Neuronal fiber bundle lengths in healthy adult carriers of the ApoE4 allele: A quantitative tractography DTI study

Lauren E. Salminen,
Department of Psychology, University of Missouri–Saint Louis, 1 University Boulevard, Stadler Hall 442 B, Saint Louis, MO 63121, USA

Peter R. Schofield,
Neuroscience Research Australia, Sydney, NSW 2031, Australia. School of Medical Sciences, University of New South Wales, Sydney, NSW 2052, Australia

Elizabeth M. Lane,
Vanderbilt University Medical Center, 1211 Medical Center Drive, Nashville, TN 37232, USA

Jodi M. Heaps,
Department of Psychology, University of Missouri–Saint Louis, 1 University Boulevard, Stadler Hall 442 B, Saint Louis, MO 63121, USA

Kerrie D. Pierce,
Neuroscience Research Australia, Sydney, NSW 2031, Australia

Ryan Cabeen,
Computer Science Department, Brown University, Providence, RI 02912, USA

David H. Laidlaw,
Computer Science Department, Brown University, Providence, RI 02912, USA

Erbil Akbudak,
Mallinckrodt Institute of Radiology, Washington University School of Medicine, 510 S. Kingshighway, St. Louis, MO 63110, USA

Thomas E. Conturo,
Mallinckrodt Institute of Radiology, Washington University School of Medicine, 510 S. Kingshighway, St. Louis, MO 63110, USA

Stephen Correia, and
Alpert Medical School, Department of Psychiatry & Human Behavior, Brown University, Box G-A, Providence, RI 02912, USA

Robert H. Paul
Department of Psychology, University of Missouri–Saint Louis, 1 University Boulevard, Stadler Hall 442 B, Saint Louis, MO 63121, USA

Lauren E. Salminen: LSalminen@mail.umsl.edu

Abstract

The epsilon 4 (e4) isoform of apolipoprotein E (ApoE) is a known genetic risk factor for suboptimal brain health. Morphometry studies of brains with Alzheimer's disease have reported

significant alterations in temporal lobe brain structure of e4 carriers, yet it remains unclear if the presence of an e4 allele is associated with alterations in the microstructure of white matter fiber bundles in healthy populations. The present study used quantitative tractography based on diffusion tensor imaging (qtDTI) to examine the influence of the e4 allele on temporal lobe fiber bundle lengths (FBLs) in 64 healthy older adults with at least one e4 allele (carriers, N=23) versus no e4 allele (non-carriers, N=41). Subtests from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) were also analyzed to examine memory performance between groups. Analyses revealed shorter FBLs in the left uncinate fasciculus (UF) (p=.038) of e4 carriers compared to non-carriers. By contrast, neither FBLs specific to the temporal lobe nor memory performances differed significantly between groups. Increased age correlated significantly with shorter FBL in the temporal lobe and UF, and with decreased performance on tests of memory. This is the first study to utilize qtDTI to examine relationships between FBL and ApoE genotype. Results suggest that FBL in the UF is influenced by the presence of an ApoE e4 allele (ApoE4) in healthy older adults. Temporal lobe FBLs, however, are more vulnerable to aging than the presence of an e4 allele.

Keywords

Introduction

Apolipoprotein E (ApoE) is a lipid-transport glycoprotein located on chromosome 19 (Nagy et al. 1995). Of the three major isoforms, the e4 allele is associated with the risk for late-onset Alzheimer's disease (AD; Nagy et al. 1995). Although the functional impact of the e4 allele on the brain is not fully understood, this allele is believed to influence the buildup of amyloid plaques and neurofibrillary tangles (Pirttila et al. 1997). Additionally, the e4 isoform influences tau phosphorylation and disrupts the neuronal cytoskeleton, leading to axon degeneration and gliosis (Adalbert et al. 2007). In studies of healthy adults, the e4 allele has been associated with enhanced beta-amyloid deposition and tau protein levels, which may explain the increased risk of AD associated with this genotype (Glodzik-Sobanska et al. 2009).

