The Relationship of Parental Longevity with the Aging Brain

- Results from UK Biobank

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Abstract:

A few studies report that parental longevity is associated with preserved cognition and physical function and lower risk of Alzheimer's disease. However, data on structural neuroimaging correlates of parental longevity and its spatial distribution are limited. This study aims to examine relationships of parental longevity with regional brain structure and to explore sex differences. We identified 12,970 UK Biobank participants (mean age=64.4, 51.5%women) with data on parental longevity, regional gray matter volumes, and white matter microstructure. Participants were categorized based on whether at least one parent lived to age 85 or older or neither parent survived to age 85. Associations of parental longevity, maternal and paternal longevity with each neuroimaging marker of interest were examined using linear regression, adjusted for demographics, APOE e4 status, lifestyle, and cardiometabolic conditions. Compared to participants whose both parents died before 85 (43%), those with at least one parent surviving to 85 (57%) had greater volumes in hippocampus, parahippocampal gyrus, middle temporal lobe, and primary sensorimotor cortex, and had lower mean diffusivity in posterior thalamic radiation and uncinate fasciculus. Associations were prominent with maternal longevity. Adjustment for cardiometabolic conditions did not affect observed associations except mean diffusivity in posterior thalamic radiation. There were no structural differences in other areas. Parental longevity is associated with preserved brain structure localized in primary sensorimotor cortex and temporal areas including hippocampus. These relationships are prominent with maternal longevity. Longitudinal studies are needed to determine whether changes in these brain structures account for the association between parental longevity and dementia.

Keywords: Parental longevity, neuroimaging, MRI, DTI, brain structure, aging

1. Introduction

Over the past decade, a number of studies demonstrated that parental longevity is associated with better health and survival of offspring, and it was suggested that both genetic and shared environmental factors contribute to such association [1-9]. Recent GWAS studies point to loci associated with parental longevity that play key roles in cellular senescence, inflammation, as well as lipid metabolisms and cardiovascular conditions [10, 11]. Indeed, individuals with long-lived parents are more likely to have more favorable health profiles and healthy aging, such as better lipid profiles, a lower prevalence of cardiovascular disease, hypertension, diabetes, and stroke, compared to those whose parents did not survive to an older age.

A few recent studies have reported that parental longevity is associated with less cognitive decline, lower odds of white matter hyperintensities, and lower risk of Alzheimer's disease [12-15]. However, it is still unclear whether parental longevity predicts cognitive related outcomes in offspring through specific structural and functional brain changes.

Published neuroimaging studies focused on global measures of brain structure, such as white matter hyperintensities and total brain volume, one specific region of interest instead of mapping specific gray matter and white matter areas [15, 16]. Hence, whether structural changes in some areas of the brain gray and white matter are more strongly associated with parental longevity than others remain unanswered. Recent studies suggest that parental longevity is associated with memory, attention, and also physical performance, such as gait speed [13, 15, 17, 18]. These findings raise the possibility that parental longevity is associated with brain structure localized in areas important for memory and motor function, such as the prefrontal cortex and hippocampus of the gray matter and the superior longitudinal fasciculus and uncinate fasciculus of the white matter. Notably, neuroimaging in one of the published studies was performed 1- or 1.5T, and the low resolution of this technology limits the accuracy of regional measures [15]. Also, whether parental longevity is associated with brain microstructure measured by the diffusion tensor imaging (DTI), which may be more sensitive to detect subtle structural changes than conventional MRI imaging, is unknown [19, 20].

One interesting and relatively unexplored question is whether the effect of parental longevity on brain health is different between men and women. One recent study reported that mothers' longevity is associated with a lower risk of dementia while father's longevity is not [21], suggesting possible mechanisms of sex differences in health care and/or a role of maternal transmission of mitochondrial DNA mutations or heteroplasmy.

In this study, we aimed to (1) examine the relationship of parental longevity with neuroimaging markers of brain structure using a multimodal neuroimaging approach, including MRI volumetric measures and microstructural measures by DTI, (2) to determine the spatial distribution of grey and white

matter areas associated with parental longevity, (3) to examine possible contributing factors of nature (APOE genotype), nurture (smoking status, physical activity) and health profile (cardiovascular disease, diabetes, hypertension, white matter hyperintensities) on the relationships between parental longevity and multimodal neuroimaging markers, and (4) to test sex differences.

