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In vivo assessment of amyloid-β deposition in non-demented very elderly subjects

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Abstract

Objective—This study examined amyloid-β (Aβ) deposition in 190 non-demented subjects aged 82 and older to determine the proportion of Aβ-positive scans and associations with cognition, APOE status, brain volume, and *Ginko biloba (Gb*) treatment.

Methods—Subjects who agreed to participate had a brain MRI and positron emission tomography scan with ^{11}C-labeled Pittsburgh compound B (PiB) following completion of a *Gb* treatment clinical trial. The youngest subject in this imaging study was 82, and the mean age of the subjects was 85.5 at the time of the scans;152 (80%) were cognitively normal and 38 (20%) were diagnosed with mild cognitive impairment (MCI)at the time of the PiB study.

Results—A high proportion of the cognitively normal subjects (51%) and MCI subjects (68%) were PiB-positive. The *APOE*4* allele was more prevalent in PiB-positive than in PiB-negative subjects (30% vs 6%). Measures of memory, language and attentional functions were worse in PiB-positive than in PiB-negative subjects, when both normal and MCI cases were analyzed together; however no significant associations were observed within either normal or MCI subject groups alone. There was no relationship between *Gb* treatment and Aβ deposition as determined by PiB.

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Interpretation—The data revealed a 55% prevalence of PiB-positivity in non-demented subjects age >80 and 85% PiB-positivity in the *APOE*4* non-demented elderly subjects. The findings also showed that long-term exposure to *Gb* did not affect the prevalence of cerebral Aβ deposition.

Introduction

Alzheimer's disease (AD) is the most frequent form of dementia in elderly subjects, with estimates of dementia prevalence of 7-8% of the population age <75 and 45% after age 85.[1] Although the exact causes of late-onset AD are unknown, altered amyloid-beta (Aβ) metabolism and clearance, and subsequent deposition of Aβ protein in brain likely play a central role in AD pathophysiology. Multiple neuropathological[2-4] and neuroimaging[5-7] studies have shown the presence of Aβ deposits in cognitively normal subjects, which may represent a pre-dementia state. Studies conducted in memory disorder clinics have shown that Aβ deposition, as measured with carbon-11-labeled Pittsburgh compound B (PiB), is present in approximately 25% of cognitively normal subjects over age 60[5-9], with higher rates in those age >80.[6] Both referral clinic- and community-based studies have shown a higher proportion of Aβ deposition in cognitively normal subjects carrying the apolipoprotein E4 (*APOE*4*) allele than in non-carriers.[7, 10, 11] After aging,the *APOE*4* allele is the most important predictor of incident AD.[12]

The present study extended previous observations by using PiB in a group of 190 non-demented individuals greater than 80 years of age who had been followed for up to 7 years as part of a larger study of the effect of *Ginkgo biloba*(*Gb*) on prevention of dementia.[13] Specifically, we aimed to determine the proportion of cognitively normal and MCI subjects with elevated Aβ deposition in this elderly group and its relationship to *APOE*4* status, cognitive measures, and magnetic resonance imaging (MRI) cerebral volumes.

Subjects/Materials and Methods

Participants

The present study was conducted in a subgroup of subjects who had participated in the Ginkgo Evaluation of Memory study (GEMS) from 2000 to 2008 in Pittsburgh. GEMS was a double-blind, multi-site, placebo-controlled, randomized clinical trial of 240 mg daily dose (120 mg twice daily) of *Gb* in 3,069 community-dwelling participants aged 72-96 years at study entry.[13] Exclusion criteria were reported in detail elsewhere[13] and included prevalent dementia, current cholinesterase inhibitor or other psychotropic medication use, history of bleeding disorders, severe depression, abnormal clinical laboratory screening, and disease-limited life expectancy less than 5 years. The median follow-up time from randomization was 6.1 years. A wide array of cognitive, genetic, functional, proxy-reported and medical history variables were collected.[14] The primary study outcome, that *Gb* would slow or delay the development of incident dementia, was negative.[13]

In 2009, approximately one year following GEMS closeout, 197 participants from the Pittsburgh clinical site were recruited into the GEMS Imaging Sub-Study. The inclusion criterion was completion of the GEMS protocol. Exclusion criteria were dementia at GEMS close-out or contraindications for neuroimaging. Compared to all 671 Pittsburgh site participants who completed the GEMS protocol and did not reach a dementia endpoint, the Imaging Sub-Study participants were slightly younger but otherwise comparable in sex, race, education, *APOE*4* status, estimated premorbid IQ and estimated income by zip code ($p > 0.05$). Three subjects were excluded for technical difficulties with PET scanning, three other subjects were excluded for developing dementia, and one subject could not complete cognitive testing. Thus, 190 of the 197 initial participants were entered in the present study.

Cognitive Assessment and Adjudication

At the time of PiB scanning, the participants were assessed with a subset of the GEMS neuropsychological battery.[15] Cognitive adjudication was completed blind to neuroimaging results by the GEMS Cognitive Diagnostic Center[14], taking into account historical serial cognitive assessments from the parent study. Criteria for MCI included 2 - 3 tests impaired at cutoffs of 1.5 standard deviations (SD) below age-education adjusted means.

