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Age of Childhood Onset in Type 1 Diabetes and Functional Brain Connectivity in Midlife

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Abstract

Objective—The development of type 1 diabetes (T1DM) within the first 7 years of life has been linked to poorer cognitive performance. Adults with T1DM have altered functional brain connectivity, but no studies have examined whether earlier age of T1DM onset is associated with functional connectivity later in life. Accordingly, we tested the relationship between age of onset and resting state functional connectivity in a cohort of middle-aged adults with childhood-onset T1DM.

Methods—Subjects were from a subsample of the Pittsburgh Epidemiology of Diabetes Complications cohort and included 66 adults (mean age = 47.54 years; 32 Male). Resting state blood oxygen level dependent activity was used to calculate mean connectivity for eight functional brain networks. A multivariate analysis of variance examined associations between age of onset and network connectivity. Diffusion tensor and fluid attenuated inversion recovery images were analyzed to identify microstructural alterations and white matter hyperintensity volumes.

Results—Later childhood onset of T1DM was associated with lower connectivity ($F(8,57) = 2.40, p = .026$). A significant interaction was present for current age such that an inverse association with age of onset for functional connectivity was present in older individuals ($F(8,55) = 2.88, p = .035$). Lower connectivity was associated with older age, increased white matter hyperintensity volume, and lower microstructural integrity.

Conclusions—Diagnosis of T1DM later in childhood may be associated with lower brain functional connectivity, particularly in those surviving into older ages. These alterations may be an

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Conflicts of Interest:

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early marker for subsequent cognitive decrements. Future studies are warranted to understand the pathways underlying these associations.

Keywords

brain; magnetic resonance imaging; type 1 diabetes; diffusion tensor imaging

Introduction

Mild cognitive dysfunction is a common complication of type 1 diabetes (T1DM)(1). Because the metabolic dysregulation associated with T1DM may disrupt normal brain development (2–4), it is not surprising to find evidence of neurocognitive changes in people who develop T1DM in childhood and adolescence, a period when the brain is undergoing dramatic developmental changes (5). A large literature has demonstrated that an earlier age of onset is related to poorer cognitive outcomes, and additional studies have identified relationships between earlier age of onset and microstructural white matter abnormalities in children and young adults (6). What remains unknown is if the associations between age of onset of T1DM in childhood correlate with brain connectivity later in life, particularly for those patients in the fifth and sixth decades of life. For these adults, the brain is not only exposed to the comorbidities of the disease but also the effects of chronological age.

To date, the single study to explicitly examine the relationship between age of onset and the brain focused on young adults. Earlier age of onset (defined as < 7 years of age) was associated with increased lateral ventricular volume, as well as poorer performance on measures of psychomotor speed and reasoning (7). Given their use of a less sensitive methodology, it was not possible to identify subtle changes in neuronal integrity or possible alterations in functional connectivity. Moreover, the outcome was measured closer in time to the time of diagnosis, a time when the effects of chronological age on brain integrity are less apparent. A goal of the present study was to investigate potential differences in functional brain connectivity later in life and to relate these measures to more sensitive measures of structural integrity.

Functional connectivity is a methodology that quantifies the functional associations between brain regions. When the brain is at rest (i.e. not performing an experimental task), brain activity exhibits low frequency fluctuations (8,9). These fluctuations can be correlated across brain regions to identify intrinsic connectivity networks (ICNs)(10). The identification of ICNs can be data-driven, as is done in independent component analysis, or based on regions of interest that have been mapped in previous studies. A recent study utilizing 90 functionally-defined regions of interest identified 14 ICNs that corresponded to a variety of brain functions (11). Regardless of methodology, there are several well-validated and studied ICNs. These include the salience network, involved in the monitoring of homeostasis and autonomic functioning, the default mode network, a system that tends to be more active in the absence of external stimulation, and the executive control network, involved in cognitive control processes and working memory function (12). Although the physiology underlying ICNs is not completely understood, there is evidence for structural connectivity that underlies ICNs – particularly in the resting state (13,14).

