

Association of Gray Matter Atrophy with Age, β -Amyloid, and Cognition in Aging

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Both cognitive aging and β -amyloid ($A\beta$) deposition, a pathological hallmark of Alzheimer's disease, are associated with structural and cognitive changes in cognitively normal older people. To examine independent effects of age and $A\beta$ deposition on cognition and brain structure in aging, 83 cognitively normal older adults underwent structural magnetic resonance imaging scans and neuropsychological tests and were classified as negative (PIB-) or positive (PIB+) for $A\beta$ deposition using the radiotracer Pittsburgh compound B (PIB). Weighted composite discriminant scores represented subjects' cognition. Older adults showed age-related gray matter (GM) atrophy across the whole brain regardless of $A\beta$ deposition. Amyloid burden within PIB+ subjects, however, was associated with GM atrophy in the frontal, parietal, and temporal cortices. Associations between cognition and volume in PIB- subjects were primarily seen throughout frontal regions and the striatum, while, in PIB+ subjects, these associations were seen in orbital-frontal and hippocampal regions. Furthermore, in PIB- subjects, cognition was related to putaminal volume, but not to hippocampus, while, in PIB+ subjects, cognition was related to hippocampal volume, but not to putamen. These findings highlight differential age and $A\beta$ effects on brain structure, indicating effects of age and $A\beta$ that operate somewhat independently to affect frontostriatal and medial temporal brain systems.

Keywords: aging, amyloid, cognition, Pittsburgh compound B-positron emission tomography, structure

Introduction

Advanced age is commonly associated with adverse structural changes in the brain and lower performance on diverse cognitive functions (Grady and Craik 2000; Buckner 2004). These changes are not invariably global, as age-related cognitive decline occurs selectively within specific cognitive domains, and age-related structural change is notable for regional differences (Raz et al. 1997; Good et al. 2001; Salat et al. 2004; DeCarli et al. 2005; Fjell et al. 2009). Using volumetric measures of manually defined regions-of-interest (ROIs), Raz et al. (1997) reported more prominent volumetric reduction in prefrontal cortex (PFC), superior parietal, and inferior temporal cortices with insignificant changes in primary motor and visual cortices. Studies using semiautomated measures of whole-brain cortical thickness or gray matter (GM) volume also reported greater atrophy in frontal and superior temporal cortices with relatively preserved GM in anterior cingulate and visual cortices (Good et al. 2001; Moffat et al. 2007; Fjell et al. 2009). Regional differences in brain aging are seen not only cross-sectionally, but also longitudinally. Using a large community sample, DeCarli et al. (2005) found that age-related structural changes are

quantitatively and qualitatively different across brain regions showing that changes in most of the brain regions are minimal before age 50, while the frontal lobe undergoes a linear reduction across lifespan, and that the rate and the magnitude of decline were greater for the frontal than the medial temporal lobes (MTLs). In addition, considerable age-related atrophy has been seen longitudinally in the striatum (Raz et al. 2003). These findings collectively support the notion that there is a regional difference in structural vulnerability to the aging process.

A relatively large proportion of cognitively normal older adults have been shown to harbor substantial accumulation of β -amyloid ($A\beta$), a pathological hallmark of Alzheimer's disease (AD) that can now be measured in vivo using positron emission tomography (PET) with radiotracers such as [¹¹C]-Pittsburgh compound B (PIB). Patients with AD and mild cognitive impairment (MCI) show particularly increased $A\beta$ deposition and atrophy (Kemppainen et al. 2007; Jack et al. 2008, 2009; Chetelat, Villemagne, Bourgeat, et al. 2010; Chetelat et al. 2011). Greater $A\beta$ deposition was associated with increased brain atrophy or atrophy rate in AD (Archer et al. 2006; Becker et al. 2011) and MCI (Tosun et al. 2011). Known regional atrophy in AD and MCI includes the MTL, especially hippocampus, as well as other regions such as anterior/posterior cingulate, temporal cortices, precuneus, and frontal cortices (de Leon et al. 1989; Braak and Braak 1991; Csernansky et al. 2004; Jack et al. 2008, 2009; Dickerson et al. 2009). The association of $A\beta$ deposition with GM atrophy has also been reported in cognitively intact normal elderly, showing an inverse relationship with PIB uptake in hippocampal volume (Morimino et al. 2009; Storandt et al. 2009; Bourgeat et al. 2010; Chetelat, Villemagne, Bourgeat, et al. 2010), cortical thickness or GM volume in the temporal pole and superior frontal cortex (Dickerson et al. 2009), and frontal and posterior association cortices (Becker et al. 2011; Oh et al. 2011). Similar results of cortical thinning in lateral, medial frontal, and temporal cortices and posterior cingulate were seen when cerebrospinal fluid (CSF) $A\beta$ were related to longitudinal changes in cortical thickness in cognitively intact older adults (Fjell et al. 2010).

Structural changes have been frequently associated with age-related cognitive changes. In particular, decline in working memory (WM) and executive functions (EXEs), such as perseverative behavior, has been related to volumetric differences in the PFC (Raz et al. 1997; Gunning-Dixon and Raz 2003). This specific relationship between decline in executive and frontal abilities and volumetric loss of the PFC is consistent with previous neuroanatomical studies in relation to cognition (Goldman-Rakic 1987) and further supports a selective age-related prefrontal atrophy compared with other brain regions (Fjell et al. 2006).

Cognitive aging, however, involves decline in not only frontal lobe-related cognitive functions, but also episodic memory (EM) that reflects MTL function. Consistent with these findings, advanced age has also been associated with widespread cortical thinning and volumetric reduction in MTL, including the hippocampus (Raz et al. 1997; Rajah et al. 2010). Decline in EM and brain atrophy particularly in the MTL, however, has also been frequently observed in A β -related pathological processes including AD.

