Original Investigation

Cross-sectional and Longitudinal Analysis of the Relationship Between Aβ Deposition, Cortical Thickness, and Memory in Cognitively Unimpaired Individuals and in Alzheimer Disease

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IMPORTANCE β-amyloid (Aβ) deposition is one of the hallmarks of Alzheimer disease. Aβ deposition accelerates gray matter atrophy at early stages of the disease even before objective cognitive impairment is manifested. Identification of at-risk individuals at the presymptomatic stage has become a major research interest because it will allow early therapeutic interventions before irreversible synaptic and neuronal loss occur. We aimed to further characterize the cross-sectional and longitudinal relationship between Aβ deposition, gray matter atrophy, and cognitive impairment.

OBJECTIVE To investigate the topographical relationship of Aβ deposition, gray matter atrophy, and memory impairment in asymptomatic individuals with Alzheimer disease pathology as assessed by Pittsburgh compound B positron emission tomography (PiB-PET).

DESIGN Regional analysis was performed on the cortical surface to relate cortical thickness to PiB retention and episodic memory.

SETTING The Australian Imaging, Biomarkers, and Lifestyle Study of Aging, Austin Hospital, Melbourne, Australia.

PARTICIPANTS Ninety-three healthy elderly control subjects (NCs) and 40 patients with Alzheimer disease from the Australian Imaging, Biomarkers, and Lifestyle Study of Aging cohort.

INTERVENTION Participants underwent neuropsychological evaluation as well as magnetic resonance imaging and PiB-PET scans. Fifty-four NCs underwent repeated scans and neuropsychological evaluation 18 and 36 months later.

MAIN OUTCOMES AND MEASURES Correlations between cortical thickness, PiB retention, and episodic memory.

RESULTS There was a significant reduction in cortical thickness in the precuneus and hippocampus associated with episodic memory impairment in the NC PiB-positive (NC^+) group when compared with the NC^- group. Cortical thickness was also correlated negatively with neocortical PiB in the NC^+ group. Longitudinal analysis showed a faster rate of gray matter (GM) atrophy in the temporal lobe and the hippocampi of the NC^+ group. Over time, GM atrophy became more extensive in the NC^+ group, especially in the temporal lobe.

CONCLUSIONS AND RELEVANCE In asymptomatic individuals, Aβ deposition is associated with GM atrophy and memory impairment. The earliest signs of GM atrophy were detected in the hippocampus and the posterior cingulate and precuneus regions, and with disease progression, atrophy became more extensive in the temporal lobes. These findings support the notion that Aβ deposition is not a benign process and that interventions with anti-Aβ therapy at these early stages have a higher chance to be effective.

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Alzheimer disease (AD) is the most common form of dementia, and its prevalence is doubling nearly every 20 years, increasing the economic and social burden associated with the disease.[1] Although novel therapeutic strategies are currently under evaluation, presently there is no cure for AD.[2]

Grey matter (GM) atrophy is observed in almost all patients diagnosed with AD. Identifying patients at an early stage of the disease would enable a better understanding of the pathophysiological processes at play as well as facilitate the development and testing of new drugs that may stop or delay disease onset before irreversible injury occurs. The identification of individuals at the presymptomatic stage has therefore become a major research interest.[3,4] Subjects classified as having mild cognitive impairment, often considered as a prodromal stage to AD,[5] exhibit the same pattern of GM atrophy as patients with AD.[6,7] Several studies have investigated population stratification at even earlier stages of the disease; for instance, support vector machines were used to identify AD-like GM atrophy patterns in a healthy elder patient group.[8]

β-amyloid (Aβ) deposition in the form of extracellular plaques is one of the pathological hallmarks of AD. Aβ burden has been shown to be associated with GM atrophy,[9] and several studies have reported the relationship between neocortical Pittsburgh compound B positron emission tomography (PiB-PET) and global and hippocampus atrophy.[10] Aβ deposition is a slow process that precedes the manifestation of the AD phenotype for more than 10 years.[11-14] It has been reported that early Aβ deposition is found in the posterior cingulate/precuneus (PPC) and orbitofrontal regions.[15,16] About 30% of cognitively unimpaired elderly subjects with no significant GM atrophy also present with significant PiB retention,[10,17-19] although at levels not as high as observed in AD.[13] This has been proposed by some as preclinical AD.[3,20]

Other studies[9,21] have focused on cognitively unimpaired individuals with an AD-like cerebrospinal fluid (CSF) profile or subjects with subjective memory complaints, where a significant association between GM atrophy and global and local Aβ deposition was found.[9] Most reports use GM volume as a means to quantify GM atrophy.[9,10] However, this could mask local effects and dilute statistical power, precluding any conclusion. The use of cortical thickness[22-25] provides a local specific measure of GM changes and hence allows a better regional discrimination of atrophy.

