Affect of APOE on information processing speed in non-demented elderly population: a preliminary structural...

Article *in* Brain Imaging and Behavior · July 2016

DOI: 10.1007/s11682-016-9571-0

CITATIONS
0

READS
27

9 authors, including:

Xiao Luo
Zhejiang University
9 PUBLICATIONS **3** CITATIONS
SEE PROFILE

Xin-feng Yu
The Second Affiliated Hospital of Zhejiang U...
18 PUBLICATIONS **27** CITATIONS
SEE PROFILE

Peiyu Huang
Zhejiang University
41 PUBLICATIONS **103** CITATIONS
SEE PROFILE

Minming Zhang
Zhejiang University
103 PUBLICATIONS **1,183** CITATIONS
SEE PROFILE

Brain Imaging and Behavior
DOI 10.1007/s11682-016-9571-0

ORIGINAL RESEARCH

Affect of APOE on information processing speed in non-demented elderly population: a preliminary structural MRI study

Xiao Luo[1] · Yerfan Jiaerken[1] · Xinfeng Yu[1] · Peiyu Huang[1] · Tiantian Qiu[1] · Yunlu Jia[1] · Jianzhong Sun[1] · Jiong Zhou[2] · Minming Zhang[1] · for the Alzheimer's Disease Neuroimaging Initiative (ADNI)

Abstract APOE is one of the strongest genetic factors associated with information processing speed (IPS). Herein, we explored the neural substrates underlying APOE-related IPS alteration by measuring lobar distribution of white matter hyperintensities (WMH), cortical grey matter volume (GMV) and thickness. Using the ADNI database, we evaluated 178 cognitively normal elderly individuals including 34 APOE ε2 carriers, 54 APOE ε4 carriers and 90 ε3 homozygotes. IPS was determined using Trail Making Tests (TMT). We quantified lobar distribution of WMH, cortical GM lobar volume, cortical thickness among three groups. Finally, we used Pearson's correlation and general linear models to examine structural MRI markers in relation to IPS. There were significant differences of IPS among groups, with ε4 carriers displaying the worst performance. Across groups, significant differences in frontal and parietal WMH load were observed (the highest in ε4 carriers); however, no significant differences in cortical GMV and thickness were found. Pearson's correlation analysis showed parietal WMH volume was significantly related with IPS, especially in ε4 carriers. Subsequently a general linear model demonstrated that parietal WMH volume, age and the interaction between parietal WMH volume and age, was significantly associated with IPS, even after adjusting total intracranial volume (TIV), gender and vascular risk factors. Disruption of WM structure, rather than atrophy of GM, plays a more critical role in APOE ε4 allele-specific IPS. Moreover, specific WMH loci are closely associated with IPS; increased parietal WMH volume, especially in ε4 carriers, was independently contributed to slower IPS.

Keywords APOE · Information processing speed · White matter hyperintensities · Voxel-based morphometry (VBM) · Surface-based analysis

Xiao Luo and Yerfan Jiaerken contributed equally to this work.

Data used in preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (www.adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Electronic supplementary material The online version of this article (doi:10.1007/s11682-016-9571-0) contains supplementary material, which is available to authorized users.

✉ Minming Zhang
zhangminming@zju.edu.cn

for the Alzheimer's Disease Neuroimaging Initiative (ADNI)

[1] Department of Radiology, The 2nd Affiliated Hospital of Zhejiang University School of Medicine, No.88 Jiefang Road, Shangcheng District, Hangzhou, China

[2] Department of Neurology, The 2nd Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

Introduction

Information processing speed (IPS) is a fundamental component of general intelligence and may affect quality of life in patients with neurodegenerative diseases (Barker-Collo 2006). IPS is specifically defined as the execution time needed to carry out a cognitive task. Apart from age (Tombaugh 2004), the apolipoprotein (APOE) gene is one of the strongest genetic factors associated with IPS. Individuals with different APOE genotypes may have different trajectory of IPS development (Corder et al. 1993). Epidemiologic studies have revealed that APOE ε4 allele is associated with steeper age-related IPS decline (Lyall et al. 2014; Raz et al. 2009; Staehelin et al. 1999);

Published online: 21 July 2016

while conversely, the APOE ε2 allele is associated with higher IPS performances (Staehelin et al. 1999).

According to neuroimaging studies, APOE is associated with widespread alteration of brain structure (Reinvang et al. 2013). However, few studies had investigated the neural substrates underlying APOE related IPS alteration. Regardless of the phenotype of APOE, some studies have been shown that slower IPS is associated with grey matter volume (GMV) atrophy and cortical thinning (Rosano et al. 2012; Camilleri et al. 2015; Roher et al. 2002; Tuladhar et al. 2015). Meanwhile, there is an emerging literature from diffusion studies linking the disruption of white matter structure to slower IPS (Jacobs et al. 2013; Dong et al. 2015). Increased WMH volume, particularly when distributed in brain area involving parieto-frontal pathway, has been linked to slower IPS (Brickman et al. 2014; Bornebroek et al. 1997; Schilling et al. 2013). In summary, it is unclear whether APOE related effects on GM or WM structure, or both, contribute to IPS slower.

In the current study, our team aimed to explore the role of regional WMH and GM in APOE related IPS slower. This analysis was performed by assessing Trail Making Tests (TMT), regional WMH, cortical grey matter volume and thickness in different APOE genotype groups (ε2, ε4 and ε3 homozygotes). We explored and discussed the following hypothesis: 1) APOE ε4 carriers have heavier load of WMH than ε3 homozygotes, especially in the frontal and parietal lobe; 2) larger WMH volume is an important risk factor for APOE related IPS slower.

Materials and methods

Alzheimer's disease neuroimaging initiative

Data used in this study were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians in developing new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. For up-to-date information, see www.adni-info.org.