A growing literature has begun to identify alterations in functional connectivity in individuals with T1DM. A consistent finding across these studies is that individuals with T1DM and comorbid proliferative retinopathy (a marker of microvascular damage) show decreases in functional connectivity relative to individuals with T1DM without retinopathy or age-matched healthy control participants (15). In the first study to examine ICNs using fMRI, reductions in ICN strength were localized to networks involved in attention, language and working memory. Relative to healthy controls, T1DM participants without microvascular complications had increased connectivity in sensorimotor and visual networks (16). A subsequent study using magnetoencephalography replicated these findings: participants with T1DM accompanied by microvascular complications had lower connectivity in the default mode, executive control, and sensorimotor networks relative to controls, as well as to T1DM participants without microvascular complications (17). Although the networks altered in association with T1DM have varied slightly across studies, the overall findings suggest that ICNs are altered in T1DM.

Diffusion tensor imaging (DTI) offers additional information about the microstructural architecture within the gray and white matter of the brain. Fractional anisotropy (FA) is a measurement of white matter structural organization (18), whereas mean diffusivity (MD) measures the magnitude of water diffusion, a marker of gray matter integrity (19,20). Early in life, there are well-documented increases in FA and decreases in MD in the white matter that coincide with brain development (21). Later in life, declines in FA are associated with progression of aging in healthy populations (22). Alterations in FA have been seen in patients with T1DM (23,24), and alterations in MD have been associated with diabetes complications (25). Thus, in addition to functional ICN strength, measures of FA and MD can provide additional information on the structural alterations that may coincide with altered ICN activity.

The goal of the present study was to identify associations between age of onset of T1DM and functional connectivity in adults. To investigate the relationship between age of onset and ICNs, we selected 8 networks identified by previous studies that have shown alterations in T1DM, or are commonly studied in cognition: dorsal and ventral default mode, right and left executive control, anterior and posterior salience, sensorimotor, and visuospatial. To further understand the significance of any connectivity findings, whole brain DTI parameters were evaluated. Given the literature documenting the relationship between early age of onset and impaired cognitive performance, we hypothesized that subjects who developed diabetes within the first several years of life would be more likely to show lower brain connectivity, particularly in networks that undergo maturational changes during the developmental periods of childhood and adolescence.

Methods

Participants

Participants included individuals recruited from the Epidemiology of Diabetes Complications study at the University of Pittsburgh. The cohort includes adults with childhood age of onset (< 17 years) who were seen at Children's Hospital of Pittsburgh within one year of diagnosis. Initial clinical assessments occurred in 1986–1988,

culminating in a 24-year follow up that included 263 adults. All available participants were invited to participate in a neuroimaging study. Of the 149 who volunteered to participate, 112 were MRI-eligible with N=82 providing resting blood oxygen level dependent (BOLD) data. Imaging data were collected between December 2010 and January 2013. A recent study of this cohort found that individuals diagnosed with diabetes prior to January 1, 1965 have a significantly greater risk of mortality (26). Eleven participants in the current study were diagnosed prior to that date and were thus excluded to reduce potential survivor biases. All research procedures were approved by the University of Pittsburgh Institutional Review Board and all participants provided informed consent prior to participation.

Clinical Measurements

Plasma blood glucose and HbA1c were obtained on the day of the MRI. Blood pressure was measured via three seated readings taken with a random-zero sphygmomanometer, with an average of the last two readings used for blood pressure measurements. Height (cm) and weight (kg) were measured to calculate body mass index. A variety of clinical measurements were obtained from previous study visits. Chronically elevated blood glucose levels were assessed with the glycosylated hemoglobin assay (HbA1c); a history of high HbA1c was defined by average HbA1c levels > 7.5% from the 1996–1998 visit to the time of MRI. Estimated glucose disposal rate, a surrogate marker of insulin resistance, was calculated at the 2004–2006 visit (27). Retinopathy was assessed by fundus photography and scored for the presence or absence of proliferative retinopathy (28). The retinopathy variable was dichotomized (0 = no retinopathy or background retinopathy at the 2004–2006 assessment, 1 = proliferative retinopathy or history of laser surgery). Microalbuminuria was defined as an albumin excretion rate of 20–200 µg/min (30–300 mg/24 h)(29). History of high blood pressure and lipid lowering medications were identified via self-report and examination of medical records from time of study entry through the 2004–2006 visit. Participants completed a cognitive assessment including several neuropsychological tests. A description of the tests and relationships to functional connectivity are presented in Table S1, Supplemental Digital Content 1.

