Published in final edited form as:

Am J Alzheimers Dis Other Dement. 2014 May ; 29(3): 222–235. doi:10.1177/1533317513517045.

Interactive effects of apolipoprotein e4 and diabetes risk on later myelinating white matter regions in neurologically healthy older aged adults

Jessica M. Foley^{a,b}, David H. Salat^{a,b,c}, Nikki H. Stricker^{a,d}, Tyler A. Zink^{a,b,d}, Laura J. Grande^{a,b}, Regina E. McGlinchey^{a,b}, William P. Milberg^{a,b}, and Elizabeth C. Leritz^{a,b,c,e}

^aPsychology Service, VA Boston Healthcare System, Boston, MA

^bHarvard Medical School, Department of Psychiatry, Boston, MA

^cAthinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, MA

^dDepartment of Psychiatry, Boston University School of Medicine, Boston, MA

^eDivision of Aging, Brigham & Women's Hospital, Boston, MA

Abstract

Possession of the apolipoprotein e4 (APOE4) allele and diabetes risk are independently related to reduced white matter (WM) integrity that may contribute to the development of Alzheimer's disease (AD). The purpose of this study is to examine the interactive effects of APOE4 and diabetes risk on later myelinating WM regions among healthy elderly at risk for AD. A sample of 107 healthy elderly (80 APOE4–/27 APOE4+) underwent structural MRI/ DTI data were prepared using TBSS and a-priori ROIs were extracted from T1-based WM parcellations. ROIs included later myelinating frontal/temporal/parietal WM regions and control regions, measured by fractional anisotropy (FA). There were no APOE group differences on DTI for any ROI. Within the APOE4 group, we found negative relationships between HAIC/fasting glucose and APOE4 on FA for all later myelinating WM regions, but not for early/middle myelinating control regions. Results also showed APOE4/diabetes risk interactions for WM underlying supramarginal, superior temporal, precuneus, superior parietal, and superior frontal regions. Results suggest interactive effects of APOE4 and diabetes risk on later myelinating WM regions, which supports preclinical detection of AD among this particularly susceptible subgroup.

Keywords

Alzheimer's disease; diabetes; APOE4; healthy aging; white matter

1. Introduction

Alzheimer's disease (AD) afflicts nearly 10 percent of individuals over the age of 70 and accounts for the highest proportion of total dementia cases with up to 75 percent carrying an AD diagnosis.¹ Increased attention has been given to earlier preclinical detection among individuals who are at risk for AD, which is especially important for identifying targeted treatments to alter the trajectory of neurodegeneration. Two of the most significant factors examined include genetic and cerebrovascular disease (CVD) risk. Researchers have investigated the utility of combining genetic or CVD risk factors with other biological markers, such as brain volume,^{2,3,4,5} but no studies have investigated possible interactive effects of these variables to facilitate earlier detection of AD in a subclinical sample. The most salient of the genetic risks strongly associated with the common form of AD is the apolipoprotein E-4 (APOE4) allele on chromosome 19.^{6,7,8} Structural magnetic resonance imaging (MRI) studies of nondemented APOE4 carriers have revealed brain changes that are quite consistent with findings demonstrated in AD.^{4,5,9,10,11,12,13,14,15,16,17} Similar to AD, APOE4 status is also associated with white matter (WM) abnormalities that may contribute to age- and disease-related neurodegeneration.^{18,19,20,21,22,23,24}

In addition to APOE4, conditions affecting the vascular system are also known to increase risk for AD¹ and to result in similar morphological brain changes.²⁵ In particular, diabetes mellitus (DM) is associated with neurologic dysfunction, including brain atrophy, vascular compromise, and increased risk for Alzheimer's brain pathology.² Notably, changes to brain tissue integrity can result from even subclinical levels of CVD risk factors such as blood pressure, cholesterol, and glucose regulation,^{26,27,28,29,30} and in the case of DM, dysregulated or elevated glucose has been found to be associated with reduced WM microstructural integrity. Gerald and King³¹ posit that, among metabolic factors, hyperglycemia (i.e., abnormally high glucose) can have one of the strongest effects on the development of vascular complications. These findings highlight the importance of degree of glucose dysregulation in the resulting severity of WM dysfunction, and suggest an additional target for preclinical detection of disease.

Of particular importance is the relationship between glucose abnormalities and APOE4 on the development of AD. DM and APOE4 each increase risk for dementia,³² but the combination of both factors increases the risk of AD by approximately 4 to 5.5 times,^{33,34} and has been associated with cognitive impairments,³⁵ as well as increased neuritic plaques and neurofibrillary tangles, and higher risk of cerebral amyloid angiopathy,³⁴ suggesting AD- neurodegeneration.

Interestingly, the combination of APOE4 genotype and abnormal glucose has been associated with neuritic plaque formation,³⁶ poor episodic memory,^{37,38} and increased amyloid precursor protein;³⁸ this relationship may be a function of the extent of glucose elevation or dysregulation, and not exclusively dependent upon achievement of a clinical threshold per se. However, no studies have addressed the effect of these combined risks on WM.

Preclinical detection of AD is advanced through earlier identification of neuropathological changes which may be associated with these subclinical conditions that increase AD risk. Since research has demonstrated that vascular dysfunction may precede cortical neuropathology in AD,³⁹ examination of WM changes may be most productive during the earliest stages;^{40,41,42} this additional role of WM has already been documented.^{43,44} Employing methods with greater sensitivity to detect pathological changes in at-risk individuals may reveal affected regions earlier in life and with greater specificity. It has been argued that regionally specific WM degeneration plays a role in the development of AD, and that WM breakdown in later myelinating cortices may be more rapid among those at risk for AD.^{45,46,47,48,49,50} Bartzokis et al.^{45,46} posited that since higher-order areas continue to mature over a more protracted period, these regions are more vulnerable to preferential myelin breakdown in the presence of risks including APOE4.^{45,46,50} Prior studies of DM have already shown WM reductions in later myelinating regions.^{51,52,53}

Diffusion tensor imaging (DTI) is a novel MRI method that is well equipped to assess the microstructural integrity of cerebral WM^{54,55} and has been shown to detect subtle pathology that may not be revealed with conventional MRI.^{56,57,58,59} Studies conducted in our lab demonstrate vulnerability to frontal WM in healthy elderly and those with subtle cerebrovascular risks^{60,27} and myelin pathology in parahippocampal WM in AD;⁶¹ recent studies have also found reduced WM integrity in APOE4 individuals.^{62,63,64,65,66,22}

The purpose of the current investigation was to examine the interactive effects of APOE4 and diabetes risk on WM integrity among a sample of older adults with varying (mild-moderate) levels of glucose dysregulation and without dementia. We predicted to find reduced WM integrity among later (versus early or middle) developing regions in among APOE4 individuals with abnormal glucose. The current study applies DTI methods in a largely subclinical sample in order to explore microstructural changes that may precede clinical diagnosis of AD.

2. Materials and Methods

2.1 Participants

VA Institutional Review Board guidelines for human subjects research, including obtaining informed consent and de-identifying participant data, were followed. One hundred and seven healthy elderly participants underwent structural MRI with DTI. The current sample is similar to those employed in Leritz et al^{28,67} and Williams et al.³⁰ Briefly, participants were recruited from two separate but overlapping studies examining the ways in which common cerebrovascular risk factors impact brain structure and cognition. Twenty-nine participants were selected (based on their agreement to undergo structural MRI) from a larger sample recruited by the Harvard Cooperative Program on Aging (HCPA) for the Claude Pepper Older American Independence Center (OAIC) of Harvard Medical School. Participants in this program were recruited from the community in response to an advertisement appearing in the HCPA newsletter asking for healthy community-dwelling older African Americans. Seventy eight participants were recruited through the Understanding Cerebrovascular and Alzheimer's Risk in the Elderly (UCARE) program, a study investigating how cerebrovascular risk impacts brain structure and cognition, and risk for dementia.

Participants in the UCARE study were recruited through the Boston University Alzheimer's Disease Center (BUADC) based on the initial criteria of having a first-degree family relative with dementia. Participants in both the OAIC and UCARE samples were excluded for the following reasons: a history of head trauma of “mild” severity or greater according to the criteria of Fortuny et al⁶⁸ (e.g., loss of consciousness for greater than 10 minutes), any history of more than one head injury (due to possible cumulative neuropathological effects), diagnosis of any form of dementia (i.e., Parkinson's disease, Alzheimer's disease, vascular dementia), any severe psychiatric illness, or any history of brain surgery or stroke. Participants were also excluded if they presented with the e2 allele (n=2), given its well understood protective role in Alzheimer's disease. All participants were literate with at least a 9th grade education. Mini-mental state examination (MMSE) scores ranged from 23 to 30. These scores are in a range outside of a dementia diagnosis, according to normative data for the two racial groups (Caucasian, African American) in this sample.⁶⁹

2.2 Glucose Measurement

Following informed consent, fasting blood was drawn and processed for analysis of glucose. Fasting glucose levels under 100 mg are considered “normal,” levels between 100 and 125 are considered “mild” and levels over 126 mg are considered to be indicative of potential diabetes (American Diabetes Association).⁷⁰ Glucose levels ranged from 65 to 156 mg in the current sample. In addition to glucose levels, we also obtained a measure of glycosylated hemoglobin A1C on each participant. HA1C is a form of hemoglobin that can estimate the average plasma glucose concentration over a period of 4–12 weeks. Thus, it is an indicator of how regulated glucose levels have been, and it is particularly useful in evaluating patients with diabetes. HA1C ranges from 4 to 14; levels of 7 and above are indicative of poorly controlled blood sugar, and potentially greater cerebrovascular risk (American Diabetes Association).⁷⁰ HA1C levels ranged from 4.9 to 8.4 in the current sample. Of the total sample, 85 individuals were taking medications to control cerebrovascular risk. Of these individuals, 37 (34.5%) were prescribed treatment to manage blood pressure, 25 (23.3%) were prescribed treatment to manage cholesterol, and 8 (7.5%) were prescribed treatment to manage diabetes.