Healthy elderly controls (NCs) with high PiB retention have become the focus of several studies.[10,17,26-29] Pittsburgh compound B retention was associated with cortical thickness reductions in the parietal and posterior cingulate regions extending into the precuneus in a pattern similar to AD.[27] However, no significant difference in cortical thickness was found between NCs with low and high PiB retention. Longitudinal analysis of the cortical volumes of NCs showed that the annual rate of GM atrophy is faster in subjects with high PiB retention when compared with those with low PiB retention, a rate that was significantly correlated with baseline neocortical PiB level, most prominently in the lateral temporal and posterior cingulate cortices.[28] Also, episodic memory impairment, the primary cognitive deficit observed in early AD, was found to be related to Aβ burden in individuals without dementia,[17,30] especially in the temporal cortex.[28]

In a similar population as in our previous report[28] using voxel-based morphometry, we used cortical thickness in a cross-sectional fashion followed by a longer longitudinal analysis to assess if Aβ deposition was associated with GM atrophy and memory.

Methods

Participants

One hundred thirty-three subjects (93 NCs and 40 patients with AD) were included in the study. All participants were part of the Australian Imaging, Biomarkers, and Lifestyle Study of Aging[31] undergoing both magnetic resonance imaging (MRI) and PiB-PET scans at the Austin Hospital (Melbourne, Australia). Approval for the study was obtained from the Austin Health Human Research Ethics Committee and St Vincent's Health Research Ethics Committee, and written informed consent for participation was obtained for each subject prior to the scans. Data from some of the HCs have appeared in a previous report using voxel-based morphometry.[28]

The full methods for the cohort recruitment and evaluation are detailed elsewhere.[31] Briefly, all subjects underwent clinical and neuropsychological examination, and allocation of individuals to a diagnostic group and exclusion of ineligible individuals were performed by a clinical review panel based on the screening interview and neuropsychological assessment and according to internationally agreed-on criteria: patients with AD met standard National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association clinical criteria for possible or probable AD. All NCs performed within less than 1.5 SDs of the published norms for their age group on neuropsychological tests. The neuropsychological examination included the Mini-Mental State Examination, Wechsler Test of Adult Reading, the California Verbal Learning Test, second edition, Rey Complex Figure Test, 30-item Boston Naming Test, Logical Memory II test, Digit Span subtest of the Wechsler Adult Intelligence Scale, third edition, verbal category fluency (animals and boy's names), and Stroop test (Victorian version). A composite episodic memory score was calculated by averaging the Logical Memory II and California Verbal Learning Test, second edition long delay recall scores.

MRI and PET Acquisition

All subjects underwent an MRI and a PiB-PET scan. T1-weighted MRI was obtained using the Alzheimer's Disease Neuroimaging Initiative magnetization-prepared rapid gradient echo protocol at 3 T, with in-plane resolution of 1 × 1 mm and 1.2 mm slice thickness.

The PiB-PET scans were acquired using an Allegro PET camera (Philips). Each participant was injected with 370 MBq of carbon 11–labeled PiB, and a 30-minute acquisition in 3-dimensional mode was performed starting 40 minutes after injection (6 × 5-minute frames). A transmission scan was performed for attenuation correction. The PET images were

reconstructed using a 3-dimensional row action maximum likelihood algorithm.

Image Analysis

Image Segmentation

The 3-dimensional T1-weighted images for all subjects were segmented into GM, white matter (WM), and CSF using an implementation of the expectation maximization segmentation algorithm.[22] Furthermore, topological constraints were applied to force the GM to be a continuous layer covering the WM.[32] Gray matter segmentation was also topologically corrected in deep sulci.[32]

To ensure robust and accurate segmentation results, the segmentation scheme used 9 different atlases to reduce the error due to misregistration of the atlas on the MRI.[10] Each individual MRI was then segmented 9 times and a voting scheme provided consensus for pure tissue segmentation.

Partial-Volume Effect and Cortical Thickness Estimation

Partial-volume effect in MRI is because of the limited spatial resolution of MRI compared with the size of anatomical structures. Accurate classification of mixed voxels and correct estimation of the proportion of each pure tissue helped to increase the precision of cortical thickness estimation (CTE) in regions where this measure was particularly difficult, such as deep sulci. Based on these pure tissue segmentations, a further maximum a posteriori classification of voxels into pure tissues WM, GM, and CSF and mixed tissues WM/GM and GM/CSF along the previously computed GM interface was performed, which resulted in a GM partial-volume effect map. The classification algorithm also integrated a mechanism for detecting sulci with topology-preserving operators.[32] The topological correction significantly improved the GM classification.

