

Is Verbal Episodic Memory in Elderly with Amyloid Deposits Preserved Through Altered Neuronal Function?

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A potential mechanism that enables intellectual preservation in cognitively normal elderly that harbor beta-amyloid (A β) pathology is heightened cerebral glucose metabolism. To investigate cross-sectional inter-relationships between A β , glucose metabolism, and cognition, 81 subjects (mean age: 75 \pm 7 years) underwent [¹¹C] Pittsburgh Compound-B and [¹⁸F]fluorodeoxyglucose positron emission tomography scans and neuropsychological testing. They were divided into low-A β (n = 53), intermediate-A β (n = 13) and high-A β (n = 15) groups as defined by their global cortical [¹¹C]PIB retention. Glucose metabolism was assessed using a MetaROI mask that covers metabolically critical regions in Alzheimer's disease (AD) (i.e., posterior cingulate and bilateral angular and inferior temporal gyri). Previously validated factor scores for verbal and visual episodic memory, semantic memory, working memory, and executive functioning were used to evaluate cognitive performances. Greater A β deposition in the precuneus was associated with higher metabolic activity (at trend level) and lower visual episodic memory scores. Glucose metabolism did not correlate with cognition across all subjects. However, heightened metabolic activity was associated with better verbal episodic memory performance in subjects with elevated amyloid levels. This preliminary study suggests that neural compensation, as a manifestation of brain reserve, enables elderly supposedly on the path to AD, at least temporarily, to preserve cognitive function.

Keywords: aging, [¹¹C]PIB, beta-amyloid, cognition, [¹⁸F]FDG, glucose metabolism, PET

Introduction

Deposition of amyloid-beta (A β) is a neuropathological hallmark of Alzheimer's disease (AD), but significant plaque burden is frequently present in cognitively normal elderly at autopsy as well (Price and Morris 1999; Wolf et al. 1999; Bennett et al. 2006). In vivo positron emission tomography (PET) studies employing [¹¹C]Pittsburgh compound-B (PIB, Klunk et al. 2004) confirmed that ~30% of persons over 70 years display cerebral amyloidosis (Morris et al. 2010; Villemagne et al. 2011; Jack et al. 2012). According to new research criteria, these individuals are in a preclinical stage of AD (Sperling et al. 2011). In a recently proposed biomarker model (Jack et al. 2010), it was hypothesized that A β deposition precedes tau-mediated neuronal dysfunction, brain atrophy, and cognitive deterioration that eventually lead to the onset of dementia. The estimated time between initial A β accumulation and manifestation of symptoms is 15 years (Rowe et al. 2010; Bateman et al. 2012). Following this model, it may be expected that some individuals with high A β burden already show subtle

signs of neurodegeneration. Indeed, morphological reductions in AD-specific regions were observed in elderly with amyloid deposits on structural magnetic resonance imaging (MRI) (Dickerson et al. 2009; Mormino et al. 2009; Chételat et al. 2010; Becker et al. 2011; Oh et al. 2011). Functional MRI studies, paradoxically, demonstrated increased brain activation in aging (Cabeza et al. 2002; Rosen et al. 2002; Park and Reuter-Lorenz 2009; Mormino et al. 2012a) and genetic risk populations (Bookheimer et al. 2000; Filippini et al. 2009) that potentially capture the earliest stage of AD development. Similarly in patients with mild cognitive impairment, increased cerebral glucose metabolism as measured using [¹⁸F]fluorodeoxyglucose (FDG) PET was associated with greater A β load (Cohen et al. 2009). Heightened synaptic activity could be a manifestation of cognitive brain reserve that reflects a compensatory response to counteract neurotoxic effects of A β . Increased neuronal activity may enable the brain to suppress pathological insult and maintain normal cognitive function for a longer period. In keeping with this idea, the cross-sectional effect of A β on cognition, if any, is small. Some studies showed a negative correlation between the presence of amyloid and cognitive performance in cognitively normal elderly (Pike et al. 2007; Rentz et al. 2010; Rodrigue et al. 2012), whereas others could not replicate this (Aizenstein et al. 2008; Rowe et al. 2010). There is more robust evidence for long-term effects of amyloid pathology as individuals with elevated A β are at higher risk for cognitive decline over time (Morris et al. 2009; Storandt et al. 2009; Resnick et al. 2010; Villemagne et al. 2011; Doraiswamy et al. 2012; Lim et al. 2012; Wirth et al. 2013).

[¹⁸F]FDG-PET is an eligible marker of resting-state synaptic activity and is capable of capturing up- and downregulation of brain function (Attwell and Laughlin 2001; Rocher et al. 2003). Neuronal activity as measured with [¹⁸F]FDG-PET may provide more insight in the complex relationship between A β deposition and cognitive performance. The objectives of this cross-sectional study were to investigate relationships between 1) A β load and glucose metabolism, 2) A β load and cognition, 3) glucose metabolism and cognition, and 4) glucose metabolism and cognition as a function of amyloid status in a group of cognitively normal elderly.