Imaging

MRI scanning was performed using a GE Signa 1.5 T scanner and a standard head coil using methods described previously.[16] A T1-weighted volumetric spoiled gradient recalled (SPGR) sequence was acquired (0.937 × 0.937 mm) in the sagittal (n=177, slice thickness=1.2mm/0mm interslice) or coronal (n=14, slice thickness=1.5mm/0mm interslice) planes. Voxel-based morphometry (VBM) was performed with the sagittal SPGR MRI acquisition protocol.

The MRI data were normalized to the ICBM 152 template (Montreal Neurological Institute, Montreal, Canada) and tissue priors using Statistical Parametric Mapping 8 (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Unified segmentation was not successful for 6 subjects and 13 subjects had incompatible MRI scans, and VBM was performed for 171 subjects. This subgroup was composed of 136 normal cognition (NC) (71 PiB-positive) and 35 MCI (24 PiB-positive) subjects. The resulting modulated gray matter images were smoothed (8 mm Gaussian filter).

The PiB data were acquired for 20 minutes (4 × 5 minute frames) beginning 50 minutes after injection of 15±1.5 mCi of PiB on a Siemens/CTI ECAT HR+ scanner in 3D imaging mode (63 planes with slice width 2.4 mm) equipped with a Neuro-Insert and reconstructed using filtered back-projection (Fourier re-binning and 2D back-projection with Hann filter kernel FWHM = 3 mm). Post-injection transmission scans were acquired using 68Ge/68Ga rods, and data were corrected for photon attenuation, scatter, and radioactive decay. The final reconstructed PET image resolution was about 6 mm (transverse and axial).

APOE Genotyping

APOE genotyping was performed on isolated DNA from blood as described previously.[17]

Data Analysis

The procedure for co-registration of the MRI and PiB PET images has been described.[18] Regions-of-interest (ROIs) were hand-drawn on a template that was a high-resolution MR image of a single elderly MCI subject.[19] The ROIs included five primary cortical areas [i.e., anterior cingulate (ACG), frontal cortex (FRC), lateral temporal cortex (LTC), parietal cortex (PAR), precuneus cortex (PRC) which comprised the Global-5 composite region], as well as medial temporal cortex (MTC), anterior ventral striatum (AVS), occipital cortex (OCC), occipital pole (OCP), sensorimotor cortex (SMC), thalamus (THL), subcortical white matter (SWM), pons (PON), and cerebellum (CER)]. PiB retention was measured using the standardized uptake value ratio (SUVR) over the 50-70 min scan (or SUV: scaled to injected dose and body mass) that is then normalized by the SUV of the CER reference region.

All statistical analyses were performed using SAS (version 9.2; SAS Institute Inc., Cary, NC, USA). All two-sample comparisons were evaluated using a Wilcoxon nonparametric test. In settings where the sample size was below 25 in any group, exact methods were used for the computation of the significance level. For the analysis of the neuropsychological outcomes, the significance levels for the two sample comparisons were computed from a

linear regression model including age, gender, and education. Each model was evaluated using regression diagnostics to identify potentially influential observations. When a Cook's D value greater than 0.2 was observed, the corresponding model was recomputed with the observation removed from the data set. These instances are denoted in the tables and text.

A two-way ANOVA model was performed with diagnosis (NC and MCI) and PiB status (PiB-negative and PiB-positive) as grouping factors to determine voxel-wise gray matter differences. The interaction effect between diagnosis and PiB status, and the main effects were examined using appropriate contrasts. Analysis of covariance was also performed in SPM8 to determine voxel-wise gray matter differences between groups: PIB-negative NC > PIB-positive MCI and PIB-negative NC > PIB-negative MCI. These models included age and gender as covariates and were applied to gray matter maps with intensity threshold masking of 0.3. Thresholds of 0, 0.2 and 0.3 were examined but the latter was chosen because this provided a good compromise between inclusion of gray matter and exclusion of background instabilities. Significance levels were set to $p<0.025$, FDR corrected.

Definition of PiB-positive Scan

PiB scans were conducted in a separate group of 62 younger controls (69.4 ± 11.5 yrs; range 35 to 89) using the methods described in this study. An iterative-outlier method defined subjects as PiB-positive if the Global-5 composite region SUVR was ≥1.57.[8]

Result

Effect of Gb Intervention on Aβ Deposition

Ninety-five (50%) of the GEMS Imaging Sub-Study participants had been randomized to the *Gb* intervention arm of the parent GEMS and 95 to the placebo arm. No group differences were found in demographics, mean Global-5 SUVR values, or proportion of PiB-positive cases. There also was no difference in PiB retention on a voxel-wise basis between treatment groups (Figure 2A). Therefore the two groups were combined for further analyses.