Once pure tissue segmentation and partial tissue classification were performed, the CTE of the resulting GM was computed using a combined voxel-based approach.[25] The GM partial-volume effect map was used to initialize a combined Lagrangian-Eulerian approach. The GM partial-volume effect initialization preserved the efficiency of the Eulerian approach while improving the accuracy.[22]

PiB Normalization

The PET images were coregistered with each individual's MRI using SPM5 (Wellcome Trust Centre for Neuroimaging). The cerebellum region of interest (ROI) was then manually drawn on the individual MRI and transferred to the coregistered PET images as previously described.[33] Scans were normalized using the standardized uptake value ratio (SUVR) method,[34] with each voxel divided by the mean value in the cerebellar cortex mask.

The NC group exhibited a bimodal neocortical PiB SUVR distribution. As previously described, a neocortical SUVR threshold of 1.4 was used to separate NCs with high (NC^+) and low (NC^-) PiB retention.[10] All subjects with AD in this study had a neocortical PiB retention higher than 1.4.

Surface-Based Approach

The Internet Brain Segmentation Repository labeling was propagated from the atlas to the individual subject space to separate the left and right hemispheres on all segmented maps. For each subject, left and right hemisphere meshes were generated from the WM/GM interface.[35] Meshes were topologically corrected in genus 0 surfaces using the Taglut tool.[15,35] Individual meshes were then registered to a common mesh atlas with a Multi-scale EM-ICP algorithm.[36] Individual meshes were first geometrically smoothed and EM-ICP registered to a smooth version of the atlas. Then local curvature features at different smoothing levels were iteratively introduced into the registration algorithm to better match the small and local geometric structures of the individual mesh to the atlas. The individual thickness values were then mapped from the image onto the mesh surface and then to the template surface. Hence, each vertex of the template was associated with a CTE vector corresponding to the CTE value of all individuals at the same spatial location. The full pipeline is detailed in eFigure 1 (Supplement). The processing pipeline is available as a plug-in of the open-source software MILXView.[1]

Robust Statistical Framework

A robust statistical framework was used to ensure against missegmentation and/or misregistration along the pipeline. In each group and at each vertex, the 2 first moments of the CTE distribution were calculated. Each CTE value outside the 95% likelihood of the vertex groupwise distribution might result in a missegmentation or misregistration of the associated subjects at these locations. These CTE values were replaced by the local mean values of the associated subjects. A 10-mm Laplace-Beltrami smoothing was then applied to the CTE values on the template mesh.

Statistical Analyses

Cortical thickness estimation, neocortical PiB SUVR, and memory test scores were adjusted for the effects of age. Significance was set at $P = .05$. P values resulting from all statistics were corrected for multiple comparisons using false discovery rates.[37] Data are presented as mean (SD) unless otherwise stated.

Surface ROI Statistical Analysis

First, a vertex-wise t test was performed between the NC^- and AD^+ groups. The P value map was thresholded at 5.10^{-4} and false discovery rate corrected. Vertices with significant P value– defined regions associated with a high degree of atrophy in AD (**Figure 1**). We postulated that early GM atrophy may appear in these regions. We particularly focused on 3 regions: the hippocampi, temporal lobes, and a region encompassing part of the precuneus and the posterior cingulate gyrus (PPC). These 3 anatomical regions were intersected with the T map between the NC^- and AD^+ groups to define the anatomical ROIs in which we compared the NC^+ and NC^- groups.

Surface ROI t Test on the CTE Between NC^- and NC^+

Second, to assess whether cortical thickness was different in the NC group with either low or high PiB retention, we

computed the mean CTE value for all patients in each ROI and a *t* test between the NC⁻ and NC⁺ groups was performed.

Surface ROI Correlation Between CTE, PiB Retention, and Memory Test Score in NC⁻/⁺

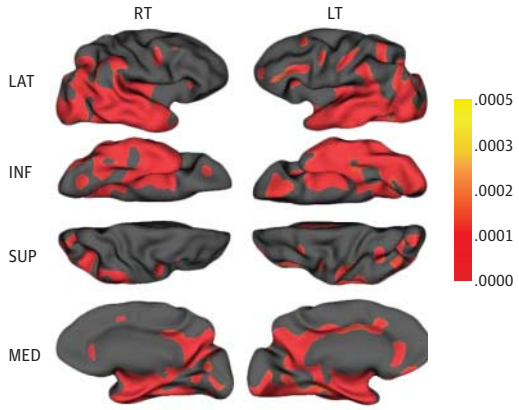
Third, to establish if a high PiB retention only affects NCs, correlations were assessed between cortical thickness in each ROI and the neocortical PiB retention score in the NC⁻, NC⁺, and AD⁺ groups. Cortical thickness is believed to be related to memory performance. Incipient GM atrophy may be associated with memory decline. Region of interest correlations were then performed between CTE and episodic memory in the different groups.

