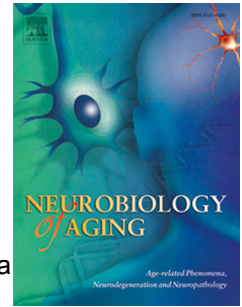


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**Cortical β -Amyloid Burden, Gray Matter, and Memory in Adults at Varying APOE $\epsilon 4$
Risk for Alzheimer's Disease**

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Abstract

Models of preclinical Alzheimer's disease (AD) propose that cerebral amyloidosis leads to neurodegeneration and subsequent cognitive decline. This study investigated whether *APOE* genotype is related to β -amyloid ($A\beta$) burden in brain regions preferentially affected by AD and whether $A\beta$ burden is associated with gray matter fraction (as a marker of neurodegeneration) and episodic memory performance in cognitively normal middle-aged individuals at varying genetic risk for AD. Three groups of cognitively normal participants aged 50-65 with a first-degree family history of AD [*APOE* genotype $\epsilon 4\epsilon 4$ (n=15), $\epsilon 3\epsilon 4$ (n=15), and $\epsilon 3\epsilon 3$ (n=15)], underwent [^{11}C]PiB PET scans to quantify cortical $A\beta$, brain MRI and neuropsychological testing. *APOE* $\epsilon 4\epsilon 4$ participants demonstrated significantly higher cortical $A\beta$ burden than *APOE* $\epsilon 3\epsilon 3$ ($p < 0.001$). Furthermore, cortical $A\beta$ burden was inversely associated with cortical gray matter fraction ($p = 0.017$), but not episodic memory performance. In cognitively normal, middle-aged individuals, $A\beta$ burden is significantly associated with gray matter fraction but not episodic memory performance. These findings are consistent with models of preclinical AD in which neurodegeneration occurs before manifest cognitive decline.

Keywords: Amyloid- β , Apolipoprotein E, Alzheimer's disease, [^{11}C]PiB, PET, Preclinical Alzheimer's disease

1. Introduction

In recent years, Alzheimer's disease (AD) has been conceptualized as a continuum of disease, beginning with a preclinical stage in which symptoms are not yet present (Sperling et al., 2011). The preclinical stage is postulated to involve accumulating brain pathology followed by very subtle cognitive decline. This stage may precede Mild Cognitive Impairment (MCI) by several years and represents an important stage for early intervention and symptom prevention. Most research in preclinical AD and prevention has focused on the 65+ population. The study of this older age group offers a high likelihood of capturing cases of preclinical AD, as the percentage of individuals with cerebral β -amyloid ($A\beta$) pathology increases from about 20% at age 65 to about 40% at age 85 (Jansen et al., 2015). AD prevention studies are already targeting this age group, which confers greater practical power to test treatments (Sperling et al., 2014).

Work to operationalize the new NIA-Alzheimer's Association diagnostic criteria has thus largely focused on adults over 65 years of age (Jack et al., 2012). Moreover, convergent evidence suggests that elderly individuals with brain $A\beta$ accumulation demonstrate subtle cortical thinning (Dickerson et al., 2009), greater rates of cortical and hippocampal atrophy (Andrews et al., 2013; Chetelat et al., 2012; Schott et al., 2010), and disruption of functional connectivity (Hedden et al., 2009; Mormino et al., 2011; Sheline et al., 2010). Finally, a number of studies have reported that individuals with elevated brain $A\beta$ perform worse on neuropsychological tests (Hedden et al., 2012; Rentz et al., 2010; Rodrigue et al., 2012; Sperling et al., 2013) and are at increased risk for cognitive decline and progression to MCI and AD dementia (Ellis et al., 2013; Knopman et al., 2012; Lim et al., 2013b; Morris et al., 2009).

However, an equally important but comparatively neglected population is that of middle-aged (50-65) individuals with preclinical AD. This younger age group may present an earlier stage of disease pathogenesis and thus a greater opportunity for early intervention. Studies of preclinical AD in the 50-65-year-old population require the use of risk factors (family history and *APOE* ϵ 4) to enrich samples for the presence of AD pathogenesis. Studies of cognitively normal individuals at high genetic risk of AD (i.e., *APOE* ϵ 4 homozygotes and heterozygotes, compared to non-carriers, mean age 64 years) have reported that cortical fibrillar A β burden is significantly associated with *APOE* ϵ 4 carrier status and *APOE* ϵ 4 dose (Reiman et al., 2009). In cognitively normal subjects enriched for parental family history and *APOE* ϵ 4 enrolled in the Wisconsin Registry for AD Prevention (mean age 60-61 years) A β status has not been associated with lower GM volume (Johnson et al., 2014), but has been linked to thinning of entorhinal cortex (Doherty et al., 2015). Moreover, elevated brain A β has not been associated with cognition cross-sectionally but confers an increased risk of MCI longitudinally and steeper rates of cognitive decline (Clark et al., 2016).