2.3 APOE Genotyping

The procedure (well established) for DNA extraction and genotyping is as follows: genomic DNA from each individual was prepared directly from peripheral blood samples using the Pure Gene (Gentra Systems, Minneapolis, MN) DNA extraction kit, with minor modifications. In the cases of buccal swabs, DNA were isolated using a kit from Epicentre Technologies. The DNA was stored and an aliquot was removed for APOE genotyping. Two hundred nanograms of DNA was added to 25 picomoles of each primer, 2.5 microliters of DiMethyl Sulfoxide and 0.5 units of AmpliTaq polymerase in 25 microliters. The PCR reaction was carried out using the following primers: 5'TCCAAGGAGCTGCAGGCGGCG 3', 5'ACAGAATTGCCCCGGCCTGGTACACTGCCA 3' under the following conditions: 94o C for 5 min for denaturing followed by 40 cycles of 65o C for 0.5 min, 70o C for 1.5 min, 94o C for 0.5 min, and a final extension at 70o C for 10 min. A 227 bp PCR fragment was produced. The amplification product was then digested with CfoI for 3 hr at 37o C. The digestion product was then electrophoresised for 2 hr on a 4 % MetaPhor Agarose gel. The

APOE alleles were distinguished from one another due to the different CfoI digestion products.

2.4 Neuroimaging Protocol

All participants received a whole-head high resolution DTI scan. Four participants were scanned using a Siemens 1.5 Tesla Sonata system, with the following parameters: magnetization-prepared rapid acquisition with gradient echo (MPRAGE); TI=1000 ms, TR=2.73 sec, TE=3.39 ms, flip angle=7°, slice thickness=1.33 mm, 128 slices, FOV=256×256 mm; DTI: repetition time (TR)=9000 ms echo time (TE)=68 ms, 60 slices total, acquisition matrix=128 × 128 (field of view; FOV=256 × 256 mm), slice thickness=2 mm (for 2 mm³ isotropic voxels) with 0 mm gap, with a b value=700 s/mm², 10 T2 and 60 diffusion weighted images, and one image, the T2-weighted “low b” image with a b-value=0 s/mm² as an anatomical reference volume. The remaining 103 participants were scanned on the upgraded Siemens 1.5 Avanto System, with slightly different parameters; MPRAGE: TI=1000 ms, TR=2.73 sec, TE=3.31 ms, flip angle=7°, slice thickness=1.3 mm, 128 slices, FOV=256×256 mm; DTI: repetition time (TR)=7200 ms echo time (TE)=77 ms, 60 slices total, acquisition matrix=128 × 128 (field of view; FOV=256 × 256 mm), slice thickness=2 mm (for 2 mm³ isotropic voxels) with 0 mm gap, with a b value=700 s/mm², 10 T2 and 60 diffusion weighted images, and one image, the T2-weighted “low b” image with a b-value=0 s/mm² as an anatomical reference volume. Acquisitions used a twice-refocused balanced echo to reduce eddy current distortions.⁷¹ The DTI scan was comprised of 10 T2 and 60 diffusion weighted images, and one image, the T2-weighted “low b” image, with a b-value=0 s/mm² as an anatomical reference volume. Total acquisition time for the DTI scan was 8 minutes 31 seconds.

2.5. Image Processing

2.5.1. DTI Preprocessing and Analysis—Preprocessing was performed with diffusion tools developed at the Martinos Center as part of the Freesurfer software package (<http://surfer.nmr.mgh.harvard.edu>) as well as tools provided with the FSL processing suite (<http://www.fmrib.ox.ac.uk/ezp-prod1.hul.harvard.edu/fsl>).⁷² See our previous work^{29,30} for additional details. Diffusion volumes were eddy current and motion corrected using FSL's Eddy Correct tool. The diffusion tensor was calculated for each voxel using a least-squares fit to the diffusion signal. The T2 weighted lowb volume was then skull stripped using FSL's Brain Extraction Tool (BET)⁷² and this volume served as a brain-mask for all other diffusion maps. The lowb structural volume was collected using identical sequence parameters as the directional volumes with no diffusion weighting, and was thus in complete register with the final diffusion maps. Maps FA were entered in voxel based analyses using the Tract Based Spatial Statistics (TBSS) procedure for inter-participant spatial normalization.⁷³

2.5.2. DTI Image Processing—Voxelwise processing of the FA data was carried out using TBSS (Tract-Based Spatial Statistics),⁷³ part of FSL.^{72,30} In this procedure, all subjects' FA data were aligned into a common space using the nonlinear registration tool FNIRT,^{74,75} which uses a b-spline representation of the registration warp field.⁷⁶ The TBSS procedure next creates a mean FA image by averaging all participants' aligned FA maps, and

then thresholds this average for voxels with an FA ≥ 0.2 to generate a mean FA skeleton which represents the centers of all tracts common to the group. This use of the FA skeleton helps avoid inclusion of regions that are likely composed of multiple tissue types or fiber orientations and may be susceptible to partial volume contamination. The next step in the TBSS processing is a projection of each participant's regional diffusion values to the appropriate location on the template skeleton, and this information was entered into voxelwise group statistics. Data along the skeleton were smoothed utilizing an anatomical constraint to limit the smoothing to neighboring data within adjacent voxels along the skeleton. Statistical maps were dilated from the TBSS skeleton for visualization.

2.5.3. ROI Analysis—The first set of regions of interest (ROIs) was generated using the Johns Hopkins University WM labels, available as part of the FSL suite. The second ROI approach employed T1 -based WM parcellations automatically created during the FreeSurfer processing stream⁷⁷ regional measures were based on gyral folding patterns⁷⁸ which were subsequently diffused from the cortex into the subjacent WM resulting in a WM parcellation for each gyral label, unique to each individual's anatomy. Registration of the T1 image to the lowb volume was performed using the FreeSurfer bbgregister tool,⁷⁹ a novel procedure that utilizes tissue contrast (gray matter (GM)/WM) as the basis of the registration cost function. WM values were extracted from voxels limited to the TBSS skeleton to correspond with voxel based analyses and to reduce the influence of partial volume contamination. The ROI-segmented mean skeleton was deprojected from TBSS standard space to each participant's native diffusion volume using the inverse of the participant's transform to standard space to extract native values. Statistics were then extracted from native diffusion maps, with each segmentation comprised of voxels representing the center of WM tracts within each region. Right and left hemisphere ROIs were averaged. See A.1. for an image depicting the tract based spatial statistics (TBSS) ROI analysis procedure.

We included seven later myelinating ROIs, since breakdown in these WM regions may be more rapid among healthy APOE4+ and associated with the development of AD degeneration.^{45,47,48,49} These regions included supramarginal, superior frontal, superior parietal, inferior temporal, middle temporal, superior temporal, and precuneus WM, which among the last to mature.^{47,80,81} The control regions including the genu and splenium are middle developing,^{82,83} and the projection fibers of the corticospinal tract (including the cerebral peduncles) are among the earliest myelinating tracts.⁸⁴

2.6. Statistical Analyses

For preliminary analyses, we used Chi-(for categorical dependent variables) and one way ANOVA (for continuous dependent variables) tests. ANOVA models were also used to squares examine APOE group differences on DTI data. We conducted bivariate Pearson's correlations between all ROIs and diabetes risk measures both genetic groups (APOE4+, APOE4-). For those regions in which WM integrity was associated with diabetes risk, a hierarchical multiple regression (MR) model was conducted to predict the interactive impact of genetic factors and diabetes risk on WM integrity. First, age was entered as a covariate (model 1), then APOE status and diabetes risk (fasting glucose, HA1C) were introduced as main effects (model 2), and finally a two-way interaction term was entered (APOE4 $\times$

glucose measure [HA1C or fasting glucose]) in the third step (model 3). Dependent variables included FA for seven study and three control regions. We did not control for multiple comparisons to allow for maximum exploration of study variables. Alpha was set to $\alpha=0.05$.

3. Results

There were no differences between APOE4 groups on demographic variables including age, education, gender and ethnicity. Average age of the total sample was $M=67.9$ years ($SD=9.1$ years) and average education was $M=14.9$ years ($SD=2.7$). Males comprised 37.0% of the APOE4+ group, and 38.8% of the APOE4- group. For the total sample, 33.6% were African American and 66.4% were Caucasian. Average fasting glucose was $M=95.3$ ($SD=17.3$) and average HA1C was $M=5.8$ ($SD=0.68$). Due to the recruitment criteria for the BUADC study, there was a high prevalence (87.9%) of individuals presenting with a positive first degree family history of dementia, placing them at higher risk of developing dementia.⁸⁵ Among the APOE4 group, 2 participants presented with two copies of the e4 allele (APOE 4/4), and the remaining 25 participants were heterozygous (APOE 3/4) for the e4 allele. With regard to glucose functioning among the total sample, twenty-four (22.4%) participants would be considered to have “mildly” elevated glucose levels, while nine (8.4%) would be considered “diabetic” according to clinical standards. Thus, 91.6% of all participants would be considered to have normal to mildly elevated fasting glucose levels. Additionally, eight individuals (7.4%) had HA1C levels of 7 and over, indicating poorly controlled sugar levels in the months preceding evaluation for these individuals. Thus, the majority of our sample had appropriately regulated glucose at the time of the assessment. With regard to global cognition, one subject had an MMSE score of 23, and only three had scores of 24, and results were not altered when eliminating these participants. Thus, it is likely that this small number of individuals with lower scores did not impact overall results or interpretation of the data. See Table A.1 for descriptive statistical data for demographic variables.