Materials and Methods

Subjects

Eighty-one cognitively normal elderly subjects with available [¹¹C]PIB and [¹⁸F]FDG-PET data were included in the present study. All volunteers were recruited through the Berkeley Aging Cohort study (BACS); a community-dwelling cohort that is a convenience sample of healthy

individuals who are older than 60 years and reside in the San Francisco Bay Area of California. BACs participants were recruited through advertisements in senior centers and in local newspapers. Inclusion criteria were independent daily living, absence of any neurological or psychiatric condition that potentially affects brain structure and function, absent cognitive complaints normal performance on cognitive tests (maximally 1.5 SD's below age-, education-, and sex-adjusted means), no use of psychoactive drugs and absence of sensory impairment that might interfere with cognitive testing. Subjects completed genotyping for apolipoprotein E (APOE) $\epsilon 4$ carrier status. The local ethics committee approved the study and subjects gave written informed consent.

Neuropsychological Testing

Seventy-four subjects underwent an extensive neuropsychological test battery, thus cognitive data were missing for 7 subjects. Previously, a principal component analysis was conducted on 189 cognitively normal elderly (mean age: 73 \pm 7 years; 63 males; mean MMSE: 29 \pm 1) and 108 young adults (mean age: 25 \pm 4 years; 62 males; mean MMSE: 29 \pm 1) in order to obtain concise and reliable cognitive component scores (Oh et al. 2012). This revealed 5 major cognitive components: 1) verbal episodic memory (Free recall trials 1–5, Short-delay free recall, Short-delay cued recall, Long-delay free recall, and Long-delay cued recall of the California Verbal Learning Test) (Delis et al. 2000), 2) visual episodic memory (Immediate recall, Delayed recall, Retention and Recognition from the Visual Reproduction Test in the Wechsler Memory Scale) (Wechsler 1997), 3) semantic memory (Category fluency “vegetables” and “animals”) (Benton et al. 1983), 4) working memory (Digit span forward and backward) (Wechsler 1997), and 5) executive functioning (“Trail B minus A” score from Trail Making Test [Reitan 1958], Symbol Digit Modalities Test [Smith 1982], and Stroop Test [Golden 1978]). Factor loadings for individual neuropsychological tests were used to calculate factor scores for participants in this study on these cognitive component scales. Factor score = 0 represents the mean of the derivation sample, with a standard deviation of 1. Negative component scores indicate worse cognitive performance and positive values mean better test scores compared to the derivation sample.

Imaging Data Acquisition

^{11}C PIB-PET

All PET scans were performed at Lawrence Berkeley National Laboratory (LBNL) using a Siemens ECAT EXACT HR scanner (Siemens, Inc., Iselin, NJ, USA) in 3D acquisition mode. The dynamic ^{11}C PIB scans consisted of 34 frames increasing progressively in duration (4 \times 15, 8 \times 30, 9 \times 60, 2 \times 180, 8 \times 300, and 3 \times 600 s) for a total scanning time of 90 min. More details on the ^{11}C PIB-PET imaging data acquisition and data analysis can be found in a previously published study (Oh et al. 2011).

^{18}F FDG-PET

^{18}F FDG-PET imaging was performed \sim 2 h after ^{11}C PIB injection. Following an injection of 6–10 mCi of the tracer, 6 \times 5 min frames of emission data were collected starting 30-min postinjection. All PET data were reconstructed using an ordered subset expectation maximization algorithm with weighted attenuation. Images were smoothed with a 4 \times 4 \times 4-mm Gaussian kernel with scatter correction.

Structural MRI

High-resolution structural MRI scans were performed at LBNL on a 1.5-T Magnetom Avanto system (Siemens, Inc.) with a 12-channel head coil run in triple mode. Three T_1 -weighted magnetization-prepared rapid gradient echo scans were collected axially for each subject (repetition time: 2110 ms; echo time: 3.58 ms; flip angle: 15°; field of view: 256 \times 256 mm; matrix size: 256 \times 256; slices: 160; voxel size: 1 \times 1 \times 1 mm³). Reference regions and regions of interest (ROI) for ^{11}C PIB and ^{18}F FDG were generated using the FreeSurfer Version 4.4 software package (surfer.nmr.mgh.harvard.edu). In

addition, total cortical gray matter volumes were obtained using the automated segmentation of the FreeSurfer software (Version 5.1) and entered as covariate to correct for potential confounding by brain atrophy in models including both ^{11}C PIB and ^{18}F FDG.

Imaging Data Analysis

^{11}C PIB

PIB-PET data analysis methods are described elsewhere (Oh et al. 2011). In summary, all PET images were preprocessed using Statistical Parametric Mapping 8 (SPM8; www.fil.ion.ucl.ac.uk/spm). Frames 6–34 collected over 90 min were realigned to the middle frame (17th frame) and co-registered to the subject's structural MRI image. Global index (encompassing frontal, temporal, parietal and anterior, and posterior cingulate cortices) and precuneus distribution volume ratio's (DVR) of ^{11}C PIB were calculated using Logan graphical analysis with cerebellar gray matter as reference region (Logan et al. 1996; Price et al. 2005). In a previous study, elderly BACs subjects were contrasted against 11 young control subjects (25 \pm 3 years) and classified as low-PIB (index DVR: <1.08), intermediate-PIB (1.08–1.16), or high-PIB (>1.16) (Mormino et al. 2012b). We adopted this classification in the present study. In previous reports, we have characterized intermediate- and high-PIB subjects as PIB-positive (PIB+) (Mormino et al. 2012b; Oh et al. 2012).