In the present study, our over-arching goal was to utilize a middle-aged sample that is highly enriched—both for family history and genetic risk of AD—to address three major hypotheses: 1) that *APOE* genotype was related to global fibrillar A β burden as measured by [^{11}C]PiB) in cognitively normal first-degree relatives; 2) that fibrillar A β burden was associated with gray matter fraction (as a marker of neurodegeneration) in brain regions known to be preferentially affected by AD; and 3) that fibrillar A β burden was associated with episodic memory (and neuropsychological test) performance. The primary analyses were performed with partial volume

corrected (PVC) PET data, but we also studied the effect of PVC on the results.

2. Methods

2.1. Participants

Cognitively normal adults aged 50-65 with a positive family history for probable AD (in at least one first-degree relative) were invited to participate. After signing informed consent, as approved by the Yale Human Investigation Committee, potentially eligible participants underwent an initial Screening Genetic Evaluation that involved a medical history questionnaire and confidential *APOE* genotyping [as previously described (van Dyck et al., 1998)] of 454 individuals. Participants were selected from each of three *APOE* genotype groups ($\epsilon 4\epsilon 4$, $\epsilon 3\epsilon 4$, and $\epsilon 3\epsilon 3$) and individually matched for age (± 2 years) and sex for further study. These individuals underwent an additional Screening Diagnostic Evaluation to ensure eligibility. Assessments included ECG, physical examination, screening laboratory studies including chemistry profile, CBC, thyroid function studies, B12, and urinalysis, as well as Mini Mental Status Examination (MMSE) (Folstein et al., 1975), Clinical Dementia Rating Scale (CDR) (Morris, 1993), Logical Memory II (Wechsler, 1987), and the Geriatric Depression Scale. Participants were excluded for possible or probable AD (McKhann et al., 1984), or MCI (Petersen, 2004) [as evidenced by $CDR > 0$ (Morris, 1993) and abnormal memory function documented by scoring 1.5 SD below education adjusted cutoff on Logical Memory II subscale from Wechsler Memory Scale – Revised (Wechsler, 1987)], or has a score on MMSE (Folstein et al., 1975) < 27 . In addition, they were excluded for any significant neurologic disease, unstable

medical condition, history of alcohol or substance abuse/dependence within the past 5 years, major psychiatric disorder, use of medications with central nervous system activity within 4 weeks, pregnancy, or contraindications to magnetic resonance imaging (MRI).

Participants then underwent a detailed neuropsychological test battery (Supplementary Table 2) to enable analysis of neuropsychological correlates of [^{11}C]PiB binding. PET and MRI scanning were then scheduled within one month. Neuropsychological testing and brain image analyses were performed by investigators blind to participant genotype.

2.2. Magnetic Resonance Imaging

MRI was performed on a 3T Trio Scanner: 1) to exclude any structural abnormalities; and 2) to co-register the PET and MRI images for image analysis and PVC. A sagittal 3D-MPRAGE-FSPGR pulse sequence with an IR prep of 300ms (TE=3.34ms, TI=1100ms, TR=2500ms, flip angle=7, slice thickness=1.0mm, 176 slices, matrix=256x256) was utilized for delineating gray matter (GM), white matter (WM), and CSF boundaries, and the small voxel size (0.98x1.00x0.98mm) provided high-resolution volumetric images.

2.3. [^{11}C]PiB PET imaging

Participants underwent [^{11}C]PiB PET scanning with the ECAT HR+ (Siemens) operating in 3D mode producing 63 slices with slice separation of 2.4mm and final image resolution of ~6mm. A

transmission scan was acquired for attenuation correction. Then 15 mCi of [^{11}C]PiB was administered by iv injection, followed by dynamic scanning for 90 min.

2.4. Image analyses

2.4.1. Reconstruction/Registration—PET images were reconstructed into 27 frames, containing 63 axial slices of 128x128 voxels (2.1x2.1x2.4mm). Reconstruction included corrections for attenuation, randoms, scatter, and deadtime. Motion correction was applied to the dynamic images, using a mutual-information algorithm (FSL-FLIRT, FSL 3.2; Analysis Group, FMRIB, Oxford, UK) by frame-by-frame registration to a summed image (0-10 min postinjection). A summed image was then created from the motion-corrected data, and registered to the participant's MR anatomical image (6-parameter affine registration, FSL-FLIRT), which was then registered to the Montreal Neurological Institute (MNI) MR template (Holmes et al., 1998) using a nonlinear transform (BioImage Suite version 2.5; www.bioimagesuite.com).