2. Methods

2.1 Study population

Participants were drawn from UK Biobank (*www.ukbiobank.ac.uk*). The UK Biobank study is a population-based study with baseline assessment of participants between 2006 and 2010 [22]. It includes 503,325 individuals between ages 40–70 years at study entry. A subset of participants are revisiting assessment centers for a brain MRI scan, which began in March 2014. At the time of analysis, 16,141 had data on neuroimaging markers by MRI, and 14,609 had data on neuroimaging markers by DTI. A total of 12,970 had data on MRI and parents' attained age (death or alive). A total of 11,727 had data on DTI and parents' attained age.

The UK Biobank study protocol was approved by the National Research Ethics Service Committee (reference 11/NW/0382). All participants provided written consent. The present study was conducted under the UK Biobank application number 14631.

2.2 Parental longevity

Participants were categorized based on whether at least one parent lived to age 85 or older or neither parent survived to age 85. Participants were also categorized based on their mothers' and father's attained age (death or alive). Maternal longevity was defined when the mother lived to age 85 or older regardless of the father's attained age (death or alive). Paternal longevity was defined when the father lived to age 85 or older regardless of mother's attained age (death or alive).

2.3 MRI Neuroimaging acquisition

Neuroimaging data were collected using a Siemens Skyra 3T running VD13A SP4 (Siemens Skyra, Siemens Healthcare, Erlangen, Germany). Imaging processing and quality control for brain volumes and DTI measures of white matter areas were conducted by the UK Biobank research team (version 1.0; Biobank Pipeline in FMRIB) [23]. Detailed imaging acquisition and quality control are available on the UK Biobank website (Brain Imaging Documentation V1.3; http://www.ukbiobank.ac.uk).

2.4 Imaging parameters

T1-weighted imaging was performed using a three-dimensional magnetization-prepared rapid acquisition with gradient echo (MP-RAGE) sequence. The sequence parameters were as follows: voxel: 1.0 × 1.0 × 1.0 mm; field of view: 208 × 256 × 256 matrix; inversion time: 880 msec; repetition time: 2000 msec.

T2-weighted fluid-attenuated inversion recovery scans were obtained using a 3-dimensional SPACE sequence. The sequence parameters were as follows: voxel: 1.05 × 1.0 × 1.0 mm; field of view: 192 × 256 × 256 matrix; inversion time: 1800 msec; repetition time: 5000 ms.

An echo-planar, single-shot Stejskal-Tanner pulse sequence (echo time: 92 msec) was applied to obtain 36 sections (voxel: 2.0 × 2.0 × 2.0 mm; field of view: 104 × 104 × 72 matrix) in 50 distinct diffusion-weighted directions (b values = 1000 and 2000 sec/mm^2). Eigenvectors, eigenvalues, and FA were calculated by feeding the b value of 1000 sec/mm^2 shell into the DTI fitting tool (DTIFIT version 2.0; the FSL diffusion tensor fitting program, FMRIB), which generated fractional anisotropy (FA) and mean diffusivity (MD) outputs. Weighted tract-averaged FA and MD values were obtained for the association, commissural, and projection fibers.

2.5 Regions of interest (ROIs)

Gray matter ROIs included selected frontal (superior, inferior, middle frontal gyri, supplementary motor cortex, precentral gyrus), parietal (postcentral gyrus, precuneus, superior parietal lobe), temporal (parahippocampal gyrus, middle temporal gyrus, inferior temporal gyrus), and subcortical areas (hippocampus, putamen, caudate, thalamus).

White matter ROIs included association tracts (anterior, superior, and posterior thalamic radiations) and projection tracts (superior longitudinal fasciculus, uncinate fasciculus, cingulate part of the cingulum, parahippocampal part of the cingulum, inferior fronto-occipital fasciculus, and inferior longitudinal fasciculus).

2.6 Other factors of interest

We were interested in whether factors of APOE e4 genotype, lifestyle and health profile contributed to the relationships of parental longevity and neuroimaging markers. Lifestyle at the time of the MRI assessment included smoking status by self-report and physical activity by the International Physical Activity Questionnaires [24].