Considering that a relatively large proportion of older adults with AD pathology may be found in a population traditionally viewed as “normal aging,” it remains unresolved to what extent age and A β pathology independently contributed to the previous findings of structural and cognitive changes in relation to age. Previously, we examined the effect of age and A β on multiple cognitive domains and found significant effects of both age and A β on overall cognition indexed by a weighted composite score of different cognitive domains (Oh et al. 2012). In the present study, we further aimed to examine independent effects of advanced age and A β on structure and structural correlates of individual differences in cognition during aging. For structural measures, we adopted 2 approaches: Surface-based cortical thickness measures and GM volume measures processed using voxel-based morphometry (VBM). Both structural measures are semiautomated methods frequently used to examine morphological changes in GM and, the converging evidence from the 2 measures would strengthen our findings. The first aim of the present study was to examine the age- and A β -related differences in brain structure as measured by cortical thickness and GM volume by assessing the effect of each independent variable while controlling for the effect of the other independent variable. The second aim of the study was to examine how structural alterations are related to the cognitive changes consequent to both age and A β deposition. We expected that age would be associated with reduction in GM volume and cortical thickness particularly in the frontal lobes, whereas A β deposition would be more associated with GM and cortical thickness reduction in the MTL, including the hippocampus. In addition, we expected that cognitive decline in older adults with and without evidence of increased A β deposition would be associated with atrophy in the MTL and frontal regions, respectively.

Materials and Methods

Subjects

Eighty-three healthy older adults (mean age = 74.4 ± 6.6 years, 53 females, mean Mini-Mental State Examination (MMSE) = 28.9 ± 1.3) who underwent PIB-PET and structural magnetic resonance imaging (MRI) participated in the study. All subjects underwent a medical interview and a detailed battery of neuropsychological tests. In order to be eligible for the study, older subjects were required to be 60 years or older, live independently in the community without neurological or psychiatric illness, and have no major medical illness or medication that influenced cognition. Apolipoprotein E (APOE)- $\epsilon 4$ carrier status was determined for most of the subjects using previously published methods (Agosta et al. 2009). Fifty-two older subjects in the present study also participated in our previous study examining the relationship between amyloid deposition, GM volume, and cognition in normal elderly people (Oh et al. 2011, 2012). All subjects provided informed consent in accordance with the Institutional Review Boards of the University of California, Berkeley and the Lawrence Berkeley National Laboratory (LBNL) prior to their participation.

Neuropsychological Tests

A detailed procedure for neuropsychological tests and scoring is described in a previously published study (Oh et al. 2012). Briefly, most of the subjects completed 17 cognitive performance test measures, whereas 9 subjects did not complete all the tests. A more concise and reliable summary measure from multiple neuropsychological test measures was developed from 17 neuropsychological test scores by applying sequential multivariate analyses using principal component analysis (PCA) and discriminant analysis. The resulting discriminant score was used to represent global cognition of each individual (detailed procedures are provided in Supplementary Methods and Results).

Imaging Data Acquisition

Pittsburgh Compound B

PIB was synthesized at the LBNL's Biomedical Isotope Facility using a previously published protocol (Mathis et al. 2003). All PET scans were performed at the LBNL using a Siemens ECAT EXACT HR PET scanner in a 3-dimensional acquisition mode. Dynamic acquisition frames were obtained over 90 min following the injection of 10–15 mCi of [^{11}C] PIB.

Structural MRI

High-resolution, structural MRI scans were collected at the LBNL on a 1.5-T Magnetom Avanto system (Siemens, Inc., Iselin, NJ, USA) with a 12-channel head-coil run in the triple mode. Three high-resolution T_1 -weighted magnetization-prepared rapid gradient-echo (MPRAGE) scans were collected axially for each subject (time repetition = 2110 ms, time echo = 3.58 ms, flip angle: 15° , field of view = 256×256 mm, matrix size: 256×256 mm, slices: 160, voxel size = $1 \times 1 \times 1$ mm 3).

Imaging Data Analysis

Pittsburgh Compound B-Positron Emission Tomography

All PET images were preprocessed using Statistical Parametric Mapping 8 (SPM8; <http://www.fil.ion.ucl.ac.uk/spm/>). ROI labeling was implemented using the FreeSurfer v4.4 software package (<http://surfer.nmr.mgh.harvard.edu/>) in order to create a reference region in the GM cerebellum and to perform subsequent ROI analyses. The first 5 PIB frames were summed, and all PIB frames including the summed image from 1 to 5 frames were realigned to the middle frame (17th frame). The subject's structural MRI image was coregistered to realigned PIB frames. A PIB distribution volume ratio (DVR) was calculated using Logan graphical analysis and a GM-masked cerebellar reference region with frames corresponding to 35–90 min postinjection (Logan et al. 1996; Price et al. 2005).

A global PIB index representing overall A β deposition across the brain was calculated in each subject's native space using DVR values across frontal (all frontal regions anterior to the precentral sulcus), temporal (superior, middle, and inferior temporal gyri), parietal (superior and inferior parietal cortices, supramarginal gyrus, and precuneus), and anterior/posterior cingulate cortices. These large ROIs were created using FreeSurfer-generated anatomical ROIs on a subject's native space.

A cutoff score of the PIB index used to classify older subjects (All Old) into either PIB positive Old (PIB+) or PIB negative Old (PIB-) group was calculated based on the PIB index of young adults as previously reported (Mormino et al. 2012). Older subjects were classified as PIB+ if their global PIB index was greater than the mean + 2 standard deviations (SDs) of the PIB index of young adults. The resulting cutoff score was 1.08. As a result, 28 older subjects were classified as PIB+ and 55 as PIB-.