A number of neuroimaging studies have been conducted to determine the extent of morphometric abnormalities among carriers of the e4 allele. Among e4 carriers with AD, region of interest (ROI) studies demonstrate enhanced atrophy of the hippocampus and amygdala, as well as overall temporal lobe volume (Honea et al. 2009). Additionally, elderly adults with an e4 allele exhibit cognitive impairment on neuropsychological assessments (Packard et al. 2007) and steeper rate of cognitive decline relative to elderly non-e4 carriers (Dik et al. 2001; Wilson et al. 2002).

Diffusion tensor imaging (DTI) studies of healthy older adults have also indicated significant white matter aberration in individuals possessing the e4 allele. Studies have reported decreased fractional anisotropy (FA) in parahippocampal white matter (Honea et al. 2009; Nierenberg et al. 2005), posterior corpus callosum, occipitofrontal fasciculus, and hippocampus of healthy e4 carriers (Persson et al. 2006). Tract-based spatial statistics have revealed increased mean diffusivity (MD) in regions including the cingulum bundle and corpus callosum of these individuals (Heise et al. 2011). Changes in these tracts indicate increased fiber degeneration in the presence of the e4 allele, likely from axonal membrane disruption or myelin loss (Taoka et al. 2006). Moreover, white matter abnormalities in e4 carriers may be tract specific, particularly in fiber bundles within the temporal stem.

Damage to white matter within the temporal stem has been linked to neurological disorders including amnesia and AD (Kier et al. 2004), yet the direct mechanism of pathology is largely unknown. However, DTI and pathway selection techniques have indicated that the course of neuropathology may vary between specific white matter pathways within this ROI (Kier et al. 2004). Of particular interest, damage to the uncinate fasciculus (UF) has been associated with severe memory impairment and post-traumatic retrograde amnesia (Kier et al. 2004; Taoka et al. 2006). Further, DTI has revealed reduced FA in the UF of adults diagnosed with probable AD (Yasmin et al. 2008). Similar reductions in FA have also been observed in the UF of healthy e4 carriers (Gold et al. 2010; Smith et al. 2010).

Although DTI scalar metrics of white matter tracts in e4 carriers have been studied, length-based tractography has not been the focus of investigation. Quantitative tractography based on DTI (qtDTI) combines traditional tractography methods (Conturo et al. 1999) with scalar metrics to detect region-specific microstructural changes in white matter fiber bundles (Correia et al. 2008). In methods previously described by Correia et al. (2008), qtDTI measures white matter fiber bundle lengths (FBLs) through a computational reconstruction of neuronal fiber pathways weighted by scalar metrics. This method may be sensitive to changes in white matter integrity of entire tracts and thus, for certain research questions, may have advantages over methods that involve placing ROIs on two dimensional scalar DTI parameter maps (Correia et al. 2008).

In the present study, we used qtDTI to determine if FBLs in the temporal lobe and UF are influenced by the presence of an e4 allele among healthy older adults. Previously, Bartzokis et al. (2006) revealed that healthy e4 carriers display a steeper rate of demyelination in temporal regions of the brain and enhanced cognitive decline relative to non-carriers. The latter study suggests a positive relationship between decreased myelinated fibers and cognitive deficits. As such, we hypothesized that individuals with at least one e4 allele would exhibit shorter mean FBLs in the temporal lobe, and would perform more poorly on tests of memory. We also anticipated shorter FBLs in the UF, since previous studies of healthy e4 carriers have reported decreased FA in this ROI (Gold et al. 2010; Smith et al. 2010). Although research has suggested that white matter pathology in e4 carriers is age-dependent (Nilsson et al. 2006; Ryan et al. 2011), the mechanism of pathology is not well understood. As an additional goal, we aimed to clarify these previously undefined variables through the unique sensitivity of qtDTI and a cross-sectional analysis of participants.