To determine whether episodic memory is correlated with cortical thickness or to Aβ deposition, we performed a multistage regression analysis.[38] We computed the partial correlation between cortical thickness and episodic memory while controlling for PiB SUVR and the partial correlation between PiB SUVR and episodic memory while controlling for cortical thickness. All partial correlations were computed with cortical thickness estimated in the PPC, temporal lobe, and hippocampus.

Vertex-wise Longitudinal Analysis of the Cortical Thickness Loss

To assess whether GM atrophy progressed differently in the NC⁺ and NC⁻ groups, we performed longitudinal analysis of the cortical thickness. We computed the vertex-wise atrophy rate of cortical thickness in both NC groups at 18 and 36 months. The comparison between the 2 points showed the progression of these patterns. Rates of GM atrophy were computed by subtracting the cortical thickness at the first or second point from the cortical thickness evaluated at baseline and dividing by the time between scans. Linear regression of the 3 points was used to estimate the global rate of atrophy over the 36 months.

Figure 1. Cortical Thickness Between the Healthy Control Pittsburgh Compound B–Negative and Alzheimer Disease Groups



P value is less than .0005 (false discovery rate corrected). *P* value maps are of a vertex-wise *t* test. Gray matter atrophy is significantly more prominent and widespread in the Alzheimer disease group than in the healthy control Pittsburgh compound B–negative group. INF indicates inferior; LAT, lateral; LT, left; MED, medial; RT, right; and SUP, superior.

Results

Table 1 and **Table 2** present the demographic data of the cohort examined in the study. There were no significant differences in sex or years of education between the groups, although the NC⁺ group was significantly older than the NC⁻

Table 1. Demographics for the Cross-sectional Analysis

	Mean (SD)		
Group	NC⁻	NC⁺	AD
Sample size	64	29	40
Male/female, No.	29/35	14/15	17/23
Age, y	72.0 (7.3)	78.2 (5.9)[a]	72.5 (10.9)
Education, y	12.9 (2.6)	12.6 (2.6)	12.0 (2.3)
MMSE score	29.0 (1.2)	28.7 (1.3)	22.4 (5.2)[a]
Neocortical SUVR	1.3 (0.1)	2.1 (0.4)[a]	2.5 (0.4)[a]
Episodic memory score	1.2 (1.9) (n = 57)	1.3 (1.8) (n = 33)	−4.7 (1.3)[a] (n = 30)

Abbreviations: AD, Alzheimer disease; MMSE, Mini-Mental State Examination; NC⁻, healthy control Pittsburgh compound B–negative; NC⁺, healthy control Pittsburgh compound B–positive; SUVR, standardized uptake value ratio.

[a] Significant difference from the NC⁻ group ($P < .05$).

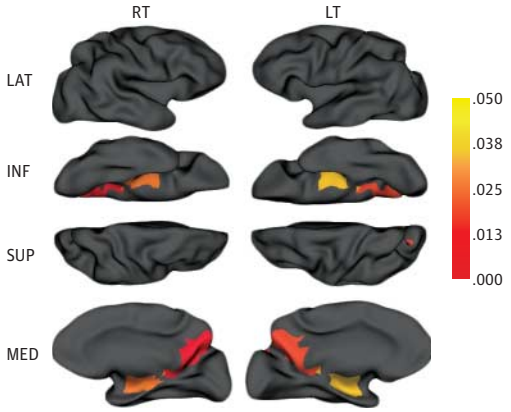
Table 2. Demographics for the Longitudinal Analysis

	Mean (SD)		
Group	NC⁻	NC⁺	AD
Sample size	38	15	4
Male/female, No.	18/20	9/6	17/23
Age at baseline, y	71.7 (7.6)	74 (5.9)[a]	72.5 (10.9)
Education, y	13.4 (2.3)	13.1 (2.5)	12.0 (2.3)
MMSE score at baseline	29.0 (1.2)	29.2 (1.2)	22.4 (5.2)
Neocortical SUVR	1.3 (0.1)	2.2 (0.4)[a]	2.6 (0.4)[a]

Abbreviations: AD, Alzheimer disease; MMSE, Mini-Mental State Examination; NC⁻, healthy control Pittsburgh compound B–negative; NC⁺, healthy control Pittsburgh compound B–positive; SUVR, standardized uptake value ratio.