^{18}F FDG-PET

The 6 ^{18}F FDG-PET frames were aligned to the first frame and averaged. Then, each ^{18}F FDG frame was realigned to the resultant mean image. The native space realigned images were summed to create one ^{18}F FDG image that was then intensity normalized to the pons, as pontine glucose metabolism is known to be preserved in AD patients (Minoshima et al. 1995).

In the present study, ^{18}F FDG data were analyzed using the MetaROI approach (Landau et al. 2011). This method comprises 5 ROIs (posterior cingulate cortex (PCC), bilateral angular gyri, and bilateral inferior temporal gyri) that were most strongly associated with metabolic and cognitive decline indicative of AD dementia in a literature review of published reports. To generate ^{18}F FDG SUVr within the MetaROI, at first, structural MRI scans were co-registered to corresponding ^{18}F FDG scans in native space. Subsequently, all co-registered MRI scans were registered to MNI space to generate a study specific template using the DARTEL tool in SPM8. Next, ^{18}F FDG scans were warped to MNI space using the flowfields obtained with the transformation of the MRI scans. Finally, a MetaROI mask was applied to extract mean ^{18}F FDG uptake values for the composite ROI and the individual regions comprising this ROI.

Statistics

Differences between groups for baseline characteristics were assessed using ANOVA and χ^2 tests, where appropriate. We adjusted the analyses for age, education, and APOE genotype given their effects on ^{11}C PIB retention, ^{18}F FDG uptake, and cognitive scores in the present (see Table 2) and in previous studies (Jagust and Landau 2012; Kantarci et al. 2012; Stern 2012; Vemuri et al. 2012). Pearson correlations were used to assess associations between age, education, APOE genotype, precuneus ^{11}C PIB, composite ^{18}F FDG MetaROI, and cognitive factor scores. Linear regression analyses, adjusted for age, education, and APOE, were used to test the relationships between precuneus ^{11}C PIB retention (as a continuous variable) and composite and regional ^{18}F FDG MetaROI uptake. In an additional model, we adjusted for partial volume effects by entering cortical gray matter volumes as covariate. We also performed a voxelwise analysis in SPM8 using a MetaROI ^{18}F FDG mask to define the search region as dependent variable, precuneus ^{11}C PIB as regressor, and age, education, APOE, and cortical gray matter volume as nuisance variables. This analysis was performed in MNI space (see subsection “ ^{18}F FDG-PET” for transformation), and results were displayed at $P < 0.05$ (2-tailed, uncorrected) with a cluster size of 10 voxels. Next, linear regression

analyses were performed to assess the relationships between precuneus [¹¹C]PIB/[¹⁸F]FDG MetaROI and the cognitive factor scores. In the first model, we entered no covariates while in the second model, we adjusted for age, education, and APOE. Finally, interactions between [¹¹C]PIB status (low, intermediate, or high) and composite [¹⁸F]FDG MetaROI on the cognitive factor scores were assessed using multivariate ANCOVA with adjustment for age, education, and APOE status. Post hoc linear regression analyses were used to further explore these relationships within [¹¹C]PIB groups.

Results

Subjects

Demographics, cognitive scores, index [¹¹C]PIB, and composite [¹⁸F]FDG are presented in Table 1. Fifty-three subjects were completely amyloid negative while the balance had evidence of Aβ deposition ranging from mild to extensive. There were no group differences in terms of age, gender, level of education, APOE genotype, MMSE, any of the cognitive factor scores, or composite [¹⁸F]FDG MetaROI. By design, the high-PIB group showed increased global [¹¹C]PIB retention compared to both intermediate-PIB and low-PIB groups ($P < 0.001$), and intermediate-PIB subjects had higher index compared to the low-PIB group ($P < 0.01$).