Neuroimaging Data Collection and Processing

Neuroimaging data were acquired on a 3T Trio TIM whole-body scanner (Siemens), equipped with a 12-channel, phased-array head coil. Functional images (described below) were coregistered and normalized to Montreal Neurological Institute space via a T1-weighted three-dimensional magnetization-prepared rapid gradient echo anatomical image (MPRAGE, field of view: 256 × 224 mm (256 × 224 matrix); repetition time: 2300 msec; inversion time: 900 msec; echo time: 3.43 msec; flip angle: 90°, 176 slices; 1 mm thick, no gap).

Resting state images were acquired with a gradient-echo echo planar image sequence (field of view = 768 × 768 mm; 128 × 128 matrix; repetition time = 2 sec; echo time = 34 msec; flip angle = 90°). During scanning, participants' ears were shielded from noise, but they were allowed to keep their eyes open while resting quietly. Twenty-eight sections (3mm thick, no gap) were obtained sequentially, yielding 150 BOLD images. Resting BOLD images were preprocessed using Statistical Parametric Mapping software (SPM8). BOLD

images were slice time corrected, and then realigned to the mean image in the series, co-registered to the MPRAGE, which was segmented and co-registered (both linear and nonlinear) to the normalized Montreal Neurological Institute space using the SPM template. Normalized images were smoothed with an 8-mm full width at half maximum isotropic Gaussian kernel, temporally band-pass filtered (0.009 to 0.08 Hz) and re-sliced to $2 \times 2 \times 2$ mm voxels.

Functional connectivity analyses were performed using CONN toolbox (30), which utilizes a component-based noise correction method (31). Regions of interest were selected from previously defined functional regions of interest defined by an independent components analysis used to identify resting state networks (11). A complete list of regions of interest and maps are available at http://findlab.stanford.edu/functional_ROIs.html. White matter, cerebrospinal fluid and motion parameters were included as covariates and a band pass filter of .008 to .09 Hz was applied. The REX (<http://web.mit.edu/swg/software.htm>) toolbox was used to extract the primary eigenvariate time-series for of each functional region of interest, then bivariate correlations were computed between all regions of interest using CONN. Correlation coefficients were Fisher z-transformed and thus a z-score was obtained for the relationship between all regions of interest. Z-scores were compiled for every participant and divided into relationships between regions within individual networks. The mean connectivity for each network was calculated by taking the mean of the z-scores between regions within each network. Mean network connectivity strength was computed for eight networks: dorsal and ventral default mode, left and right executive control, anterior and posterior salience, visuospatial and sensorimotor. A visualization of the networks is provided in Figure S1, Supplemental Digital Content 2. Some network regions were not included in the analysis due to missing data resulting from either lack of coverage or signal dropout. A list of regions included in each network is available in Table S2, Supplemental Digital Content 3.

White matter hyperintensities (WMH), normalized to total brain volume, were quantified from fluid-attenuated inversion recovery images acquired in the axial plane: repetition time = 9160 ms; echo time = 90 ms; inversion time = 2500 ms; flip angle = 150° ; field of view = 212×256 mm; slice thickness = 3 mm; matrix size = 256×212 ; number of slices = 48 slices; and voxel size = $1 \text{ mm} \times 1 \text{ mm}$. Data were analyzed using an automated segmentation algorithm as described previously (32). An Automated Labeling Pathway was used to calculate whole brain and regional counts of gray matter, white matter and cerebrospinal fluid (32). Intracranial Volume was calculated using the FMRIB Software Library's (<http://fsl.fmrib.ox.ac.uk>) Brain Extraction Tool. Whole brain gray matter was divided by intracranial volume to account for individual differences in brain volume.

Diffusion tensor images were acquired using single-short spin-echo echo planar imaging sequence with the following parameters: repetition time = 5300 ms; echo time = 88 ms; inversion time = 2500 ms; flip angle = 90° ; field of view = $256 \text{ mm} \times 256 \text{ mm}$; two diffusion values of $b = 0$ and 1000 s/mm^2 ; 12 diffusion directions; four repeats; 40 slices; matrix size = 128×128 ; voxel size = $2 \text{ mm} \times 2 \text{ mm}$; slice thickness = 3 mm; and GRAPPA = 2. The diffusion-weighted images were pre-processed using the FMRIB's Diffusion Toolbox (33) to remove unwanted distortions due to eddy current then the tensors were

computed (34) and diagonalized to determine the eigenvalues from which the FA and MD maps were computed (35). The FA map was registered to the FMRIB58_FA template using the FMRIB's non-linear image registration tool (FNIRT) (36), similar to tract-based spatial statistics (37). The transformation was also applied to the MD map. Then, using the segmentation of white matter, gray matter, and white matter hyperintensities that were obtained from the T1-weighted and T2-weighted fluid attenuated inversion recovery images, the FA and MD maps were restricted to normal appearing white and gray matter. Mean FA and mean MD were calculated for normal appearing WM and normal appearing GM. Whole brain values for FA and MD were extracted for each participant. DTI data were unavailable for six participants.