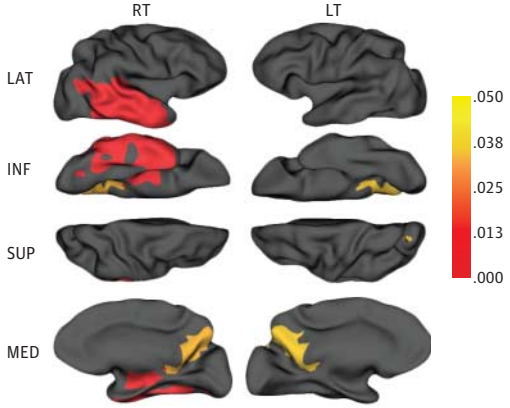
[a] Significant difference from the NC⁻ group ($P < .05$).

Figure 2. Cortical Thickness Estimation of the Healthy Control Pittsburgh Compound B–Negative (NC^-) and Healthy Control Pittsburgh Compound B–Positive (NC^+) Groups



P value is less than .05 (false discovery rate corrected). Groups were evaluated in the 3 different anatomical regions of interest. *P* value maps are of the *t* test between groups. Compared with the NC^- group, significantly greater atrophy was observed in the hippocampus and precuneus and posterior cingulate gyrus of the NC^+ group. INF indicates inferior; LAT, lateral; LT, left; MED, medial; RT, right; and SUP, superior.

Figure 3. Correlation Between Cortical Thickness and Neocortical Pittsburgh Compound B in the Healthy Control Pittsburgh Compound B–Positive Group



Data are reported in *P* value maps. *P* value is less than .05 (false discovery rate corrected). Gray matter atrophy was significantly associated with neocortical standardized uptake value ratio in the healthy control Pittsburgh compound B–positive group bilaterally in the precuneus and posterior cingulate gyrus and in the right temporal lobe and hippocampus. INF indicates inferior; LAT, lateral; LT, left; MED, medial; RT, right; and SUP, superior.

group. Pittsburgh compound B retention was significantly different between the NC and AD groups. As expected, Mini-Mental State Examination scores were lower in the AD group. There were no significant differences in episodic memory between the NC^+ and NC^- groups, but the NC^+ group presented with slightly higher scores.

Cross-sectional Analysis

Significant differences between the NC^- and AD groups ($P < .0005$ corrected) were found in most regions: the temporal, occipital, and parietal lobes, as well as the hippocampus, parahippocampus, and amygdala (Figure 1). Significant differences ($P < .05$ corrected) in CTE between the NC^- and NC^+ groups were found in the PPC and hippocampus in both hemispheres (**Figure 2**). The *P* values were slightly smaller in the right hemisphere.

The mean cortical thickness in the hippocampus and PPC was significantly more atrophic in the NC^+ and AD^+ groups compared with the NC^- group (eFigure 2). The AD group had significantly greater GM atrophy than both NC groups in both regions.

Correlations between CTE and neocortical SUVR in the NC^+ group were significant in the PPC bilaterally and in the temporal lobe and hippocampus in the right hemisphere (**Figure 3**). The correlation between neocortical PiB and PPC PiB SUVR was 0.94 (after correction). However, correlations between regional PPC PiB SUVR and CTE were not significant (not shown). No correlations were found in the NC^- group (not shown).

There were no significant correlations between cortical thickness and episodic memory scores in the NC^- group (not shown). Correlations were moderate ($r > 0.4$) in the NC^+ group in the right temporal lobe and right PPC and but lower ($r \approx 0.2$) and not significant in the left hemisphere (eFigure 3). The correlation was significant in the PPC ($P < .01$) and in the temporal lobe ($P < .02$). The hippocampi had low correlation with episodic memory in both NC groups ($P = .22$ and $P = .10$, for the right and left hippocampus, respectively).

In the NC^+ group, the correlation between CTE and neocortical PiB SUVR was significant in each anatomical ROI of **Table 3**, as well as the correlation between cortical thickness and episodic memory except in the hippocampus. When controlling for neocortical PiB retention, the correlation between cortical thickness and episodic memory was lower but still significant in the PPC and temporal lobe. When controlling for cortical thickness, the correlation between neocortical PiB retention and episodic memory was lower and not significant ($P = .15$). Cortical thickness in the hippocampus was not associated with episodic memory.