3.1. ANOVA Models

See Table A.2. for descriptive statistical data for groups on ROIs. One way ANOVA analyses revealed no differences between APOE groups (APOE4+, APOE4-) on any study ROI (for FA).

3.2. Pearson's Bivariate Correlations

Correlational analyses revealed distinct relationships for the APOE4 group; when APOE groups were examined independently, significant relationships emerged for glucose and HA1C with late myelinating ROIs for the APOE4 group only. In particular, higher glucose levels and higher HA1C levels were associated with lower FA in the following regions: supramarginal WM (HA1C $r=-0.48$, $p=0.01$; fasting glucose $r=-0.46$, $p=0.02$), inferior temporal (HA1C $r=-0.41$, $p=0.03$; fasting glucose $r=-0.47$, $p=0.01$), middle temporal (HA1C $r=-0.47$, $p=0.01$; fasting glucose $r=-0.47$, $p=0.01$), superior temporal (HA1C $r=-0.37$, $p=0.05$; fasting glucose $r=-0.43$, $p=0.02$), precuneus (HA1C $r=-0.43$, $p=0.03$; fasting glucose $r=-0.50$, $p=0.008$), superior frontal (HA1C $r=-0.42$, $p=0.03$; fasting glucose $r=-0.48$, $p=0.01$), and superior parietal (HA1C $r=-0.42$, $p=0.03$; fasting glucose $r=-0.50$, $p=0.008$) WM. These relationships were not significant for the early developing regions (p

> .05 for genu, splenium and cerebral peduncles) or for any relationship in the APOE4-group ($p>0.05$ for genu, splenium, cerebral peduncles). We also examined relationships to other cerebrovascular risk variables for the APOE4 group, and findings did not reveal significant relationships (although some approached statistical significance) with WM integrity for any of these variables. In particular, *blood pressure* yielded no significant relationships to WM: [systolic blood pressure] FA supramarginal WM ($r=-0.18$, $p=0.37$), FA inferior temporal WM ($r=-0.25$, $p=0.20$), FA middle temporal WM ($r=-0.28$, $p=0.16$), FA superior temporal WM ($r=-0.12$, $p=0.56$), FA superior frontal WM ($r=-0.16$, $p=0.42$), FA precuneus WM ($r=-0.33$, $p=0.10$), FA superior parietal ($r=-0.33$, $p=0.09$). *Cholesterol* yielded no significant relationships to WM: [total cholesterol] FA supramarginal WM ($r=-0.08$, $p=0.70$), FA inferior temporal WM ($r=-0.20$; $p=0.33$), FA middle temporal WM ($r=-0.10$, $p=0.62$), FA superior temporal WM ($r=-0.21$, $p=0.29$), FA precuneus WM ($r=-0.02$, $p=0.93$), FA superior frontal WM ($r=-0.14$, $p=0.50$), FA superior parietal WM ($r=0.07$, $p=0.72$); [low density lipoprotein] FA supramarginal WM ($r=-0.12$, $p=0.54$), FA inferior temporal WM ($p=-0.15$, $r=0.46$), FA middle temporal WM ($r=-0.13$; $p=0.51$), FA superior temporal WM ($r=-0.22$, $p=0.27$), FA precuneus WM ($r=-0.32$, $p=0.88$), FA superior frontal WM ($r=-0.16$, $p=0.44$), FA superior parietal WM ($r=-0.02$, $p=0.91$); [triglycerides] FA supramarginal WM ($r=-0.14$, $p=0.50$), FA inferior temporal WM ($r=-0.09$, $p=0.67$), FA middle temporal WM ($r=-0.25$, $p=0.21$), FA superior temporal WM ($r=0.06$, $p=0.77$), FA precuneus WM ($r=-0.05$, $p=0.81$), FA superior frontal WM ($r=-0.12$, $p=0.56$), FA superior parietal WM ($r=-0.19$, $p=0.34$). Finally, *body weight* yielded no significant relationships to WM ([body mass index] FA supramarginal WM ($r=-0.24$, $p=0.27$), FA inferior temporal WM ($r=-0.04$, $p=0.86$), FA middle temporal WM ($r=-0.32$, $p=0.13$), FA superior temporal WM ($r=0.04$, $p=0.86$), FA precuneus WM ($r=-0.13$, $p=0.56$), FA superior frontal WM ($r=-0.15$, $p=0.48$), FA superior parietal WM ($r=-0.31$, $p=0.14$).

3.3. Hierarchical Multiple Regression Analyses

Separate hierarchical MR analyses were then performed for all study (but not control) regions, given their significance on correlational tests. Independent variables were examined for collinearity. Results of the variance inflation factor (all less than 2.0) and collinearity tolerance (all greater than .76) suggest that the estimated β s are well established.

In step 2 of the (age-controlled) analyses, significant main effects were found for glucose in supramarginal (HA1C: $p=0.044$), middle temporal (fasting glucose: $p=0.010$, HA1C: $p=0.022$), precuneus (fasting glucose: $p=0.030$), and superior frontal (fasting glucose: $p=0.018$, HA1C: $p=0.006$) WM, suggesting that elevated glucose is independently (controlling for age/APOE status) associated with poorer WM integrity (lower FA) in these regions. There were no main effects for APOE4 status in the step two.

A significant (age-controlled) interactive effect for fasting glucose $\times$ APOE4 was found for supramarginal ($p=0.020$), inferior temporal ($p=0.043$), superior temporal ($p=0.037$), precuneus ($p=0.022$), superior parietal ($p=0.014$), and superior frontal ($p=0.014$) WM, suggesting that APOE4 and higher fasting glucose level predicted poorer WM integrity of these regions. A glucose $\times$ APOE4 effect approached significance for middle temporal ($p=0.096$) WM, suggesting that elevated fasting glucose among APOE4+ participants, but

not among APOE4⁻ participants, was marginally associated with poor WM integrity in this region.

A significant (age-controlled) interactive effect for HA1C $\times$ APOE4 was found for supramarginal ($p=0.012$), middle temporal ($p=0.046$), precuneus ($p=0.009$), and superior parietal ($p=0.009$) WM, suggesting that APOE4 status and glucose dysregulation (HA1C) predicted poorer WM integrity of these regions. An HA1C $\times$ APOE4 effect approached significance for the inferior temporal ($p=0.069$), superior temporal ($p=0.065$), and superior frontal ($p=0.070$) WM, suggesting that elevated glucose (HA1C) in APOE4⁺ was marginally associated with poor WM integrity in these regions. See Table A.3. for direct and interactive relationships of APOE4 status and diabetes risk on FA for individual ROIs.

See Figure A.2. for scatterplots depicting significant relationships between glucose variables (HA1C, fasting glucose) and supramarginal WM for each APOE group. See Figure A.3. for scatterplots depicting relationships between glucose variables (HA1C, fasting glucose) and precuneus WM for each APOE group.

4. Discussion

The current results suggest interactive effects of genetic and CVD risk factors for AD (APOE4 and glucose dysregulation) on later myelinating WM regions in healthy elderly; in particular, the presence of APOE4 and elevated fasting glucose was more strongly associated with WM deterioration versus either risk factor alone. Negative relationships were found between glucose and FA in the APOE4⁺ group for all seven later myelinating WM regions, but not for the three (middle or earlier myelinating) control regions. Further, no relationships were shown between glucose measures and FA in any region for the APOE4⁻ group. Regression analysis further supported these findings by revealing that greater evidence of glucose dysregulation was associated with reduced WM integrity in supramarginal, superior temporal, precuneus, superior parietal, and superior frontal regions, in the APOE4⁺ group only.

The current results demonstrated that glucose dysregulation, a significant risk factor for DM and vascular disease, is particularly detrimental in individuals with the APOE4 allele. Indeed, prior work has also documented a synergistic impact of APOE4 and diabetes on AD risk, with a five fold increase in the development of dementia among those affected with both contributions,³⁴ whereas diabetes alone may be associated with less significant, moderate, risk for AD.⁸⁶ The interaction of diabetes and APOE4 on WM dysfunction as documented in the present study reflects neurodegeneration that is consistent with AD and supports a possible pathological mechanism for some individuals who will develop this disease. This apparent association between APOE4 and metabolic dysregulation may be related to the capacity of the e4 allele to regulate vascular functioning. The e4 allele provides a modulatory influence on a variety of vascular factors (e.g., diabetes, blood pressure, dyslipidemia, atherosclerosis⁸⁷), and may mediate AD risk by decreasing resting cerebral blood flow prior to dementia onset.⁸⁸ Previous work has demonstrated an effect of glucose dysregulation on brain WM integrity, namely increased WM hyperintensities,^{89,90,91,92,93} and a general decrease in WM volume in frontal and temporal

regions.^{94,95} DTI studies have also revealed that DM is associated with reduced WM integrity in the temporal stem,^{53,96} frontal lobe,^{51,96} cingulate, occipital lobe, and cerebral peduncles.⁹⁶ Thus, our current results suggest that APOE4 may be associated with WM change in the context of vascular burden. Previous work has also revealed preferential impact of these risks (APOE4 and DM),³² particularly when combined,^{33,34} in the development of dementia and AD (increased pathology in the cortex and hippocampus³⁴). Moreover, the combined impacts of both risks on brain structure have also been supported even when considering subclinically dysregulated glucose in the absence of clinical DM, with evidence for neuritic plaque formation,³⁶ and increases in amyloid precursor protein,³⁸ alongside cognitive changes.^{37,38} Thus, the modulatory influence of CVD risk, and particularly, glucose dysregulation, on APOE4 risk may be exerted even in the absence of overt diabetes, suggesting an earlier stage of impact and an additional avenue for preclinical detection in this particularly susceptible at-risk group.