2.4.2. Regions of Interest (ROIs)—The Anatomical Automatic Labeling (AAL) algorithm for SPM2 (Tzourio-Mazoyer et al., 2002) was used to define ROIs for both PET images and MRI. For our primary outcome measure, a mean cortical ROI consisting of frontal, posterior cingulate, precuneus, lateral parietal, and lateral temporal ROIs was used. Based on the published list of AAL regions (Tzourio-Mazoyer et al., 2002), the frontal ROI included frontal, anterior cingulate, middle cingulate, and insular cortex regions 3–34; the posterior cingulate ROI regions 35–36, the precuneus ROI regions 67–68; the lateral temporal ROI regions 79–90; the lateral parietal ROI regions 59–66; and the cerebellar reference ROI regions 91–115.

2.4.3. MRI Segmentation—Prior to transformation to MNI template space, MR images were segmented into GM, WM, and CSF using FAST— FMRIB’s Automated Segmentation Tool (The Analysis Group, FMRIB, Oxford, UK). To quantify cortical GM within each ROI while accounting for intersubject variability in brain size, we applied inverse transformations of the AAL from MNI to subject space and calculated GM fraction as the number of voxels segmenting as GM divided by the total number of voxels in a region. GM fractions (ranging between 0.00 and 1.00) were thus generated for the mean cortical ROI and component ROIs.

2.4.4. Partial Volume Correction (PVC)—Some studies of cognitively intact adults have shown GM reduction in *APOE* carriers relative to non-carriers (Wishart et al., 2006). Therefore, we applied PVC to PET images and also analyzed the effects of PVC. In this approach (Muller-Gartner et al., 1992), binary mask images of GM and WM were smoothed to the system resolution (~6mm). For each dynamic PET frame, GM voxels were corrected for spill-in and spill-out of activity, assuming activity in CSF was zero and WM activity was uniform and was estimated from each image time frame.

2.4.5. Tracer Kinetic Modeling—Parametric images of BP_{ND} (the ratio at equilibrium of specifically bound radioligand to that of nondisplaceable radioligand in tissue (Innis et al., 2007)) were generated using SRTM2 (Wu and Carson, 2002) using whole cerebellum as reference region for both uncorrected and partial volume corrected PET scans. BP_{ND} was calculated so that a value of 0 reflects no specific binding, i.e., tracer uptake no greater than that in the reference region. This is directly related to the distribution volume ratio (DVR) reported

by other investigators (Reiman et al., 2009), in that $DVR=BP_{ND}+1$. BP_{ND} images were created from both original, uncorrected data, and from partial-volume corrected image data. Three sets of BP_{ND} values were extracted: i) uncorrected BP_{ND} from the full AAL region, ii) uncorrected BP_{ND} from the AAL regions masked to only include GM voxels, and iii) PVC- BP_{ND} images, again with GM masking. In secondary analyses, we investigated the effect of PVC on measurement of $A\beta$ binding. Unless otherwise noted, BP_{ND} refers to the calculation using PVC images.

2.5. Statistical analyses

Differences among genotype groups were assessed using ANOVA for continuous variables and χ^2 tests for categorical variables. To investigate the association between *APOE* genotype and $A\beta$ burden, a multivariable generalized linear model was fit for mean cortical BP_{ND} with *APOE* genotype as the main explanatory variable and age and sex as covariates. A natural logarithm link was used for the right-skewed outcomes. In addition, to account for clustering introduced by matching on age and sex, a robust variance estimator was used by invoking the quasi-likelihood estimation method of generalized estimating equations. Secondary analyses examined the association between *APOE* genotype and BP_{ND} for each of the five component ROIs.

The association between $A\beta$ burden and cortical GM fraction within the mean cortical ROI was assessed using a general linear model with mean cortical BP_{ND} as the main explanatory variable and age and sex as covariates. For the association between $A\beta$ burden and episodic memory performance, an episodic memory score was calculated (by averaging the z-scores for California

Verbal Learning Test free delayed recall and Logical Memory II) and was assessed using the same general linear model as for GM fraction. Secondary analyses explored the association between either *APOE* genotype or mean cortical A β burden and performance on each of the neuropsychological tests. Since individual test scores were not all normally distributed, the Kruskal-Wallis test and Spearman's rank correlation were utilized.

Finally, the effect of PVC on mean cortical A β values was explored. Spearman's rank correlation coefficient was used to assess the association between cortical GM fraction and the change in BP_{ND} from uncorrected to PVC. In addition, model fits of BP_{ND} were examined using separate general linear models with *APOE* genotype as the main explanatory variable, as well as age and sex covariates. Williams t-test was used to compare the differences in correlation between GM fraction and BP_{ND} values for the uncorrected, GM masked, and PVC conditions (Weaver and Wuensch, 2013).