Longitudinal Analysis of the CTE

The global rate of atrophy over 36 months for the NC^- and NC^+ groups is shown in **Figure 4**. While the NC^- group exhibited some cortical thickness loss, the loss was greater in the NC^+ group, especially in the temporal, PPC, insula, temporo-occipital, and hippocampal regions. In the NC^- group, the GM loss ranged between 0.0 and 0.015 mm/y in most brain regions with the exception of the insula, hippocampi, and right PPC, where the GM loss ranged between 0.015 and 0.04 mm/y. In the NC^+ group, the rate of atrophy was larger in the hippocampus, parahippocampus, temporal lobes, insula, and right PPC. No significant cortical thickness loss was observed in the frontal areas in any of the groups.

Figure 5 shows the significantly different anatomical ROI *t* test on the rate of GM atrophy between the NC^- and NC^+ groups. The rate of atrophy in the NC^+ group was significantly faster in both the temporal lobe and hippocampi.

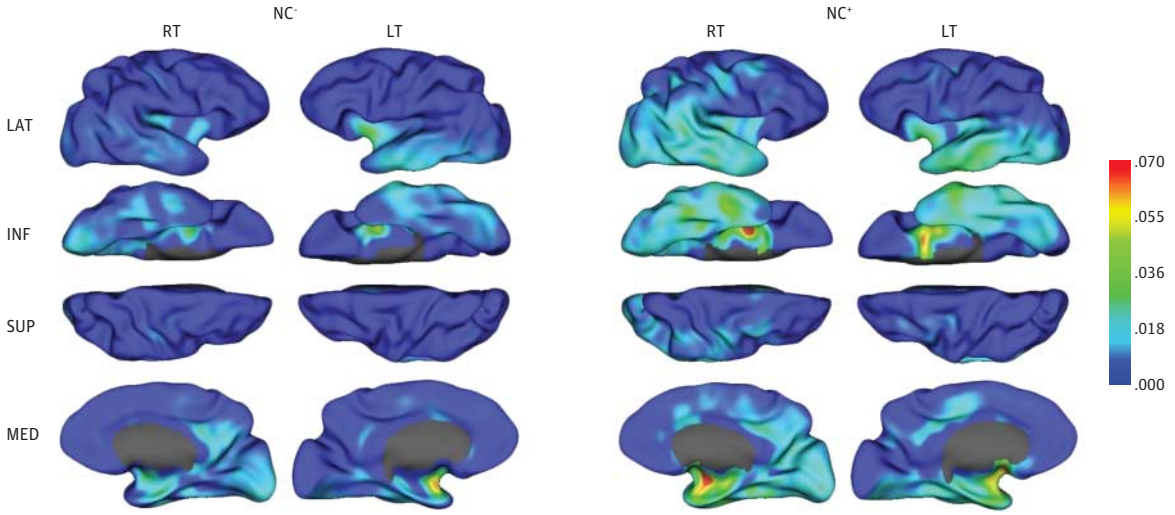
Table 3. Correlations and Partial Correlations Between CTE, PiB SUVR, and EM in the Right Hemisphere of the NC+ Group

AROI From the Right Hemisphere	r(CTE,PiB)	r(CTE,EM)	r(CTE,EM)/PiB	r(PiB,EM)	r(PiB,EM)/CTE
PPC	−0.43[a]	0.43[a]	0.38[a]	−0.19	−0.014
TL	−0.53[a]	0.41[a]	0.36[a]	−0.19	0.03
Hippocampus	−0.68[a]	0.07	−0.09	−0.19	−0.20
PPC + TL	−0.56[a]	−0.48[a]	0.45[a]	−0.19	0.10

Abbreviations: AROI, anatomical region of interest; CTE, cortical thickness estimation; EM, episodic memory; NC+, healthy control Pittsburgh compound B–positive; PiB, Pittsburgh compound B; PPC, precuneus and posterior cingulate gyrus; r(a,b)/c, partial correlation between a and b while controlling for c; SUVR, standardized uptake value ratio; TL, temporal lobe.

[a] Significant correlation.

Figure 4. Gray Matter Atrophy in the Healthy Control Pittsburgh Compound B–Negative (NC−) and Healthy Control Pittsburgh Compound B–Positive (NC+) Groups



Rates are reported in millimeters per year. Gray matter loss over 36 months was more extensive, especially in the temporal, precuneus and posterior cingulate gyrus, and occipital cortices, in the NC+ group compared with the NC− group. Faster rates of gray matter loss were observed in the hippocampal regions. INF indicates inferior; LAT, lateral; LT, left; MED, medial; RT, right; and SUP, superior.