We did not find any significant differences between APOE4 groups in WM integrity. Prior work investigating the impact of APOE4 on brain WM changes using DTI methodology has revealed somewhat conflicting findings; Bendlin et al⁶² found no effect of APOE4 on any brain WM region, while others have reported reduced microstructural integrity in individuals with the APOE4 allele among several brain WM regions.^{63,64,22,65,97} This inconsistency may be attributable to the moderating effect of CVD risk factors, given the results of the present study.

Our results suggested particular impact of AD and CVD risk among the most advanced (i.e., latest developing) brain WM areas. Indeed, DTI studies have revealed decreasing diffusion metrics through late childhood and young adulthood within frontal, temporal, and parietal association regions.⁸¹ In particular, the temporal regions included in this study are known to mature even after other association regions are well developed.⁸⁰ In addition, Bartzokis⁴⁷ showed that anterior frontal lobe WM myelination peaks at age 44.6, but the anterior temporal lobe WM peaks even later (age 47.5), suggesting very late development of these association regions. In contrast, regions including the corticospinal tract and the genu and splenium develop early in maturation;^{98,99,83} for example, Partridge et al.⁸⁴ documented that projection fibers of the corticospinal tract included the lowest diffusion values and these values further decreased from 30 weeks gestational age to at-term. The corpus callosum has been shown to reach adult myelination by the third year of life,⁸³ although recent studies have shown continued development into young adulthood (peak FA by ages 21 and 25 for genu and splenium, respectively),⁸² suggesting that these structures might serve as developmentally intermediate WM regions. The seven association regions included in our analyses are among the latest areas to develop, whereas the three control regions are known to be complete by very early childhood. Our results are consistent with the work of Bartzokis et al,^{45,46,47,48,49} who argued that WM breakdown in developmentally later myelinating association cortices may occur earlier among healthy older adults presenting with the APOE4 allele and associated with AD-related neurodegeneration; of note, however, is that the cross sectional nature of this study prevents interpretation of any possible rate of change over time. Also in support of the retrogenesis model, research in healthy APOE4 has revealed a particular predilection for association regions,⁹⁷ alongside accelerated loss of subcortical WM integrity.⁹⁷ Although no direct APOE group differences were documented,

the pattern of our current findings (i.e., affecting later but not earlier myelinating regions, and corticocortical areas before commissural and projection areas) may be potentially explainable by retrogenesis in APOE4 when mediated by CVD risk.

The impact of a disrupted blood brain barrier (BBB) should also be highlighted when considering the results of the present study, as previous work has revealed a potential common mechanism supporting the observed pathological WM changes. There is increasing evidence supporting anatomic, metabolic, and inflammatory mechanisms for BBB dysfunction as a result of DM.^{100,101,102} Even in the absence of clinical diabetes, episodes of hyperglycemia disrupt BBB permeability and edema formation, and precipitate neuropathological compromise.¹⁰⁰ Furthermore, APOE deficiency leads to BBB compromise¹⁰³ and APOE4 increases the susceptibility of the BBB to injury by regulating the integrity of tight junctions.¹⁰⁴ These results suggest BBB disruption among metabolically dysregulated and genetically at-risk individuals, and an underlying mechanism for microstructural pathology and dementia may be supported.

While GM atrophy in AD is now well understood, newer work suggests an additional role of brain WM which precedes these long observed GM changes. Despite the cross sectional nature of this study, the current work suggests that DTI may reveal pathological WM changes, particularly in individuals with co-occurring CVD risk, before the more prominent dysfunction associated with AD becomes apparent and visible on conventional MRI,^{56,57,59} and also highlights the prominence of cerebrovascular changes associated with a range of glucose dysregulation. Research during the preclinical phase is particularly important since vascular dysfunction may precede cortical neuropathology;³⁹ therefore, it is during this critical period that investigative efforts may be most fruitful. Our results support earlier preclinical detection among this susceptible subgroup, and suggest that such identification may serve as a critical biomarker for AD.

The present results suggest that APOE4 and diabetes risk, a significant CVD risk factor, are associated with deterioration among later myelinating WM regions. Findings highlight the importance of even mild metabolic dysregulation in moderating this relationship. Since vascular disease may accelerate WM changes and potentiate neurodegeneration in individuals at genetic risk for AD, inclusion of cerebrovascular risks will be important for advancing future research.

4.1 Limitations and Future Directions

Several limitations deserve comment. First, bias may exist in our sample when considering the higher prevalence of individuals with a positive first degree family history of dementia (87.9%), who are known to be at higher risk for dementia;⁸⁵ our data might thus reflect stronger associations between predictor variables and brain microstructure. This study also included a large proportion (33.6%) of African Americans, who are known to be at higher risk for vascular conditions^{105,106} and increased WM burden.¹⁰⁷ The relationships between cerebrovascular disease and brain WM integrity might not be fully generalizable or may be attenuated in the population. However, this sample characteristic might also be interpreted as a strength as it allowed us to more directly tap factors relevant to vascular risk which

might not be feasible in a lower risk group. Nonetheless, we recommend consideration of this demographic distribution.

The current study is also limited by its cross sectional design as we are unable to determine how genetics and vascular dysregulation confer longitudinal brain changes, particularly at the time of disease conversion. Although previous work has investigated early detection of AD through genetic status and brain volume,^{4,108} none have longitudinally investigated the impact of multiple (genetic, cerebrovascular) risks on WM microstructure.

Moreover, while the majority of participants presented with normal or mildly elevated glucose, a small percentage showed clinically elevated glucose and would be considered diabetic by clinical standards (i.e., nine [8.4%] had elevated fasting glucose, and eight [7.4%] had elevated H_{A1C} levels); thus, this sample reflects a wider range of vascular compromise than might be suggested by a strictly subclinical sample. Future research should be conducted with individuals presenting at an earlier stage of disease to investigate the limits of these findings. Additionally, data on the duration of vascular risk was not available, which has been shown to be related to WM integrity among DMII;⁵¹ thus, our ongoing work is now collecting this critical information.

Additionally, due to insufficient within cell sample size (APOE 3/4=25, APOE 4/4=2), we were unable to examine dose dependent relationships of the number of copies of the e4 allele on WM. Nevertheless, our results were not driven solely by the two homozygous participants, and thus the presence of only one copy appears sufficient to confer preferential WM degeneration. Among those studies which have more directly addressed this relationship, results have been conflicting; while some investigations have failed to detect dose dependent differences in brain volume,^{4,11,14,16,109} cross-sectional studies of nondemented persons with APOE4 do in fact demonstrate this relationship,^{110,111} and thus the relative impact of the number of copies of the e4 allele remains an important area for future investigation.

It is also possible that very mild cases of dementia were undetected given that only brief screens were conducted to rule out notable cognitive compromise and given that few participants presented with subclinically low MMSE scores (one participant with a score of 23 and three with a score of 24). Clearly the presence of even mild cognitive difficulties would be expected to impact microvascular integrity. However, all cases of frank dementia (based on MMSE screens) were ruled out. Our future work will consider any impact of the present neuropathological findings on cognition. Indeed, investigation into potential cognitive consequences of APOE4 and diabetes risk warrants future attention as existing data are limited, although current evidence suggests relationships of APOE4 and DM on cognition, particularly in the presence of both risks,^{112,113} and these risks appear to interact with WM change in predicting cognitive impairment.^{66,97} Further research is needed to expand upon these findings and investigate the combined impacts of both metabolic and genetic risk factors on cognition and its relationship WM change.

4.2. Conclusions

In summary, the results of the present study suggest interactive effects of APOE4 and diabetes risk on WM integrity, which supports aggressive management of cerebrovascular risk factors among this particularly susceptible subgroup. The combination of metabolic and genetic risk appears to be particularly deleterious for late myelinating WM integrity among healthy elderly, thus suggesting a critical neuroimaging biomarker for earlier disease detection among individuals who are particularly vulnerable to developing AD.

Acknowledgements

This work was supported by the National Institute of Neurologic Disorders and Stroke

(K23NS062148), the National Institute of Nursing Research (R01NR010827), the National Institute on Aging (P60AG08812 and P01AG004390), American Psychological Association Division 40, The Rosalind and Arthur Gilbert Foundation/AFAR New Investigator Award in Alzheimer's Disease, and by Medical Research Service VA Merit Review Awards to William Milberg and Regina McGlinchey.

