Title

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Abstract

Importance— -Amyloid (A) deposition and vascular brain injury (VBI) frequently co-occur and are both associated with cognitive decline in aging. Determining whether a direct relationship exists between them has been challenging. We sought to understand VBI's influence on cognition

and clinical impairment, separate from and in conjunction with pathologic changes associated with Alzheimer disease (AD).

Objective—To examine the relationship between neuroimaging measures of VBI and brain A deposition and their associations with cognition.

Design and Setting—A cross-sectional study in a community- and clinic-based sample recruited for elevated vascular disease risk factors.

Participants—Clinically normal (mean age, 77.1 years [N=30]), cognitively impaired (mean age, 78.0 years [N=24]), and mildly demented (mean age, 79.8 years [N=7]) participants.

Interventions—Magnetic resonance imaging, A (Pitts-burgh Compound B–positron emission tomographic [PiB-PET]) imaging, and cognitive testing.

Main Outcome Measures—Magnetic resonance images were rated for the presence and location of infarct (34 infarct-positive participants, 27 infarct-negative participants) and were used to quantify white matter lesion volume. The PiB-PET uptake ratios were used to create a PiB index by averaging uptake across regions vulnerable to early A deposition; PiB positivity (29 PiB-positive participants, 32 PiB-negative participants) was determined from a data-derived threshold. Standardized composite cognitive measures included executive function and verbal and nonverbal memory.

Results—Vascular brain injury and A were independent in both cognitively normal and impaired participants. Infarction, particularly in cortical and subcortical gray matter, was associated with lower cognitive performance in all domains (*P*<.05 for all comparisons). Pittsburgh Compound B positivity was neither a significant predictor of cognition nor interacted with VBI.

Conclusions and Relevance—In this elderly sample with normal cognition to mild dementia, enriched for vascular disease, VBI was more influential than A in contemporaneous cognitive function and remained predictive after including the possible influence of A . There was no evidence that VBI increases the likelihood of A deposition. This finding highlights the importance of VBI in mild cognitive impairment and suggests that the impact of cerebrovascular disease should be considered with respect to defining the etiology of mild cognitive impairment.

Deposition of -amyloid (A) and vascular brain injury (VBI) are the 2 most common pathologic changes seen in the aging brain. They frequently co-occur[1]; however, determining whether a direct relationship exists between them has proven challenging. Although the presence of A is a diagnostic criterion for Alzheimer disease (AD),[2,3] a significant portion of clinically normal elderly individuals have A (approximately 25%).[1,4,5] Thus, the deleterious effects of A may be dependent on a subsequent "cascade" of events that lead to dementia.[6] However, both postmortem and in vivo neuroimaging measures of A have been inconsistently associated with cognitive deficits.[7–15]

Most studies to date that have examined the relationship between A and cognition exclude individuals with evidence of VBI. The few neuroimaging studies that have directly examined VBI and A found no relationship between the 2 entities.[16–18] Two of these studies[16,18] considered only clinically normal individuals; because the presence of an infarct and A in the same individual may increase the likelihood of clinical impairment,[1] evidence of a relationship might have escaped their detection.

We sought to understand VBI's influence on cognition and clinical impairment separate from and in conjunction with AD pathologic changes.[19,20] The aim of this study was to define how neuroimaging measures of A deposition and VBI separately and together affect cognition in a cognitively heterogeneous population. Specifically, we asked: (1) Is there a

relationship between A and VBI that is dependent on cognitive status or lesion type? (2) What are the distinct contributions of A and VBI to specific cognitive domains in a group of individuals ranging from normal cognition to mild dementia?