Significant differences in the rate of cortical thickness loss after a vertex-wise *t* test between the NC+ and NC− groups were observed at both the 18-month (**Figure 6A**) and 36-month (Figure 6B) follow-up. While significant atrophy in the NC+ group was restricted to a small area of the right occipital and temporal lobes at the 18-month follow-up (about 17% of the right temporal lobe) (Figure 6A), there was more extensive atrophy in the same areas at the 36-month follow-up (about 77% of the right temporal lobe) (Figure 6B) showing a steady progression of cortical thickness loss. At the 36-month follow-up, significantly faster GM atrophy was also found in the PPC, hippocampus, and some areas of the frontal lobe (Figure 6B).

The rate of GM loss in the NC− group was the same when evaluated at 36 months and 18 months, while the NC+ group showed a faster rate of atrophy at 36 months. eFigure 4 shows the average annual rate of atrophy in the right temporal lobe for NCs. The rate of atrophy was significantly faster in the NC+ group than the NC− group in the right temporal lobe at 36 months.

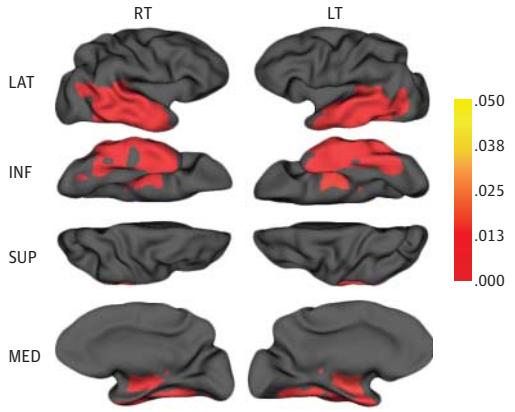
Discussion

There was a significant difference in cortical thickness between the NC+ and the NC− groups. The NC+ group exhibited significantly lower CTE in the hippocampus and the PPC. These findings are in agreement with a previous report showing an association between PiB retention and cortical thickness in the PPC of NCs.[27] This region is also part of the default network,[39,40] which has been implicated in memory-related functions altered in AD.[41]

In contrast, no significant association was found between PiB retention and cortical thickness when considering the whole NC group.[27] This discrepancy is probably due to the large cortical thickness variability in the NC− group, probably attributable to the heterogeneity of non-AD-related pathological processes in this group where there was no correlation between cortical thickness and PiB retention. However, a significant correlation was found in the NC+ group bilater-

ally in the PPC and in the temporal lobe and hippocampus of the right hemisphere. These regions are known to be associated with early Aβ deposition.[15,16] This finding suggests that Aβ deposition has a direct effect on GM very early in the disease process, even before overt symptoms are manifested. A previous study[10] had already showed a direct association between global PiB retention and GM atrophy in AD; however, our results show that this atrophy, especially in the PPC, occurs at the presymptomatic stages of the disease.

Figure 5. Significant Differences in the Global Rate of Gray Matter Atrophy Between the Healthy Control Pittsburgh Compound B–Negative (NC^-) and Healthy Control Pittsburgh Compound B–Positive (NC^+) Groups



Data are reported in *P* value maps. The rates of atrophy in the NC^+ group over 36 months were significantly faster than in the NC^- group in both temporal lobes and the hippocampi. INF indicates inferior; LAT, lateral; LT, left; MED, medial; RT, right; and SUP, superior.

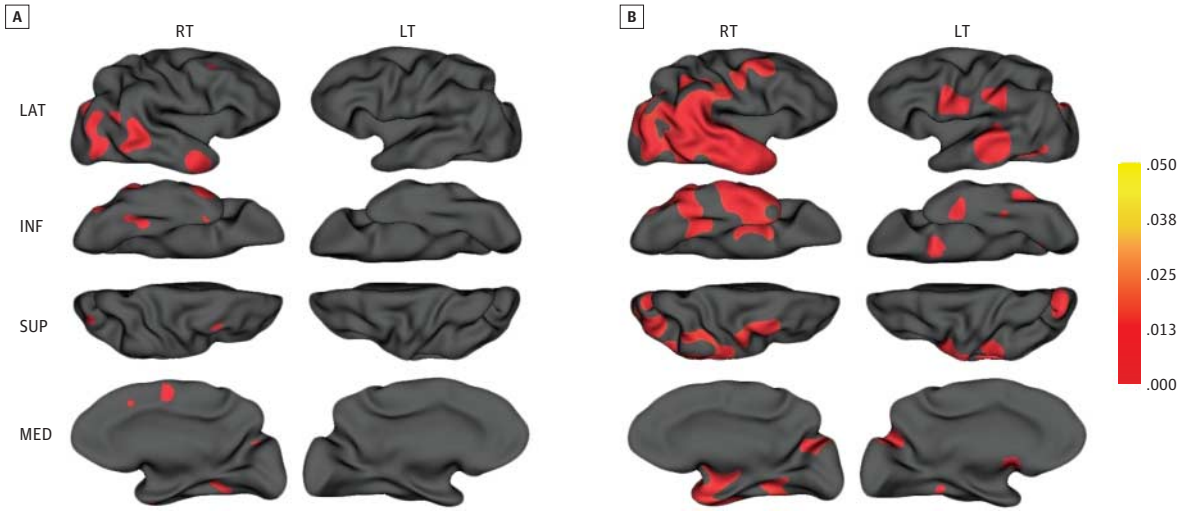
In the NC^+ group, while PiB retention was not significantly asymmetric, the cortex of the left hemisphere appeared consistently less affected than the right hemisphere. This is in agreement with a previous study reporting a rightward asymmetry in cortical thickness in NCs in the inferior temporal lobe and the medial posterior regions.[42]