P-values <0.05 for two-sided tests were interpreted as statistically significant. Analyses used either SPSS version 21.0 (IBM Corp.) or Matlab R2015a Statistics Toolbox (Mathworks, Inc.).

3. Results

3.1. Participant characteristics

The final study sample consisted of 45 cognitively normal FDRs who were enrolled in three *APOE* genotype groups: $\epsilon 3\epsilon 3$ (n=15), $\epsilon 3\epsilon 4$ (n=15), and $\epsilon 4\epsilon 4$ (n=15). Table 1 summarizes the

demographics and clinical characteristics of each group. As they were individually matched for age and sex, the *APOE* groups did not differ with respect to these variables. In addition, they did not differ in education, WRAT-3 Reading subtest standard score as an estimate of premorbid intelligence, MMSE, full scale IQ score, or GDS score.

3.2. Association between *APOE* Genotype and Cortical A β Burden (BP_{ND})

As depicted in Figure 1, *APOE* $\epsilon 4\epsilon 4$ participants had significantly higher mean cortical BP_{ND} (0.455) than those with $\epsilon 3\epsilon 3$ (0.187) ($p < 0.001$), and $\epsilon 3\epsilon 4$ participants (0.346) were marginally higher than those with $\epsilon 3\epsilon 3$ ($p = 0.125$), but $\epsilon 4\epsilon 4$ and $\epsilon 3\epsilon 4$ groups did not differ ($p = 0.317$). A significant linear trend ($p < 0.005$) indicated that as the $\epsilon 4$ allele number increased, cortical A β burden increased proportionally. Results for the individual brain ROIs that comprise the mean cortical ROI are presented in Supplementary Table 1.

3.3. Association between Cortical A β Burden (BP_{ND}) and Cortical Gray Matter Fraction

The unadjusted association between mean cortical BP_{ND} and cortical GM fraction values within the mean cortical ROI in the overall sample is displayed in Figure 2A by a linear regression line and its 95% confidence interval. Mean cortical BP_{ND} was inversely associated with GM fraction (regression coefficient = -0.046, $p = 0.017$) in a general linear model with adjustments for age and sex covariates. Post hoc analysis showed that this association was also present prior to PVC for GM masked mean cortical BP_{ND} (regression coefficient = -0.046, $p = 0.048$, Figure 2C).

3.4. Association between Cortical A β Burden (BP_{ND}) and Episodic Memory

Performance

The unadjusted association between BP_{ND} and episodic memory performance values within the mean cortical ROI in the overall sample is displayed in Figure 2B by a linear regression line and its 95% confidence interval. There was no statistically significant association between mean cortical BP_{ND} and episodic memory performance (regression coefficient = -0.317, $p = 0.558$) in a general linear model with adjustments for age and sex. Post hoc analysis showed that this association was also non-significant prior to PVC for GM masked mean cortical BP_{ND} (regression coefficient = 0.127, $p = 0.846$, Figure 2D).

Exploratory analysis was performed using the larger neuropsychological battery. *APOE* genotype was not associated with any of the neuropsychological test performance measures (Supplementary Table 2). In addition, there were no significant correlations between any neuropsychological test and mean cortical A β burden (BP_{ND}) in the overall sample (Supplementary Table 3).

3.5. Effect of Partial Volume Correction on BP_{ND}

As expected, PVC tended to increase values of BP_{ND} in the overall participant sample (N=45). Figure 3 demonstrates the effect of PVC on BP_{ND} images of participants with high and low A β load. Values of mean cortical BP_{ND} increased from 0.10 ± 0.18 uncorrected, to 0.13 ± 0.20 GM masked, to 0.28 ± 0.24 with PVC. Not surprisingly, the increase in mean cortical BP_{ND} produced

by PVC (from uncorrected to PVC-corrected) was highly inversely associated with the cortical GM fraction (Spearman $r = -0.46$, $p < 0.002$). I.e., uncorrected analyses may underestimate A β burden to a greater extent in individuals with lower cortical GM fraction. Although *APOE* $\epsilon 4$ allele number is associated with increased cortical amyloid even prior to PVC, PVC improved the goodness of fit (R^2) for the overall model (Table 2). In addition, the association between cortical GM fraction and cortical A β burden is significantly greater when PVC is performed compared with GM mask correction alone (Williams t-score = 2.15, $p = 0.04$) or with no correction (Williams t-score = 3.04, $p = 0.004$).