METHODS

PARTICIPANTS

Participants were recruited for an ongoing multisite research program, the Aging Brain project, designed to recruit individuals with substantial vascular disease risk factors and VBI. Inclusion criteria have previously been described in detail.[19]

The 61 participants in the present study included 30 who were clinically normal (mean [SD] age, 77.1 [7.3] years), 24 who were cognitively impaired (mean age, 78.0 [7.4] years; 7 with amnestic mild cognitive impairment [MCI], 13 with nonamnestic MCI, and 4 with other impairment), and 7 individuals with a diagnosis of dementia (mean age, 79.8 [3.3] years). For research purposes, cognitive status was defined by dividing participants into 2 groups according to their Clinical Dementia Rating (CDR) status (CDR = 0 [N = 30]; CDR 0.5 [N=31]). All participants underwent cognitive testing, Pitts-burgh Compound B–positron emission tomography (PiB-PET), and magnetic resonance imaging (MRI). Participants were monitored longitudinally, and the MRI and cognitive session closest to the PiB imaging date were used. The mean time between all imaging and cognitive examinations was approximately 2 months.

The study was approved by the institutional review boards of all participating institutions. Written informed consent was obtained from all participants or their legal representatives following institutional review board–approved protocols.

COGNITIVE TESTING

The Mini-Mental State Examination (MMSE) provided a measure of global cognitive functioning; the Geriatric Depression Scale, a measure of depressive symptoms.

Each participant completed a broad battery of standardized neuropsychological tests. Previously developed composite measures of executive function, verbal memory, and nonverbal memory were used. The scale of these composite measures was transformed so that each had a mean of 100 and an SD of 15. These scales were created using item response theory methods to attain psychometrically matched scales with linear measurement properties and high reliability across a 4-SD range of ability. Specific methods have been previously described.[19,21]

MAGNETIC RESONANCE IMAGING

Acquisition—Fifty-one participants underwent MRI using a 3-T scanner (Magnetom Trio System; Siemens) with an 8-channel head coil. Acquired images included a T1-weighted, volumetric, magnetization-prepared rapid gradient-echo (MPRAGE) image (repetition time [TR], 2500 milliseconds; echo time [TE], 2.94 or 2.98 milliseconds; inversion time [T1], 1100 milliseconds) and a fluid-attenuated inversion recovery (FLAIR) image (TR, 5000 milliseconds; TE, 403 milliseconds; TI, 1700 milliseconds; 1.0×1.0 mm^2 in-plane resolution with 1.00-mm thickness). Three participants underwent scanning using a 1.5-T system (Signa Genesis; GE Healthcare). Each session included a T1-weighted, 3-dimensional, spoiled gradient recalled–echo scan (TR, 9 milliseconds; TE, 1.9 milliseconds); data from FLAIR images were not used owing to technical difficulties. Seven participants underwent scanning with a 4-T system (MedSpec System; Siemens) with an 8-channel head coil. A T1-weighted volumetric MPRAGE image (TR, 2300 milliseconds; TE, 2.84 or 3.37

milliseconds; TI, 950 milliseconds) and a FLAIR image (TR, 6000 milliseconds; TE, 405 milliseconds; TI, 2050 milliseconds; 1.0×1.0 mm^2 in-plane resolution with 2.00-mm thickness) were acquired.

Image Analysis—The T1-weighted MRIs were used to identify infarcts and to assist with PiB-PET processing. Image analysis software (FreeSurfer, version 5.1.0; http:// surfer.nmr.mgh.harvard.edu/) was used to process the T1-weighted MRIs for each participant following procedures previously described.[22] A cerebellar gray matter mask was also derived from each participant's native brain space to serve as a reference region for PiB processing. Each mask was manually edited to remove noncerebellar tissue.

White Matter Hyperintensity Quantification—The skull was removed from FLAIR images and a manually edited binary mask was created using the remaining brain. FLAIR images were corrected for image intensity inhomogeneity,[23] and then white matter hyperintensities (WMHs) were segmented using location (guided by the brain mask) and an image intensity histogram.[24] The WMH lesion segmentations were visually inspected to ensure that they included at least 80% of observed WMH.