Structural MRI

GM Volume Analysis. We performed VBM implemented with SPM8 running under Matlab 7.7 (Mathworks, Natick, MA, USA) on structural images. Briefly, VBM is a semiautomated procedure in which tissue classification, bias correction, and nonlinear warping are

combined. Detailed methods describing the implementation of VBM for the current study are provided in Supplementary Methods.

Cortical Thickness Analysis. In order to measure cortical thickness, we processed the averaged single structural T_1 image for each subject using a surface-based processing stream provided by the FreeSurfer v4.4 software package (<http://surfer.nmr.mgh.harvard.edu/>; for further details, see Supplementary Methods).

Imaging Data Statistical Analysis

GM Volume Analysis

Prior to any statistical analyses, total intracranial volume (TIV) was calculated by summing the volumes of GM, white matter (WHM), and CSF derived from non-normalized segmented images. Only voxels with a GM value >0.1 (maximum value, 1) were included in subsequent analyses to avoid possible edge effects around the border between GM, WHM, and CSF (Sorg et al. 2007). To assess the effects of age and amyloid deposition on GM volume, we used the general linear model (GLM) and conducted multiple regressions with age, PIB index, gender, education, and TIV as regressors. The resulting maps were thresholded at $P < 0.05$, corrected for multiple comparisons using the false discovery rate (FDR) correction method (Genovese et al. 2002). In addition, in order to examine the regions that are negatively associated with the global PIB index only in PIB+ subjects, we constructed a multiple regression model with the PIB index as a covariate of interest and age, gender, education, and TIV as covariates that are controlled for. The resulting statistical maps were thresholded at $P < 0.005$ uncorrected for multiple comparison correction, followed by cluster correction at $P < 0.05$.

To assess the relationship between GM volume and cognition, we conducted multiple regression analyses in which voxel-wise GM volume was regressed on subjects' cognitive performance as measured by discriminant scores. We applied a threshold of $P < 0.05$, corrected for multiple comparisons using an FDR for All Old and PIB- groups and a threshold of $P < 0.005$, uncorrected at a voxel level, followed by cluster-level correction at $P < 0.05$, for the PIB+ group. A more lenient threshold was applied for PIB+, because the sample size was smaller compared with All Old and PIB- groups. These analyses controlled for age, gender, education, and TIV.

Cortical Thickness Analysis

Statistical analysis was performed on the FreeSurfer-processed cortical thickness data using the GLM as implemented in FreeSurfer. To assess the effect of age, multiple regressions were constructed with age as predictors of interest and PIB index, gender, and education as nuisance variables. The effect of amyloid deposition on cortical thickness was assessed by a multiple regression model with the PIB index as predictors of interest with age, gender, and education being controlled. To assess the relationship between cognition and cortical thickness within All Old, PIB-, and PIB+ groups, multiple regressions were conducted with discriminant scores as predictors of interest and age, gender, and education as nuisance variables.

ROI Analysis

In order to further confirm the relationship between subcortical structures and cognition observed in VBM analysis, we conducted ROI analyses using subcortical ROIs provided by FreeSurfer, with a particular focus on putamen and hippocampus bilaterally. In addition, we conducted exploratory ROI analyses using 40 Desikan cortical ROIs provided by FreeSurfer to assess whether aggregated cortical thickness measures within an ROI might show statistically significant relationships with cognition even though they did not reach significance at a whole-brain level. For cortical ROIs, a mean cortical thickness measure within each ROI was calculated; for subcortical ROIs, volume of the selected ROIs was first adjusted by estimated intracranial volume (eICV) following previously published methods (Mathalon et al. 1993; Mormino et al. 2009) prior to being entered into a multiple regression model. Although eICV provided by FreeSurfer and TIV measured by SPM are highly correlated, we adjusted subcortical

FreeSurfer ROI volumes using eICV. Therefore, eICV-adjusted FreeSurfer ROI volumes were used in subsequent multiple regressions in relation to cognition.

Multiple Regressions with Cognitive Test Scores

All nonimage analyses, including ROI analysis, were conducted using the SPSS software (version 19). Differences between PIB+ and PIB- groups for gender and APOE genotypes were assessed by χ^2 tests. Independent sample T -tests were used to compare means between PIB- and PIB+ groups. Multiple regressions were further conducted to assess the relationship between global PIB index and cognitive performance and between cortical/subcortical ROI measures and cognition. Multiple regressions with global PIB index and cognitive performance resulted in a total of 6 multiple regressions for 5 cognitive factors and 1 discriminant score as dependent measures. For ROI measures, 3 multiple regression models (for All Old, PIB-, and PIB+ groups) were run for each ROI. Age was controlled in all analyses. Statistical significance was determined at $\alpha = 0.05$, 2-tailed.

Results

Characteristics of Participants

Demographics, global PIB index, and MMSE scores for all older subjects are summarized in Table 1. PIB+ versus PIB- groups did not differ on measures such as age, gender, education, APOE genotypes, and MMSE.

Neuropsychological Test Scores by Principal Components and Discriminant Scores

PCA revealed 5 components that, based on the tests that loaded most heavily on each component, we called verbal EM, visual episodic memory (VM), semantic memory, WM, and EXEs. These 5 components accounted for 78.6% of the total variance of the data. The component loadings are shown in Supplementary Table 1. Group differences between PIB+ and PIB- adults were not significant in any cognitive domain ($P_s > 0.05$). Using the PIB index as a continuous variable, multiple regression controlling for age revealed that PIB index significantly predicted VM scores, $\beta = -0.22$, $P < 0.05$, but not any other cognitive scores ($P_s > 0.1$). When PIB index was controlled for, age by itself significantly predicted VM scores, $\beta = -0.37$, $P < 0.05$.