Study participants

This study was approved by all of the participating institution, and informed written consent was obtained from all participants at each site. And this study was also approved by the Medical Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine. At the time of analysis, individuals carrying at least one APOE ε4 allele (genotype ε4/ε4 and ε4/ε3) were classified as APOE ε4 carriers and carrying at least one ε2 allele (genotype ε2/ε2 and ε2/ε3) were classified as APOE genotype ε2 carriers. Moreover, individuals with genotype ε3/ε3 were classified as the controls. Given the possible confounding APOE-related effect, individuals with the APOE genotype ε2/ε4 were excluded (Suri et al. 2013a). Using the ADNI GO and ADNI 2 databases, 193 right-handed cognitively intact healthy participants, comprised of 35 APOE ε2 carriers, 59 APOE ε4 carriers and 99 non-carriers, who had undergone 3D MPRAGE T1-weighted structural scans, T2 FLAIR scans, and neuropsychological assessments, were identified. These study data were downloaded from the ADNI publically available database prior to November 15, 2015. According to the ADNI manual, the classification of cognitive normal were: the subject had an MMSE between 24 and 30 (inclusive), a clinical dementia rating (CDR) score of 0;, the subjects were also required to meet distinctive cutoffs for Wechsler Memory Scale-Logical Memory (WMS-LM) delay score (in detail: ≥ 9 for subjects with 16 or more years of education; ≥ 5 for subjects with 8–15 years of education; and ≥3 for 0–7 years of education). Additionally, no signs of depression (geriatric depression scale score < 5), or dementia were present. All subjects were screened and excluded for history of obvious head trauma that could impair cognitive function, history of addictions, neurologic or psychiatric disease, or treatments that would affect cognitive function.

After careful screening, 3 participant was excluded due to depression (geriatric depression scale score > 6); 1 subject was excluded because of disease-related occupation in the occipital lobe, 11 subjects were excluded due to poor image quality, often caused by excess head motion. Importantly, the subjects in this study were not preselected for presence or absence of WMH. Table 1 presents the demographic data for the remaining 178 subjects.

Neuropsychological assessment and APOE genotyping

The neuropsychological assessment used in the current study was downloaded from the ADNI database. The cognitive tests included the MMSE as a global measure for cognitive performance. Processing speed was determined using TMT (including the Part A and Part B). TMT is a standard component of Halstead-Reitan Neuropsychological Test Battery. Part A requires the subjects to draw lines to connect 25 consecutive numbers (i.e. 1–2-3…) while Part B requires drawing lines between both number and letters (i.e. 1-A, 2-B, 3-C…)

Table 1 Comparison among three subgroups of demographic and behavior data

	ε2 carriers	ε4 carriers	Controls	F/χ^2	P
Number	34	54	90		
Demographic characteristics					
Age, y, mean (SD)	74.92 ± 5.61	74.59 ± 7.33	74.53 ± 5.71	0.05	0.95
Female, n(%)	16(0.47)	28(0.52)	43(0.48)	0.28	0.87
Education, y, mean (SD)	16.97 ± 2.54	16.11 ± 2.74	16.71 ± 2.54	1.37	0.26
Vascular risk factors, n(%)					
Smoking history	11 (0.32)	13 (0.24)	18 (0.20)	2.1	0.35
Diabetes	1 (0.03)	1 (0.02)	7 (0.08)	2.81	0.25
Hachinski Ischemic Score	0.53 ± 0.79	0.44 ± 0.50	0.46 ± 0.56	0.24	0.79
Cognitive scores					
MMSE	28.21 ± 5.13	28.25 ± 4.12	28.56 ± 4.48	1.09	0.34
Log-transformed TMT A	1.47 ± 0.12	1.53 ± 0.13	1.48 ± 0.10	3.71	0.03*
Log-transformed TMT B	1.85 ± 0.11	1.89 ± 0.17	1.83 ± 0.16	2.12	0.12
TIV	1361.81 ± 134.83	1362.45 ± 148.15	1342.34 ± 127.11	0.38	0.69

MMSE Mini-Mental State Examination, *TMT* Trail Making Test, *TIV* Total intracranial volume

*represent $P < 0.05$

(Miner and Ferraro 1998). The score on each part represents the amount of time required to complete the task. Memory functioning was assessed using WMS-LM tests (including Immediate and Delayed part) for subjects screening. Depression was assessed by geriatric depression scale. Vascular disease was ascertained by self-report, which incorporated current or past diagnosis and treatment of diabetes. The risk of cerebrovascular component was assessed by Hachinski Ischemic Score (HIS). Detailed information of vascular factors could be found in ADNI database.

Genotyping of all subjects for APOE allele status was performed using DNA extracted from peripheral blood cells. The cells were collected in 1 EDTA plastic tubes (10 ml) and sent by overnight delivery, at room temperature, to the University of Pennsylvania AD Biofluid Bank Laboratory. Please see the ADNI-1 Procedures manual for more detailed information.

Data acquisition

Both the 3D MPRAGE T1-weighted and T2 FLAIR scans were acquired across sites following a standardized protocol that was validated across platforms. All participants were scanned using a 3.0-Tesla MRI scanner. The ADNI MRI scanner protocols are available for GE, Philips and Siemens devices. Given potential differences among these MRI scanners, the scanner types were controlled as a covariate in following statistical analysis. The 3D MPRAGE T1-weighted sequence were acquired using the following parameters: repetition time (TR) =2300 ms; echo time (TE) =2.98 ms; inversion time (TI) =900 ms; 170 sagittal slices; within plane FOV = 256 × 240 mm^2; voxel size = 1.1 × 1.1× 1.2 mm^3; flip angle = 9°; bandwidth = 240 Hz/pix. The T2 FLAIR scans were obtained using an echo-planar imaging sequence with the following parameters: TR = 9000 ms, TE = 90 ms, and TI = 2500 ms. Additional details regarding MRI acquisition are available elsewhere (http://adni.loni.usc.edu/methods/documents/mri-protocols/).