Methods

Participants

Data were collected from 64 primarily Caucasian healthy men (N=22) and women (N=42), selected for a longitudinal study of healthy cognitive aging. Participants were recruited from local advertisements emphasizing "healthy aging," and the Research Participant Registry of the Washington University Institute of Clinical and Translational Sciences (ICTS). All participants were English-speaking adults above the age of 50. Participants were evaluated for neurological and medical conditions via self-report questionnaires. All physiological data were collected at the time of assessment. Medical records were obtained for individuals who indicated relevant medical issues at the time of assessment. Subjects with a history of neurological disease were excluded, along with other neurological conditions capable of influencing cognition (e.g., Huntington's Disease). Additional exclusion criteria involved treatment-dependent diabetes, history of head injury with loss of consciousness greater than 30 min, substance abuse disorders, and severe psychiatric diagnoses (e.g., all Axis I and II disorders with the exception of controlled depression), and contraindications for MRI including claustrophobia. Individual MRIs were examined by a physician for gross

radiological abnormalities (atrophy, normal pressure hydrocephalus, etc.) and individuals with evidence of such abnormalities were excluded from the study.

All participants provided informed consent before participation in the study, and all were given financial compensation for their involvement. The research was approved by the local Institutional Review Boards of the corresponding institutions.

Genotyping

Genomic DNA was extracted from saliva samples purified using the Oragene DNA collection kit (DNA Genotek, Ottawa, Canada) and processed using the Autopure LS nucleic acid purification system (QIAgen).

ApoE isoform genotypes were determined for all subjects based on analysis of two C/T single-nucleotide polymorphisms (SNPs), rs429358 (amino acid position 112) and rs7412 (amino acid position 158), which comprise the e2/e3/e4 polymorphism (Weisgraber et al. 1981). The SNP composition for each isoform is e2 = rs429358 T and rs7412 T; e3 = rs429358 T and rs7412 C and e4 = rs429358 C and rs7412 C. SNPs were determined using the Sequenom MassArray system. The allelic frequencies of both SNPs were within Hardy-Weinberg equilibrium (rs429358, $c^2 = 1.05$, d.f. = 1, P=0.31; rs7412, c^2=1.83 $d.f.$=1 P=0.18).

Neuropsychological testing

Subjects completed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al. 1998) to examine memory performance between e4 carriers and non-carriers. This test has been validated as a sensitive tool for detecting cognitive impairment in non-clinical populations (Duff et al. 2005). The RBANS consists of 12 subtests used to examine five essential cognitive domains: immediate memory, visuospatial/visuoconstruction ability, language, attention, and delayed memory (Randolph et al. 1998). The present study focused on raw scores of immediate and delayed memory, since previous research has associated e4 status with significant decline in episodic memory among healthy adults (De Blasi et al. 2009). Raw scores of language were also analyzed since deficits in this domain have been observed in MCI and mild AD (Petersen et al. 2001). Raw scores were analyzed instead of index scores to allow for analysis of true age-related impact on memory function. Subtests of the immediate memory index include list learning and story memory; delayed memory subtests include list recall, list recognition, and story recall; language subtests include picture naming and semantic fluency (Randolph et al. 1998).

Neuroimaging acquisition

Imaging acquisition was performed at Washington University–St. Louis, using a head-only Magnetom Allegra 3 T MRI scanner (Siemens Medical Solutions, Erlangen, Germany). For consistent results, the same MRI scanner, vendor operating software level, acquisition protocols, and pulse sequences were used throughout the duration of the study. Daily quality-assurance tests were also performed to assure consistent MRI performance. Structural images were obtained from the following methods: a T1-weighted magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) sequence, T2-weighted turbo spin echo (TSE) sequence; and T2-weighted fluid-attenuated inversion-recovery (FLAIR), as detailed in (Paul et al. 2011). Slice coverage and field of view (FOV) were established from an initial pilot study involving the same participants.

Diffusion-weighted imaging (DWI) acquisition

Axial diffusion-weighted images were collected using a custom single-shot multislice echo-planar tensor-encoded pulse sequence. Diffusion gradients were applied in 31 non-colinear

directions comprised of 24 main directions (diffusion weighing of b=996 s/mm^2) and 5 I_0 acquisitions (b=0 s/mm^2). The following parameters were used: *TE*=86.2 ms; *TR*=7.82 s; 64 contiguous 2.0-mm slices; and an acquisition matrix of 128×128 with a FOV of 256×256 mm (isotropic 2.0×2.0× 2.0 mm voxels). Raw (k-space) data were stored and reconstructed into floating-point DWIs.