4. Discussion

We studied cognitively normal middle-aged individuals with a first-degree family history of AD and varying *APOE* risk to investigate the relationship between A β deposition, GM fraction, and neuropsychological test performance in this unique population. *APOE* $\epsilon 4\epsilon 4$ participants demonstrated significantly higher mean cortical A β burden (PVC BP_{ND}) than $\epsilon 3\epsilon 3$ participants, with $\epsilon 3\epsilon 4$ marginally higher than $\epsilon 3\epsilon 3$ participants. In the overall sample, A β burden was inversely associated with GM fraction within the mean cortical ROI. Reported results show no statistically significant association between mean cortical A β burden and episodic memory performance. PVC increased values of BP_{ND} and led to a statistically significant increase in the association between cortical A β burden and GM fraction.

4.1. Comparison with In Vivo Imaging Studies

Our results corroborate and extend observations by Reiman et al (Reiman et al., 2009), but with a somewhat reduced *APOE* $\epsilon 4$ effect on A β deposition in this younger sample (mean age 59 vs. 64). Our findings are also consistent with those of Johnson et al. (Johnson et al., 2014) and demonstrate that in high-risk individuals, considerable A β deposition begins by the early 50s, and earlier than has generally been reported in large series of cognitively normal participants (Morris et al., 2010; Rowe et al., 2010).

Neuropsychological test results confirmed the full cognitive “normality” of many at risk participants with considerable fibrillar A β burden. Mean cortical BP_{ND} was unrelated to an index of episodic memory performance for the pooled sample of 45 participants. These results agree with those of Johnson et al. (Johnson et al., 2014), who also observed no relationship between A β status and any of several cognitive measures in an at-risk middle aged sample (mean age 60.1 years). In other A β imaging studies of cognitively normal elderly individuals (generally > age 65), A β binding has been shown to be associated with cognitive performance in some (Hedden et al., 2012; Rentz et al., 2010; Rodrigue et al., 2012; Sperling et al., 2013), but not all (Harrington et al., 2013) previous studies. In some studies, an association has been observed with episodic memory only in females (Pike et al., 2011) or in *APOE* $\epsilon 4$ carriers (Lim et al., 2013a).

Our finding of an inverse association between A β deposition and GM fraction within the A β susceptible brain regions—in the absence of a cognitive association—is somewhat unexpected. Previous studies have demonstrated that cognitively normal elderly individuals with brain A β accumulation demonstrate subtle cortical thinning (Dickerson et al., 2009), greater rates of cortical and hippocampal atrophy (Andrews et al., 2013; Chetelat et al., 2012; Schott et al.,

2010), and disruption of functional connectivity (Hedden et al., 2009; Mormino et al., 2011; Sheline et al., 2010). However, these studies generally involve the older age range (>65 years), in which A β burden has also been associated with cognitive function. Our results differ from those of Johnson et al. (Johnson et al., 2014), who observed no association between A β status and GM volume in subjects of similar age. This divergence may relate to different methods of evaluating gray matter (GM fraction within the A β susceptible ROIs versus voxel based morphometry) or our analysis of A β deposition as a continuous rather than categorical variable.

A major difference between our subject sample and those of most of the other referenced studies is that our participants are significantly younger and largely non-overlapping in age with other samples. They may simply fall at an earlier stage of preclinical disease without “subtle cognitive decline” (Sperling et al., 2011). Alternatively, they may exhibit lesser aging effects in comparison to the older participants in other studies. Age-related atrophy occurs partly in AD-specific brain regions and may have additive effects with AD-related neurodegeneration (Bakkour et al., 2013). Thus, our middle-aged subjects may have greater “brain reserve” compared to older preclinical samples and may not manifest cognitive effects of A β deposition and early neurodegeneration. The preclinical stage of AD has been theorized to include sub-stages of A β deposition with and without neuronal damage and subtle cognitive symptoms (Sperling et al., 2011). Thus our findings are fully consistent with this theoretical model. They suggest that future prevention studies may benefit from intervention at a younger age and an earlier preclinical stage than the current A4 study (Sperling et al., 2014). Enrichment of samples through family history and *APOE* genotyping will likely be necessary.

4.2. Implications for Early Intervention

Our finding that A β burden is inversely associated with GM fraction prior to an association with any cognitive measures has particular implications for future prevention strategies. A limitation of the present study is its cross-sectional design, which cannot fully establish the temporal relationship implicated in the association of A β burden with GM losses. Longitudinal studies that span the emergence of A β pathogenesis may be necessary to establish whether the early steps in this process are already associated with GM reductions and other markers of neuronal injury. However, the definition of this stage will be critical to determine the optimal period for intervention strategies. A broad range of potential interventions—including anti-A β strategies or attempts to repair structural defects of *APOE* ϵ 4 (Mahley and Huang, 2012)—should ultimately be implemented prior to earliest neurodegeneration. It presently remains unclear whether an early stage of A β pathogenesis fully precedes neuronal injury and thus whether detection of fibrillar A β deposition in the brain by a screening test is a sufficient condition for identifying candidates for early intervention studies.