WMH segmentation and quantification

For each subject, WMH lesion map was automatically created based on 3D MPRAGE T1-weighted and T2 FLAIR image using Lesion Segmentation Toolbox in SPM8 (Schmidt et al. 2012). To be specific, this software classifies the tissue into gray matter, white matter and cerebrospinal fluid based on the 3D MPRAGE T1-weighted image. Then the T2 FLAIR intensity was used to determine lesion beliefs. Next, a conservative lesion belief is expanded; neighboring voxels are added to lesion under certain threshold and the likelihood of the voxel being WM or GM is weighed against the likelihood of being lesion. This process will repeat iteratively until no new voxels are added to the lesions (Schmidt et al. 2012).

The masks were then manually corrected by two experienced neuroradiologists (MMZ, HPY) using ITK-SNAP software (www.itksnap.org). Then we coregistered the 3D MPRAGE T1 image, T2 FLARI and corrected masks to the standard atlas (UNC adult brain atlas template, created by University of North Carolina at Chapel Hill, www.nitrc.org). We combined our corrected masks with the UNC lobar parcellation mask, separating WMH ROI into the 4 brain lobes (fontal, occipital, temporal and parietal lobe, Fig. 1). Notably, WMH in the subcortical region were not taken into account, which may influence our result. The WMH volume in each brain lobe was subsequently calculated by multiplying voxel numbers in each lobar ROI by voxel size.

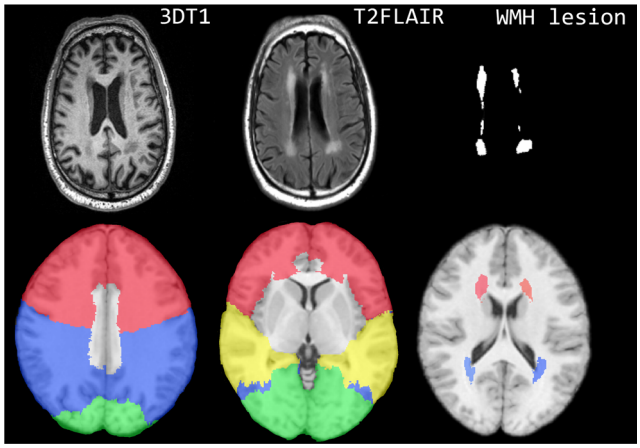

Fig. 1 For each subject, WMH lesion map was automatically created based on 3D T1-weighted and T2 FLAIR image. We coregistered the 3D T1 scan, T2-FLAIR and corrected masks to the standard atlas. Then, we combined our corrected masks with the UNC lobar parcellation mask (www.nitrc.org), separating WMH ROI into the 4 brain lobes (red color represents the frontal lobe, yellow represent the temporal lobe, green color represent occipital lobe and blue represent parietal lobe)

The mean of all corrected and coregistered WMH masks in each group was calculated using the MRIcroN software (www.mricro.com Version 4 April 2011). Figure 2 represents the cumulative WMH maps in each group.

Surface-based association analysis

Cortical GM segmentation data were downloaded from the ADNI database. Surface-based cortical analyses were performed with the FreeSurfer software package, version 5.1 (http://surfer.nmr.mgh.harvard.edu). These procedures have been fully described in previous publications (Fischl and Dale 2000). Surface-based analyses in FreeSurfer involved the removal of non-brain tissue by a hybrid watershed algorithm, and automated Talairach transformation, segmentation of subcortical WM and GM, intensity normalization, tessellation of GM/WM boundary, automated correction of topological defects, and surface deformation to form the GM and WM boundary. Regional cortical volume was determined as the difference between the pial and WM surface. Cortical thickness were also obtained using Freesurfer, by measuring the distance between reconstructed representations of the inner and the outer surface of the cortical mantle. Subjects with quality control result of "Partial" or "Fail" are excluded from further analysis. After screening, 164 subjects remained in the study (including 84 controls, 29 APOE ε2 carriers and 51 APOE ε4 carriers. More detail in Supplement A). Please see the ADNI-1 Procedures manual for more detailed information (http://www.adni-info.org). Finally, the results of regional GMV and cortical thickness were shown in Supplement A.

VBM

Scans were processed with VBM in SPM8, using previously described methods (Nho et al. 2012). Briefly, 3D-MPRAGE scans were aligned to the T1-weighted template image. We segmented them into GM, WM, and CSF compartments with bias correction. Finally, the GM density maps were normalized to Montreal Neurological Institute atlas space as 1 mm × 1 mm × 1 mm voxels and smoothed using 8 mm FWHM Gaussian kernel. Then, modulated GM maps were generated and analyzed. A threshold of $p < 0.05$ (corrected by FWE) and minimum cluster size of 10 voxels was considered significant.