Table 1
Characteristics of participants

	All Old	PIB-	PIB+
<i>N</i>	83	55	28
Age (year)	74.3 \pm 6.6(60–96)	73.6 \pm 6.3(60–88)	75.5 \pm 7.6(61–96)
Education (year)	17 \pm 1.9(12–20)	17.2 \pm 1.8 (12–20)	16.5 \pm 2(12–20)
Gender, <i>n</i> , F/M ^a	53/30	36/19	17/11
PIB index	1.1 \pm 0.2(0.8–1.8)	1.0 \pm 0.1(0.8–1.07)	1.3 \pm 0.2(1.08–1.8)
APOE- ϵ 4, <i>n</i> (%) ^b	25 (30.9%)	13 (24.1%)	12 (44.4%)
TIV (mL)	1610.7 \pm 168 (1226.6–2047.4)	1630 \pm 179 (1226.6–2047.4)	1572.8 \pm 139 (1285–1827)
MMSE	28.9 \pm 1.3 (25–30)	29 \pm 1.2(25–30)	28.8 \pm 1.3(26–30)

Note: Values are presented as mean \pm SD (range).

^a $\chi^2 = 0.18$, $P > 0.5$.

^bProportion of individuals with APOE genotypes ϵ 3/4 or ϵ 4/4, $\chi^2 = 3.5$, $P > 0.05$.

^cClassified as PIB+ when PIB index was greater than mean + 2 SD of the PIB index of young adults. The resulting cutoff score was 1.08.

TIV: total intracranial volume; PIB: Pittsburgh compound B; MMSE: Mini-Mental Status Examination.

The discriminant score largely reflected the VM and EXE scores (Supplementary Results). No significant group difference between PIB+ and PIB- adults was found for the discriminant scores ($P=0.11$, once age was controlled for). Using the PIB index as a continuous variable, multiple regressions revealed a significant relationship between PIB index and discriminant scores ($\beta=-0.24$, $P<0.05$), which was not significant once age was included in the model ($P=0.10$). When PIB index was controlled, age itself significantly predicted discriminant scores, $\beta=-0.43$, $P<0.001$. Subjects' discriminant scores were used as a proxy for global cognition in association with GM measures.

Effect of Age on GM Volume and Cortical Thickness

Age-related GM volume changes are depicted in Figure 1A. GM volume reduction was observed throughout most of the brain, but with preservation in primary somatosensory and motor areas and primary visual cortex. Peak coordinates were found in inferior frontal cortex bilaterally, caudate, and right superior and middle temporal cortices. For cortical thickness, similar results to GM volume were obtained for age-related reduction, showing greater cortical thinning in widespread regions including frontal, parietal, and temporal cortices (Fig. 1B).

Effect of A β on GM Volume and Cortical Thickness

Neither group comparison between PIB- and PIB+ nor multiple regression with PIB index as a continuous variable revealed any suprathreshold voxels even with a very lenient threshold ($P=0.005$, uncorrected for multiple comparisons). When we examined the effect of A β on GM volume and cortical thickness only within PIB+ adults, however, the PIB index was negatively associated with GM volume in the right middle frontal cortex (MFC), superior and inferior parietal cortices bilaterally, right angular gyrus, right inferior, middle, and superior temporal gyrus, precuneus bilaterally, and middle cingulate cortices, as shown in Figure 2. A similar association between PIB index and cortical thickness was found (data not shown).

Relationship Between GM and Cognition in All Old

We examined the relationship between regional GM measures and individual differences in cognition of older adults across both PIB+ and PIB- groups. When cognition, as indexed by discriminant scores, was correlated with GM volume, a positive association between GM volume and cognition was observed in right inferior and middle frontal gyri, orbital cortex bilaterally, left superior frontal and medial gyri, left temporal pole, left hippocampus, and putamen bilaterally (Fig. 3A). For