Subject Characteristics

Demographics, genetic status, and cognitive scores are shown in Table 1; *APOE* genotype was available for 176 of the 190 cases entered in the analysis. The cohort was composed of NC (n=152; 80%) and MCI (n=38; 20%) at the time of PiB scan. The youngest subject was 82, and the average group age was not different between NC (mean 85.44, SD 2.83) and MCI (mean 85.87, SD 2.78) groups. Over half (55%) of these very elderly subjects were PiB-positive (see Table 1). The proportion of PiB-positive subjects was higher in the MCI group (68%) than in the NC group (51%). However, this difference did not reach statistical significance (p=0.058).

There were no differences between PiB-positive and PiB-negative subjects as a function of age, gender, race, education level or MMSE score except the PiB-positive MCI subjects were significantly older than MCI PiB-negative subjects (Table 1). PiB-positive subjects were significantly more likely to be *APOE*4* allele carriers, when analyzed across all subjects as well as in both the NC and MCI groups. A positive *APOE*4* status was similar in MCI and NC subjects. In contrast, PiB-positivity in the three groups was not significantly effected by *APOE*2* status (Table 1). In addition, 85% of all *APOE*4* carrier subjects were PiB-positive, while 46% of all *APOE*4* non-carriers were PiB-positive.

When comparing the cognitive test scores for all subjects (n=190), those who were PiB-positive had worse scores on animal fluency (p=0.0496) and Trail Making A (p=0.046) tests

than those who were PiB negative (Table 2). There were no significant differences in neuropsychological test performance between the PiB-positive and PiB-negative subsets within each of the NC and MCI groups separately (Table 2). Of note, regardless of significance level, all mean test scores were in the predicted direction (worse performance by PiB-positive subjects), except for letter fluency.

The MCI group showed higher PiB retention than NC in the following brain areas: Global-5, anterior cingulate, frontal cortex, lateral temporal cortex, parietal cortex, precuneus, anterior ventral striatum, occipital cortex, and sensorimotor cortex (Table 3a). *APOE*4* carriers showed significantly higher levels of PiB retention in the brain areas typically found to have increased Aβ-deposition in AD [20]: anterior cingulate, frontal cortex, lateral temporal cortex, parietal cortex, precuneus and anterior ventral striatum (Table 3b). Similar findings were observed when the NC and MCI groups were examined separately, except the occipital cortex showed significantly higher PiB retention in the *APOE*4* carriers of the MCI group. Figure 1 shows a scatter plot of the Global-5 SUVR values of all subjects, highlighting the higher average values for the NC and MCI *APOE*4* carriers relative to non-carriers.

When the association of *APOE*4* with PiB retention was limited to those subjects who were PiB-positive (NC and MCI groups combined), the same general trends as those described above were observed, but the findings were blunted (Supplementary Table 1). Within the PiB-positive group, the *APOE*4* allele was associated with significantly higher PiB retention only in the anterior cingulate (p=0.014), the frontal cortex (p=0.048), the precuneus (p=0.048), and the Global-5 composite region (p=0.024).

Association Between PiB Retention and Diagnostic Group

In this very elderly cohort, there was very little difference in PiB retention between subjects with normal cognition and subjects with MCI at the time of the scan. This was true when all controls (n=152) and all MCI subjects (n=38) were compared (Figure 2B), or when either the PiB-positive controls (n=78) were compared to the PiB-positive MCI subjects (n=26) or when the PiB-negative controls (n=74) were compared to the PiB-negative MCI subjects (n=12) (data not shown). The topography of the average PiB retention in the PiB-negative controls (n=74) and PiB-negative MCI subjects (n=12) was typical of that reported in other studies (Figures 2C and 2D) and consisted of non-specific white matter retention[5, 8, 21]. The topography of the average PiB retention in the PiB-positive controls (n=78) and PiB-positive MCI subjects (n=26) was similar to the topography previously reported in MCI and AD[22-24].

Association Between Brain Volume and PiB Retention

Figure 3 shows the results of VBM analyses of 171 subjects with MRI data available for analysis. Two-way ANOVA did not reveal any significant diagnosis by PiB status interaction effect (p<0.025, FDR corrected). Figure 3A and 3B show the main effect results from the two-way ANOVA model analysis performed with diagnosis (NC, n=136; or MCI, n=35) and PiB status (negative, n=76 negative; or positive, n=95) as grouping factors. As has been shown in previous studies[25], the main effect of diagnosis (NC vs. MCI) was observed in the mesial temporal lobes where the MCI subjects showed greater atrophy (see Supplementary Table 2A-D for SPM peak-levels and statistics). Figure 3B shows that there was no significant main effect of PiB status on brain volume across all subjects. Figure 3C shows that PiB-positive MCI subjects (n=24) demonstrated enhanced atrophy relative to PiB-negative NC (n=65) predominantly in the mesial temporal lobes. In contrast, PiB-negative MCI subjects (n=11) differed from PiB-negative NC in a more diffuse manner with the most significant differences observed in the frontal lobes (Fig 3D). No significant differences were observed when PiB-negative and PiB-positive MCI subjects were directly

compared (data not shown). Nor was a significant volume difference observed between PiB-positive NC and PiB-positive MCI subjects under the conditions of this analysis ($p<0.025$ with FDR correction and 100 contiguous voxels).