Table 1

Demographics, cognition, [¹¹C]PIB index, and composite [¹⁸F]FDG

	All (n = 81)	Low-PIB (n = 53)	Intermediate-PIB (n = 13)	High-PIB (n = 15)
Age	75.0 ± 6.6	74.8 ± 6.2	72.4 ± 6.9	78.1 ± 7.0
Gender (male/female)	29/52	19/34	5/8	5/10
Education	17.0 ± 1.8	17.2 ± 1.8	16.9 ± 1.6	16.5 ± 1.8
APOE ε4 carriers (%)	27	21	25	47
MMSE	29.0 ± 1.2	29.1 ± 1.2	29.5 ± 0.7	28.5 ± 1.2
Verbal episodic memory	-0.04 ± 1.04	-0.05 ± 1.1	-0.21 ± 0.85	0.10 ± 1.07
Visual episodic memory	-0.15 ± 0.89	-0.05 ± 0.89	0.04 ± 0.93	-0.61 ± 0.73
Working memory	-0.04 ± 1.05	-0.08 ± 1.08	0.17 ± 1.20	-0.10 ± 0.83
Semantic memory	0.03 ± 1.18	-0.10 ± 1.09	0.41 ± 1.52	0.15 ± 1.15
Executive functions	-0.28 ± 1.03	-0.27 ± 1.00	-0.36 ± 0.54	-0.26 ± 1.42
[¹¹ C]PIB index	1.11 ± 0.18	1.02 ± 0.04	1.11 ± 0.02*	1.43 ± 0.18*
Composite [¹⁸ F]FDG	1.65 ± 0.18	1.65 ± 0.18	1.61 ± 0.17	1.67 ± 0.18

Note: Data are presented as mean ± standard deviation unless indicated otherwise.

Differences between groups were assessed using ANOVA with post hoc Bonferroni tests (age, education, MMSE, cognitive factor scores, index PIB, and composite FDG) and χ^2 (gender, APOE genotype).

*Intermediate-PIB > low-PIB: $P < 0.01$.

**High-PIB > low-PIB and intermediate-PIB: $P < 0.001$.

Across groups, Pearson correlations revealed significant associations between age and precuneus [¹¹C]PIB ($r = 0.23$), age and composite [¹⁸F]FDG MetaROI ($r = -0.25$), education and executive functions ($r = 0.25$), APOE genotype and precuneus [¹¹C]PIB ($r = 0.28$), precuneus [¹¹C]PIB, and visual episodic memory ($r = -0.30$), executive functions and semantic memory ($r = -0.29$, all $P < 0.05$), and between age and visual episodic memory ($r = -0.39$, $P < 0.01$). No other significant correlations were found (Table 2).

Correlations Between Precuneus PIB and FDG MetaROI

Linear regression analysis with adjustment for age, education, and APOE showed an association at trend level between precuneus [¹¹C]PIB retention and composite [¹⁸F]FDG MetaROI (standardized β : 0.21, $P = 0.10$, Fig. 1A). Additional adjustment for partial volume effects using cortical gray matter volumes revealed an even stronger association (standardized β : 0.33, $P < 0.05$). Precuneus [¹¹C]PIB retention was significantly correlated with PCC (standardized β : 0.36, $P < 0.05$) and right angular (standardized β : 0.28, $P < 0.05$) [¹⁸F]FDG uptake, which was confirmed in a voxelwise analysis in SPM8 within MetaROIs (Fig. 1B). Precuneus [¹¹C]PIB retention did not correlate significantly with left angular gyrus (standardized β : 0.16, $P = 0.25$) and left (standardized β : 0.19, $P = 0.15$) and right (standardized β : 0.17, $P = 0.18$) inferior temporal gyri uptake.

Precuneus PIB and Cognitive Factor Scores

Linear regression analysis showed a negative association between precuneus [¹¹C]PIB retention and performance on visual episodic memory tasks across groups (standardized β : -0.30, $P < 0.05$, Fig. 2A). This result was no longer significant after adjustment for age, education, and APOE (standardized β : -0.19, $P = 0.12$). Post hoc analysis revealed a borderline significant correlation between precuneus [¹¹C]PIB and visual episodic memory factor scores in the high-PIB group (adjusted: standardized β : -0.55, $P = 0.08$; unadjusted: standardized β : -0.64, $P < 0.05$), whereas this association was absent in intermediate-PIB (standardized β : -0.17, $P = 0.69$) and low-PIB (standardized β : 0.12, $P = 0.43$) groups. Across and within groups, there were no associations between precuneus [¹¹C]PIB retention and verbal episodic memory, working memory, semantic memory, and executive functions (all $P > 0.05$).

Table 2

Correlations between age, education, APOE genotype, [¹¹C]PIB, [¹⁸F]FDG, and cognition

	Age	Education	APOE	[¹¹ C]PIB	[¹⁸ F]FDG	Verbal EM	Visual EM	WM	SM	EXE
Age	X									
Education	-0.05	X								
APOE ε4 status	-0.03	0.17	X							
Precuneus [¹¹ C]PIB	0.23*	-0.18	0.28*	X						
Composite [¹⁸ F]FDG MetaROI	-0.25*	0.10	0.02	0.11	X					
Verbal episodic memory	-0.15	-0.03	0.01	0.10	0.12	X				
Visual episodic memory	-0.39**	0.01	-0.10	-0.30*	0.03	-0.18	X			
Working memory	0.15	0.02	0.03	-0.07	0.10	-0.15	-0.13	x		
Semantic memory	-0.15	0.09	0.10	0.01	0.13	0.05	0	-0.03	X	
Executive functions	-0.07	0.25*	0.13	0.04	0.01	0.12	-0.19	-0.16	-0.29*	X

Associations between age, education, APOE genotype, [¹¹C]PIB, [¹⁸F]FDG, and cognition were assessed using Pearson correlations.

* $P < 0.05$.