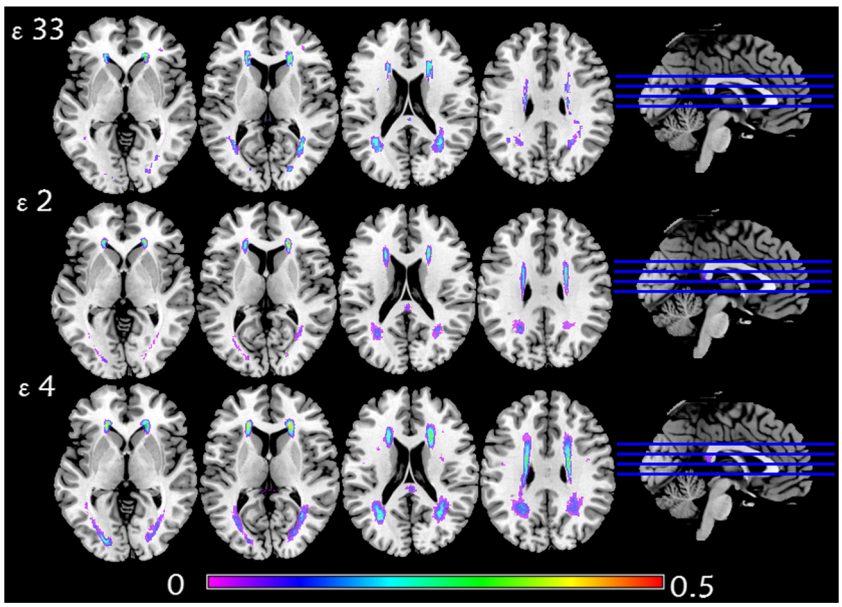

Fig. 2 Cumulative WMH map in (**a**) APOE ε2 carrier group, (**b**) the controls and (**c**) APOE ε4 group. Only areas with WMH in at least 5 % of the patients are shown. Compared with the controls, APOE ε4 carriers have more WMH burden, especially in the parietal and frontal lobe

Statistical analysis

All statistical analyses were performed using IBM SPSS19 statistical software on Windows (http://www-01.ibm.com/software/analytics/spss). Descriptive statistics on the subjects were given as means ± SD for continuous variables and percent prevalence for dichotomous variables. The TMT scores were log-transformed due to positively skewed distribution. Gender data, vascular risk factors and MRI scanner type were analyzed using a Chi-square test. Differences in age, education, log-transformed TMT scores, lobar WMH volume, cortical GMV, cortical thickness, TIV among three groups were examined by one-way analysis of variance (ANOVA). Using Bonferroni correction, post-hoc pair wise T tests was performed if ANOVA was significant ($p < 0.05$). To assess the possible correlation between MRI markers and IPS, Pearson's correlation was firstly performed across the entire sample and in subgroup level. Then the general lineal model was used. With dependent variable was log transformed TMT-A ranking; fixed factors were: gender, smoking (yes/no), diabetes (yes/no), ε4 carrying and ε2 carrying. Covariates were WMH volume, intracranial volume, HIS, age, education attainment and MRI scanners. The impact of interaction between 1) age and WMH 2) WMH and ε4 carrying 3) WMH and ε2 carrying were also tested.

Results

Demographics and behavioral data

An overview of demographic variables and neuropsychological performance is presented in Table 1. There were no significant differences among groups in MMSE, gender distribution, age or educational status. Additionally, there was no significant difference in the cardiovascular risk profile among groups as determined by the HIS, smoking history and diabetes. As expected, there was significant difference in log-transformed TMT-A ($P = 0.026$). The post-hoc T test showed that ε4 carriers had inferior TMT-A than controls ($p = 0.032$, corrected by Bonferroni). However, there was no significant difference among groups in log-transformed TMT-B ($p > 0.05$).

Comparison of WMH burden, cortical grey matter volume and thickness

The frequency maps of WMH in three groups are shown in Fig. 2. Following an ANOVA analysis, significant differences in global WMH volume across groups were observed ($p = 0.017$). Subsequent post-hoc T test demonstrated that ε4 carriers had more global WMH volume than controls ($p = 0.017$, corrected by Bonferroni). The analysis result of Freesurfer demonstrated that there were no differences in any regional cortical GMV or cortical gray matter thickness among three groups (details in Supplement A). Similarly, VBM analysis did not identify any differences in grey matter density among three groups (Cluster size > 10 voxel, $P < 0.05$, corrected by FWE).

Further comparison of lobar WMH volume showed significant differences in parietal and frontal lobe between groups ($p < 0.05$). The post-hoc T test demonstrated that APOE ε4 carriers displayed significantly increased WMH volume in parietal and frontal lobe ($p < 0.05$, corrected by Bonferroni) as compared to controls (Fig. 3).

Correlation between WMH volume and IPS

Across groups, a correlation analysis noted that global WMH volume was significantly related with log-transformed TMT-A ($r = 0.15, p < 0.05$), and only the parietal WMH volume was significantly related with log-transformed TMT-A ($r = 0.224$, $p = 0.006$). In subgroup level, parietal WMH volume was significantly related with log-transformed TMT-A in ε4 carriers ($r = 0.32$, $p = 0.032$, Fig. 4). However, there was no statistically significant association between parietal WMH volume and log-transformed TMT-A observed in ε2 carriers and controls ($p > 0.05$).

Subsequent GLM showed that parietal WMH volume, age, and the interaction between parietal WMH volume and age was significantly associated with log-transformed TMT-A. However, gender, total intracranial volume (TIV), HIS, frontal WMH volume, MRI scanners and the interaction of APOE genotype with WMH volume had no impact on log transformed TMT-A (Table 2).

Discussion

Although the neurobiological underpinnings are poorly understood, many epidemiological studies had suggested there exist an APOE-related effect on IPS. The current study aimed to explore

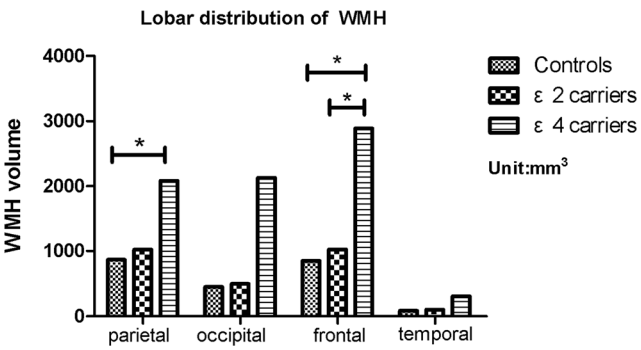

Fig. 3 Lobe distribution of mean WMH volume across groups. The histogram showing ε4 carriers had significant increased WMH burden in parietal and frontal regions relative to controls. *represents $p < 0.05$, corrected by Bonferroni