Discussion

We studied a group of non-demented elderly subjects who had participated in the *Gb* therapeutic trial and found a number of highly relevant findings in this, the oldest (mean age 85.5) and largest elderly cohort studied with Aβ imaging and cognitive testing. First, the long-term use of *Gb* treatment, in the most commonly used dose, had no effect on Aβ deposits as indexed by PiB retention (Figure 2A). Second, over half of this elderly cohort had significant PiB retention, as 55% of these elderly subjects were PiB-positive (51% of the cognitively normal subject and 68% of those with MCI), and elevated PiB retention was seen in a regional pattern typical of that previously described in MCI and AD patients (Figures 2C & 2D)[22, 26, 27]. Third, PiB retention was not extensively greater in the MCI subjects than in the subjects with normal cognition (Figure 2B). Fourth, PiB retention occurred more frequently in subjects carrying the *APOE*4* allele. Fifth, semantic fluency and psychomotor speed were associated with PiB retention. Finally, no significant differences in brain volumes were found between PiB-negative and PiB-positive subjects.

GEMS showed that regardless of mechanism, *Gb* did not decrease the risk of incident dementia.[13] The present study showed that *Gb* did not modify Aβ deposition, and consequently, its use will not affect the outcome of future neuroimaging studies of Aβ deposition. In this very elderly cohort, 51% of cognitively normal subjects and 68% of MCI subjects were found to have elevated PiB retention consistent with having significant brain Aβ deposition. These prevalence percentages are higher than those typically reported in most younger NC cohorts (~25% across a range of studies[7, 8, 19, 22, 28-39]) and younger MCI cohorts (~60% across a range of studies[7, 19, 28, 33, 39-43]). Our findings that Aβ deposition and its prevalence continues to increase with age are consistent with previous observations that showed that AD pathology can be seen in a high proportion of autopsied NC subjects after age 80+.[2, 4, 44] Bennett and colleagues reported that 66% of normal elderly subjects and 68% of those with MCI (age 81 – 85) met the CERAD criteria for possible, probable or definite AD.[45] Similarly, Savva and colleagues found an attenuated association between neocortical neuritic plaques and dementia in subjects age 95+, which was due primarily to increased pathology in the cognitively normal subjects. Nevertheless, the primary cause of dementia in this group was AD pathology.[46]

The dynamics of the association between cognition and Aβ deposition in cross-sectional neuroimaging studies as well as in neuropathological studies are difficult to determine with certainty, since there is no follow-up to determine whether the development of dementia is imminent or whether the subjects will remain cognitively normal despite the presence of significant amounts of Aβ in the brain. We hypothesize that the normal subjects with Aβ deposition on neuroimaging studies will progress to a dementia syndrome.

The previously reported observation of a higher prevalence of the *APOE*4* allele among younger PiB-positive subjects[10] was observed also in this very elderly cohort. The 5-fold increased prevalence of the *APOE*4* allele in PiB-positive individuals with an average age of ~85 was similar to *APOE*4* prevalence among PiB-positive subjects in their 60's and 70's.[10] This implies that the *APOE*4* effect is still a strong risk factor for Aβ deposition in the mid-80's. The region-specific nature of the *APOE*4*-associated elevations in PiB retention adds additional support for the clear interaction between *APOE*4* and Aβ-deposition.[10] It should be noted that the *APOE*4* allele carrier frequency in this population

(20.6%) is within the range (20-30%) of what is seen in elderly subjects participating of epidemiological studies in the U.S.[47, 48]

The VBM analyses suggest that this very elderly MCI cohort is no different than younger cohorts in that mesial temporal atrophy is the most prominent structural change compared to age-matched controls.[25, 49] PiB-positive MCI appeared to be more associated with mesial temporal atrophy, as are AD[50, 51], while PiB-negative MCI appeared to be associated with a more diffuse pattern of atrophy that included frontal lobes. However, this conclusion remains speculative because when directly compared, the atrophy patterns of PiB-positive and PiB-negative MCI did not significantly differ, most likely due to the small samples sizes of these two MCI groups.

In these very elderly subjects with no (i.e., controls) or minimal (i.e., MCI) cognitive changes, increased atrophy was not readily apparent in the PiB-positive subjects relative to the PiB-negative subjects (Figure 3B). This could be considered consistent with the hypothesis that Aβ deposition precedes atrophy in the pathophysiological sequence of AD.[52] However, even more likely in this very elderly cohort, is the possibility that extensive age-related atrophy was present in both PiB-negative and PiB-positive subjects. That is, brain atrophy was being driven by factors other than or in addition to Aβ deposition. Still, the MCI subjects had greater brain atrophy than the cognitively normal controls (Figure 3A). In contrast, both the controls and the MCI subjects had extensive PiB retention, and the level of PiB retention in MCI subjects was not significantly greater than that in controls (Figure 2B). Taken together, the in vivo evidence of increased atrophy and lack of evidence for increased Aβ deposition in the MCI subjects of this very elderly cohort is consistent with the postmortem findings of Savva et al. [4]. Savva et al. suggested that increasing plaque and tangle pathology with increasing age in non-demented subjects tended to obscure differences in these pathologies between demented and non-demented subjects above age 90 years of age, a finding consistent with other studies [53, 54]. However, Savva et al. also found a consistent difference in atrophy between demented and non-demented subjects even in subjects above 90 years of age.