Statistical Methods

Multivariate analysis of variance (MANOVA) was utilized to investigate the relationship between age of onset and composite network connectivity. Due to the high degree of correlation between age of onset and age at the time of MRI scanning ($r = .49$), separate models were run for age, age of onset and duration of disease (age – age of onset). Significant results from the MANOVA were explored via post hoc general linear models that assessed relationships between functional connectivity and the effects of clinical and demographic variables on the model. Separate MANOVAs were conducted to investigate the influence of demographic and clinical characteristics and brain measures (GM atrophy, WMH) on the models. For comparison between functional ICN and structural integrity measures (FA and MD), ICNs that were significant in the original analysis were combined into a composite average and correlated with FA and MD measures. Whole brain atrophy was included as a covariate in analyses involving MD. WMH values were log-transformed to reduce skew inherent in the data. A supplementary data analysis was performed by matching participants on current age and sex and splitting on age of onset (Supplemental Digital Content 4).

Results

Participant Characteristics

A summary of participant demographic and clinical characteristics is displayed in Table 1. Individuals who were excluded were older ($t(116) = 3.94, p < .001$) and had longer duration of disease ($t(116) = 4.38, p < .001$) but were not significantly different from participants in body mass index, age at onset, systolic or diastolic blood pressure. There was no difference in sex between included and excluded participants ($\chi^2(1) = .002, p = .97$).

Age of Disease Onset and ICN Connectivity

Later age of onset was associated with lower functional brain connectivity ($F(8,57) = 2.40, p = .026$, Wilks' $\lambda = .75, \eta^2 = .25$). Neither disease duration ($F(8,57) = 0.88, p = .55$, Wilks' $\lambda = .89, \eta^2 = .11$) nor age at time of MRI visit ($F(8,57) = 1.61, p = .14$, Wilks' $\lambda = .82, \eta^2 = .19$) were predictive of functional connectivity. Examination of the significant age of onset result revealed an age of onset x age at time of MRI interaction ($F(8,55) = 2.28, p = .04$, Wilks' $\lambda = .75, \eta^2 = .25$). To explore this interaction, the data were split into two groups based on median age at time of scanning (47.2 years old). As displayed in Table 2, the

relationship between later age of onset and lower functional brain connectivity was only present for older participants. The interaction term was significant for every network with the exception of the sensorimotor ($p = .11$) and ventral default mode ($p = .12$) networks. The interaction between age of onset and duration of disease was non-significant ($F(8,55) = 1.12, p = .36$, Wilks' $\lambda = .86$, $\eta^2 = .14$).

Influence of Clinical and Demographic Variables on ICN Connectivity

To investigate the potential influence of clinical and demographic factors, these variables were entered as covariates in the MANOVA predicting the eight networks. Results are displayed in Table 3. The main effect of age of onset in predicting lower brain connectivity was marginally reduced, but still trended towards significance. To investigate the moderating effect of age, a model that included age of onset, age, and the age x age of onset interaction term was conducted. Neither age of onset ($F(8,42) = 1.40, p = .23$, Wilks' $\lambda = .79$, $\eta^2 = .21$), age ($F(8,42) = .88, p = .54$, Wilks' $\lambda = .86$, $\eta^2 = .14$) nor the age of onset x age interaction term ($F(8,42) = 1.53, p = .17$, Wilks' $\lambda = .77$, $\eta^2 = .23$) were predictive of network connectivity.

Influence of Atrophy and White Matter Hyperintensities on ICN Connectivity

A separate MANOVA was conducted with age of onset, GM atrophy and whole brain WMH volume predicting ICN connectivity for the eight networks. Age of onset trended toward predicting connectivity ($F(8,50) = 2.02, p = .068$, Wilks' $\lambda = .76$), but atrophy ($p = .23$) and WMH volume ($p = .99$) were not predictive of connectivity. When the age and age x age of onset interaction terms were included in the model, the interaction term was attenuated but continued to trend towards significance ($F(8,48) = 1.94, p = .075$, Wilks' $\lambda = .76$, $\eta^2 = .24$).