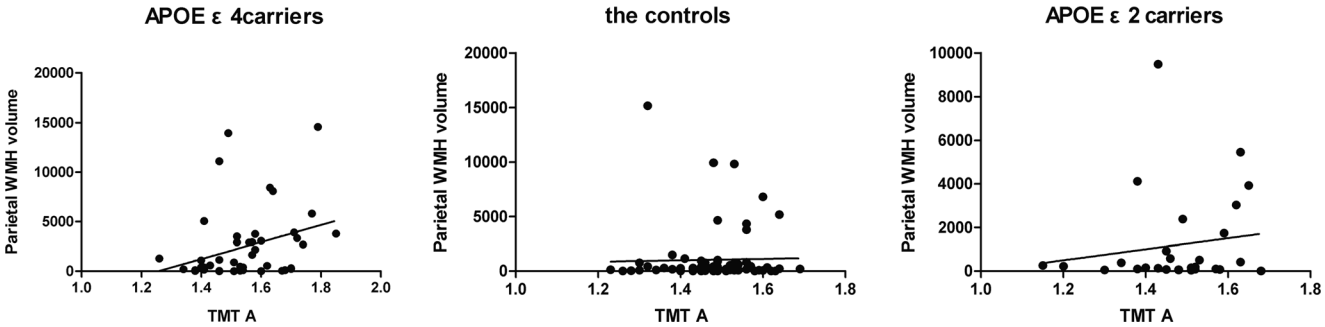

Fig. 4 Scatter plot association between parietal WMH volume and TMT-A score in all subgroup. Parietal WMH volumes was significantly associated with log-transformed TMT-A score (r = 0.32, p = 0.032) in ε4 carriers. No significant associations existed between parietal WMH volume and log-transformed TMT-A score in controls and ε2 carriers

the neural basis underlying APOE related IPS alteration by measuring lobar distribution of WMH and regional cortical volume in cognitively normal elderly population. Our results demonstrated that: (1) ε4 carriers had more WMH volume than controls, particularly in frontal and parietal lobe; (2) parietal WMH volume was associated with IPS, especially in ε4 carriers.

The effects of APOE on lobar distribution of WMH

In the present study, irrespective of regional distribution, the APOE ε4 carriers had significantly increased global WMH volume relative to controls. It is known that APOE ε4 allele is associated with aggregation of Aβ protein and decreased clearance of Aβ deposition relative to ε3 allele (Jiang et al. 2008; Reinvang et al. 2013). One of the physiological interpretations of our observations is that, relative increased Aβ deposition in ε4 carriers affect arterial wall and reduce vessel lumen, leading to chronic hypoperfusion and formation of WMH (Kalaria 1997; Schilling et al. 2013). Additionally, the mechanism by which APOE ε4 allele is linked to increased WMH volume can also be considered from the perspective of myelin metabolism. ApoE is the most abundant cholesterol transporter in the brain, and cholesterol is an essential component of myelin sheaths (Han 2007; Mahley 1988). Since the number of apoE molecules in ε4 is 12 % lower than controls, the decrement in myelin repair process of APOE ε4 carriers may also contribute to formation of WMH (Boyles et al. 1989; Poirier 2005).

Notably, APOE ε4 carriers had more WMH volume than controls in frontal and parietal lobe rather than in other lobes.

Table 2 General linear model for TMT-A score (log10-transformed)

Factors	Type III sum of square	F value	Sig.
ε2 carrying	0.006	0.534	0.466
ε4 carrying	0.014	1.185	0.278
Age	0.153	12.829	<0.001*
Gender (female or male)	0.011	0.943	0.333
Education(years)	0.00005483	0.005	0.946
HIS	0.008	0.679	0.411
Diabetes (yes or no)	0.004	0.346	0.558
Smoking (yes or no)	0.006	0.469	0.495
MRI scanner	0.009	0.377	0.687
Parietal WMH volume (mm^3)	0.058	4.824	0.03*
Frontal WMH volume (mm3)	0.009	0.748	0.389
ε2 carrying × parietal WMH volume	0.006	0.505	0.479
ε2 carrying × frontal WMH volume	0.008	0.643	0.424
ε4 carrying × parietal WMH volume	0.021	1.745	0.189
ε4 carrying × frontal WMH volume	0	0.014	0.906
age × parietal WMH volume	0.056	4.684	0.032*
age × frontal WMH volume	0.01	0.865	0.354
TIV	0.032	2.724	0.101

WMHs white matter hyperintensities, *HIS* Hachinski Ischemic Score, *TIV* Total intracranial volume

*represent $P < 0.05$

This was broadly in line with one recent study, which showed ε4 carriers had higher WMH in parietal in 1233 subjects (including 1178 healthy elderly) (Brickman et al. 2014). As for the regional selectivity of WMH, the exact mechanism is still unclear, but may stem from the perilous blood supply (Wen and Sachdev 2004). Specifically, the supply vessels of frontal and parietal WM come from two origins: superficially from the subarachnoid circulation, and at the base of the brain, from the large vessel as arterial perforators. The two systems, passing cortical layers and the deep gray structures respectively, converge towards each other at the periventricular WM (mostly located in parietal and frontal lobe). Anastomoses in this area are scarce and arterioles are tortuous (Yoshita et al. 2006). Given the possible effect of APOE ε4 status on perfusion alteration, the frontal and parietal WM may particularly susceptible to ischemic events resulting from APOE ε4 status (Pantoni 2010; Pantoni and Garcia 1997).

It should be noted that we did not identify any protective effects of ε2 allele on WM; rather, we found that APOE ε4 carriers and ε2 carriers had a similar WMH volume. Moreover, one recent study reported that healthy ε2 allele carriers had larger frontal WMH volume than ε3 homozygotes and even ε4 carriers. Intriguingly, a number of studies using resting state functional MRI or DTI approach also revealed ε4 and ε2 carriers exhibited similar brain function alterations relative to ε3 homozygotes, rather than showing opposite effects (Suri et al. 2013b; Westlye et al. 2012). Although the mechanism remains unclear, our findings support the hypothesis that APOE ε2 may have other effects on the brain, beyond the originally reported protective function (Suri et al. 2013b).