Fiber bundle length extraction

Each DWI volume was corrected for subject motion and eddy current artifacts by affine registration to the first I_0 volume using FSL FLIRT with mutual information (Jenkinson et al. 2012). The orientations of the diffusion-encoding vectors were corrected by the rotation induced by these registrations, and brain tissue was extracted using FSL's Brain Extraction Tool. Diffusion tensors were fit from the linearly interpolated volumes (Zhukov and Barr 2002), and the major eigenvector was used for tracking with one random seed per voxel, second-order Runge–Kutta integration, an angle threshold of 35°, an FA threshold of 0.15, and a minimum-length threshold of 10 mm. The ICBM lobe atlas and the JHU DTI white matter atlas were mapped to each subject through affine registration with mutual information to the FA image (Wakana et al. 2007). In this analysis, each reconstructed track line represents a local macroscopic bundle of neuronal fibers. Fiber bundles in the temporal lobe were segmented by connectivity criteria using custom software, in which a track was included if either endpoint was within one voxel of ICBM temporal gray matter. The UF was segmented volumetrically with custom software, including a track if the corresponding JHU atlas region contained 80 % or more of its arc length. The complexity of the UF and neighboring fiber bundles such as the inferior longitudinal fasciculus and superior longitudinal fasciculus make the specificity of fiber extraction difficult without probabilistic tractography maps. We used the JHU-DTI atlas to ensure confidence that no other surrounding fiber tracks would be included in our measurement of UF FBL. For both types of segmentation, fiber bundles were culled by removing random tracks within a distance of 0.8 mm of an existing track (Zhang et al. 2003).

All FBLs were normalized to intracranial volume (ICV) prior to statistical analyses. Estimates of ICV were obtained through the summation of three probability maps of voxel identity. FBL values were then corrected for head size through normalized algorithms for the number of streamtubes, total summed length of streamtubes, and total weighted length metrics for linear and fractional anisotropy in the temporal lobe and UF. Normalized algorithms are explained in detail elsewhere (Correia et al. 2008).

FBLs of the temporal lobe were measured across both hemispheres. Thus, temporal FBL values are a measure of mean length, weighted across the left and right hemispheres. FBLs of the UF were measured separately in the right and left hemispheres.

Data analysis

Influence of the e4 isoform on brain structure and function was examined by comparing subjects possessing at least one e4 allele (*N*=23; 5 males and 18 females) versus subjects possessing no e4 alleles (*N*=41; 17 males and 24 females). Of the 23 individuals with at least one e4 allele, one participant possessed the homozygous e4 genotype (two e4 alleles). Subjects containing either one or two e4 alleles were all classified as "carriers" because there was no phenotypic manifestation of the e4 allele (i.e., all participants met the neurological inclusion/exclusion criteria). An independent samples *t*-test was performed to determine if age or years of education were needed as covariates in the primary analyses. Ethnicity was not analyzed due to the dominant cell size of Caucasian participants with an e4 allele (*N*=20 out of 23). While years of education did not differ significantly between e4

carriers and non-carriers, participants with an e4 allele were significantly younger than non-carriers ($p<.05$). As such, age was utilized as a covariate for the main analyses. See Table 1.

In order to investigate the functional relationship between the e4 allele and FBL, we performed two separate multivariate analyses of co-variance (MANCOVA) with age as the covariate. The e4 carrier status served as the independent variable for both MANCOVAs, with imaging and neuropsychological indices serving as the respective dependent variables in the two separate MANCOVAs. We hypothesized that individuals with higher memory scores would have longer mean fiber bundle lengths, demonstrating the functional relevance of FBL in the temporal lobe and UF. Pearson's correlation coefficients were also computed to examine the degree of shared variance between age and each of the dependent variables.

Results

The MANCOVA examining e4 influence on FBL revealed a significant multivariate main effect for shorter UF bundle lengths in the left hemisphere (Wilks' =.917 $F(3, 59)= 1.790$[a], $F=4.496$ $p=.038$) and a trend effect for shorter mean UF bundle lengths in the right hemisphere ($F=3.506$ $p=.066$) of e4 carriers. Temporal FBLs did not differ significantly between carrier groups. See Table 2. The MANCOVA examining memory also revealed no significant main effect from the e4 allele. See Table 3. The results for both MANCOVAs were corrected for multiple comparisons using Sidak confidence interval adjustments.

