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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 T 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 ($n = 45$, $p \leq 0.001$) 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 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.

1. 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 (McCrimmon, Ryan, & Frier, 2012; van Harten, De Leeuw, Weinstein, Scheltens, & Biessels, 2006). With better therapies and increased longevity in T1D, there is a marked increase in the number of adults with T1D who are aging (Diabetes Atlas, 2007; Pambianco et al., 2006) 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 (Pell, Lin, Wellard, et al., 2012). 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 (Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003; Ziegler et al., 2012) although there is a very high degree of individual variability in both rate and degree of change over time (Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010). Similar relationships between increasing age and decreasing gray matter volume have also been reported in several subcortical structures, including the putamen,

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thalamus, nucleus accumbens and hippocampus (Goodro, Sameti, Patenaude, & Fein, 2012; Walhovd, Westlye, Amlien, et al., 2011).

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 (Musen, Lyoo, Sparks, et al., 2006) studied 82 young adults (mean age = 32 years) with a childhood-onset of diabetes and found ~ 5% less gray matter volume (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 (Wessels, Simsek, Remijnse, et al., 2006)) or nonexistent (Brands, Kessels, Biessels, et al., 2006). 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 (Pell et al., 2012). 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.

2. Methods

2.1. 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 (Orchard et al., 1990a,b). 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 (Gianaros, Onyewuenyi, Sheu, Christie, & Critchley, 2012). 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.

2.2. 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 3 T Siemens Tim Trio MR scanner using identical protocols. Details on the protocol of acquisition are described in greater detail elsewhere (Venkatraman, Aizenstein, Newman, et al., 2011). 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.

2.3. Automated Labeling Pathway (ALP) technique

The automated labeling technique delimitated forty-five regions of interest defined by the Montreal Neurological Institute (MNI) labeled single-subject high-resolution anatomical brain template (Tzourio-Mazoyer, Landeau, Papathanassiou, et al., 2002). A series of automated nonlinear warpings of the brain template was 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" (Jenkinson, Pechaud, & Smith, 2005) and was used to account for head size differences between subjects. GM atrophy was calculated as the ratio of GMV/ICV, with smaller values indicating more GM atrophy.

2.4. Regions of interest

Among the forty-five anatomically-defined brain regions of interest (Tzourio-Mazoyer et al., 2002), 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.

2.5. Laboratory and clinical measures

Waist circumference in centimeters, height in centimeters, weight in kilograms, blood pressure, glucose, creatinine, albumin and lipids were measured at time of MRI. Blood pressure was measured with a random zero sphygmomanometer after a five minute rest (Hypertension Detection and Follow-Up Program Cooperative Group, 1976) and hypertension was defined as blood pressure ≥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) (Warnick & Albers, 1978), cholesterol and triglycerides (Bucolo & David, 1973). 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®