Physiological interpretation of APOE related effects on IPS

In the current study, ε4 carriers had significantly reduced TMT A score relative to controls. However, when age and WMH are included as covariant in the GLM, the ε4 carrying status no longer had any impact on IPS., GLM suggested that parietal WMH load, age and the interaction between parietal WMH load and age exerted significant effect on IPS. Therefore our results suggest that differences in IPS observed between APOE genotype groups were mainly driven by WMH volume. The parietal regions served as the "hubs" within the brain functional network (Buckner et al. 2009; Drzezga et al. 2011), which had disproportionately numerous connections to other brain regions. In particular, the parieto-frontal connection is necessary for the processing of the visual scene and is pivotal for IPS (Thiebaut et al. 2005). Thus, we speculated that the primary mechanism underlying the association of parietal WMH with IPS could be considered as a functional "disconnection" symptom. The deficits in superior longitudinal fasciculus of parieto-frontal connection may influence the efficiency of integrating diverse informational sources and manifested as reduced IPS (O'Sullivan et al. 2001).

Notably, we did not identify any significant differences in regional cortical GMV or cortical thickness among groups, despite differences in WMH among groups. This suggest WM may be more susceptible to the modification effects of ε4 allele, before volume changes are detectable by GM. Similar result had been reported by a previous study, which examined both the WM integrity and GM volume in cognitively normal APOE ε4 carriers and found only decreased WM integrity (Gold et al. 2010). Several factors may influence in our findings. First, GM having better perfusion than WM and thus more resilient to ischemic event may account for our findings (Wright et al. 2015). Second, APOE ε4 allele is linked with myelin metabolisms in central neuron system and may interfere with myelin repairing, which may partially explain the selective damage on myelin-rich WM rather than GM (Wen and Sachdev 2004). However, some prior studies carried out on healthy elderly have shown that slowed IPS was associated with both WM deterioration and GM atrophy (Schiavone et al. 2009; Chee et al. 2009; Eckert et al. 2010; Hong et al. 2015). Apart from the effects of APOE genotype, several reasons may also account for the discrepancy between our results and these works. Firstly, the rate of brain atrophy can be influenced by the difference of education, ethnic group or environmental factors (Brickman et al. 2008; Staff et al. 2006). Compared to these studies, we found that the subjects of our study, downloaded from ADNI database, were mainly composed of Caucasian (92.9 %) and had relative higher educational attainment (mean 16.58 ± 2.6 years). Secondly, the relatively simple neuropsychological test of IPS (TMT A&B) and different brain structure measures (WMH volume) may also attribute to the discrepancy.

It is important to note that there exist several limitations with this exploratory analysis. The current cross-sectional study has limited ability to draw definitive conclusions about causal relationships of APOE status and brain structural, and thus, longitudinal studies are needed. Moreover, although ε4 carriers had more frontal WMH volume than controls, no significant association between frontal WMH and log-transformed TMT A score was observed. Thus, further studies to detect the relationship between IPS and microstructure of WM obtained by DTI data are needed. Furthermore, to acquire more information on brain structure, more sensitive measures such as Vertex-wise analysis of cortical thickness should be done in the further. Finally, despite the large sample size, the number of APOE ε2 carriers was relative low and therefore not powerful enough to detect small differences.

Thus, our results should be confirmed in future studies using a larger subject cohort, ideally with more ε2 carriers (including subjects with APOE ε2/ε4 genotype).

Conclusion

Our findings revealed that APOE ε4 allele has a detrimental effect on parietal and frontal WM in cognitively normal elderly; and we demonstrate that IPS deficits can be explained by parietal WMH volume, age and interaction between parietal WMH volume and age. Clinically, this research may provide additional insight into therapy of cognitive decline diseases by developing drug targeting WMH progression.

Acknowledgments Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.;Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Eisai Inc.; ElanPharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd. and its affiliatedcompany Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen AlzheimerImmunotherapy Research & Development, LLC.; Johnson & Johnson PharmaceuticalResearch & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; MesoScaleDiagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis PharmaceuticalsCorporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; andTransition Therapeutics. The Canadian Institutes of Health Research is providing funds tosupport ADNI clinical sites in Canada. Private sector contributions are facilitated by theFoundation for the National Institutes of Health (www.fnih.org). The grantee organization isthe Northern California Institute for Research and Education, and the study is coordinatedby the Alzheimer's Disease Cooperative Study at the University of California, San Diego.ADNI data are disseminated by the Laboratory for Neuro Imaging at the University ofSouthern California.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Informed consent Written informed consent was obtained from all participants and/or authorized representatives and the study partners before any protocol-specific procedures were carried out in the ADNI study. More details in http://www.adni-info.org.

Funding This study was funded by the 12th Five-year Plan for National Science and Technology Supporting Program of China (Grant No. 2012BAI10B04), Zhejiang Provincial Natural Science Foundation of China (Grant No. LZ14H180001 and Grant No. Y16H090026).

References

Barker-Collo, S. L. (2006). Quality of life in multiple sclerosis: does information-processing speed have an independent effect? *Archives of Clinical Neuropsychology, 21*, 167–174.

Bornebroek, M., Haan, J., Van Duinen, S. G., Maat-Schieman, M. L., Van Buchem, M. A., Bakker, E., Van Broeckhoven, C., & Roos, R. A. (1997). Dutch hereditary cerebral amyloid angiopathy: structural lesions and apolipoprotein E genotype. *Annals of Neurology, 41*, 695–698.

Boyles, J. K., Zoellner, C. D., Anderson, L. J., Kosik, L. M., Pitas, R. E., Weisgraber, K. H., Hui, D. Y., Mahley, R. W., Gebicke-Haerter, P. J., Ignatius, M. J., & Et, A. (1989). A role for apolipoprotein E, apolipoprotein A-I, and low density lipoprotein receptors in cholesterol transport during regeneration and remyelination of the rat sciatic nerve. *Journal of Clinical Investigation, 83*, 1015–1031.