Independent of e4 status, Pearson's correlation coefficients demonstrated that increased age is significantly correlated with shorter FBLs in the temporal lobe and UF, as well as decreased performance on tests of memory. See Table 4. A significant positive relationship between temporal FBL and memory scores was evident on the list learning task but no other cognitive indices. A significant positive relationship was also evident between semantic fluency and UF FBL of the left hemisphere but no other cognitive scores. No significant differences were observed between UF FBL of the right hemisphere and cognitive performance. See Table 5.

Discussion

The study herein is the first to investigate the structural integrity of temporal white matter FBLs among healthy adult carriers of the ApoE e4 genotype. Our results reveal that the mean FBL of the UF is significantly shorter in individuals with an e4 allele, but the overall mean FBL associated with the temporal lobe does not differ significantly between carriers and non-carriers. Performances on tests of memory were similar between groups. Further analyses, however, revealed that increased age was significantly correlated with both shorter UF and temporal FBL and lower scores of memory performance. A significant relationship between FBL and memory was only evident in fibers specific to the temporal lobe. Results indicate that the mean FBL of the UF is vulnerable to an e4 allele among healthy adults, which is independent of age. Conversely, the overall mean temporal FBL is more vulnerable to aging than to the impact of an e4 allele.

Previous studies have utilized diffusion tensor tractography to examine scalar metrics of specific white matter tracts involved in neurodegenerative disease, including the UF. The UF is a cortico-cortical white matter tract, and disruption of this structure is related to severe deficits in semantic memory (Yasmin et al. 2008). The latter study revealed reduced FA in the UF of individuals with early stage AD, which is consistent with a preliminary study by Taoka et al. (2006). The relationship between the e4 allele and AD has led to investigations of UF integrity among clinical populations of e4 carriers (Gold et al. 2010; Smith et al. 2010), but few studies have examined UF integrity among healthy individuals. Our study

demonstrates that FBL of the UF is influenced by the e4 allele of ApoE in healthy populations.

Several theories have attempted to identify the mechanism by which the e4 polymorphism impairs white matter integrity. Adalbert et al. (2007) reported a complex relationship between isoform e4, beta-amyloid deposition, and tau deposits. Specifically, isoform e4 stimulates the transformation of beta-amyloid to fibrillar forms that increase neuritic dystrophy (Adalbert et al. 2007). Both beta-amyloid and e4 increase tau phosphorylation that can alter axonal transport resulting in axon degeneration (Adalbert et al. 2007). In animal studies, accumulation of beta-amyloid and phosphorylated tau proteins have shown to disrupt white matter through direct damage to oligodendrocytes (Desai et al. 2009; Tesseur et al. 2000). These microphysiological changes have also been observed in e4 carriers in the very early stages of AD (Glockner et al. 2002).

Differences in mean FBL in the UF of e4 carriers suggest that the UF fibers are more influenced by ApoE status compared to other white matter tracts within the temporal lobe. It is possible that temporal FBLs have high durability to damage due to functional compensation processes within this lobe. A study by Glockner et al. (2002) suggested that presence of the e4 allele contributes to decreases in neuronal repair and re-modeling, initiating a plastic response that counteracts neuronal loss. Recently, Tuminello and Han (2011) proposed that the physiological impact of an e4 allele might differ throughout the adult lifespan as a mechanism of compensatory recruitment. With increased age, e4 carriers demonstrate enhanced recruitment of widespread brain regions during cognitive tasks compared to non-carriers; yet performance levels do not significantly vary (Tuminello and Han 2011). This model is consistent with fMRI studies of ApoE pathology. Bookheimer et al. (2000) and Bondi et al. (2005) demonstrated that atrophic regions of the hippocampus, parietal cortex, and PFC show enhanced activation during working memory tasks. As such, compensatory recruitment may be responsible for structural preservation of the temporal lobe FBLs and attenuated cognitive decline in our sample of relatively young e4 carriers.