Relationships Between ICN Connectivity, and Structural Integrity Measures

The relationship between composite ICN connectivity (the mean of the six networks that exhibited a significant age x age of onset interaction) and FA was investigated using Pearson correlation. Bivariate relationships are displayed in Table 4. There was a positive correlation between ICN connectivity and FA. The relationship between ICN connectivity and whole brain gray matter MD was investigated via partial correlation controlling for individual differences in atrophy. There was a strong negative correlation between ICN connectivity and gray matter MD, $r(57) = -.48, p < .001$. Age of onset was negatively correlated with whole brain FA and positively correlated with gray matter MD, but controlling for age eliminated the associations (FA: $r(57) = -.10, p = .44$; MD: $r(56) = .18, p = .18$). In a multiple regression, after controlling for age and age of onset, the age of onset x age interaction term was not significant for whole brain FA ($F_{change}(1,56) = 1.13, p = .29$), gray matter MD (additionally covarying for atrophy, $F_{change}(1,55) = 1.29, p = .26$), or WMH volume ($F_{change}(1,57) = .09, p = .77$).

Discussion

Individuals with T1DM are living longer (26), but how T1DM interacts with the aging process in the brain is not fully understood. Earlier age of onset of T1DM has been associated with reduced cognition in children and adults, which suggests that an earlier age

of onset would also be associated with reductions in brain connectivity. The aim of the present study was to identify if age of onset of T1DM relates to functional brain connectivity in midlife. Contrary to our hypothesis, we found that later age of onset was associated with lower functional ICN connectivity, and this relationship was moderated by a significant interaction with the age of the participant at the time of the study. That is, the strength of the association between later age at onset and poorer connectivity was weaker for younger participants but stronger in older participants. This relationship was present for six of the eight networks. These findings suggest that individuals with a later age of childhood onset T1DM may be more susceptible to decreases in functional ICN connectivity as they progress in the aging process.

Previous studies have demonstrated that T1DM patients with microvascular complications had decreased functional connectivity compared to patients without microvascular complications (15,16). In the present study, age of onset displayed a unique association with functional connectivity, independent of microvascular status and additional clinical indicators of diabetes comorbidities. These findings slightly diverge from the previous studies, which covaried for age of onset. A potential source of this discrepancy is a difference in the participant sample. The current study utilized a sample drawn from a childhood-onset cohort with age of onset less than 17 years of age who were between 32 and 58 years of age at the time of MRI. Other studies included participants with onset after 17 years of age, as well as individuals as young as 18 at time of assessment, which may limit direct comparisons with our aging sample. Future studies will be necessary to understand the longitudinal dynamics of functional brain activity throughout the lifespan and how alterations are moderated by disease comorbidities, aging, and potential implications for cognitive decline.

Functional connectivity provides information about statistical coupling between brain regions, but does not provide direct information about the neuronal integrity underlying the connections. In order to understand the structural brain integrity underlying the functional connectivity, DTI measures of FA and MD were compared to age of onset and ICN strength. Lower ICN connectivity was associated with lower FA values, indicating poorer white matter integrity, and higher MD values, indicating poorer gray matter integrity. This association replicates previous studies that have found associations between measures of structural integrity and functional connectivity (38,39). Although there were no relationships between age of onset and whole brain FA or MD after covarying for age, it is possible that these effects could be confined to specific white matter tracts or gray matter regions. Recent studies have found that the structural variation in individual networks can help account for individual variations in ICN strength across subjects (40) and future studies utilizing multimodal neuroimaging paradigms can continue to help understand the impact of diseases, such as T1D, on brain structure and function.

The mechanisms underlying the current findings are likely multifactorial. Early childhood, adolescence and late adulthood represent three critical periods for brain development and degeneration (41). The present study is unable to delineate the underlying pathophysiological mechanisms, but the findings are supported by previous literature on brain development in T1DM and brain degeneration in type 2 diabetes as well as other

pathologies of brain aging. It has been suggested that diabetes results in structural compensatory mechanisms in the brain, but this remodeling may draw upon the reserve capacity thereby making the brain more susceptible to later insults (42). Another possibility is that T1DM onset close to puberty is more detrimental than exposure during childhood due to the maturation of connectivity taking place around this time. Secondly, the effects of age of onset on connectivity may become manifest as individuals enter their fifth and sixth decades of life and begin to exhibit effects of the chronological aging process. Longitudinal studies, as well as studies with carefully matched controls, will be necessary to identify the clinical implications of these findings.