Prevalent diseases at the time of MRI assessment included a history of myocardial infarction (MI), hypertension, type 2 diabetes, and stroke. Diagnoses were identified by self-report of pre-existing diseases at baseline and from linked medical records to hospital inpatient data (hospital episode statistics) from baseline to the date of the MRI assessment. Hospital data were coded according to the International Classification of Diseases 10th revisions (ICD-10) using the following codes: MI (I20-I25), hypertension (I10-I15), type 2 diabetes (E11) and stroke (G45-G46; I61; I63). Total white matter hyperintensity volume by MRI is often considered as a surrogate marker of cerebral small vessel disease [25].

2.7 Statistical analysis

To examine the relationship between parental longevity and each neuroimaging marker of interest, we used linear regression with parental longevity category being the independent variable and each neuroimaging marker of interest being the dependent variable.

We first adjusted for age, sex, ethnicity (white and non-white), and education. To examine possible contributing factors of nature, nurture, and health profile on these relationships, we additionally adjusted for APOE e4 status, smoking status, physical activity, the prevalence of MI, hypertension, type 2 diabetes, stroke, and total white matter hyperintensity volume.

To test sex differences, we examined the relationships of maternal and paternal longevity with neuroimaging markers that were significantly associated with combined parental longevity using linear regression, adjusted for age, sex, ethnicity, education, and APOE e4 status.

In this exploratory analysis, all results were reported. With multiple neuroimaging markers of interest being examined in a relatively large sample, we set significance at $p < 0.005$. All statistical analyses were performed using SAS v9.4 (SAS Institute, Inc., Cary, NC).

3. Results

Compared to participants whose both parents died before 85 (43%), those with at least one parent surviving to 85 (57%) were more likely to have greater education, less likely to have prevalent MI, type 2 diabetes, stroke, and hypertension, and less likely to be current smokers, in low physical activity category, and APOE e4 carriers (Table 1).

Compared to participants whose both parents died before 85, those with at least one parent surviving to 85 had significantly greater volumes in the precentral gyrus, postcentral gyrus, hippocampus, parahippocampal gyrus, and middle temporal gyrus after adjustment for age, sex, ethnicity, and education (Table 2, Model 1). Associations remained largely unchanged after further adjustment for APOE e4, smoking status, physical activity, history of MI, hypertension, type 2 diabetes, stroke, and total white matter hyperintensity volume (Table 2, Model 2-4). Volumes in other ROIs, including inferior, superior, and middle frontal gyri, precuneus, superior parietal lobe, inferior temporal lobe, putamen, caudate, and thalamus, were not statistically different between those whose both parents died before 85 and those with at least one parent surviving to 85 (Table 2).

Compared to participants whose both parents died before 85, those with at least one parent surviving to 85 had lower MD in posterior thalamic radiation and uncinate fasciculus, after adjustment for age, sex, ethnicity, education, APOE e4, smoking status, and physical activity (Table 3, Model 1-3). Additional adjustment for health profile, including a history of MI, hypertension, type 2 diabetes, stroke, and total white matter hyperintensity volume, a surrogate marker of cerebral small vessel disease, did not affect the association with MD in the uncinate fasciculus but attenuated the association with MD in the posterior thalamic radiation (Table 3, Model 4). The associations of parental longevity with MD in the

anterior and superior thalamic radiations were marginally significant (Table 3, Model 1; p=0.005 and p=0.006, respectively). DTI measures in other white matter ROIs were not statistically different between those whose both parents died before 85 and those with at least one parent surviving to 85 (Table 3).

Neuroimaging markers that were significantly associated with the combined parental longevity remained similarly associated with maternal longevity, while some associations with paternal longevity were attenuated (Table 4). However, associations of neuroimaging markers important for memory, including volumes of the hippocampus and parahippocampal gyrus, remained statistically significant with both maternal and paternal longevity (Table 4).

4. Discussion

In this cross-sectional study that included information on parental longevity in more than 12,000 adults who underwent a brain MRI scan demonstrates for the first time that parental longevity is associated with preserved brain structure localized in areas important for memory and motor function, both on a macro- and microstructural level. These associations are robust albeit moderate, especially for memory-related areas, independent of demographics, APOE e4 status, lifestyle factors, and health profile. Interestingly, the effect of maternal longevity on brain structural integrity appears to stronger than paternal longevity for some specific areas.