As a group, PiB-positive subjects had lower performance on executive and attention tests. The neuropsychological battery was used to define “normal cognition”, and it was difficult to determine statistical differences between NC subjects with and without Aβ deposition. While there were no statistical differences between MCI subjects with and without Aβ deposition, including tests of memory, attention and language functions, trend level differences were observed.

One of the strengths of this study is that the present group of elderly subjects is different from previous cohorts in several important ways. This cohort is much older on average than those included in previous studies. Consequently these subjects are at increased risk of dementia and having Aβ plaque deposits in the brain. This cohort includes both NC subjects as well as subjects with MCI, which allows us to examine two different levels of cognitive function within a group of non-demented subjects. Finally, this cohort had been followed for up to 9 years with detailed annual cognitive and neuropsychiatric evaluations prior to and concurrent with the PiB scan, which strengthened the characterization of the NC and MCI diagnoses.

Taken together, the data from this study extend previous studies of progressive Aβ deposition in a population-based cohort of aging, non-demented subjects. Our data indicate that the increased prevalence of Aβ deposition with age continues at least into the ninth decade of life and that even at these ages, some PiB-positive individuals do not show cognitive symptoms, consistent with the pathological findings of the Religious Orders

Study.[2] Although these findings support the need for early preventive therapeutic strategies, it is difficult to determine when these interventions should take place. Further longitudinal evaluations of this cohort will provide important information about development of new Aβ deposition in the PiB-negative cases, the risk of dementia in PiB-positive MCI subjects, and outcomes over time in PiB-positive and PiB-negative NC cases. Such information will provide further guidance for intervention trials of PiB-positive and PiB-negative NC and MCI subjects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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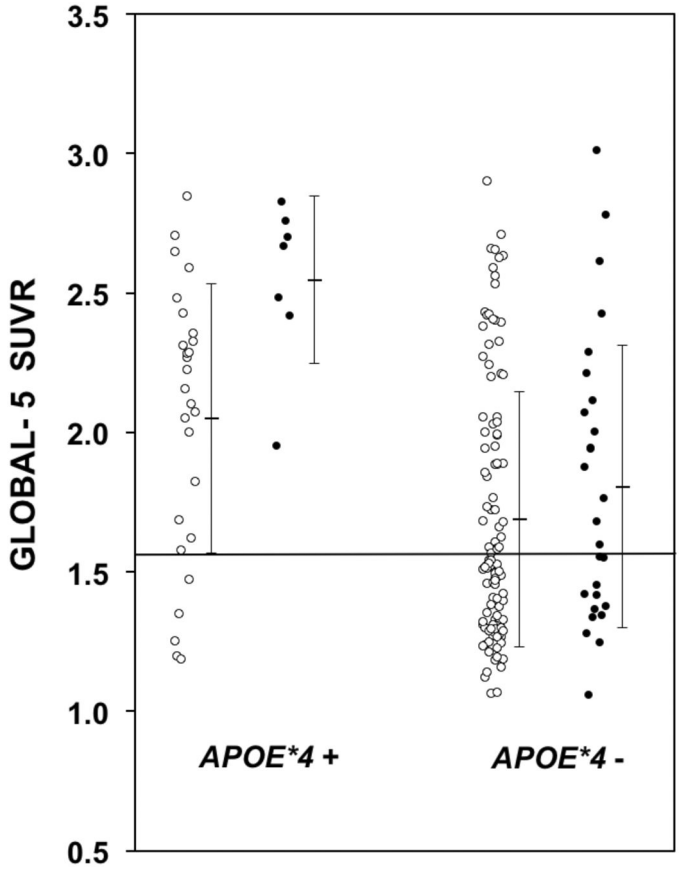

Figure 1.

Scatter plot of the Global-5 SUVR values of normal cognition (NC) (○) and mild cognitive impairment (MCI) (●) subjects, highlighting the higher average values for both the NC and MCI *APOE*4*-positive subjects relative to the *APOE*4*-negative NC and MCI subjects. The horizontal line at a Global-5 SUVR of 1.57 represents the line defining PiB-positivity.

