%
Model 2									-8.2%
Superior gyrus									2.9%
Inferior gyrus									-3.6%
Angular gyrus									-5.8%
Precuneus									-2.2%

	T1D Participants (n=104)		Control Participants (n=151)		Mean difference	95% Confidence Limits		Percent mean difference	
	LSmeans	SE	LSmeans	SE		Lower	Upper		p-value
Superior gyrus	22504	227	23480	183	-976	-1596	-356	0.002	-4.2%
Heschel's gyrus	2401	43	2561	34	-160	-277	-44	0.007	-6.3%
Middle gyrus	38005	329	39199	265	-1193	-2093	-294	0.010	-3.0%
Inferior gyrus	32003	303	33183	244	-1180	-2009	-351	0.005	-3.6%
Superior pole	12522	150	12715	121	-192	-602	217	0.355	-1.5%
Middle pole	9823	149	10317	120	-494	-902	-86	0.018	-4.8%
Occipital lobe									
Superior gyrus	9808	132	10059	106	-251	-612	110	0.172	-2.5%
Middle gyrus	19854	268	20969	216	-1115	-1848	-383	0.003	-5.3%
Inferior gyrus	9317	159	9772	128	-455	-888	-21	0.039	-4.7%
Cuneus	12477	176	12042	141	436	-44	915	0.075	3.6%
Calcarine	16337	235	15983	189	354	-288	997	0.279	2.2%
Lingual gyrus	19237	243	18936	196	301	-364	966	0.374	1.6%
Fusiform gyrus	26916	250	26748	201	168	-516	851	0.629	0.6%

LSmeans (SE) = least squares means and standard errors from multivariable linear regression models.

Model 2 – Further adjusted for waist circumference, years of education, sitting systolic blood pressure, fasting serum cholesterol and smoking status.

* Asterisks indicate the regions hypothesized to differ with age.