** $P < 0.01$.

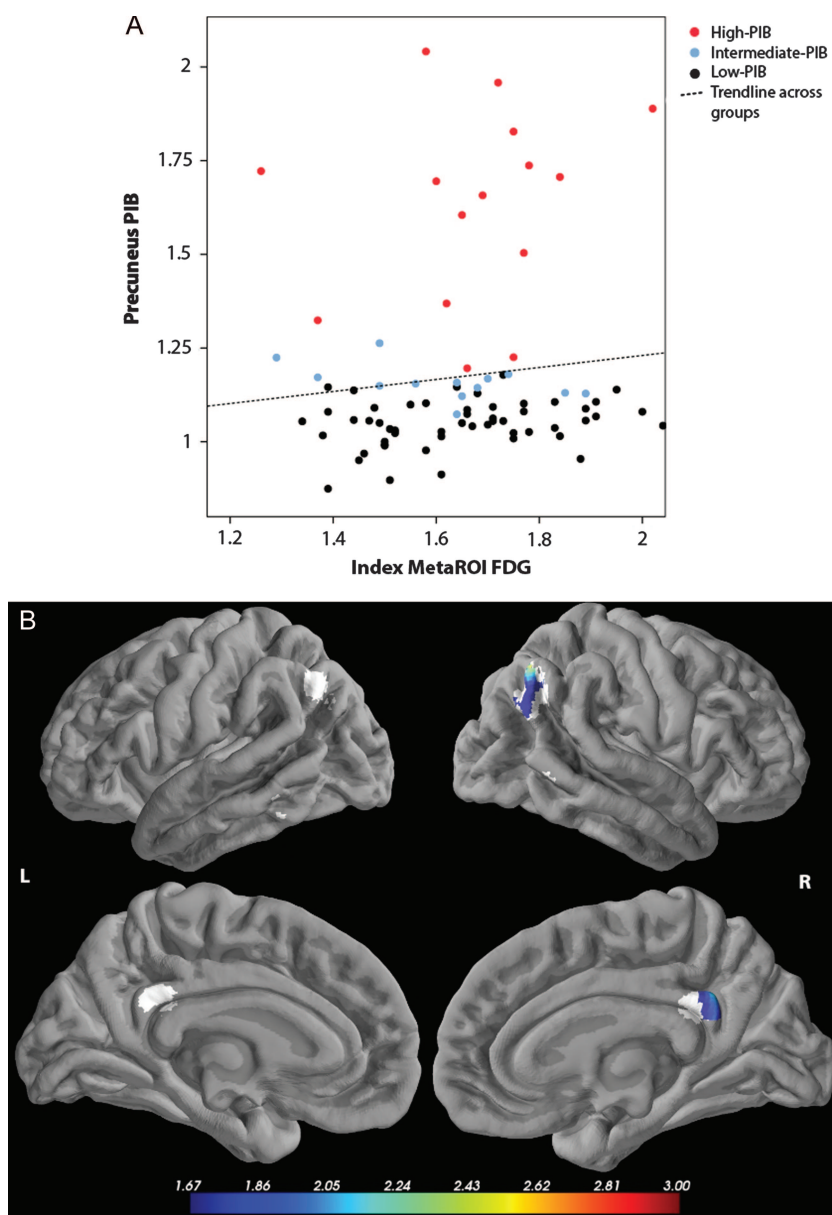


Figure 1. Linear regression analyses, with adjustment for age, education, and APOE, showed an association at trend level between precuneus [^{11}C]PIB DVR and composite [^{18}F]FDG MetaROI (A) (standardized β : -0.21 , $P = 0.10$). Additionally, we performed a voxelwise regression analysis within MetaROI regions (in white), thresholded at an uncorrected $P < 0.05$ ($k > 10$ voxels) (B). Color maps represent mean T -values. Effects in the right angular gyrus and posterior cingulate mainly drive the relationship between precuneus [^{11}C]PIB and composite [^{18}F]FDG MetaROI.

MetaROI FDG and Cognitive Factor Scores

Linear regression analyses, irrespective of whether or not adjusted for age, education, and APOE, showed no association between the composite and regional [^{18}F]FDG MetaROI and any of the cognitive factor scores across groups (all $P > 0.05$).

Relationships Between FDG and Cognition According to PIB Status

Multivariate ANOVA with adjustment for age, education, and APOE status showed a significant interaction between [^{11}C]PIB status (low, intermediate, or high) and composite [^{18}F]FDG MetaROI on verbal episodic memory ($P < 0.05$), but not on other cognitive factor scores (all $P > 0.05$). Post hoc linear regression analyses with adjustment for age, education, and

APOE, revealed strong associations between the composite ROI (standardized β : 0.68 , $P < 0.01$, Fig. 2B) and left (standardized β : 0.80 , $P < 0.01$, Fig. 2C) and right (standardized β : 0.68 , $P = 0.01$, Fig. 2D) angular gyrus [^{18}F]FDG uptake and verbal episodic memory in subjects with intermediate [^{11}C]PIB retention. Moderate, albeit nonsignificant, correlations with verbal episodic memory were found in the left (standardized β : 0.52 , $P = 0.11$) and right (standardized β : 0.59 , $P = 0.17$) inferior temporal gyri and in the PCC (standardized β : 0.28 , $P = 0.38$) of intermediate-PIB subjects (Table 3). In addition, we found an association between left angular gyrus [^{18}F]FDG uptake and working memory scores (standardized β : 0.76 , $P < 0.05$). In the high-PIB group, there was an association between left inferior medial temporal [^{18}F]FDG uptake and verbal episodic memory (standardized β : 0.57 , $P < 0.05$).