4.3. Importance of Partial Volume Correction

Finally, our results underscore the importance of PVC for A β PET imaging, even in the preclinical stages of AD. The fact that A β burden is inversely associated with GM fraction at a preclinical stage inherently entails that uncorrected analyses will underestimate A β burden in the very individuals with the greatest burden. Indeed, our additional analyses confirm that the increase in mean cortical BP_{ND} yielded by PVC is highly inversely associated with the fraction of

GM within the mean cortical ROI. Additional support for performing PVC in the present study is provided by the improved overall model fit of BP_{ND} values vs. *APOE* genotype (Table 2), i.e., PVC enlarges group differences in A β burden. Although PVC has not been widely employed in A β PET imaging—and has been essentially absent from preclinical investigations—these results highlight the advantages of correcting for partial volume effects when performing A β imaging in the preclinical stages.

Recently, interest has mounted in performing PVC for A β PET (Gonzalez-Escamilla et al., 2017; Shidahara et al., 2017). The optimal method of PVC for PET imaging remains a topic of investigation (For review, see (Erlandsson et al., 2012)), with alternatives including region-based methods such as the regional spread function (RSF) method (Rousset et al., 2008), as well as voxel-based methods such as the Muller-Gartner algorithm used here. The selection of a PVC method is based on several factors, including the system point-spread function and its spatial variation, assumptions about uniformity of tracer uptake within regions, and the accuracy of registrations and segmentations. As an example, Su et al. (Su et al., 2015) compared 2 PVC methods, the 2-compartment image-based method (Meltzer et al., 1990) which corrects for GM loss but not for spill-in between WM and GM, and RSF, and concluded that RSF performed better. However, this conclusion was based in part on a simulation study, for which the validity may be limited to the chosen simulation conditions. Here, we used the Muller-Gartner method, which is of intermediate complexity between the methods compared by Su et al. This method can account for the time-varying spill-in of activity from WM to GM, which is particularly important for A β PET due to the high WM uptake.

4.4. Conclusion

In cognitively normal, middle-aged individuals at varying genetic risk for AD, A β burden is significantly associated with gray matter fraction but not episodic memory performance. These findings are consistent with models of preclinical AD in which neurodegeneration occurs before manifest cognitive decline.

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Table 1. Participant demographics and characteristics by *APOE* genotype

	APOE Genotype						F/ χ^2 ^a	p-value
	$\epsilon 3, \epsilon 3$ (n=15)		$\epsilon 3, \epsilon 4$ (n=15)		$\epsilon 4, \epsilon 4$ (n=15)			
	Mean/ Count	\pm SD/%	Mean/ Count	\pm SD/%	Mean/ Count	\pm SD/%		
Demographic								
Age (y)	59.1	± 4.4	59.2	± 4.6	59.1	± 5.4	.00	.99
Female Sex	8	53	8	53	8	53	.00	1.00
Education (y)	16.5	± 1.6	16.3	± 2.3	16.3	± 1.8	.06	.95
Clinical								
MMSE	29.7	± 0.5	29.3	± 0.8	29.1	± 1.2	1.43	.25
WAIS-III FSIQ	113.5	± 14.4	118.8	± 14.8	112.9	± 10.5	.90	.42
WRAT-3 Reading	109.4	± 8.7	109.2	± 9.4	109.8	± 11.3	.01	.99
Geriatric Depression Scale	0.7	± 0.7	0.4	± 0.6	1.1	± 1.9	1.1	.35

F statistics and p-values for means are from ANOVA significance tests; χ^2 statistics and p-values for counts are from chi-square significance tests. SD=standard deviation.

Table 2: Effect sizes of overall models* and *APOE* genotype for mean cortical A β burden (BP_{ND}) (N=45)

	Overall Model R ²	<i>APOE</i> Genotype Bias-Corrected Semi-Partial Correlation Ratio [†]	<i>APOE</i> Genotype Correlation Ratio 95% Confidence Interval	p-value
BP _{ND} -Uncorrected	0.327	0.127	0.012, 0.303	0.013
BP _{ND} -Gray Matter Masked	0.368	0.134	0.015, 0.308	0.009
BP _{ND} -Partial Volume Corrected	0.393	0.128	0.011, 0.300	0.009

*These statistics are obtained from separate general linear models in which *APOE* genotype is the main explanatory variable and age and sex are covariates.