During development, the natural history of T1DM likely differs between those with early versus late age of onset, possibly resulting from genetic factors, hormonal changes associated with growth factors, changes in insulin sensitivity associated with puberty, and rates of disease progression (43). Adolescence is a critical time for the establishment of long-range brain connectivity (44) and during the aging process later in life, even in healthy individuals, these connections begin to become less efficient (45). One possible explanation for our finding of later age of onset being associated with lower connectivity is that the onset of T1DM and the associated changes in glycemic control may have coincided with this period. Several studies of children with T1DM have detected differences in regional brain volumes (46–48) and a study of young T1DM patients (< 10 years) found a negative association between age of onset and radial diffusivity, suggesting that earlier age of onset was associated with less myelin integrity (6). We are unaware of any published studies that have investigated functional connectivity in children with T1DM and such studies will be necessary to more fully understand the functional implications of the structural alterations that are being documented.

The present study possesses several strengths including a well-characterized cohort of individuals with T1DM, a multi-modal imaging dataset and the ability to account for a variety of clinical characteristics that may have influenced the findings. There are, however, several limitations that must be considered in the interpretation and consideration of the findings. The current study is cross-sectional and lacked a control group that limits the interpretation as to whether the level of connectivity is stronger or weaker relative to non-T1DM participants. Future longitudinal studies will need to identify any clinical significance of lower connectivity, possibly as a biomarker for future cognitive problems. In order to increase interpretation of the findings, global DTI measures were included, and future studies will need to utilize more specific regional measurements of FA and MD. Finally, individuals with T1DM have a higher mortality risk relative to healthy controls throughout adulthood (49). In the present cohort, a significantly increased risk of mortality has been found in individuals diagnosed prior to 1965 (26). These factors suggest that the older participants in the study may thus reflect a survivor bias. Although we excluded participants diagnosed before 1965, a survivor bias may still remain.

An additional methodological limitation is the use of theory-driven ICN network selection. An assumption of the theory-driven method is that the regions that comprise the networks in T1DM are similar to healthy controls. Given the size of the regions of interest in the present study, as well as the extraction of the principle eigenvariate to characterize the signal of the

region of interest, it is less likely that subtle differences in network composition would bias the findings. One advantage of this method is that it allows reproducibility of the method and regions to other samples, however data driven approaches such as independent components analysis may reveal different results and more fully characterize the composition of the networks that are associated with the variables of interest. Additionally, the use of a mean composite score to represent functional connectivity may have masked subtler sub-network changes. Future studies using smaller network components, as well as dynamic network changes during cognitive tasks may increase our understanding of the brain alterations that occur in T1DM. Two networks – the sensorimotor and ventral default mode network – did not achieve statistical significance, but exhibited a trend in the same direction. It is unclear if the lack of association in these two networks have clinical relevance, but future longitudinal studies, or studies that involve task-evoked changes in ICN activity may provide information to clarify these associations.

There are several clinical implications for the present study. Individuals with T1DM are living longer and it is important to identify predictors of potential future neurological and cognitive problems. Resting state functional connectivity has been associated with cognition (12,50) and disruption of these networks is a common feature of several neurodegenerative diseases(51). Thus, the lower connectivity associated with later age of onset as participants become older may serve as an early marker of upcoming cognitive issues. Additionally, if late age of onset affects functional connectivity later in life, it will be important to identify potential moderators of this association that may provide opportunities for mitigating the effects. The present study found that the age of onset effect strengthened in older individuals, yet the participants in the present study are of relatively “young” older age. Thus it will be essential to continue to follow individuals with T1DM as they proceed through the aging process to understand what additional cognitive and neurological risks T1DM conveys on an aging population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

BOLD	Blood Oxygen Level Dependent
DTI	Diffusion Tensor Imaging
FA	Fractional Anisotropy
fMRI	Functional Magnetic Resonance Imaging

GM	gray matter
ICN	Intrinsic Connectivity Network
MANOVA	Multivariate Analysis of Variance
MD	Mean Diffusivity
MPRAGE	Magnetization-Prepared Rapid Gradient Echo
SPM	Statistical Parametric Mapping
T1DM	Type 1 Diabetes Mellitus
HbA1c	hemoglobin A1c, a 3-month measure of blood glucose levels