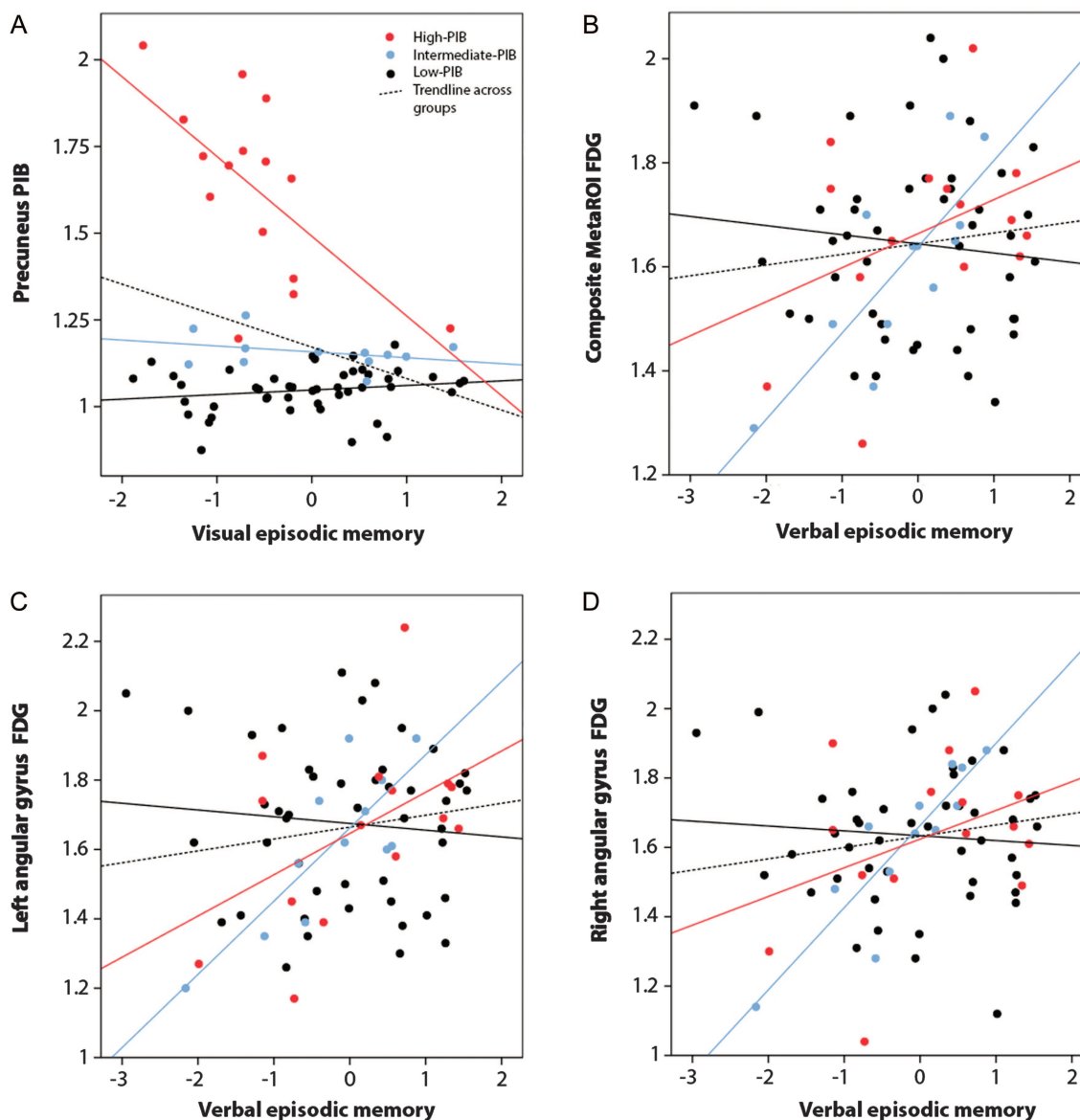


Figure 2. Linear regression analysis showed an association between increased [^{11}C]PIB retention in the precuneus and lower visual episodic memory factor scores (A) (standardized β : -0.30 , $P < 0.05$). Across groups, there was no effect of [^{18}F]FDG on cognition. In subjects with intermediate-PIB levels, verbal episodic memory performance was positively associated with (B) composite (standardized β : 0.68 , $P < 0.01$), (C) left (standardized β : 0.80 , $P < 0.01$), and (D) right (standardized β : 0.68 , $P = 0.01$) angular gyri [^{18}F]FDG SUVr.