[†]This ratio represents the proportion of total variation accounted for by the allele group factor.

Figure Legends

Figure 1. Box plots of mean cortical A β burden (BP_{ND}) by APOE genotype. Boxes define the interquartile range. The black horizontal lines indicate medians and the white diamonds indicate the means. Plotted values are unadjusted means and statistical analysis was performed using a generalized linear model adjusted for age and sex. The APOE genotype variable is significant with $p = 0.003$ ($n = 15$ per group).

Figure 2. Association between cortical A β burden (BP_{ND}) and cortical gray matter (GM) fraction (A, C) or episodic memory performance (B, D). Plotted values are partial volume corrected BP_{ND} for the mean cortical ROI (A) and unadjusted cortical gray matter fraction (regression coefficient = -0.046, $p = 0.017$) or (B) episodic memory performance (regression coefficient = -0.317, $p = 0.558$). Gray matter masked BP_{ND} without partial volume correction for the mean cortical ROI (C) and unadjusted cortical gray matter fraction (regression coefficient = -0.046, $p = 0.048$) or (D) episodic memory performance (regression coefficient = 0.1271, $p = 0.846$) are also shown. Episodic memory performance is the average of z-scores for CVLT free delayed recall and Logical Memory II. The figure displays unadjusted linear regression lines with their 95% confidence intervals. Statistical analysis was performed using general linear models adjusted for age and sex.

Figure 3. Effect of partial volume correction on BP_{ND} images with [¹¹C]PiB. Images are for cognitively normal, first-degree relatives of AD patients with high A β load and low A β load. Mask images of gray and white matter were smoothed to the system resolution (~6mm). For each dynamic PET frame, GM voxels were corrected for spill-in and spill-out of activity, assuming

activity in CSF was zero and WM activity was uniform and was estimated from the centrum semiovale. Finally, SRTM2 was re-applied to the PVC-images to produce PVC-corrected BP_{ND} values. In the resulting PVC images, values in white matter voxels are not corrected.

Figure 1.