Studies of healthy e4 carriers have observed an age-dependent relationship between the e4 allele, white matter abnormalities, and cognitive decline (Ryan et al. 2011). Ryan et al. (2011) utilized DTI to examine the apparent diffusion coefficient (ADC) and FA in healthy older e4 carriers. Results revealed that e4 carriers exhibit differences in ADC and FA in frontal, temporal, and parietal white matter regions relative to non-carriers (Ryan et al. 2011). Additionally, differences in memory were further amplified by decade in e4 carriers showing that age was a significant predictor of enhanced ADC and decreased FA in temporal regions of e4 individuals (Ryan et al. 2011). This study suggests that e4 does not produce an exacerbated effect on brain integrity across the adult age range, but instead changes the trajectory of normal aging (Ryan et al. 2011).

The significantly younger age range in our e4 group is noteworthy. Previous research has indicated that the frequency of an e4 allele in cognitively normal populations is significantly reduced after age 70 (Davidson et al. 2007; Ryan et al. 2011; Sando et al. 2008), which may reflect increased mortality (De Benedictis et al. 2001) or late-onset cognitive effects associated with e4 status. Consistent with previous research, only one e4 carrier in our population sample was above the age of 70, compared to 14 non-carriers above age 70. Our group may have been represented by younger individuals with an e4 allele because older individuals with an e4 allele may have been excluded from the study due to the presence of neurologic disease or dementia.

In addition to young age, it is possible that e4 carriers did not display white matter abnormalities due to e4 heterozygosity in the majority of the carriers. Possession of two e4

alleles increases the risk for white matter abnormalities. Godin et al. (2009) reported significantly higher white matter lesion (WML) volumes in homozygous e4 carriers compared to heterozygous individuals and non-carriers. Homozygous carriers also displayed a higher increase in WML volume over a four-year period relative to non-carriers and heterozygous participants (Godin et al. 2009). It is possible that more robust differences in memory and imaging indices would be observed among larger samples of individuals with two e4 alleles, compared to the sample of predominately heterozygous e4 carriers represented in our study.

Independent of ApoE status, we observed a significant correlation between shortened temporal FBL and advancing age. This correlation is consistent with previous postmortem studies demonstrating that advanced age is associated with significant loss of myelinated fiber lengths (Tang et al. 1997). Marner et al. (2003) reported a 45 % reduction in the length of myelinated axons with old age, primarily in smaller nerve fibers. Although these histologic changes were observed at autopsy, all individuals were free of neurologic and psychiatric disease, or any other condition affecting the central nervous system at the time of death (Tang et al. 1997; Marner et al. 2003). These studies support our finding that shorter FBL is associated with aging in healthy older adults.

Degeneration of white matter FBL in healthy older adults is important for how we understand and perceive normative brain functions in aging populations. Although shorter tracts may cause deficits in information processing, encoding, and retrieval of new memories (Bartzokis 2004), it is unclear what directly leads to these changes throughout the adult lifespan. While it has been suggested that shorter fiber lengths may correlate with decreased cognitive performance (Peters 2002), a study by Jørgensen et al. (2008) did not find any difference in myelinated fiber lengths between subjects with AD and healthy controls. This suggests that shorter fiber bundles are not necessarily a preclinical symptom of neurodegenerative disorders, but reflect aging processes rather than disease, per se.

A few limitations are present in this study. The relatively small sample size of e4 carriers may have contributed to a lack of significant group differences in temporal FBLs. Additionally, overall preservation of temporal FBLs may not accurately depict hemispheric differences in white matter integrity since FBL measures were collapsed across both hemispheres. It also remains unclear whether allele load influences white matter changes observed in our study, since nearly all participants possessed only one copy of isoform e4.

Although this is not the first study to use qtDTI (Correia et al. 2008; Tate et al. 2010), we acknowledge a few limitations associated with this technique. The use of affine registration to the ICBM atlas may have resulted in missed fibers or inclusion of extra fibers that terminate farther than a few voxels from the gray matter-white matter boundary. Structural stability of fibers may also have been compromised from our segmentation parameters of one seed per voxel and lack of more advanced techniques such as high angular resolution diffusion imaging.