Our work lays a foundation for parental longevity being linked to brain aging and the development of neurodegenerative diseases. We advanced prior knowledge by examining multiple brain areas of interest that are important for cognition and sensorimotor function, by examining volumetric measures of gray matter and microstructural integrity of white matter, and by accounting for potential contributing factors of brain health. The strong associations with parental longevity are localized in the primary sensorimotor cortex and selected temporal area including the hippocampus, parahippocampal gyrus, and uncinate fasciculus, suggesting a specific pattern of “inheritance” for the brain. These findings confirm early reports suggesting that parental longevity is associated with preserved cognition and physical performance [13, 15, 17, 18].

Previous research on parental longevity and brain health has mostly focused on global white matter, such as total white matter volume or total white matter hyperintensity volume, while regional white matter microstructural abnormalities were not addressed. We filled in this gap in knowledge by examining specific white matter tracts using two metrics, FA and MD. Previous research has suggested that the use of a combination of DTI metrics may advance the understanding of tissue pathology [26]. FA describes the directionality of the white matter tracts, and MD quantifies the diffusion magnitude of water molecules within tracts. Several conditions may lead to increased MD, such as increased water tissue, inflammation, and necrosis, [26]. We observed the associations were present in MD and not in FA, which

may indicate parental longevity may protect against inflammation and cell necrosis in the central nervous system.

Of multiple white matter tracts examined in this study, parental longevity may be specifically associated with the uncinate fasciculus and projection tracts connecting the thalamus to cortical gray matter areas, where the primary sensorimotor cortex and middle and medial temporal lobes are located. Specifically, the posterior thalamic radiation runs between the caudal part of the thalamus and parietal and occipital lobes. The superior thalamic radiation runs between the ventral part of the thalamus and the primary sensorimotor cortex. The anterior thalamic radiation connects the anterior and middle portions of the thalamus with the frontal lobe [27]. The uncinate fasciculus is localized in the anterior portion of the temporal lobe and also links to the frontal lobe. Notably, associations with these DTI markers except the uncinate fasciculus MD were attenuated after additional adjustment for cardiometabolic conditions, such as a history of MI, hypertension, diabetes, stroke, and white matter hyperintensities which were considered vascular origin. Because cardiovascular burden has been associated with low white matter microstructural integrity and structural decline [28-33], these cardiometabolic conditions may account for some of the observed associations. It is also possible that cardiometabolic conditions are shared causal pathways underlying parental longevity and brain aging.

Another interesting finding is that these neuroimaging correlates are more prominent with maternal longevity than those with parental longevity. Limited data have shown that maternal longevity, but not paternal longevity, predicts a lower risk of dementia. Possible mechanisms, including maternal inheritance of mitochondrial DNA mutations and/or heteroplasmy, were proposed but not yet investigated. One recent study has reported a significant association of mitochondrial DNA copy number between centenaries and their offspring, suggesting a higher mitochondrial DNA copy number is likely inheritable [34]. Future studies are warranted to confirm sex differences in the relationship of parental longevity with brain structure and investigate underlying mechanisms. It is important to note that neuroimaging markers localized in the temporal lobe, including volumes of the hippocampus and parahippocampal gyrus, remained significant with paternal longevity. We also note that there may be a potential power issue as the longevity is not the same for both parents (maternal longevity 43%; parental longevity 26%). However, given that associations were similar in some areas and different in other areas, the observed sex differences may not be due to the power.

This study has limitations. The cross-sectional design does not imply any causation. Although setting the significance level at $p < 0.005$ to correct for multiple testing reduced the chance of false-positive findings, we may have missed some associations. UK Biobank participants tend to be healthier than the general population at study entry [35]. This study has several strengths. A comprehensive examination of both gray matter and white matter allows us to determine the spatial distribution with

parental longevity. Both FA and MD metrics provide rich information on white matter microstructural integrity. This study has a large imaging sample which provides good statistical power. The wealth of other factors, such as genotype, lifestyle, and health conditions, allows us to investigate the strength of these relationships.

5. Conclusions

Parental longevity is associated with preserved brain structure with a specific spatial distribution in the primary sensorimotor cortex and the temporal lobe including the hippocampus and parahippocampal gyrus. Observed relationships are robust, independent of demographics, APOE e4 genotype, lifestyle, and cardiometabolic conditions, while associations with white matter microstructure are attenuated by cardiometabolic conditions. Maternal longevity may be more strongly associated with brain structure than paternal longevity. Whether parental longevity predicts brain aging and whether sex differences exist warrant further investigations.

Declarations:

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Conflict of Interest: None declared.