Appendix A

Table A.1

Descriptive Statistics by Group for Demographic and Diabetes Data

	Group		Significance
	APOE4+ (n=27)	APOE4- (n=76)	P
Demographic	Mean (SD)	Mean (SD)	
Age	67.9 (8.6)	67.9 (9.4)	NS 0.98
Education	14.9 (2.9)	15 (2.7)	NS 0.90
Gender (male %)	37.0	38.8	NS 0.87
Ethnicity (%)	44.4 AA 55.6 C	30.0 AA 70.0 C	NS 0.17
Family History AD (%)	85.2	88.8	NS 0.97
MMSE	27.5	28.1	NS 0.12
Diabetes Measures			
Glucose	94.9 (18.7)	95.5 (16.9)	NS 0.87
HA1C	5.88 (8.0)	5.79 (0.6)	NS 0.54

AA=African American; C=Caucasian

Table A.2

Descriptive Statistics by Group for Regions of Interest

	Group		F	P
	APOE4+ Mean (SD)	APOE4- Mean (SD)		
ROIs (FA)				
Supramarginal	0.329 (0.26)	0.332 (0.022)	0.295	0.59
Inferior Temporal	0.341 (0.025)	0.342 (0.022)	0.036	0.85

	Group		<i>F</i>	<i>P</i>
	APOE4+	APOE4–		
<i>ROIs (FA)</i>	Mean (SD)	Mean (SD)		
Middle Temporal	0.327 (0.023)	0.330 (0.019)	0.262	0.61
Superior Temporal	0.344 (0.023)	0.344 (0.018)	<0.001	0.99
Precuneus	0.356 (0.031)	0.357 (0.027)	0.020	0.89
Superior Parietal	0.377 (0.027)	0.380 (0.023)	0.382	0.54
Superior Frontal	0.364 (0.028)	0.364 (0.018)	0.003	0.96
<i>Control ROIs (FA)</i>				
Cerebral Peduncles	0.606 (0.040)	0.608 (0.040)	0.061	0.81
Genu	0.661 (0.035)	0.642 (0.054)	3.052	0.08
Splenium	0.721 (0.030)	0.719 (0.041)	0.032	0.86

Table A.3

Direct and interactive relationships of APOE4 status and diabetes risk on FA for individual ROIs

ROI	<i>F</i> <i>M1</i> <i>M2</i> <i>M3</i>	<i>R</i> ²	Age		APOE4		Diabetes measure		AxD Interaction	
			<i>b</i>	<i>t</i>	<i>b</i>	<i>t</i>	<i>b</i>	<i>t</i>	<i>b</i>	<i>t</i>
<i>Glucose</i>										
Supra-marginal	9.195** 4.051** 4.565**	0.081 0.106 0.153	–0.285 –0.272 –0.284	–3.032** –2.091** –3.088**	–0.047 1.100	–0.500 2.224*	–0.153 –0.014	–1.630 –0.126	–1.17	–2.359*
Inferior Temporal	4.111* 2.660+ 3.106*	0.038 0.073 0.110	–0.195 –0.180 –0.190	–2.028* –1.882+ –2.018*	–0.015 1.005	–0.158 1.983	–0.186 –0.062	–1.945+ –0.555	–1.04	–2.048*
Middle Temporal	4.479* 3.942** 3.717**	0.041 0.104 0.128	–0.203 –0.183 –0.191	–2.116* –1.946+ –2.052*	–0.043 0.786	–0.462 1.567	–0.248 –0.147	–2.637** –1.329	–0.85	–1.682+
Superior Temporal	1.936 1.583 2.350+	0.018 0.044 0.085	–0.135 –0.122 –0.133	1.392 –1.259 –1.392	0.004 1.074	0.042 2.089*	–0.162 –0.032	–1.671+ –0.285	–1.09	–2.118*
Precuneus	15.812*** 7.017*** 6.846***	0.132 0.171 0.182	–0.363 –0.347 –0.358	–3.976*** –3.841*** –4.043***	–0.009 1.082	–0.099 2.296*	–0.198 –0.066	–2.193* –0.626	–1.12	–2.328*
Superior Parietal	14.493 6.170 6.432	0.122 0.154 0.171	–0.350*** –0.336*** –0.348***	–3.807*** –3.673*** –3.896***	–0.052 1.128	–0.573 2.351*	–0.170 –0.027	–1.865+ –0.256	–1.21	–2.503*
Superior Frontal	1.497 2.440+ 3.486**	0.014 0.067 0.121	–0.119 –0.101 –0.113	–1.224 –1.049 –1.029	–0.001 1.237	–0.008 2.455*	–0.230 –0.080	–2.401* –0.720	–1.27	–2.499*

ROI	F M1 M2 M3	R ²	Age		APOE4		Diabetes measure		AxD Interaction	
			<i>b</i>	<i>t</i>	<i>b</i>	<i>t</i>	<i>b</i>	<i>t</i>	<i>b</i>	<i>t</i>
Cerebral Peduncles	0.132 1.516 1.230	0.001 0.043 0.046	-0.150 -0.140 -0.142	-1.551 -1.441 -1.445	0.020 0.205 0.150	0.205 0.284 0.284	-0.128 -0.113 -0.113	-1.319 -0.969 -0.969	-0.13	-0.251
Genu	17.270*** 7.712*** 5.882***	0.142 0.185 0.189	-0.377 -0.370 -0.374	-4.156*** -4.129*** -4.151***	0.176 0.514	1.968 ⁺ 1.062	-0.105 -0.064	-1.167 -0.595	-0.35	-0.710
Splenium	2.406 1.398 1.054	0.023 0.039 0.040	-0.150 -0.140 -0.142	-1.551 -1.441 -1.445	0.020 0.205 0.150	0.205 0.284 0.284	-0.128 -0.113 -0.113	-1.319 -0.969 -0.969	-0.13	-0.251
<i>HAIC</i>										
Supra- marginal	8.315** 4.323** 5.040***	0.073 0.112 0.165	-0.271 -0.287 -0.299	-2.884** -3.075** -3.288***	-0.041 1.789	-0.440 2.473*	-0.190 -0.025	-2.035* -0.228	-1.86	-2.550*
Inferior Temporal	3.736 ⁺ 2.557 ⁺ 2.807*	0.034 0.069 0.099	-0.185 -0.201 -0.210	-1.933 ⁺ -2.106* -2.225*	-0.007 1.364	-0.073 1.815 ⁺	-0.187 -0.064	-1.958 -0.551	-1.39	-1.838 ⁺
Middle Temporal	3.670 ⁺ 3.168* 3.469*	0.034 0.084 0.120	-0.184 -0.202 -0.212	-1.916 ⁺ -2.135* -2.272*	-0.036 1.453	-0.384 1.956 ⁺	-0.221 -0.087	-2.331* -0.759	-1.52	-2.021*
Superior Temporal	1.680 1.432 1.970	0.016 0.040 0.035	-0.126 -0.139 -0.148	-1.296 -1.430 -1.545	0.010 1.422	0.102 -0.253	-0.157 -0.030	-1.615 -0.253	-1.44	-1.865 ⁺
Precuneus	14.834*** 5.679** 6.276***	0.124 0.142 0.198	-0.352 -0.363 -0.376	-3.852*** -3.963*** -4.215***	-0.005 1.866	-0.052 2.630**	-0.135 0.033	-1.469 0.306	-1.90	-2.658**
Superior Parietal	12.822*** 4.954** 5.681***	0.109 0.126 0.182	-0.330 -0.340 -0.352	-3.581*** -3.673*** 3.915***	-0.052 1.827	-0.567 2.551*	-0.118 0.051	-1.272 0.463	-1.91	-2.645**
Superior Frontal	1.196 3.078* 3.200*	0.011 0.082 0.111	-0.106 -0.128 -0.138	-1.093 -1.355 -1.466	0.011 1.368	0.166 1.832 ⁺	-0.268 -0.146	-2.822** -1.268	-1.38	-1.832 ⁺
Cerebral Peduncles	0.186 0.993 1.082	0.002 0.028 0.041	-0.042 -0.055 -0.061	-0.432 -0.569 -0.631	-0.014 0.876	-0.148 1.130	-0.161 -0.081	-1.652 -0.680	-0.91	-1.158
Genu	16.156*** 7.016*** 5.882***	0.133 0.170 0.187	-0.365 -0.373 -0.380	-4.019*** -4.139*** -4.238***	0.174 1.232	1.937 ⁺ 1.725 ⁺	-0.089 0.006	-0.983 0.058	-1.08	-1.493
Splenium	2.234 0.883 0.755	0.021 0.025 0.029	-0.144 -0.150 -0.153	-1.495 -1.532 -1.559	0.002 0.504	0.222 0.646	-0.063 0.020	-0.643 -0.162	-0.49	-0.623

Standardized Beta reported

M1: Model 1 (age); M2: Model 2 (APOE4 status, diabetes risk); M3: Model 3 (APOE4 status, diabetes risk, APOE4 status x diabetes risk)

* Significant at $p \leq 0.05$;

** Significant at $p \leq 0.01$;

*** Significant at $p \leq 0.001$;

⁺ Approaches significance (< 0.10)

Figure A.1.
Tract based spatial statistics (TBSS) ROI analysis procedure

*Scatterplot depicting multiple regression interaction of APOE4 and fasting glucose on WM integrity for the supramarginal region.
FA=fractional anisotropy; WM=white matter
 $p=0.020$

*Scatterplot depicting multiple regression interaction of APOE4 and HA1C on WM integrity for the supramarginal region.
 FA=fractional anisotropy; WM=white matter
 $p=0.012$

Figure A.2.
 Interaction between APOE status and glucose on Supramarginal WM

*Scatterplot depicting multiple regression interaction of APOE4 and fasting glucose on WM integrity for the Precuneus.
 FA=fractional anisotropy; WM=white matter
 $p=0.022$

*Scatterplot depicting multiple regression interaction of APOE4 and HA1C on WM integrity for the Precuneus.
 FA=fractional anisotropy; WM=white matter
 $p=0.009$

Figure A.3.