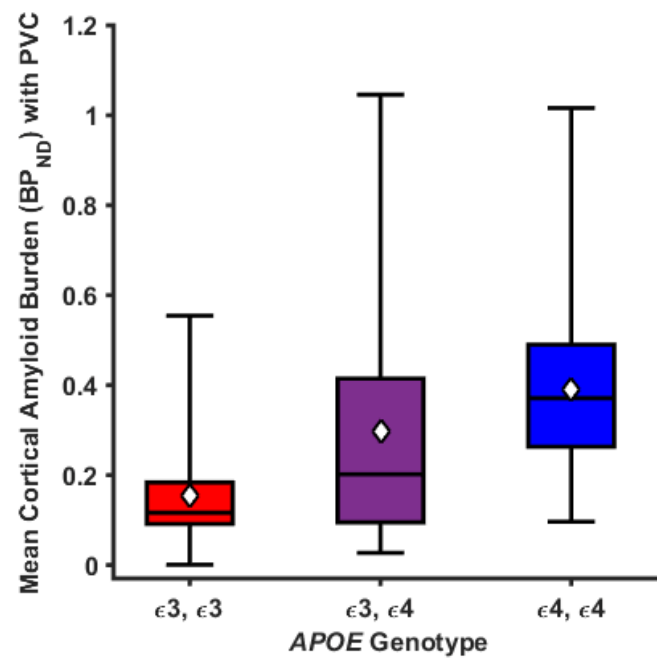


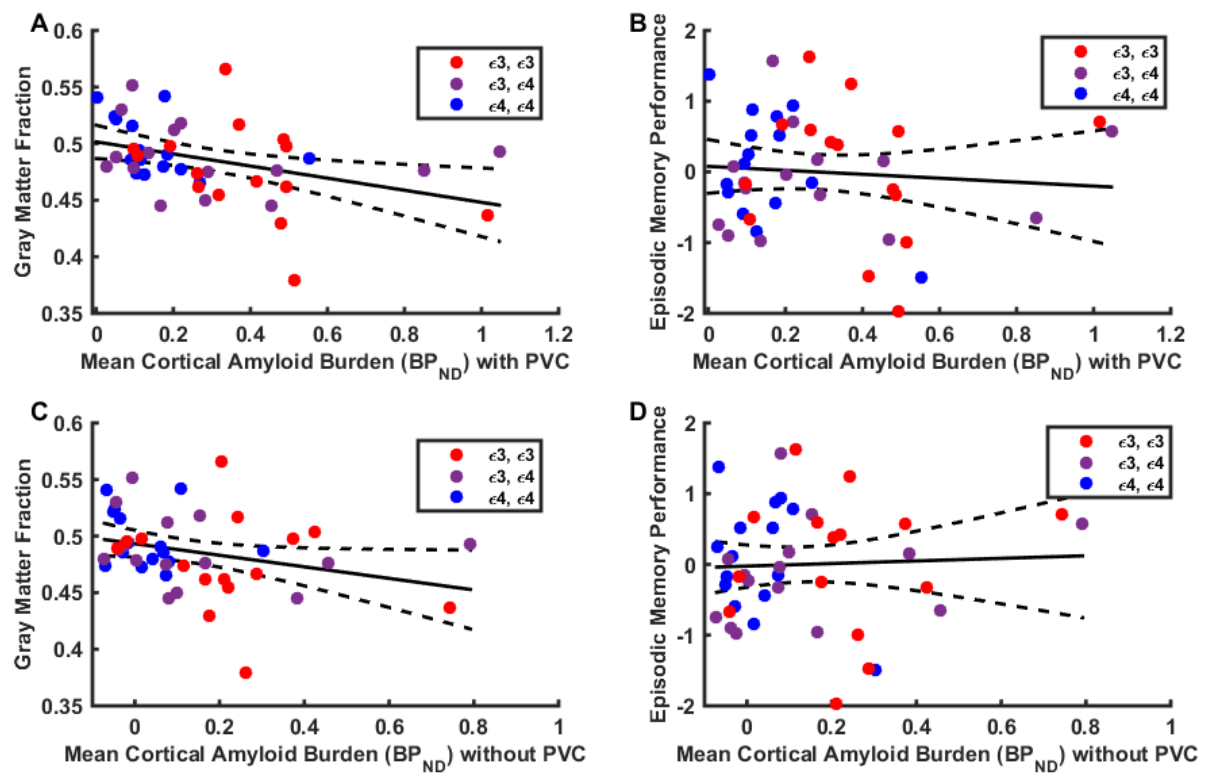
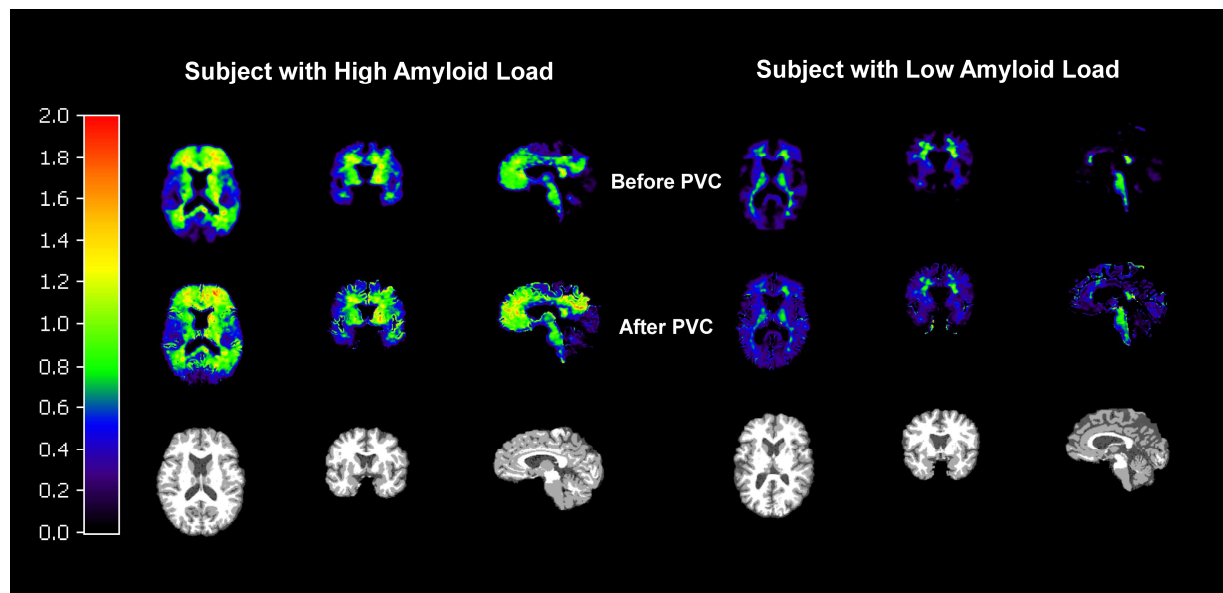
Figure 2.

Figure 3.

Highlights

- Cognitively normal adults with *APOE* $\epsilon 4\epsilon 4$ genotype had higher $A\beta$ burden than $\epsilon 3\epsilon 3$.
- Cortical $A\beta$ burden was inversely associated with gray matter fraction.
- There was no significant association of cortical $A\beta$ burden with episodic memory.