Availability of data and material: Upon request

Code availability: Upon request

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Table 1. Sample characteristics at the time of brain MRI (n=12,970)

	Participants whose both parents died before 85 (n=5,610)	Participants with at least one parent surviving to 85 (n=7,360)
	Mean (standard deviation) or N (%)	
Demographics		
Age, years	64.6 (6.8)	64.4 (6.4)
Women	2,808 (50%)	3,874 (53%)
White	5,471 (97.5%)	7,206 (97.9%)
Body mass index, kg/m2	27.0 (4.5)	26.3 (4.3)
>High school education	3,212 (57%)	4,866 (66%)
Health-related conditions		
Prevalent MI	439 (7.8%)	359 (4.9%)
Prevalent stroke	115 (2.1%)	112 (1.5%)
Prevalent type 2 diabetes	241 (4.3%)	222 (3.0%)
Prevalent hypertension	1,979 (35.3%)	1,957 (26.6%)
Lifestyle		
Current smokers	211 (3.8%)	240 (3.3%)
IPAQ, MET per week	2,956 (2,723)	2,887 (2,545)
Low physical activity category	529 (9.4%)	655 (8.9%)
Genotype		
APOE e4 carriers	1,411 (25.2%)	1,678 (22.8%)
Global neuroimaging marker		
Total brain volume (normalized by head size), cm3	1,492 (71)	1495 (70)
Total white matter hyperintensity volume, cm^3	5.3 (6.2)	4.9 (6.1)

Note. IPAQ=International Physical Activity Questionnaire. MET=metabolic equivalent.

Table 2. Associations between parental longevity and regional gray matter volumes.

		Model 1: adjusted for age, sex, ethnicity, education, and total brain volume	Model 2: model 1+ nature (APOE e4)	Model 3: model 1 + nurture (smoking, PA)	Model 4: Model 1+ health profile (MI, hypertension, diabetes, stroke, and WMH)
		Standardized beta (p-value)			
Frontal	**Superior frontal gyrus**	0.012 (0.146)	0.012 (0.153)	0.012 (0.151)	0.010 (0.207)
	Inferior frontal gyrus	0.010 (0.231)	0.010 (0.231)	0.010 (0.232)	0.008 (0.323)
	Middle frontal gyrus	0.024 (0.019)	0.019 (0.023)	0.018 (0.025)	0.020 (0.016)
	Supplementary motor cortex	0.011 (0.204)	0.011 (0.191)	0.010 (0.216)	0.008 (0.369)
	Precentral gyrus	*0.027 (0.0006)*	*0.027 (0.0005)*	*0.027 (0.0007)*	0.022 (0.006)
Parietal	**Postcentral gyrus**	*0.031 (0.0001)*	*0.031 (0.0001)*	*0.031 (0.0002)*	*0.025 (0.002)*
	Precuneus	0.012 (0.128)	0.012 (0.112)	0.012 (0.133)	0.012 (0.113)
	Superior parietal lobe	0.012 (0.149)	0.012 (0.151)	0.012 (0.153)	0.010 (0.234)
Temporal	**Interior temporal gyrus**	0.015 (0.058)	0.014 (0.060)	0.014 (0.062)	0.013 (0.083)
	Middle temporal gyrus	*0.036 (5.14E-06)*	*0.036 (4.93E-06)*	*0.036 (5.34E-06)*	*0.032 (4.56E-05)*
	Parahippocampal gyrus	*0.034 (1.10E-05)*	*0.033 (1.27E-05)*	*0.033 (1.25E-05)*	*0.030 (0.0001)*
Subcortical	**Hippocampus**	*0.031 (8.42E-05)*	*0.031 (9.35E-05)*	*0.031 (9.66E-05)*	*0.028 (0.0003)*
	Putamen	0.004 (0.640)	0.004 (0.625)	0.004 (0.667)	0.008 (0.362)
	Caudate	-0.011 (0.182)	-0.011 (0.190)	-0.011 (0.189)	0.002 (0.790)
	Thalamus	0.008 (0.332)	0.008 (0.363)	0.008 (0.329)	0.011 (0.183)

Note. The italic number indicates significant associations at p<0.005. PA=physical activity. WMH=white matter hyperintensity.

Table 3. Associations between parental longevity and DTI measures of white matter regions of interest.