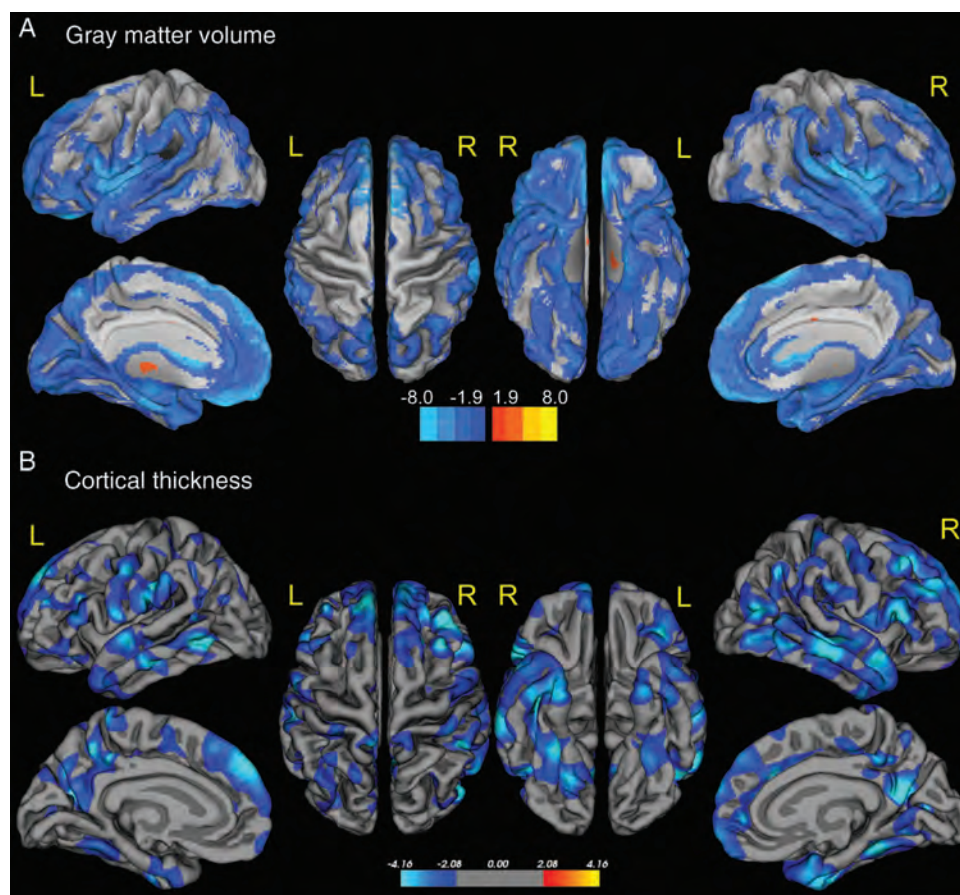


Figure 1. Effect of age on GM volume and cortical thickness. Brain regions showing associations between age and GM volume (A) and cortical thickness (B). Maps for both GM volume and cortical thickness were thresholded at FDR = 0.05, corrected for multiple comparisons. Panel of GM volume (A) shows suprathreshold regions on the lateral, medial, dorsal, and ventral surfaces of an average brain in MNI space, controlling for PIB index, gender, education, and TIV. For cortical thickness (B), PIB index, gender, and education were controlled. Warm and cool colors represent positive and negative associations between age and GM volume/cortical thickness. The color bars represent T -values. L: left hemisphere; R: right hemisphere.

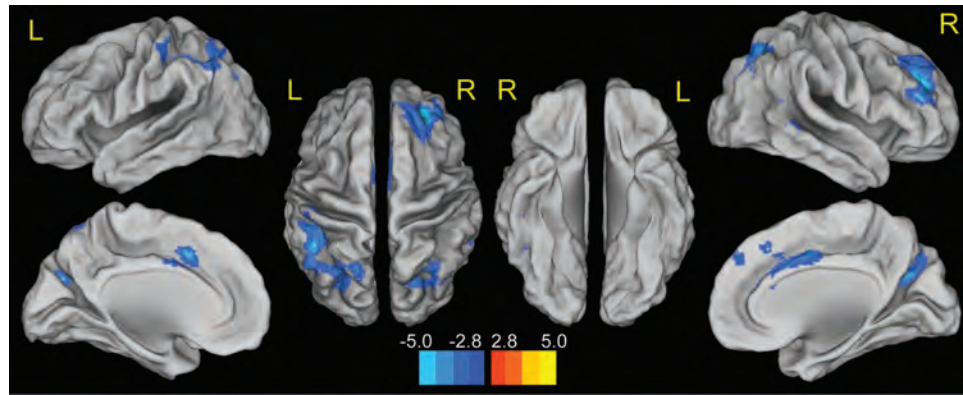


Figure 2. Negative association between PIB index and GM volume in PIB+ adults. Regions showing a negative association between GM volume and PIB index in the PIB+ group. Suprathreshold regions controlling for age, gender, education, and TIV are shown on the cortical surface of an average brain in MNI space. Maps were thresholded at $P < 0.005$ with cluster size correction ($P < 0.05$, 600 or more contiguous voxels). Warm and cool colors represent positive and negative associations between GM volume and PIB index. The color bars represent T -values.

cortical thickness measures, cognition was associated with greater cortical thickness in the right middle frontal gyrus, superior temporal gyri bilaterally, left temporal pole, lateral occipital cortices, medial orbital cortex, and parahippocampal gyri bilaterally (Fig. 3D).

Relationship Between GM and Cognition by A β Measures

To examine associations between GM volume and cognition in older people with little amyloid deposition, we repeated this analysis within the PIB- subjects. We found positive associations between discriminant scores and GM volume mainly in a frontostriatal network, including inferior and MFC bilaterally, left superior medial cortex, orbital cortex bilaterally, and left and right putamen. GM volume in the left inferior parietal, supramarginal, and precuneus also showed a positive relationship with cognition (Fig. 3B).

Consistent with GM volume results, better cognitive performance in the PIB- subjects was associated with greater cortical thickness in the right frontal cortex, while left lateral occipital gyrus and left temporal pole were also positively associated with cognition (Fig. 3E). The adjusted putamen subcortical ROI volume further confirmed a positive relationship between cognition and GM volume as shown in the VBM data (left putamen: $\beta = 0.37$, $P < 0.05$ and right putamen: $\beta = 0.39$, $P < 0.05$; Fig. 4). Association between the adjusted hippocampal volume and cognition was not significant (left hippocampus: $\beta = 0.08$, $P = 0.62$ and right hippocampus: $\beta = 0.20$, $P = 0.21$; Fig. 4). Within PIB+, cognition was positively associated with GM volume in hippocampus bilaterally, inferior medial frontal cortex, and putamen bilaterally (Fig. 3C). A similar relationship between structure and cognition was also found in cortical thickness (Fig. 3F). Adjusted hippocampal volume processed by Freesurfer further confirmed a positive relationship between cognition and hippocampal GM volume only within PIB+ (left hippocampus: $\beta = 0.50$, $P < 0.05$ and right hippocampus: $\beta = 0.41$, $P < 0.05$; Fig. 4). The adjusted putamen ROI volumes were not significantly associated with cognition ($P_s > 0.5$; Fig. 4). The slopes between putamen volume and cognition and between hippocampal volume and cognition did not significantly differ between PIB groups.

Exploratory analyses on cortical ROIs provided complementary findings for the voxel- and vertex-based whole-brain analyses while identifying additional anatomical regions that were missed in the whole-brain analyses. These regions included posterior cingulate cortices bilaterally and isthmus cingulate. Associations between cortical ROIs and cognition by All Old, PIB-, and PIB+ groups are provided in Supplementary Table 3.