The longitudinal analysis confirmed the regional cross-sectional findings, further complementing them by showing a faster GM atrophy in the NC^+ group. The rate of atrophy was particularly fast in the insula in both hemispheres and in the hippocampus and PPC of the right hemisphere. Both the hippocampus and PPC exhibited significantly faster GM atrophy in the NC^+ group than in the NC^- group, thinning that was significantly associated with PiB retention. As reported previously, this significant difference suggests an early effect of Aβ deposition on cortical thickness.[27] Furthermore, these findings also validate the results on our previous report based on a shorter follow-up on some of the same NCs.[28]

Gray matter atrophy was already present in several regions of the brain of the NC^- group, with rates of GM loss around 0.02 mm/y, whereas no significant correlation between cortical thickness and neocortical PiB retention was found. The mesial temporal cortex was slightly affected by GM loss in the NC^- group and the rate of GM loss was constant over the 36-month period. This is in agreement with previous reports on the rates of atrophy associated with aging,[43] suggesting that the GM atrophy in the NC^- group was not driven by AD pathology.

In the NC^+ group, the small significant patterns of GM loss in the temporal lobe extended from about 17% of the total surface of the lobe at 18 months to about 77% at 36 months, where longitudinal analysis of PiB retention also showed that Aβ deposition is highest.[33]

Figure 6. Significant Cortical Thickness Loss in the Healthy Control Pittsburgh Compound B–Positive Group at the 18-Month and 36-Month Follow-ups



Panel A indicates 18-month and panel B indicates 36-month follow-ups. Data are reported in *P* value maps. In the healthy control Pittsburgh compound B–positive group, there was a steady progression of cortical thickness loss. INF indicates inferior; LAT, lateral; LT, left; MED, medial; RT, right; and SUP, superior.

In the NC+ group, cortical thickness was also significantly associated with episodic memory scores in the temporal lobe and PPC of the right hemisphere. These results suggest that while the NC+ group is still performing within the normal range for these tests, there is a direct association between cortical thickness and memory performance, even at the presymptomatic stage of the disease. These results are consistent with previous reports showing that atrophy in the mesial temporal cortex is associated with the appearance of objective cognitive impairment.[44,45] A previous study already showed an association between local PiB retention in the temporal lobe and memory impairment.[46] The different correlation and partial correlations between PiB deposition, cortical thickness, and memory decline showed some evidence of a sequential relationship, where Aβ deposition locally leads to GM atrophy, which itself results in memory decline, similar to a previous report in subjects without dementia.[38] While longitudinal assessments of episodic memory performance are needed to confirm these findings, they support the push for early therapeutic intervention with anti-Aβ therapy in NC+ individuals[47] to reduce the risk of memory decline.

In summary, the present study using a different methodological approach to measure GM atrophy confirms and further validates in a larger cohort and longer longitudinal evaluation our previous reports showing the relation between Aβ deposition, GM atrophy, and cognition.[9,10,28] We have demonstrated that high Aβ deposition is associated with fast GM atrophy in the PPC and hippocampus in cognitively unimpaired individuals, atrophy that occurs very early in the disease process. Moreover, rates of atrophy were faster in the NC+ group, and with disease progression, atrophy became more extensive, especially in the temporal lobes. Furthermore, GM atrophy in NCs+ is associated with episodic memory impairment. These results support the notion that that Aβ deposition is not a benign process and that cognitively unimpaired subjects with substantial Aβ deposition in the brain likely represent a group at a significantly higher risk of developing dementia.[3]

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