White matter hyperintensity volume was regressed onto total cranial volume (derived from the image analysis software) to minimize the effect of head size,[25] and the resulting unstandardized residuals were retained. After adding a constant (12 000) to the residuals to eliminate negative values, the residuals were then log transformed to normalize the data. The log-transformed residuals were used in subsequent analyses. Nine individuals did not have WMH data because of technical problems.

Infarct Classification—Infarcts were identified by a vascular neurologist (N.S.) blind to any other participant data by using the T1-weighted and FLAIR MRIs. Infarcts were categorized according to the vascular territory affected, structures involved, size (small, 3– 10 mm; large, >10 mm), and severity (cystic, not cystic). Infarcts were then labeled: *cortical gray matter* (affecting any cortical region), *white matter* (affecting any subcortical white matter region and/or internal capsule), *subcortical gray matter* (affecting the basal ganglia, thalamus, amygdala, and/or hippocampus), and *other* (affecting the midbrain, pons, medulla, and/or cerebellum). The number of infarcts was also noted (range, 0–4 infarcts) and was recoded into a categorical variable with 3 levels: 0 infarcts (n=27), 1 infarct (n=24), and more than 1 infarct (n=10).

PET IMAGING

Acquisition—The PiB radiotracer was synthesized at Lawrence Berkeley National Laboratory, Berkeley, California, using a previously published protocol.[26] Ninety minutes of dynamic PiB-PET data were acquired on a high-resolution PET scanner (ECAT EXACT; Siemens).

Image Analysis—Pittsburgh Compound B data were preprocessed with procedures previously described[16] using a gray matter cerebellar reference region to calculate distribution volume ratio images[27,28] that were then warped to MNI (Montreal Neurological Institute) space using the SPM (Statistical Parametric Mapping) T1 template. The Global PiB Index was generated from the mean distribution volume ratios from regions of interest vulnerable to early Aβ deposition, which include the frontal cortex (anterior to the precentral gyrus), lateral parietal cortex, lateral temporal cortex, posterior cingulate, and precuneus.[22,29] The occipital cortex was also examined because of its susceptibility to cerebral amyloid angiopathy. Areas that overlapped with the stroke and peristroke regions in the individuals with cortical infarct were manually excluded. In individuals with cerebellar

infarct, the contralesional cerebellar hemisphere served as the reference region. This method was validated by demonstrating that the ratio of PiB uptake in the pons (a region generally spared from PiB binding) to the contralesional cerebellar hemisphere was similar to that ratio in subjects without infarct when comparing both a single cerebellar hemisphere and the entire gray matter cerebellum.

PiB Positivity—To define PiB as a dichotomous variable, 11 young adults (mean [SD] age, 24.5 [3.4] years) underwent PiB-PET imaging using the same acquisition and processing procedures already described. Global PiB Index values 2 SDs above the average (>1.114) were established as defining values of PiB positivity.

STATISTICAL ANALYSIS

All analyses were conducted using SPSS statistical software (version 20; SPSS Inc). Differences between infarct (positive vs negative) and PiB (positive vs negative) groups were tested using Pearson χ^2 tests for dichotomous variables and independent-sample t tests for continuous variables. Spearman ρ, Pearson R, and linear regressions were used to assess relationships between continuous variables. Independent measures analyses of variance were used to explore the relationship between infarct and PiB uptake. The Kolmogorov-Smirnov test with Lilliefors correction was used to test normality of distribution of cognitive measures.

We used a multistage multiple regression approach to evaluate the contributions of vascular- and amyloid-related measures to neuropsychological test performance. The independent variables were the neuroimaging measures of vascular injury (infarct number [0, 1, or >1] and location and WMH) and Aβ deposition (Global PiB Index). The dependent variables were composite cognitive test performance (verbal and nonverbal memory and executive function). The baseline stage of the model included demographic variables: sex, age, and educational level. In the second stage, we evaluated whether each marker of pathologic change (infarcts, WMH, and PiB), considered separately, was associated with cognition. There were multiple indicators of infarct status (ie, cortical gray matter, subcortical gray matter, white matter, other, and number of infarcts) that were distributed in overlapping patterns; we evaluated each separately and, if more than 1 indicator was significant, in simple combinations to identify the best infarct predictor for each cognitive outcome. In the third stage, we evaluated the joint and independent effects of pathologic markers by adding all (PiB, WMH, and the best infarct predictor) to the baseline demographic model. This approach was adopted to describe the effects of each type of pathologic change when considered alone, then to investigate their independent contributions when considered together. A 2-tailed α level of .05 was used to determine statistical significance.