		Model 1: adjusted for age, sex, ethnicity, and education	Model 2: model 1+ nature (APOE e4)	Model 3: model 1 + nurture (smoking, PA)	Model 4: Model 1+ health profile (MI, hypertension, diabetes, stroke, and WMH)
		Weighted mean FA (higher=better) Standardized beta (p-value)			
Projection tracts	**Anterior thalamic radiation**	0.010 (0.258)	0.010 (0.267)	0.010 (0.269)	-0.001 (0.895)
	Superior thalamic radiation	0.009 (0.300)	0.010 (0.283)	0.009 (0.303)	0.005 (0.563)
	Posterior thalamic radiation	0.019 (0.040)	0.018 (0.046)	0.018 (0.043)	0.006 (0.463)
Association tracts	**Superior longitudinal fasciculus**	0.018 (0.045)	0.018 (0.053)	0.018 (0.046)	0.007 (0.441)
	Uncinate fasciculus	0.023 (0.013)	0.023 (0.012)	0.022 (0.013)	0.017 (0.059)
	Inferior fronto-occipital fasciculus	0.013 (0.140)	0.013 (0.149)	0.013 (0.146)	0.003 (0.732)
	Inferior longitudinal fasciculus	0.024 (0.007)	0.024 (0.008)	0.024 (0.007)	0.015 (0.088)
	Cingulate part of the cingulum	0.005 (0.566)	0.005 (0.568)	0.005 (0.577)	0.001 (0.925)
	Parahippocampal part of cingulum	-0.005 (0.595)	-0.005 (0.557)	-0.005 (0.591)	-0.008 (0.393)
		Weighted mean MD (lower=better) Standardized beta (p-value)			
Projection tracts	**Anterior thalamic radiation**	-0.023 (0.005)	-0.023 (0.006)	-0.023 (0.006)	-0.009 (0.211)
	Superior thalamic radiation	-0.024 (0.006)	-0.024 (0.006)	-0.024 (0.007)	-0.011 (0.175)
	Posterior thalamic radiation	*-0.025 (0.0042)*	*-0.024 (0.005)*	*-0.025 (0.0047)*	-0.014 (0.084)
Association tracts	**Superior longitudinal fasciculus**	-0.019 (0.035)	-0.018 (0.040)	-0.018 (0.037)	-0.004 (0.602)
	Uncinate fasciculus	*-0.033 (0.0002)*	*-0.033 (0.0002)*	*-0.033 (0.0002)*	*-0.026 (0.0031)*
	Inferior fronto-occipital fasciculus	-0.015 (0.085)	-0.015 (0.093)	-0.015 (0.089)	-0.004 (0.614)
	Inferior longitudinal fasciculus	-0.018 (0.048)	-0.017 (0.056)	-0.017 (0.0499)	-0.008 (0.353)
	Cingulate part of the cingulum	-0.009 (0.325)	-0.009 (0.344)	-0.009 (0.333)	-0.002 (0.856)
	Parahippocampal part of cingulum	0.005 (0.588)	0.005 (0.591)	0.005 (0.566)	0.009 (0.324)

Note. The italic number indicates significant associations at p<0.005. PA=physical activity. WMH=white matter hyperintensity.

Table 4. Associations of maternal and paternal longevity with neuroimaging markers that were associated with combined parental longevity.

		Maternal longevity	Paternal longevity
		Standardized beta (p-value)	
Gray matter volume (higher=better)	**Precentral gyrus**	*0.025 (0.0017)*	0.008 (0.321)
	Postcentral gyrus	*0.029 (0.0005)*	0.009 (0.267)
	Hippocampus	*0.028 (0.0004)*	*0.023 (0.004)*
	Parahippocampal gyrus	*0.027 (0.0004)*	*0.025 (0.0013)*
	Middle temporal gyrus	*0.033 (1.14E-05)*	0.019 (0.0156)
White matter mean diffusivity (lower=better)	**Anterior thalamic radiation**	*-0.026 (0.0020)*	-0.016 (0.0643)
	Superior thalamic radiation	*-0.026 (0.0029)*	-0.013 (0.141)
	Posterior thalamic radiation	*-0.027 (0.0022)*	-0.017 (0.057)
	Uncinate fasciculus	*-0.040 (5.83E-06)*	-0.023 (0.010)

Note. All models were adjusted for age, sex, ethnicity, education, and APOE e4. For regional gray matter volume, models were additionally adjusted for total brain volume (normalized to head size). The italic number indicates significant associations at $p<0.005$.