Brickman, A. M., Schupf, N., Manly, J. J., Luchsinger, J. A., Andrews, H., Tang, M. X., Reitz, C., Small, S. A., Mayeux, R., & DeCarli, C. (2008). Brain morphology in older African Americans, Caribbean Hispanics, and whites from northern Manhattan. *Archives of neurology, 65*, 1053–1061.

Brickman, A. M., Schupf, N., Manly, J. J., Stern, Y., Luchsinger, J. A., Provenzano, F. A., Narkhede, A., Razlighi, Q., Collins-Praino, L., Artero, S., Akbaraly, T. N., Ritchie, K., Mayeux, R., & Portet, F. (2014). APOE epsilon4 and risk for Alzheimer's disease: do regionally distributed white matter hyperintensities play a role? Alzheimers. *Dementia, 10*, 619–629.

Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F. M., Liu, H., Hedden, T., Andrews-Hanna, J. R., Sperling, R. A., & Johnson, K. A. (2009). Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *Journal of Neuroscience, 29*, 1860–1873.

Camilleri, J. A., Reid, A. T., Muller, V. I., Grefkes, C., Amunts, K., & Eickhoff, S. B. (2015). Multi-modal imaging of neural correlates of motor speed performance in the trail making test. *Frontiers in Neurology, 6*, 219.

Chee, M. W., Chen, K. H., Zheng, H., Chan, K. P., Isaac, V., Sim, S. K., Chuah, L. Y., Schuchinsky, M., Fischl, B., & Ng, T. P. (2009). Cognitive function and brain structure correlations in healthy elderly east Asians. *NeuroImage, 46*, 257–269.

Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G.W., Roses, A.D., Haines, J.L., Pericak-Vance, M.A., 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261, 921–923.

Dong, C., Nabizadeh, N., Caunca, M., Cheung, Y. K., Rundek, T., Elkind, M. S., DeCarli, C., Sacco, R. L., Stern, Y., & Wright, C. B. (2015). Cognitive correlates of white matter lesion load and brain atrophy: the northern Manhattan study. *Neurology, 85*, 441–449.

Drzezga, A., Becker, J. A., Van Dijk, K. R., Sreenivasan, A., Talukdar, T., Sullivan, C., Schultz, A. P., Sepulcre, J., Putcha, D., Greve, D., Johnson, K. A., & Sperling, R. A. (2011). Neuronal dysfunction and disconnection of cortical hubs in non-demented subjects with elevated amyloid burden. *Brain, 134*, 1635–1646.

Eckert, M. A., Keren, N. I., Roberts, D. R., Calhoun, V. D., & Harris, K. C. (2010). Age-related changes in processing speed: unique contributions of cerebellar and prefrontal cortex. *Frontiers in Human Neuroscience, 4*, 10.

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America, 97*, 11050–11055.

Gold, B. T., Powell, D. K., Andersen, A. H., & Smith, C. D. (2010). Alterations in multiple measures of white matter integrity in normal women at high risk for Alzheimer's disease. *NeuroImage, 52*, 1487–1494.

Han, X., 2007. Potential mechanisms contributing to sulfatide depletion at the earliest clinically recognizable stage of Alzheimer's disease: a tale of shotgun lipidomics. Journal of Neurochemistry 103 Suppl 1, 171–179.

Hong, Z., Ng, K. K., Sim, S. K., Ngeow, M. Y., Zheng, H., Lo, J. C., Chee, M. W., & Zhou, J. (2015). Differential age-dependent associations of gray matter volume and white matter integrity with processing speed in healthy older adults. *NeuroImage, 123*, 42–50.

Jacobs, H. I., Leritz, E. C., Williams, V. J., Van Boxtel, M. P., van der Elst, W., Jolles, J., Verhey, F. R., McGlinchey, R. E., Milberg, W. P., & Salat, D. H. (2013). Association between white matter microstructure, executive functions, and processing speed in older adults: the impact of vascular health. *Human Brain Mapping, 34*, 77–95.

Jiang, Q., Lee, C.Y., Mandrekar, S., Wilkinson, B., Cramer, P., Zelcer, N., Mann, K., Lamb, B., Willson, T.M., Collins, J.L., Richardson, J.C., Smith, J.D., Comery, T.A., Riddell, D., Holtzman, D.M., Tontonoz, P., Landreth, G.E., 2008. ApoE promotes the proteolytic degradation of Abeta. Neuron 58, 681–693.

Kalaria, R. N. (1997). Cerebrovascular degeneration is related to amyloid-beta protein deposition in Alzheimer's disease. *Annals of the New York Academy of Sciences, 826*, 263–271.

Lyall, D. M., Harris, S. E., Bastin, M. E., Munoz, M. S., Murray, C., Lutz, M. W., Saunders, A. M., Roses, A. D., Valdes, H. M. C., Royle, N. A., Starr, J. M., Porteous, D. J., Wardlaw, J. M., & Deary, I. J. (2014). *Are APOE varepsilon genotype and TOMM40 poly-T repeat length associations with cognitive ageing mediated by brain white matter tract integrity? Transl psychiatry 4* (p. e449).

Mahley, R. W. (1988). Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science, 240*, 622–630.

Miner, T., & Ferraro, F. R. (1998). The role of speed of processing, inhibitory mechanisms, and presentation order in trail-making test performance. *Brain and Cognition, 38*, 246–253.

Nho, K., Risacher, S. L., Crane, P. K., DeCarli, C., Glymour, M. M., Habeck, C., Kim, S., Lee, G. J., Mormino, E., Mukherjee, S., Shen, L., West, J. D., & Saykin, A. J. (2012). Voxel and surface-based topography of memory and executive deficits in mild cognitive impairment and Alzheimer's disease. *Brain Imaging and Behavior, 6*, 551–567.