Discussion

In the present study, we aimed to characterize the independent effects of age and A β deposition on GM atrophy and relationships between atrophy and cognition among cognitively normal older adults. The novel findings include: (1) Independent of A β deposition, age-related GM atrophy was observed widely throughout the brain; (2) while there was no difference in regional atrophy between those classified as PIB+ and PIB-, there was an association between higher levels of A β and regional atrophy in those classified as PIB+; (3) Individual differences in cognition in older adults were related to brain atrophy in selective regions, and the pattern of relationships between brain regions and cognition differed between those who had evidence of brain A β and those who did not.

Age-Related Structural Changes

Advanced age has been commonly associated with reduction in cortical volume or thickness that may be associated with age-related decline in diverse cognitive functions (Grady and Craik 2000; Buckner 2004). In addition, age is generally associated with greater GM volume reduction in the association cortices including prefrontal, parietal, temporal cortices and medial temporal regions, and with relatively preserved GM volume in the primary sensory and motor regions including occipital cortex and pre- and postcentral gyri (Raz et al. 1997; Good et al. 2001; Gunning-Dixon and Raz 2003; DeCarli et al. 2005; Fjell et al. 2009). Because many previous studies of brain aging could have been contaminated by the inclusion of older people with brain A β deposition, it has been unclear whether age-related structural GM reduction is purely due to age without an influence of AD pathology.

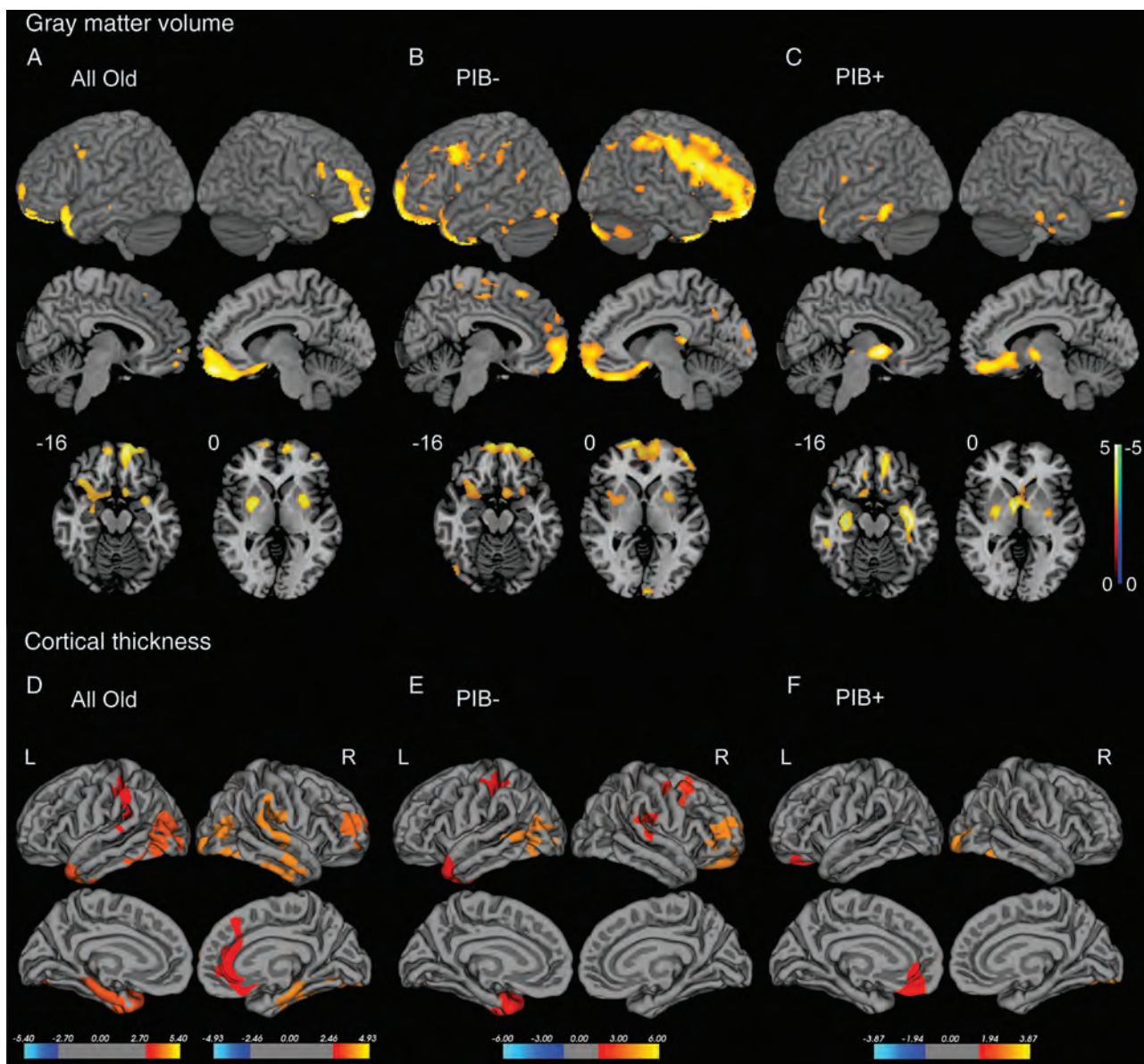


Figure 3. GM volume and cortical thickness associated with cognition measured by discriminant scores in All Old (A and D), PIB– (B and E), and PIB+ (C and F) groups. Regions showing a positive association between GM volume and cognition within All Old (A), PIB– (B), and PIB+ (C) groups. Suprathreshold regions controlling for age, gender, education, and TIV are shown on lateral and medial surfaces and axial slices (with corresponding z coordinates in mm) in MNI space. Maps were thresholded at $P < 0.05$ with multiple comparison correction using the FDR (A and B) and $P = 0.005$ with cluster size correction (1000 or more contiguous voxels) (C). Regions showing a positive association between cortical thickness and cognition in All Old (D), PIB– (E), and PIB+ (F) groups. Suprathreshold regions controlling for age, gender, and education are shown on the lateral and medial surfaces of the left and right hemispheres. Clusters of vertices were thresholded at $P < 0.05$ with cluster wise correction using 5000 instances of a Monte Carlo simulation.