Interactions between APOE status and glucose on Precuneus WM

References

1. Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. *Dialogues of Clinical Neuroscience*. 2009; 11(2):111–28.
2. Götz J, Ittner LM, Lim YA. Common features between diabetes mellitus and Alzheimer's disease. *Cellular and Molecular Life Sciences*. 2009; 66(8):1321–1325. [PubMed: 19266159]
3. Hämäläinen A, Grau-Olivares M, Tervo S, Niskanen E, Pennanen C, Huuskonen J, et al. Apolipoprotein E epsilon 4 allele is associated with increased atrophy in progressive mild cognitive impairment: a voxel-based morphometric study. *Neurodegenerative Disorders*. 2008; 5(3–4):186–189.
4. Jack CR Jr, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, et al. Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. *Neurology*. 1998; 51(4):993–999. [PubMed: 9781519]
5. Plassman BL, Welsh-Bohmer KA, Bigler ED, Johnson SC, Anderson CV, Helms MJ, et al. Apolipoprotein E epsilon 4 allele and hippocampal volume in twins with normal cognition. *Neurology*. 1997; 48(4):985–989. [PubMed: 9109888]
6. Blacker D, Haines JL, Rodes L, Terwedow H, Go RC, Harrell LE, et al. ApoE-4 and age at onset of Alzheimer's disease: the NIMH genetics initiative. *Neurology*. 1997; 48:139–147. [PubMed: 9008509]
7. Hsiung GY, Sadovnick AD, Feldman H. Apolipoprotein E epsilon4 genotype as a risk factor for cognitive decline and dementia. *Canadian Medical Journal Association*. 2004; 171:863–867.
8. Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology*. 1993; 43(8):1467–1472. 1993. [PubMed: 8350998]

9. Cherbuin N, Leach LS, Christensen H, Anstey KJ. Neuroimaging and APOE genotype: a systematic qualitative review. *Dementia and Geriatric Cognitive Disorders*. 2007; 24(5):348–62. [PubMed: 17911980]
10. Reiman EM, Uecker A, Caselli RJ, Lewis S, Bandy D, de Leon MJ, et al. Hippocampal volumes in cognitively normal persons at genetic risk for Alzheimer's disease. *Annals of Neurology*. 1998; 44:288–291. [PubMed: 9708558]
11. Jernigan TL, Archibald SL, Fennema-Notestine C, Gamst AC, Stout JC, Bonner J, et al. Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiology of Aging*. 2001; 22:581–594. [PubMed: 11445259]
12. Morra JH, Tu Z, Apostolova LG, Green AE, Avedissianm C, Madsen SK, et al. Automated mapping of hippocampal atrophy in 1-year repeat MRI data from 490 subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls. *Neuroimage*. 2009; 45(1):S3–15. [PubMed: 19041724]
13. Serra-Grabulosa JM, Salgado-Pineda P, Junqué C, Solé-Padullés C, Moral P, López-Alomar A, et al. Apolipoproteins E and C1 and brain morphology in memory impaired elders. *Neurogenetics*. 2003; 4(3):141–146. [PubMed: 12736801]
14. Schmidt H, Schmidt R, Fazekas F, Semmler J, Kapeller P, Reinhart B, et al. Apolipoprotein E e4 allele in the normal elderly: neuropsychologic and brain MRI correlates. *Clinical Genetics*. 1996; 50(5):293–299. [PubMed: 9007313]
15. Tohgi H, Takahashi S, Kato E, Homma A, Niina R, Sasaki K, et al. Reduced size of right hippocampus in 39- to 80-year-old normal subjects carrying the apolipoprotein E epsilon4 allele. *Neuroscience Letters*. 1997; 236(1):21–24. [PubMed: 9404942]
16. Convit A, de Asis J, de Leon MJ, Tarshish CY, De Santi S, Rusinek H. Atrophy of the medial occipitotemporal, inferior, and middle temporal gyri in non-demented elderly predict decline to Alzheimer's disease. *Neurobiology of Aging*. 2000; 21(1):19–26. [PubMed: 10794844]
17. Burggren AC, Zeineh MM, Ekstrom AD, Braskie MN, Thompson PM, Small GW, et al. Reduced cortical thickness in hippocampal subregions among cognitively normal apolipoprotein E e4 carriers. *Neuroimage*. 2008; 41(4):1177–1183. [PubMed: 18486492]
18. de Leeuw FE, Richard F, de Groot JC, van Duijn CM, Hofman A, Van Gijn J, et al. Interaction between hypertension, apoE, and cerebral white matter lesions. *Stroke*. 2004; 35(5):1057–1060. [PubMed: 15060316]
19. Høgh P, Garde E, Mortensen EL, Jørgensen OS, Krabbe K, Waldemar G. The apolipoprotein E epsilon4-allele and antihypertensive treatment are associated with increased risk of cerebral MRI white matter hyperintensities. *Acta neurologica Scandinavica*. 2007; 115(4):248–253. [PubMed: 17376122]
20. Kim JS, Han SR, Chung SW, Kim BS, Lee KS, Kim YI, et al. The apolipoprotein E epsilon4 haplotype is an important predictor for recurrence in ischemic cerebrovascular disease. *Journal of the Neurological Sciences*. 2003; 206(1):31–37. [PubMed: 12480082]
21. Liu Y, Laakso MP, Karonen JO, Vanninen RL, Nuutinen J, Soimakallio S, et al. Apolipoprotein E polymorphism and acute ischemic stroke: a diffusion- and perfusion-weighted magnetic resonance imaging study. *Journal of Cerebral Blood Flow Metabolism*. 2002; 22(11):1336–42. [PubMed: 12439291]
22. Nierenberg J, Pomara N, Hoptman MJ, Sidtis JJ, Ardekani BA, Lim KO. Abnormal white matter integrity in healthy apolipoprotein E epsilon4 carriers. *Neuroreport*. 2005; 16(12):1369–1372. [PubMed: 16056141]
23. Tesseur I, Van Dorpe J, Bruynseels K, Bronfman F, Sciort R, Van Lommel A, et al. Prominent axonopathy and disruption of axonal transport in transgenic mice expressing human apolipoprotein E4 in neurons of brain and spinal cord. *American Journal of Pathology*. 2000; 157(5):1495–1510. [PubMed: 11073810]
24. Wen HM, Baum L, Cheung WS, Mok V, Lam WW, Tomlinson B, et al. Apolipoprotein E epsilon4 allele is associated with the volume of white matter changes in patients with lacunar infarcts. *European Journal of Neurology*. 2006; 13(11):1216–1220. [PubMed: 17038035]
25. Raz N, Rodrigue KM. Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neuroscience and Biobehavioral Reviews*. 2006; 30(6):730–748. [PubMed: 16919333]

26. Kennedy KM, Raz N. Pattern of normal age-related regional differences in white matter microstructure is modified by vascular risk. *Brain Research*. 2009; 1297:41–56. [PubMed: 19712671]
27. Leritz EC, Salat DH, Milberg WP, Williams VJ, Chapman CE, Grande LJ, et al. Variation in blood pressure is associated with white matter microstructure but not cognition in African Americans. *Neuropsychology*. 2010; 24(2):199–208. [PubMed: 20230114]
28. Leritz EC, Salat DH, Williams VJ, Schnyer DM, Rudolph JL, Lipsitz L, et al. Thickness of the human cerebral cortex is associated with metrics of cerebrovascular health in a normative sample of community dwelling older adults. *Neuroimage*. 2011; 54(4):2659–2671. [PubMed: 21035552]
29. Salat DH, Williams VJ, Leritz EC, Schnyer DM, Rudolph JL, Lipsitz LA, et al. Inter-individual variation in blood pressure is associated with regional white matter integrity in generally healthy older adults. *Neuroimage*. 2012; 59(1):181–92. [PubMed: 21820060]
30. Williams, VJ.; Leritz, EC.; Shepel, J.; McGlinchey, RE.; Milberg, WP.; Rudolph, JL., et al. Human Brain Mapping. 2012. Interindividual variation in serum cholesterol is associated with regional white matter tissue integrity in older adults. Epub ahead of print
31. Geraldles P, King GL. Activation of protein kinase C isoforms and its impact on diabetic complications. *Circulation Research*. 2010; 106(8):1319–1331. [PubMed: 20431074]
32. Akomolafe A, Beiser A, Meigs JB, Au R, Green RC, Farrer LA, et al. Diabetes Mellitus and risk of developing Alzheimer Disease: Results from the Framingham Study. *Archives of Neurology*. 2006; 63(11):1551–5. [PubMed: 17101823]
33. Irie F, Fitzpatrick AL, Lopez OL, Kuller LH, Peila R, Newman AB, et al. Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE epsilon4: the cardiovascular health study cognition study. *Archives of Neurology*. 2008; 65(1):89–93. [PubMed: 18195144]
34. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies. *Diabetes*. Apr.2002 51:1256–62. [PubMed: 11916953]
35. Caselli RJ, Dueck AC, Locke DE, Sabbagh MN, Ahern GL, Rapcsak SZ, et al. Cerebrovascular risk factors and preclinical memory decline in healthy APOE ε4 homozygotes. *Neurology*. 2011; 76(12):1078–84. [PubMed: 21325652]
36. Matsuzaki T, Sasaki K, Tanizaki Y, Hata J, Fujimi K, Matsui Y, et al. Insulin resistance is associated with the pathology of Alzheimer disease: The Hisayama Study. *Neurology*. 2010; 75(9):764–70. [PubMed: 20739649]
37. Craft S, Asthana S, Cook DG, Baker LD, Cherrier M, Purganan K, et al. Insulin dose–response effects on memory and plasma amyloid precursor protein in Alzheimer's disease: Interactions with apolipoprotein E genotype. *Psychoneuroendocrinology*. 2003; 28(6):809–22. [PubMed: 12812866]
38. Craft S, Asthana S, Schellenberg G, Baker L, Cherrier M, Boyt AA, et al. Insulin effects on glucose metabolism, memory, and plasma amyloid precursor protein in Alzheimer's disease differ according to Apolipoprotein-E genotype. *Annals New York Academy of Sciences*. 2000; 903:222–8.
39. de la Torre JC. Alzheimer's disease: how does it start? *Journal of Alzheimer's Disease*. 2002; 4(6): 497–512.
40. Burns JM, Church JA, Johnson DK, Xiong C, Marcus D, Fotenos AF, et al. White matter lesions are prevalent but differentially related with cognition in aging and early Alzheimer disease. *Archives of Neurology*. 2005; 62(12):1870–6. [PubMed: 16344345]
41. Esiri MM, Nagy Z, Smith MZ, Barnettson L, Smith AD. Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. *Lancet*. 1999; 354(9182):919–20. [PubMed: 10489957]
42. Gold BT, Johnson NF, Powell DK, C.D. Smith. White matter integrity and vulnerability to Alzheimer's disease: preliminary findings and future directions. *Biochimica et Biophysica Acta*. 2012; 1822(3):416–22. [PubMed: 21803153]
43. Hirano N, Kitagaki H, Kazui H, Hashimoto M, Mori E. Impact of white matter changes on clinical manifestation of Alzheimer's disease: A quantitative study. *Stroke*. 2000; 31(9):2182–8. [PubMed: 10978049]