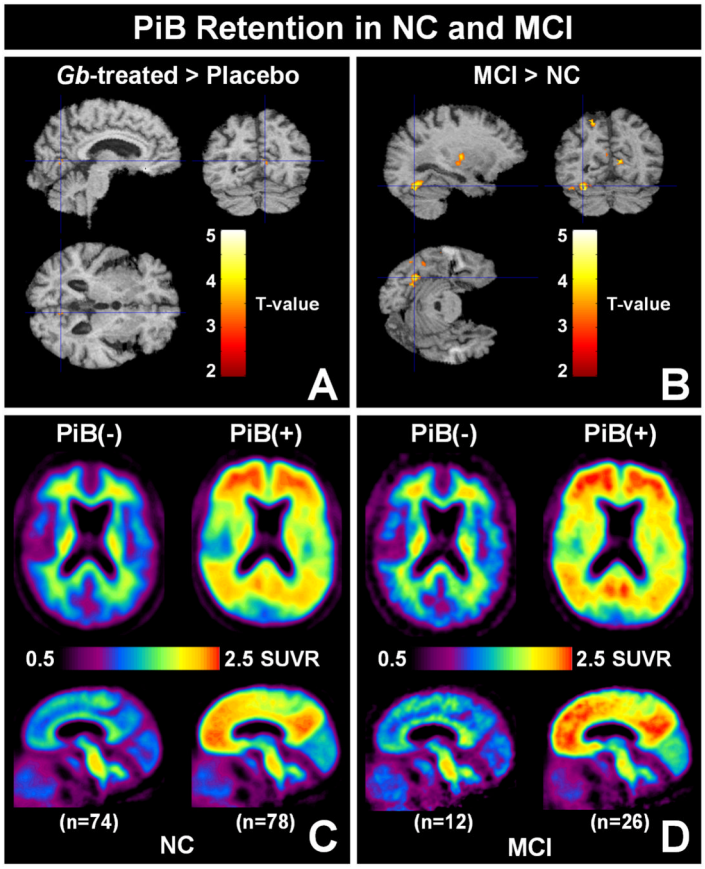

Figure 2.

(A & B) Results of voxel-wise analysis of PiB retention. The t-maps show the three orthogonal views of the slice containing the point of peak significance overlaid on the MCI template. Both A & B correspond to k=50 contiguous voxels; $p<0.001$ uncorrected. No significant voxels are detected at $p<0.001$ with FDR correction. (A) Comparison of PiB retention in *Gb*-treated (n=95) and placebo-treated subjects (n=95); Contrast: *Gb*-treated > placebo-treated shown, no significant voxels for *Gb*-treated < placebo-treated. (B) Comparison of PiB retention in all controls (n=152) with all MCI subjects (n=38); Contrast: MCI > controls; no significant voxels for controls > MCI. (C & D) The topography of PiB retention in control (C) and MCI subjects (D). The average PiB retention (SUVR) is shown in an axial plane (top) and a sagittal plane (bottom) in PiB-negative (left) and PiB-positive subjects (right).

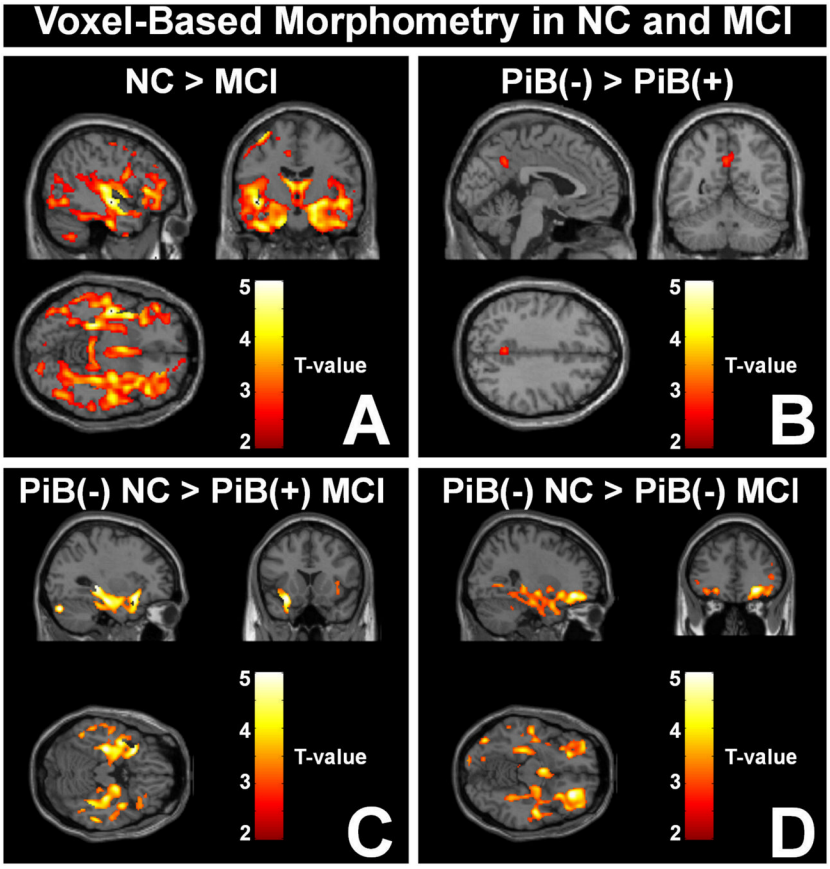

Figure 3.