When we associated age with GM measures while controlling for the effect of A β deposition, we found a similar pattern of GM changes to previous studies. Thus, it is clear that age, independent of A β deposition, is associated with near-global GM reduction that spares primary sensory and motor areas.

A β -Related Structural Changes in AD and Cognitively Normal Older Adults

Studies examining relationships between brain atrophy and A β using amyloid PET ligands have reported an association between brain atrophy and amyloid deposition as A β -related disease status progresses from healthy normals to MCI, and

AD and even within cognitively normal older adults. In this study, we did not find an effect of A β deposition on GM measures by treating A β deposition as either a dichotomous or continuous variable when we included all older subjects. We found, however, an inverse relationship between GM measures and A β deposition within the PIB+ group in anterior and middle cingulate, temporal cortices, precuneus, right MFC, and lateral parietal cortices, bilaterally. The association between GM atrophy and A β deposition is consistent with recent findings showing A β deposition is negatively associated with GM volume particularly in posterior cingulate, anterior cingulate, temporal cortex, or hippocampus (Storandt et al. 2009; Becker et al. 2011; Oh et al. 2011). Interestingly,

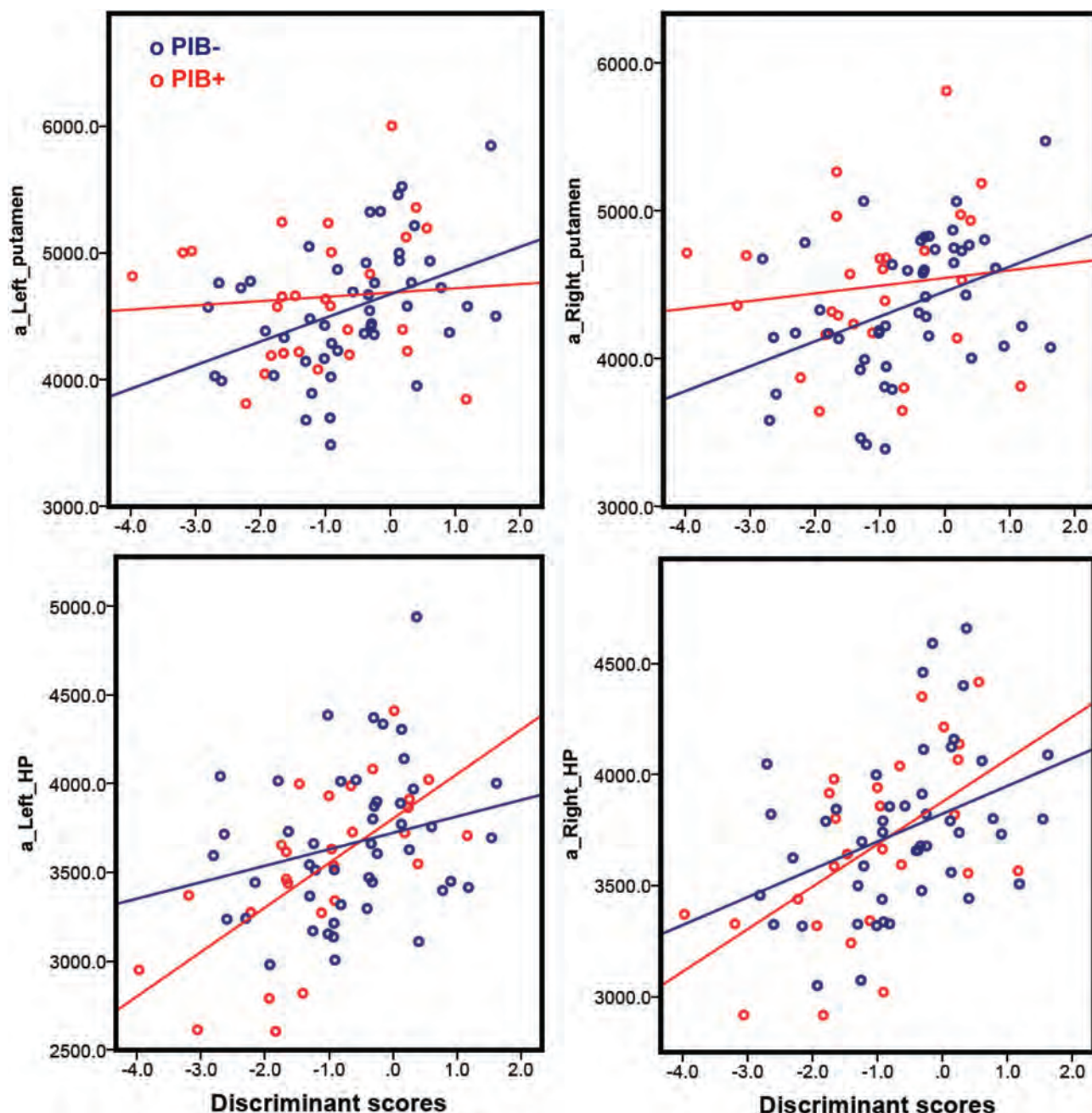


Figure 4. Subcortical ROIs showing significant relationships between GM volume and cognition differentially for PIB⁻ and PIB⁺ groups. GM volume in the putamen was significantly related to cognition in PIB⁻, but not in PIB⁺. GM volume in the hippocampus was significantly related to cognition in PIB⁺, but not in PIB⁻. These relationships, however, did not significantly differ from one another (for an interaction term, a_Left_putamen: $P > 0.1$; a_Right_putamen: $P > 0.1$; a_Left_HP: $P = 0.059$; a_Right_HP: $P > 0.1$). a_Left_putamen: eICV-adjusted left putamen; a_Right_putamen: eICV-adjusted right putamen; a_Left_HP: eICV-adjusted left hippocampus; a_Right_HP: eICV-adjusted right hippocampus. For a_Left_putamen, PIB⁻: $R^2 = 0.165$, $P < 0.05$; PIB⁺: $R^2 = 0.006$, $P > 0.1$. For a_Right_putamen, PIB⁻: $R^2 = 0.158$, $P < 0.05$; PIB⁺: $R^2 = 0.015$, $P > 0.1$. For a_Left_HP, PIB⁻: $R^2 = 0.059$, $P > 0.1$; PIB⁺: $R^2 = 0.428$, $P < 0.05$. For a_Right_HP, PIB⁻: $R^2 = 0.145$, $P > 0.1$; PIB⁺: $R^2 = 0.319$, $P < 0.05$.

an A β -related decrease in GM volume was also found in the right MFC, consistent with a recent finding that there was more profound age-related reduction in the right MFC compared with the left MFC in cognitively older adults compared with young individuals (Rajah et al. 2011). The study, however, did not measure the level of A β deposition in the older sample, therefore, although speculative, it is possible that the age-related volumetric reduction in the right MFC and the differential functional MRI activity pattern in association

with right MFC volume may have been driven by older adults with high A β deposition.

Inconsistent with other studies that show A β -related atrophy collapsing across all older subjects, we did not find a significant difference in brain atrophy in association with A β deposition when all older subjects were included. One possibility for the lack of group effect of A β deposition on GM in our sample may be that some older adults who are PIB⁺ show relatively low levels of A β deposition because of our

choice of thresholds. Our PIB cutoff score based on young adults' PIB indices is quite low compared with other studies, so that it is possible that some individuals considered PIB+ in this fashion might be misclassified. However, those classified as PIB- are highly likely to reflect brain aging without the presence of any fibrillar A β . Furthermore, the evidence suggests that even very low levels of brain A β might be biologically significant (Mormino et al. 2012). It is also possible that soluble forms of A β could contribute to brain atrophy in PIB- subjects. Another possibility is that some PIB+ subjects in the current sample may have high levels of brain reserve possibly as more GM, which permits normal cognition, but diminishes differentiation from PIB- in GM measures. Consistent with this possibility, some studies have reported larger GM volume in PIB+ compared with PIB- in cognitively normal elderly (Chetelat, Villemagne, Pike, et al. 2010). Because our sample consisted of very high functioning older adults, it is possible that relatively small differences in GM measures might not have been detected.