44. Sjöbeck M, Englund E. Glial levels determine severity of white matter disease in Alzheimer's disease: a neuropathological study of glial changes. *Neuropathology and Applied Neurobiology*. 2003; 29(2):159–169. [PubMed: 12662323]
45. Bartzokis G. Age-related myelin breakdown: A developmental model of cognitive decline and Alzheimer's disease. *Neurobiological Aging*. 2004; 25:5–18.
46. Bartzokis G.; Lu, PH. Brain Volume: Age-related Changes. In: Squire, LR., editor. *New Encyclopedia of Neuroscience*. Academic Press; Oxford: 2007. p. 417–427.
47. Bartzokis G, Lu PH, Geschwind DH, Edwards N, Mintz J, Cummings JL. Apolipoprotein E genotype and age-related myelin breakdown in healthy individuals: implications for cognitive decline and dementia. *Archives of General Psychiatry*. 2006; 63:63–72. [PubMed: 16389198]
48. Bartzokis G, Lu PH, Geschwind DH, Tingus K, Huang D, Mendez MF, et al. Apolipoprotein E affects both myelin breakdown and cognition: implications for age-related trajectories of decline into dementia. *Biological Psychiatry*. 2007; 62:1380–1387. [PubMed: 17659264]
49. Bartzokis G, Lu PH, Mintz J. Human brain myelination and amyloid beta deposition in Alzheimer's disease. *Alzheimer's & Dementia: Journal of the Alzheimer's Association*. 2007; 3:122–125.
50. Lenroot RK, Giedd JN. Brain development in children and adolescents: insights from anatomical magnetic resonance imaging. *Neuroscience and Biobehavioral Reviews*. 2006; 30(6):718–729. [PubMed: 16887188]
51. Hsu JL, Chen YL, Leu JG, Jaw FS, Lee CH, Tsai YF, et al. Microstructural white matter abnormalities in type 2 diabetes mellitus: A diffusion tensor imaging study. *NeuroImage*. 2012; 59(2):1098–105. [PubMed: 21967726]
52. Reisberg B, Franssen EH, Hasan SM, Monteiro I, Boksay I, Souren LE, et al. Retrogenesis: clinical, physiologic, and pathologic mechanisms in brain aging, Alzheimer's and other dementing processes. *European Archives of Psychiatry and Clinical Neuroscience*. 1999; 249(S3):28–36. [PubMed: 10654097]
53. Yau PL, Javier D, Tsui W, Sweat V, Bruehl H, Borod JC, et al. Emotional and neural declarative memory impairments and associated white matter microstructural abnormalities in adults with type 2 diabetes. *Psychiatry Research*. 2009; 174(3):223–230. [PubMed: 19906514]
54. Basser PJ. Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. *NMR in Biomedicine*. 1995; 8(7–8):333–344. [PubMed: 8739270]
55. Sen PN, Basser PJ. A model for diffusion in white matter in the brain. *Biophysical Journal*. 2005; 89(5):2927–38. [PubMed: 16100258]
56. Bronge L. Magnetic resonance imaging in dementia. A study of brain white matter changes. *Acta Radiologica Supplement*. 2002; 428:1–32.
57. Schiavone F, Charlton RA, Barrick TR, Morris RG, Markus HS. Imaging age-related cognitive decline: A comparison of diffusion tensor and magnetization transfer MRI. *Journal of Magnetic Resonance Imaging*. 2009; 29(1):23–30. [PubMed: 19097099]
58. Sjöbeck M, Elfgren C, Larsson EM, Brockstedt S, Lätt J, Englund E, et al. Alzheimer's disease (AD) and executive dysfunction. A case-control study on the significance of frontal white matter changes detected by diffusion tensor imaging (DTI). *Archives of Gerontological Geriatrics*. 2010; 50(3):260–6.
59. Ukmar M, Makuc E, Onor ML, Garbin G, Trevisiol M, Cova MA. Evaluation of white matter damage in patients with Alzheimer's disease and in patients with mild cognitive impairment by using diffusion tensor imaging. *Radiological Medicine*. 2008; 113(6):915–922.
60. Salat DH, Tuch DS, Hevelone ND, Fischl B, Corkin S, Rosas HD, et al. Age-related changes in prefrontal white matter measured by diffusion tensor imaging. *Annals of the New York Academy of Sciences*. 2005; 1064:37–49. [PubMed: 16394146]
61. Salat DH, Tuch DS, van der Kouwe AJ, Greve DN, Pappu V, Lee SY, et al. White matter pathology isolates the hippocampal formation in Alzheimer's disease. *Neurobiology of Aging*. 2010; 31(2):244–256. [PubMed: 18455835]
62. Bendlin BB, Ries ML, Canu E, Sodhi A, Lazar M, Alexander AL, et al. White matter is altered with parental family history of Alzheimer's disease. *Alzheimer's Dementia*. 2010; 6(5):394–403.

63. Honea RA, Vidoni E, Harsha A, Burns JM. Impact of APOE on the healthy aging brain: a voxel-based MRI and DTI study. *Journal of Alzheimer's Disease*. 2009; 18(3):553–564.
64. Kanchibhotla SC, Mather KA, Wen W, Schofield PR, Kwok JB, Sachdev PS. Genetics of ageing-related changes in brain white matter integrity: a review. *Ageing Research Reviews*. 2013; 12(1): 391–401. [PubMed: 23128052]
65. Persson J, Nyberg L, Lind J, Larsson A, Nilsson LG, Ingvar M, et al. Structure-function correlates of cognitive decline in aging. *Cerebral Cortex*. 2006; 16(7):907–915. [PubMed: 16162855]
66. Westlye ET, Hodneland E, Haász J, Espeseth T, Lundervold A, Lundervold AJ. Episodic memory of APOE ϵ 4 carriers is correlated with fractional anisotropy, but not cortical thickness, in the medial temporal lobe. *Neuroimage*. 2012; 63(1):507–516. [PubMed: 22796460]
67. Leritz, EC.; Shepel, J.; Williams, VJ.; Lipsitz, LA.; McGlinchey, RE.; Milberg, WP., et al. Human Brain Mapping. 2013. Associations between T(1) white matter lesion volume and regional white matter microstructure in aging. Epub ahead of print
68. Fortuny LA, Briggs M, Newcombe F, Ratcliff G, Thomas C. Measuring the duration of post traumatic amnesia. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1980; 43(5):377–9.
69. Bohnstedt M, Fox PJ, Kohatsum ND. Correlates of Mini-Mental Status Examination scores among elderly demented patients: the influence of race-ethnicity. *Journal of Clinical Epidemiology*. 1994; 47(12):1381–7. [PubMed: 7730847]
70. American Diabetes Association. 2009.
71. Reese TG, Heid O, Weisskoff RM, Wedeen VJ. Reduction of eddy-current-induced distortion in diffusion MRI using a twice-refocused spin echo. *Magnetic Resonance Medicine*. 2003; 49(1): 177–182. 2003.
72. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*. 2004; 23(suppl 1):S209–9.
73. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage*. 2006; 31:1487–1505. [PubMed: 16624579]
74. Andersson, JLR.; Jenkinson, M.; Smith, S. Non-linear optimisation. FMRIB technical report TR07JA1 from. 2007a. www.fmrib.ox.ac.uk/analysis/techrep
75. Andersson, JLR.; Jenkinson, M.; Smith, S. Non-linear registration, aka Spatial normalisation FMRIB technical report TR07JA2. 2007b. from www.fmrib.ox.ac.uk/analysis/techrep
76. Rueckert D, Sonoda LI, Hayes C, Hill DL, Leach MO, Hawkes DJ. Nonrigid registration using free-form deformations: application to breast MR images. *IEEE transactions on medical imaging*. 1999; 18:712–721. [PubMed: 10534053]
77. Salat DH, Greve DN, Pacheco JL, Quinn BT, Helmer KG, Buckner RL, et al. Regional white matter volume differences in nondemented aging and Alzheimer's disease. *Neuroimage*. 2009; 44(4):1247–1258. [PubMed: 19027860]
78. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006; 31(3):968–80. [PubMed: 16530430]
79. Greve DN, Fischl B. Accurate and robust brain image alignment using boundary-based registration. *Neuroimage*. 2009; 48(1):63–72. [PubMed: 19573611]
80. Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *PNAS*. 2004; 101(21): 8174–8179. [PubMed: 15148381]
81. Qiu D, Tan L, Zhou K, Khong P. Diffusion tensor imaging of normal white matter maturation from late childhood to young adulthood: Voxel-wise evaluation of mean diffusivity, fractional anisotropy, radial and axial diffusivities, and correlation with reading development. *Neuroimag*. 2008; 41:223–232.
82. Lebel C, Gee M, Camicioli R, Wieler M, Martin W, Beaulieu C. Diffusion tensor imaging of white matter tract evolution over the lifespan. *Neuroimage*. 2012; 60:340–352. [PubMed: 22178809]