Future investigations of FBL should include volumetric analysis to examine the relationship between FBL and regional atrophy particularly in longitudinal designs. Studies should also include congruent numbers of heterozygous and homozygous e4 carriers to investigate the relationship between FBL and e4 allele load.

Conclusions

White matter FBLs of the uncinate fasciculus are significantly shorter in healthy older adults with an e4 allele of the ApoE gene, compared to no e4 allele. However, FBLs specific to the temporal lobe and memory performance are not influenced by the presence of an e4 allele in

this sample of relatively healthy adults. Because of the age range of our e4 participants, it remains unclear whether tract degeneration manifests more rapidly in e4 carriers after age 70. Shortened temporal FBL appears to be a function of normal aging independent of e4 status. Future investigations should longitudinally examine healthy elderly adults with and without e4 alleles in order to determine if the e4 allele mediates the normal trajectory of aging in white matter FBL.

Acknowledgments

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Table 1

Age distribution of the sample (total sample size N=64)

ApoE e4 status	Mean (SD)	Minimum	Maximum
Carriers[a] (N=23)	58.78 (6.65)	51	78
Non-carriers (N=41)	64.71 (8.60)	51	81

[a] In this study, a carrier is defined as a participant who has a mutation but no disease phenotype. Of the 23 carriers, 22 had one e4 allele (heterozygous), while one had two e4 alleles (homozygous)

Table 2

ApoE e4 carrier group and mean fiber bundle lengths (mm)

ROI	Carrier group mean (SD)	Non-carrier group mean (SD)	Group difference	F	p value	Partial eta squared
Left UF	46.71 (4.65)	49.64 (4.90)	−2.851	4.496	0.038[*]	0.069
Right UF	49.66 (6.14)	51.86 (6.69)	−3.309	3.506	0.066	0.054
Temporal lobe	28.08 (2.93)	27.72 (2.63)	−0.123	0.028	0.869	0.000

[*]
Stastically significant $p<0.05$

Table 3

Neurocognitive performance

RBANS subtest	Mean raw score, carriers (SD)	Mean raw score, non-carriers (SD)	*p* value
List learning	27.91 (4.17)	27.78 (4.40)	0.694
Story memory	18.26 (3.35)	17.59 (3.65)	0.617
Semantic fluency	23.39 (4.93)	21.85 (4.41)	0.232
Picture naming	9.74 (0.62)	9.73 (0.50)	0.719
List recognition	18.65 (1.34)	19.00 (1.41)	0.254
List recall	5.91 (2.37)	5.46 (2.20)	0.696
Story recall	9.83 (1.56)	9.24 (1.84)	0.564

*
Statistically significant *p*<0.05

Table 4

Correlations with age

	r	*p* value
Brain region for mean FBL measurement:		
Left uncinate fasciculus	−0.188	0.048[*]
Right uncinate fasciculus	−0.159	0.198
Temporal lobe	−0.328	0.004[*]
RBANS memory scores:		
List learning	−0.284	0.003[*]
Story memory	−0.165	0.084
Semantic fluency	−0.156	0.102
Picture naming	−0.026	0.783
List recognition	−0.133	0.165
List recall	−0.224	0.018[*]
Story recall	−0.290	0.002[*]

[*] Statistically significant $p < 0.05$

Table 5

Correlations with FBL

	r	*p* value
RBANS memory scores and temporal FBL:		
List learning	0.240	0.035 [*]
Story memory	0.019	0.868
Semantic fluency	0.154	0.181
Picture naming	0.216	0.059
List recognition	0.116	0.315
List recall	0.157	0.174
Story recall	0.093	0.421
RBANS memory scores and UF FBL (left, right):		
List learning	0.105, 0.085	0.272, 0.492
Story memory	0.012, −0.099	0.901, 0.427
Semantic fluency	0.237, −0.004	0.012 [*], 0.974
Picture naming	0.039, −0.051	0.685, 0.684
List recognition	−0.057, −.095	0.552, 0.446
List recall	0.106, −0.125	0.270, 0.315
Story recall	0.032, −0.097	0.740, 0.433

[*] Statistically significant $p<0.05$