Table 3

Relationships between [^{18}F]FDG uptake and verbal episodic memory scores according to [^{11}C]PIB status

	Low-PIB	Intermediate-PIB	High-PIB
Verbal episodic memory versus			
Composite [^{18}F]FDG MetaROI	-0.14	0.68^{**}	0.33
Right angular gyrus	-0.10	0.80^{**}	0.31
Left angular gyrus	-0.10	0.68^{*}	0.44
PCC	-0.16	0.28	-0.10
Right inferior temporal gyrus	-0.11	0.59	0.57^{*}
Left inferior temporal gyrus	-0.01	0.52	0.36

Associations between composite and regional MetaROI [^{18}F]FDG with verbal episodic memory according to [^{11}C]PIB status were assessed using linear regression analyses. Estimates are presented as standardized β -values, to allow comparison of effect sizes. All analyses were adjusted for age, education, and APOE genotype.

* $P < 0.05$

** $P < 0.01$.

No other significant correlations were found in any of the groups between composite or regional [^{18}F]FDG uptake and cognitive factor scores (see Supplementary Material).

Discussion

In the present study, cognitively normal subjects underwent [^{11}C]PIB and [^{18}F]FDG-PET and extensive neuropsychological testing, allowing exploration of the inter-relationships between amyloid burden, glucose metabolism, and cognition. We found that greater A β pathology was associated with heightened metabolic activity in AD-specific regions (at trend level) and worse performance on visual episodic memory tasks. Across all subjects, cerebral glucose metabolism was not associated with cognitive performance. In individuals with intermediate or high amyloid burden, however, metabolic activity in several

AD-specific regions was positively correlated to verbal episodic memory scores. This potential mechanism of cognitive brain reserve may reflect neural compensation that suppresses neurotoxic effects of A β pathology. These findings suggest that asymptomatic elderly with cerebral amyloidosis are, at least temporarily, able to preserve cognitive function through increased brain activity.

A β Burden and Glucose Metabolism

In the present study, we used highly sensitive PET measures to detect biological processes related to AD. [^{11}C]PIB retention was used to quantify fibrillar amyloid plaque deposition in the precuneus, one of the regions earliest affected in AD (Mormino et al. 2012b). In addition, we used a meta-analysis based approach (MetaROI) for [^{18}F]FDG to measure cerebral glucose metabolism in AD-specific regions (Landau et al. 2011). The association between heightened metabolic activity and increased amyloid deposition is consistent with other functional imaging studies showing elevated brain activation in aging, mild cognitive impairment, and genetic risk populations (Bookheimer et al. 2000; Cabeza et al. 2002; Rosen et al. 2002; Cohen et al. 2009; Filippini et al. 2009; Park and Reuter-Lorenz 2009; Mormino et al. 2012a). There are at least 2 mechanisms that may account for this phenomenon. The first is that the brain starts to recruit neuronal resources more intensively as a response to neurotoxicity of A β . This neural compensation may be an appearance of cognitive brain reserve, a concept that is often used to explain why some individuals can tolerate substantial pathological burden longer before showing cognitive loss, whereas others have less resilient brain capacity and decline earlier (Stern 2006, 2012). A second interpretation of our data is that increased neural activity leads to A β accumulation in the brain (Jagust and Mormino 2011). Animal studies have shown that a state of wakefulness and long-term unilateral vibrissal stimulation in transgenic mice enhance A β release and the formation and growth of amyloid plaques (Kang et al. 2009; Bero et al. 2011). In addition, A β plaques preferentially accumulate in metabolically highly active regions found in multimodal association cortices and the default mode network in the human brain (Buckner et al. 2005). The link between increased neural activity and amyloid pathology could not be attributed separately to low-, intermediate-, or high-PIB groups. In a previous study (Drzezga et al. 2011), amyloid-positive cognitively normal elderly had minor metabolic reductions compared to their amyloid-negative counterparts. Discrepancies with the present study may be explained by the fact that we used [^{11}C]PIB as a continuous variable and both studies selected different target regions to assess glucose metabolism. In addition, we included only subjects with cerebral amyloidosis who had glucose metabolism (and cognitive function) in the normal range. Potentially, the relationships between A β deposition and metabolic activity change along the spectrum of preclinical AD.

A β Burden and Cognition

Primarily driven by subjects with high [^{11}C]PIB retention, greater precuneus A β burden was associated with worse visual episodic memory performance. This result was no longer significant after adjustment for age, education, and APOE genotype, and there were no associations with other

cognitive functions, including verbal episodic memory performance. It could be speculated that the discrepancy between modalities is a consequence of a higher degree of complexity of our visual episodic memory task or, alternatively, it may be harder to process visual information rather than verbal stimuli. This would be consistent with a recent study (Rentz et al. 2011) showing that highly demanding cognitive tasks increase the sensitivity to detect subtle A β -related impairment. Previous reports on the effect of amyloid burden on cognition have been equivocal; some have shown significantly lower memory scores in subjects with A β (Pike et al. 2007; Rentz et al. 2010; Rodrigue et al. 2012), whereas others did not (Aizenstein et al. 2008; Rowe et al. 2010). Assuming that A β deposition eventually leads to clinical symptoms, mediating factors are needed to explain the weak cross-sectional association between amyloid plaques and cognition. These mediators could boost the effects of A β pathology (e.g. neuroinflammation, tau pathology, or vascular damage) (Desikan et al. 2012) or, conversely, suppress them by means of cognitive brain reserve factors.