83. Schneider JFL, Il'yasov KA, Hennig J, Martin E. Fast quantitative diffusion-tensor imaging of cerebral white matter from the neonatal period to adolescence. *Neuroradiology*. 2004; 46:258–266. [PubMed: 14999435]
84. Partridge SC, Mukherjee P, Henry RG, Miller SP, Berman JI, Jin H, et al. Diffusion tensor imaging: serial quantitation of white matter tract maturity in premature newborns. *Neuroimage*. 2004; 22:1302–1314. [PubMed: 15219602]
85. Huang W, Qiu C, von Strauss E, Winblad B, Fratiglioni L. APOE genotype, family history of dementia, and Alzheimer disease risk: a 6-year follow-up study. *Archives of Neurology*. 2004; 61(12):1930–4. [PubMed: 15596614]
86. Luchsinger JA, Tang MX, Stern Y, Shea S, Mayeux R. Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *American Journal of Epidemiology*. 2011; 154(7):635–641. [PubMed: 11581097]
87. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, et al. Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. *Annals of Internal Medicine*. 2002; 137(3):149–155. [PubMed: 12160362]
88. Thamisetty M, Beason-Held L, An Y, Kraut MA, Resnick SM. APOE epsilon4 genotype and longitudinal changes in cerebral blood flow in normal aging. *Archives of Neurology*. 2010; 67(1): 93–98. [PubMed: 20065135]
89. Espeland MA, Bryan RN, Goveas JS, Robinson JG, Siddiqui MS, Liu S, et al. Influence of type 2 diabetes on brain volumes and changes in brain volumes: Results from the Women's Health Initiative Magnetic Resonance Imaging studies. *Diabetes care*. 2013; 36(1):90–7. [PubMed: 22933440]
90. Jongen C, van der Grond J, Kappelle LJ, Biessels GJ, Viergever MA, Pluim JP, et al. Automated measurement of brain and white matter lesion volume in type 2 diabetes mellitus. *Diabetologia*. 2007; 50(7):1509–16. [PubMed: 17492428]
91. Manschot SM, Brands AMA, van der Grond J, Kessels RP, Algra A, Kappelle LJ. Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. *Diabetes*. 2006; 55:1106–13. [PubMed: 16567535]
92. Reijmer YD, van den Berg E, de Bresser J, Kessels RP, Kappelle LJ, Algra A, et al. Accelerated cognitive decline in patients with type 2 diabetes: MRI correlates and risk factors. *Diabetes Metabolism Research and Reviews*. 2011; 27:195–202. [PubMed: 21294241]
93. Seo SW, Lee JM, Im K, Park JS, Kim SH, Kim ST, et al. Cardiovascular risk factors cause cortical thinning in cognitively impaired patients: Relationships among cardiovascular risk factors, white matter hyperintensities, and cortical atrophy. *Alzheimer's Disease and Associated Disorders*. 2012; 26(2):106–12.
94. Chen Z, Li L, Sun J, Ma L. Mapping the brain in type II diabetes: Voxel-based morphometry using DARTEL. *European journal of radiology*. 2012; 81(8):1870–6. [PubMed: 21546180]
95. Last D, Aslop DC, Abduljalil AM, Marquis RP, de Bazelaire C, Hu K, et al. Global and regional effects of type 2 diabetes on brain tissue volumes and cerebral vasoreactivity. *Diabetes Care*. 2007; 30(5):1193–9. [PubMed: 17290035]
96. Yau PL, Javier DC, Ryan CM, Tsui WH, Ardekani BA, Ten S, et al. Preliminary evidence for brain complications in obese adolescents with type 2 diabetes mellitus. *Diabetologia*. 2010; 53(11):2298–306. [PubMed: 20668831]
97. Ryan L, Walther K, Bendlin BB, Lue LF, Walker DG, Glisky EL. Age-related differences in white matter integrity and cognitive function are related to APOE status. *Neuroimage*. 2011; 54(2): 1565–77. [PubMed: 20804847]
98. Hermoye L, Saint-Martin C, Cosnard G, Lee SK, Kim J, Nassogne MC, et al. Pediatric diffusion tensor imaging: normal database and observation of the white matter maturation in early childhood. *Neuroimage*. 2006; 29(2):493–504. [PubMed: 16194615]
99. Paus T, Collins DL, Evans AC, Leonard G, Pike B, Zijdenbos A. Maturation of white matter in the human brain: a review of magnetic resonance studies. *Brain Reserve Bulletin*. 2001; 54(3):255–66.

100. Serlin Y, Levy J, Shalev H. Vascular pathology and blood brain barrier disruption in cognitive and psychiatric complications of type 2 diabetes mellitus. *Cardiovascular Psychiatry and Neurology*. 2011; 2011 doi: 10.1155/2011/609202.
101. Zlokovic BV. New therapeutic targets in the neurovascular pathway in Alzheimer's disease. *Neurotherapeutics*. 2009; 5(3):409–414. [PubMed: 18625452]
102. Starr JM, Wardlaw J, Ferguson K, MacLulich A, Deary IJ, Marshall I. Increased blood-brain barrier permeability in type II diabetes demonstrated by gadolinium magnetic resonance imaging. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2003; 74(1):70–6.
103. Zipser BD, Johanson CE, Gonzalez L, Berzin TM, Tavares R, Hulette CM, et al. Microvascular injury and blood-brain barrier leakage in Alzheimer's disease. *Neurobiology of Aging*. 2007; 28(7):977–86. [PubMed: 16782234]
104. Nishitsuji K, Hosono T, Nakamura T, Bu G, Michikawa M. Apolipoprotein E Regulates the Integrity of Tight Junctions in an Isoform-dependent Manner in an in Vitro Blood-Brain Barrier Model. *The Journal of Biological Chemistry*. 2011; 286(20):17536–17542. [PubMed: 21471207]
105. DeCarli C, Reed BR, Jagust W, Martinez O, Ortega M, Mungas DB. Brain behavior relationships among African Americans, whites, and Hispanics. *Alzheimer's Disease and Associated Disorders*. 2008; 22(4):382–391.
106. He J, Farias S, Martinez O, Reed B, Mungas D, DeCarli C. Differences in brain volume, hippocampal volume, cerebrovascular risk factors, and apolipoprotein E4 among mild cognitive impairment subtypes. *Archives of Neurology*. 2009; 66(11):1393–1399. [PubMed: 19901172]
107. Brickman AM, Schupf N, Manly JJ, Luchsinger JA, Andrews H, Tang MX, et al. Brain morphology in older African Americans, Caribbean Hispanics, and Whites from Northern Manhattan. *Archives of Neurology*. 2008; 65(8):1053–1061. [PubMed: 18695055]
108. Okonkwo OC, Alosco ML, Jerskey BA, Sweet LH, Ott BR, Tremont G, et al. Cerebral atrophy, apolipoprotein E4, and rate of decline in everyday function among patients with amnesic mild cognitive impairment. *Alzheimer's Dementia*. 2010; 6(5):404–411.
109. Cherbuin N, Anstey KJ, Sachdev PS, Maller JJ, Meslin C, Mack HA. Total and regional gray matter volume is not related to APOE*E4 status in a community sample of middle-aged individuals. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. [PubMed: 18511754]
110. Hashimoto M, Yasuda M, Tanimukai S, Matsui M, Hirono N, Kazui H, et al. Apolipoprotein E epsilon 4 and the pattern of regional brain atrophy in Alzheimer's disease. *Neurology*. 2001; 57(8):1461–6. [PubMed: 11673590]
111. Mori E, Lee K, Yasuda M, Hashimoto M, Kazui H, Hirono N, et al. Accelerated hippocampal atrophy in Alzheimer's disease with apolipoprotein E epsilon4 allele. *Annals of Neurology*. 2002; 51(2):209–214. [PubMed: 11835377]
112. Caselli RJ, Dueck AC, Locke DE, Sabbagh MN, Ahern GI, Rapcsak SZ, et al. Cerebrovascular risk factors and preclinical memory decline in healthy APOE ε4 homozygotes. *Neurology*. 2011; 76(12):078–84.
113. Stewart R, Russ C, Richards M, Brayne C, Lovestone S, Mann A. Apolipoprotein E genotype, vascular risk and early cognitive impairment in an African Caribbean population. *Dementia and Geriatric Cognitive Disorders*. 2001; 12(4):251–6. [PubMed: 11351136]