Cognitive Consequences of Structural Changes in Cognitively Normal Elderly

Age-related decline in executive and frontal functions such as WM and inhibition has been related to age-related structural differences in the PFC (Raz et al. 1997; Gunning-Dixon and Raz 2003). This selective volumetric loss supports the view that executive and frontal abilities decline relatively more with advancing age than other cognitive functions, termed the "frontal-executive hypothesis" (Schretlen et al. 2000; Salat et al. 2002; Fjell et al. 2006). It is worth noting that, in our study, the discriminant scores reflecting cognition were most heavily weighted by VM and EXE, and that brain regions that were associated with cognition include large areas of the PFC and striatum. PFC and striatum have strong structural and functional links (Alexander et al. 1986) comprising a well-integrated system subserving frontal/EXEs. These associations in PIB- subjects suggest that the well-recognized frontal-executive hypothesis of aging includes both PFC and striatum, and is not A β -dependent. The etiology of this atrophy is unclear, but could involve cerebrovascular disease (Gunning-Dixon and Raz 2003; Tullberg et al. 2004) or age-related dopamine loss (Fearnley and Lees 1991).

The relationship between regional GM volume and cognition showed dissociation in the relationships between brain regions and cognition by PIB groups. Voxel-wise data show an association between discriminant scores and volumes in the hippocampus in the PIB+ group, which was absent in the PIB- subjects. In addition, the relationship between discriminant scores and regional putamen volume was seen in the absence of A β , but not in its presence. In those with A β , on the other hand, the statistically significant inverse relationship between regional GM volume and cognition was found in hippocampus bilaterally, which was not seen in the PIB- subjects, consistent with the whole-brain data. These results replicate previous findings showing relationships between hippocampal atrophy and EM decline in cognitively normal older adults (Rajah et al. 2010), but further extend the findings by showing that this relationship might have been driven by PIB+ subjects. It is important to note that these results need to be interpreted in relation to the volume of the whole structure, because the VBM results show some significant

voxels within the putamen in relation to cognition within PIB+, possibly reflecting the effect of both age and A β . In addition, because our study is cross-sectional, it is possible that individuals who are PIB+ may develop AD, as previous studies have suggested (Storandt et al. 2009). In order to characterize a cognitive and structural trajectory, longitudinal follow-up of these older adults in our sample is needed. Taken together, these results indicate that age-related cognitive decline independent of A β is more related to the frontal-executive network, while A β -related cognitive decline involves a medial temporal network including the hippocampus.

Conclusions

In this study, we examined independent influences of age and brain A β deposition on brain structure measured by GM volume and cortical thickness and cognition. We found that age plays a major role in brain atrophy as measured by GM volume and thickness regardless of the level of amyloid deposition, while in those with higher levels of amyloid deposition, A β is associated with reduced GM. Brain structure and cognition relationships among older adults were affected by the level of A β deposition: A frontostriatal network GM was positively associated with cognition in older adults with no A β deposition, and hippocampal GM with cognition in older adults with enhanced A β deposition. Findings from the present study suggest that a combination of a global effect of age and a regional effect of A β deposition on brain atrophy occurs during aging and highlights A β -related differential structure and cognition relationships in cognitively normal older adults.

Supplementary Material

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

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Notes

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