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Table 1

Participant Characteristics

Variable	N	M ± SD (Range)
Age (years)	66	45.54 ± 5.9 (32.2 – 58.5)
Age of Onset (years)	66	8.29 ± 4.2 (0.7 – 15.9)
Disease Duration (years)	66	39.26 ± 4.2 (31.5 – 46.5)
Gender	66	32 M/34 F
Years of Education	64	15.06 ± 2.3 (12 – 20)
HbA1c (%)	63	7.45 ± 1.2 (4.9 – 10.1)
Average HbA1c History ^a	66	7.87 ± 1.3 (5.4 – 11.9)
Body Mass Index (kg/m ²)	65	27.22 ± 4.8 (18.3 – 38.9)
Systolic Blood Pressure (mmHg)	63	117.56 ± 15.31 (86 – 146)
Diastolic Blood Pressure (mmHg)	63	65.52 ± 9.6 (40 – 86)
Glucose Before MRI Scan (mg/dL)	64	170.42 ± 79.9 (34 – 379)
Estimated Glucose Disposal Rate (mg/kg/min)	66	7.89 ± 2.52 (1.5 – 12.5)
<i>Medication History</i>		
History of Lipid Lowering Medications (n, %)	66	21 (31.8)
History of Blood Pressure Medications (n, %)	66	19 (28.8)
<i>Diabetes Complications</i>		
Microalbuminuria (n, %)	66	40 (60.6)
Proliferative Retinopathy (n, %)	66	31 (47.0)

^a Average of HbA1c readings at study visits since the 1996–1998 exam.

Table 2Age of Onset Predicting Mean Network Connectivity^a

	Age Below Median		Age Above Median		Interaction	
	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>
Anterior Salience	.17	.36	-.40	.02		.007
Posterior Salience	.05	.79	-.37	.04		.027
Dorsal DMN	-.06	.73	-.42	.01		.004
Ventral DMN	.01	.96	-.26	.15		.11
Left Executive Control	.14	.44	-.36	.04		.006
Right Executive Control	.14	.43	-.39	.02		.001
Sensorimotor	.23	.20	-.21	.23		.12
Visuospatial	.24	.17	-.36	.04		.003

DMN = default mode network; β = Standardized regression coefficient

^aIn the MANOVA, a significant interaction was present for age of onset x age. To explore this interaction, a median split was performed (median age = 47.2 years) and mean network connectivity was regressed on age of onset. Interaction p-values indicate the interaction term value for the full sample age x age of onset term.

Table 3
Association Between Age of Onset and ICN Connectivity Including Clinical Factors as Covariates^a

Variable	Wilks' λ	F	df	Error df	p
Age of Onset	.74	2.12	8	44	.054
HbA1c ^b	.96	.25	8	44	.98
HbA1c History ^c	.94	.33	8	44	.95
EGDR	.87	.82	8	44	.59
Retinopathy	.84	1.02	8	44	.44
Microalbuminuria	.78	1.54	8	44	.17
Lipid Medication	.93	.42	8	44	.91
BP Medication	.80	1.40	8	44	.22
BMI	.85	.94	8	44	.50
Sex	.78	1.51	8	44	.18

EGDR = Estimated glucose disposal rate; BP = Blood pressure; BMI = Body Mass Index

^a MANOVA predicting network connectivity of eight intrinsic connectivity networks while simultaneously covarying clinical factors.

^b HbA1c at time of MRI.

^c Average of HbA1c readings at study visits since the 1996–1998 exam.

Table 4

Pearson Correlations Between Age, Age of Onset and Neuroimaging Variables

	Age of Onset	ICN	WMH ^b	Atrophy	MD ^c	FA ^c
Age	.70***	-.27*	.25	-.16	.48***	-.35**
Onset		-.34**	.33*	-.06	.44**	-.31*
ICN			-.02	.17	-.50*** ^d	.41*** ^d
WMH				-.09	-.01	.00
Atrophy					-.21	.07
MD						-.52**

* p < .05,
** p < .01,
*** p < .001

ICN = Mean connectivity of the six intrinsic connectivity networks that were associated with the age x age of onset interaction term; WMH = log transformed white matter hyperintensity volume; MD = gray matter mean diffusivity; FA = whole brain fractional anisotropy. N = 66 unless otherwise noted.

^b n = 61,
^c n = 60,
^d n = 59