Glucose Metabolism and Cognition

Across all subjects, metabolic activity was not associated with cognitive factor scores. The majority (53 of 81 subjects) of subjects in the present study showed no in vivo evidence of cerebral amyloidosis. These subjects with low [^{11}C]PIB retention, however, displayed comparable basal cerebral glucose metabolism as subjects with intermediate and high levels of A β (Fig. 1A), and there was a wide dynamic range. Relatively, low metabolic activity in these subjects is most likely independent of AD pathology and could be due to developmental factors or life-long experiences. Stronger correlates with cognition may be expected in prodromal AD or AD dementia patients who have crossed the threshold for abnormal [^{18}F]FDG uptake and display clinical symptoms (Chételat et al. 2003; Landau et al. 2012; Ossenkoppele et al. 2012).

Glucose Metabolism and Cognition as a Function of A β

Looking specifically at subjects harboring A β pathology in the brain, there was a positive correlation between metabolic activity and verbal episodic memory scores. This was most prominent in the intermediate-PIB group, that comprised individuals with [^{11}C]PIB retention 2–4 standard deviations above the mean distribution volume ratio of young healthy controls. In a previous study, it was shown that this elevation of [^{11}C]PIB occurred in a pathologically confirmed AD like pattern and is therefore of likely biological relevance (Mormino et al. 2012b). In this group, composite (weighted average of the 5 MetaROIs) and bilateral angular gyri [^{18}F]FDG uptake related strongly to one of the earliest cognitive functions affected in AD, namely, verbal episodic memory (Salmon 2000). In other words, among elderly supposedly on the path to AD, those who display heightened cerebral glucose metabolism have better preserved cognitive function than those with lower metabolic activity. It is unclear if increased neuronal activity is an adaptive response of the brain to the presence of A β pathology or that individuals just start out differently and show distinct cognitive trajectories when A β comes into play.

In high-PIB subjects, [^{18}F]FDG uptake in the left inferior temporal lobe correlated with verbal episodic memory

performance. In addition, moderate correlations were appreciated for the metabolic composite, bilateral angular gyri, and right inferior temporal cortex, but due to small sample size, the statistical threshold was not reached. The pattern of better cognitive performance in individuals with higher metabolic activity was thus similar to that seen in the intermediate-PIB group, only to a smaller extent. Longitudinal imaging studies have shown amyloid plaque growth in normal elderly, particularly in those that already have substantial A β load (Sojkova et al. 2011; Villemagne et al. 2011; Vlassenko et al. 2011). Individuals with strongly elevated [^{11}C] PIB retention are potentially more advanced in the amyloid cascade model and thus closer toward entering the clinical stage of AD (Jack et al. 2010). This could imply that neural compensation is temporarily beneficial but long-term exposure of A β will eventually tip over glucose metabolism and subsequent cognitive performance. This model fits well with previous studies that report only a modest effect of A β on cross-sectional cognitive performance (Pike et al. 2007; Aizenstein et al. 2008; Rentz et al. 2010; Rodrigue et al. 2012; Rowe et al. 2010), whereas subjects harboring A β are consistently more prone to longitudinal cognitive deterioration (Morris et al. 2009; Storandt et al. 2009; Resnick et al. 2010; Villemagne et al. 2011; Doraiswamy et al. 2012; Lim et al. 2012; Wirth et al. 2013). An alternative explanation is that these elderly with cerebral amyloidosis—but normal cognitive function—are “survivors” and are protected against cognitive deterioration not only via neuronal mechanisms but also by interactions of currently unknown genetic and environmental factors.

Limitations

The main limitation of the present study is the relatively small sample size of the intermediate- ($n = 13$) and high-PIB ($n = 15$) groups. The results, however, seem not to be driven by outliers and effects are often appreciated in multiple brain regions, indicating a certain robustness of the findings. Also, the cross-sectional design of this study does only allow speculation that individuals with A β pathology who are no longer capable of compensation through neural circuits are the most likely to decline cognitively. Longitudinal studies that include more subjects could help to test this hypothesis. Finally, the present study was not designed to assess the impact of cognitive reserve variables on preservation of cognitive function by means of increased metabolic function.

Conclusions

We found relationships between presence of A β pathology and higher metabolic activity (at trend level) and lower visual episodic memory scores. Glucose metabolism did not correlate with cognition across all subjects, but heightened metabolic activity was associated with better verbal episodic memory performance in subjects with moderately elevated amyloid levels. This preliminary study indicates that neural compensation, as a manifestation of cognitive brain reserve reflected in measures of glucose metabolism, is a mechanism that enables elderly with amyloid deposits to preserve cognitive function.

Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>

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