Results of VBM analyses. The t-maps show the three orthogonal views of the slice containing the point of peak significance overlaid on the MNI template. **(A & B)** Two-way ANOVA model with diagnosis (control, n=136; or MCI, n=35) and PiB status (negative, n=76; or positive, n=95) as grouping factors to determine voxel-wise gray matter differences. No interaction effect was found between diagnosis and PiB status. **(A)** Main effect of diagnosis. Contrast: Controls > MCI. **(B)** Main effect of PiB status. Contrast: PiB-negative > PiB-positive. **(C)** Comparison of PiB-negative controls (n=65) with PiB-positive MCI subjects (n=24); Contrast: PiB-negative Controls >PiB-positive MCI. **(D)** Comparison of PiB-negative controls with PiB-negative MCI subjects (n=11); Contrast: PiB-negative Control > PiB-negative MCI. All figures correspond to k=100 contiguous voxels and $p<0.025$ after FDR correction, except (B) that corresponds to k=100 contiguous voxels and $p<0.01$ without FDR correction. For the comparison in (B), it is important to note that no significant voxels are detected at $p<0.025$ with FDR correction.

Table 1

Demographic and clinical characteristics by PiB status for all participants

	All Subjects			Normal Cognition			MCI		
	PiB-negative (n=86)	**PiB-positive (n=104)**	***P***	**PiB-negative (n=74)**	**PiB-positive (n=78)**	***P***	**PiB-negative (n=12)**	**PiB-positive (n=26)**	***P***
Age, mean (SD), y	85.2 (2.5)	85.8 (3.0)	.3711	85.5 (2.6)	85.4 (3.1)	.5964	83.8 (1.2)	86.8 (2.8)	**.0012**
Sex (n, % male)	54 (62.8%)	59 (56.7%)	.3971	44 (59.5%)	44 (56.4%)	.7035	10 (83.3%)	15 (57.7%)	.1578
Race									
white	83 (96.5%)	101 (97.1%)	.8128	73 (98.7%)	77 (98.7%)	.9701	10 (83.3%)	24 (92.3%)	.5773
Education, mean (SD), y	14.6 (2.7)	14.7 (2.5)	.9452	14.8 (2.7)	14.8 (2.6)	.8955	13.8 (3.1)	14.2 (2.3)	.5082
*APOE*4* allele carrier (n/ available, %)	5/81 (6.2%)	29/95 (30.5%)	**<.0001**	5/69 (7.2%)	22/73 (30.1%)	**.0005**	0/12 (0%)	7/22 (31.8%)	**.0356**
*APOE*2* allele carrier (n/ available, %)	14/81 (17.3%)	7/95 (7.4%)	.0608	11/69 (15.9%)	6/73 (8.2%)	.1989	3/12 (25%)	1/22 (4.6%)	.2733
MMSE score, mean (SD)	27.8 (2.1)	27.4 (2.1)	.1700	28.2 (1.7)	27.9 (1.6)	.1981	25.3 (2.8)	26.0 (2.6)	.5878

Table 2

Concurrent neuropsychological test performance (mean, SD) by PiB status

† Models adjusted for age, education, sex, race and CESD depression score.

	All Subjects			Normal Cognition			MCI		
	PiB-negative (n=86)	**PiB-positive (n=104)**	***p***	**PiB-negative (n=74)**	**PiB-positive (n=78)**	***p***	**PiB-negative (n=12)**	**PiB-positive (n=26)**	***p***
Memory									
CVLT sum of learning trials (range, 0-80)	44.9 (11.6)	41.5 (12.1)	.074	47.3 (10.5)	44.1 (11.4)	.094	30.7 (6.9)	33.6 (10.8)	.094
CVLT delayed recall (range, 0-16)	8.5 (3.7)	8.0 (3.7)	.365	9.2 (3.1)	9.1 (3.2)	.679	3.8 (3.2)	4.7 (3.4)	.221
Rey figure immediate recall (range, 0-24)	16.7 (3.8)	15.6 (4.0)	.077	17.1 (3.7)	16.8 (3.4)	.405	14.0 (3.9)	12.0 (3.3)	.669
Rey figure delayed recall (range, 0-24)	16.2 (4.1)	15.8 (4.1)	.736	16.6 (3.8)	16.9 (3.3)	.560	13.5 (4.8)	12.3 (4.0)	.734
Visuospatial construction									
Rey figure copy (range, 0-24)	20.7 (2.4)	20.2 (2.2)	.131	20.9 (2.2)	20.8 (1.7)	.683	19.8 (3.1)	18.5 (2.7)	.509
Executive functions									
Trail Making B, s to completion (sample range, 43-240)	106.7 (45.4)	123.3 (51.9)	.059	97.5 (35.5)	108.2 (41.9)	.229	163.4 (59.0)	168.5 (53.4)	.437
Language									
Animal fluency, no. of words generated in 60 s	15.8 (3.7)	14.4 (4.0)	**.0496**	15.9 (3.6)	15.4 (3.6)	.717	15.3 (4.5)	11.2 (3.4)	.098
Letter fluency (sum F & S), average no. of words generated in 60 s	27.3 (8.6)	28.3 (8.0)	.336	27.9 (8.3)	28.7 (7.9)	.250	23.3 (10.0)	27.2 (8.1)	.290
Attention									
Trail Making A, s to completion (sample range 20-94)	42.3 (15.0)	48.5 (17.8)	**.046**	42.2 (15.2)	45.3 (16.6)	.388	42.8 (14.3)	58.2 (18.3)	.095