O'Sullivan, M., Jones, D. K., Summers, P. E., Morris, R. G., Williams, S. C., & Markus, H. S. (2001). Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology, 57*, 632–638.

Pantoni, L. (2010). Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurology, 9*, 689–701.

Pantoni, L., & Garcia, J. H. (1997). Pathogenesis of leukoaraiosis: a review. *Stroke, 28*, 652–659.

Poirier, J. (2005). Apolipoprotein E, cholesterol transport and synthesis in sporadic Alzheimer's disease. *Neurobiology of Aging, 26*, 355–361.

Raz, N., Rodrigue, K. M., Kennedy, K. M., & Land, S. (2009). Genetic and vascular modifiers of age-sensitive cognitive skills: effects of COMT, BDNF, ApoE, and hypertension. *Neuropsychology, 23*, 105–116.

Reinvang, I., Espeseth, T., & Westlye, L. T. (2013). APOE-related biomarker profiles in non-pathological aging and early phases of Alzheimer's disease. *Neuroscience and Biobehavioral Reviews, 37*, 1322–1335.

Roher, A. E., Weiss, N., Kokjohn, T. A., Kuo, Y. M., Kalback, W., Anthony, J., Watson, D., Luehrs, D. C., Sue, L., Walker, D., Emmerling, M., Goux, W., & Beach, T. (2002). Increased a beta peptides and reduced cholesterol and myelin proteins characterize white matter degeneration in Alzheimer's disease. *Biochemistry, 41*, 11080–11090.

Rosano, C., Studenski, S. A., Aizenstein, H. J., Boudreau, R. M., Longstreth, W. J., & Newman, A. B. (2012). Slower gait, slower information processing and smaller prefrontal area in older adults. *Age and Ageing, 41*, 58–64.

Schiavone, F., Charlton, R. A., Barrick, T. R., Morris, R. G., & Markus, H. S. (2009). Imaging age-related cognitive decline: a comparison of diffusion tensor and magnetization transfer MRI. *Journal of Magnetic Resonance Imaging, 29*, 23–30.

Schilling, S., DeStefano, A. L., Sachdev, P. S., Choi, S. H., Mather, K. A., DeCarli, C. D., Wen, W., Hogh, P., Raz, N., Au, R., Beiser, A., Wolf, P. A., Romero, J. R., Zhu, Y. C., Lunetta, K. L., Farrer, L., Dufouil, C., Kuller, L. H., Mazoyer, B., Seshadri, S., Tzourio, C., & Debette, S. (2013). APOE genotype and MRI markers of cerebrovascular disease: systematic review and meta-analysis. *Neurology, 81*, 292–300.

Schmidt, P., Gaser, C., Arsic, M., Buck, D., Forschler, A., Berthele, A., Hoshi, M., Ilg, R., Schmid, V. J., Zimmer, C., Hemmer, B., & Muhlau, M. (2012). An automated tool for detection of FLAIR-hyperintense white-matter lesions in multiple sclerosis. *NeuroImage, 59*, 3774–3783.

Staehelin, H. B., Perrig-Chiello, P., Mitrache, C., Miserez, A. R., & Perrig, W. J. (1999). Apolipoprotein E genotypes and cognitive functions in healthy elderly persons. *Acta Neurologica Scandinavica, 100*, 53–60.

Staff, R. T., Murray, A. D., Deary, I. J., & Whalley, L. J. (2006). Generality and specificity in cognitive aging: a volumetric brain analysis. *NeuroImage, 30*, 1433–1440.

Suri, S., Heise, V., Trachtenberg, A. J., & Mackay, C. E. (2013a). The forgotten APOE allele: a review of the evidence and suggested mechanisms for the protective effect of APOE varepsilon2. *Neuroscience and Biobehavioral Reviews, 37*, 2878–2886.

Suri, S., Heise, V., Trachtenberg, A. J., & Mackay, C. E. (2013b). The forgotten APOE allele: a review of the evidence and suggested mechanisms for the protective effect of APOE varepsilon2. *Neuroscience and Biobehavioral Reviews, 37*, 2878–2886.

Thiebaut, D. S. M., Urbanski, M., Duffau, H., Volle, E., Levy, R., Dubois, B., & Bartolomeo, P. (2005). *Direct evidence for a parietal-frontal pathway subserving spatial awareness in humans* (Vol. 309, pp. 2226–2228). Science.

Tombaugh, T. N. (2004). Trail Making Test A and B: normative data stratified by age and education. *Archives of Clinical Neuropsychology, 19*, 203–214.

Tuladhar, A. M., Reid, A. T., Shumskaya, E., de Laat, K. F., van Norden, A. G., van Dijk, E. J., Norris, D. G., & de Leeuw, F. E. (2015). Relationship between white matter hyperintensities, cortical thickness, and cognition. *Stroke, 46*, 425–432.

Wen, W., & Sachdev, P. (2004). The topography of white matter hyperintensities on brain MRI in healthy 60- to 64-year-old individuals. *NeuroImage, 22*, 144–154.

Westlye, L. T., Reinvang, I., Rootwelt, H., & Espeseth, T. (2012). Effects of APOE on brain white matter microstructure in healthy adults. *Neurology, 79*, 1961–1969.

Wright, S. N., Hong, L. E., Winkler, A. M., Chiappelli, J., Nugent, K., Muellerklein, F., Du, X., Rowland, L. M., Wang, D. J., & Kochunov, P. (2015). Perfusion shift from white to gray matter may account for processing speed deficits in schizophrenia. *Human Brain Mapping, 36*, 3793–3804.

Yoshita, M., Fletcher, E., Harvey, D., Ortega, M., Martinez, O., Mungas, D. M., Reed, B. R., & DeCarli, C. S. (2006). Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. *Neurology, 67*, 2192–2198.