Abbreviations: CVLT, California Verbal Learning Test

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Table 3

a. SUVR values by diagnosis

Region	All Subjects		
	NC (n=152)	MCI (n=38)	*P*
Global-5	1.75 (0.48)	1.97 (0.54)	.0251
ACG	1.71 (0.59)	1.95 (0.64)	.0448
FRC	1.84 (0.53)	2.06 (0.58)	.0380
LTC	1.72 (0.39)	1.91 (0.49)	.0221
PAR	1.74 (0.45)	1.93 (0.49)	.0418
PRC	1.75 (0.52)	1.99 (0.58)	.0177
AVS	1.59 (0.47)	1.82 (0.52)	. 0191
MTC	1.18 (0.16)	1.19 (0.15)	.6295
PON	2.08 (0.30)	2.00 (0.27)	.0812
OCC	1.49 (0.23)	1.60 (0.27)	.0348
OCP	1.70 (0.22)	1.75 (0.21)	.4060
SMC	1.47 (0.28)	1.59 (0.33)	.0418
SWM	1.94 (0.33)	1.93 (0.28)	.5904
THL	1.44 (0.22)	1.44 (0.19)	.8653

b. SUVR values by *APOE*4* carrier status

Region	All Subjects			Normal Cognition			MCI		
	*APOE*4*+ (n=34)	*APOE*4*-(n=142)	*P*	*APOE*4*+ (n=27)	*APOE*4*-(n=115)	*P*	*APOE*4*+ (n=7)	*APOE*4*-(n=27)	*P*
Global-5	2.15 (0.49)	1.71 (0.46)	<.0001	2.05 (0.48)	1.69 (0.46)	.0014	2.54 (0.30)	1.81 (0.51)	.0013
ACG	2.22 (0.57)	1.65 (0.56)	<.0001	2.11 (0.56)	1.62 (0.56)	.0003	2.65 (0.40)	1.76 (0.59)	.0014
FRC	2.26 (0.55)	1.80 (0.50)	<.0001	2.16 (0.54)	1.77 (0.50)	.0031	2.66 (0.38)	1.90 (0.54)	.0028
LTC	2.05 (0.43)	1.69 (0.38)	<.0001	1.94 (0.42)	1.67 (0.37)	.0040	2.48 (0.29)	1.77 (0.45)	.0004
PAR	2.08 (0.47)	1.72 (0.43)	.0001	2.00 (0.48)	1.69 (0.42)	.0041	2.40 (0.28)	1.79 (0.47)	.0011
PRC	2.15 (0.50)	1.71 (0.51)	<.0001	2.05 (0.51)	1.69 (0.51)	.0018	2.53 (0.24)	1.81 (0.56)	.0014
AVS	1.94 (0.51)	1.57 (0.44)	.0001	1.84 (0.49)	1.54 (0.43)	.0018	2.29 (0.46)	1.69 (0.47)	.0087
MTC	1.22 (0.15)	1.18 (0.16)	.1110	1.22 (0.15)	1.18 (0.16)	.1837	1.24 (0.14)	1.18 (0.15)	.4505
PON	2.03 (0.22)	2.10 (0.28)	.2200	2.06 (0.19)	2.11 (0.30)	.3124	1.92 (0.31)	2.02 (0.26)	.3537

b. SUVR values by *APOE*4* carrier status

Region	All Subjects			Normal Cognition			MCI		
	***APOE*4*+ (n=34)**	***APOE*4*-(n=142)**	***P***	***APOE*4*+ (n=27)**	***APOE*4*-(n=115)**	***P***	***APOE*4*+ (n=7)**	***APOE*4*-(n=27)**	***P***
OCC	1.58 (0.23)	1.51 (0.23)	.0424	1.52 (0.18)	1.49 (0.22)	.2700	1.80 (0.25)	1.55 (0.26)	.0332
OCP	1.77 (0.23)	1.71 (0.20)	.1421	1.74 (0.23)	1.71 (0.21)	.5544	1.88 (0.23)	1.72 (0.19)	.0264
SMC	1.67 (0.33)	1.46 (0.27)	.0006	1.60 (0.32)	1.44 (0.26)	.0130	1.91 (0.27)	1.52 (0.31)	.0060
SWM	1.90 (0.28)	1.98 (0.31)	.2144	1.92 (0.27)	1.97 (0.32)	.4011	1.80 (0.31)	1.97 (0.27)	.2981
THL	1.48 (0.23)	1.44 (0.21)	.4098	1.46 (0.23)	1.44 (0.21)	.7398	1.54 (0.23)	1.43 (0.18)	.2565