RESULTS

PARTICIPANT CHARACTERISTICS

The demographic data, apolipoprotein E (*APOE*) allele status, and clinical status of participants stratified by PiB status are summarized in Table 1. The same characteristics stratified by infarct status are summarized in Table 2. Overall, 34 of the 61 participants (56%) had an MRI-identified infarct, and 29 (48%) were classified as PiB-positive. Participants classified as PiB-negative (n=32) and PiB-positive (n=29) did not differ in age, educational level, CDR, MMSE score, or Geriatric Depression Scale score. Participants who were PiB-positive were more likely to be male (*P*=.046) and to carry the *APOE* ε4 allele (*P* =.02). There was a significant positive relationship between increasing age and PiB status (ρ=0.27; *P*=.04).

Infarct-negative (n = 27) and infarct-positive (n = 34) participants did not differ in age, sex, educational level, *APOE* allele status, MMSE score, or Geriatric Depression Scale score. There was a trend toward worse cognitive status in infarct-positive participants (*P* = .055), which was especially apparent in individuals with a cortical infarct (CDR = 0: 2 of 11 participants [18%]; CDR   0.5: 9 of 11 [82%]; *P* = .02). Of the 34 infarct-positive individuals, 11 had infarcts in cortical gray matter, 19 in subcortical gray matter, 23 in cortical white matter, and 14 in another location. These numbers do not sum to 34 because 10 individuals had more than 1 infarct (mean [range], 2.7 [2–4] infarcts), and most infarcts affected multiple regions. Cortical gray matter infarcts primarily affected the frontal lobe (n = 9). All subcortical gray matter infarcts occupied the basal ganglia, with most specifically affecting the striatum (n = 17). Three participants had a lesion in cortical white matter only and 4 in subcortical gray matter only. No participant had an isolated cortical gray matter lesion. Five participants had infarcts affecting both cortical gray and white matter, 9 had lesions affecting subcortical gray and cortical white matter, and 6 had lesions affecting all 3 regions (cortical gray, white, and subcortical gray matter). The mean WMH volume as a percentage of total cranial volume across the sample was 0.7%. Infarct-positive individuals had greater WMH volume than did infarct-negative individuals (*P* = .02). The WMH volume did not differ by MRI field strength (between 3-T and 4-T scans; *P* = .20).

VBI RELATIONSHIP WITH PiB

Presence of an infarct did not increase the likelihood that an individual was PiB-positive (*P* = .26 [Figure]). Dividing participants by cognitive status (CDR = 0 vs CDR   0.5) revealed no relationship between having an infarct and PiB uptake in normal (*P* = .64) or impaired (*P* = .16) individuals. There was no effect of infarct location (*P* >.30 for all comparisons) or cognitive status (*P* = .50) on PiB uptake and no interaction between presence of an infarct and cognitive status (*P* = .81 [Figure]). Individuals with a cortical gray matter infarct did not have greater Global PiB Index values (*P* = .96) and were not more likely to be PiB-positive compared with persons without a cortical gray matter infarct (*P* = .61). Infarct-positive and infarct-negative participants did not differ in any of the individual regions of interest constituting the Global PiB Index (*P* >.12 for all comparisons) or the occipital lobe (*P* = .44).

White matter hyperintensity burden showed no bivariate relationship with Global PiB Index (= −0.07; *P* = .63). In addition, there was no relationship between the number of infarcts (0, 1, or >1) and the Global PiB Index (*P* = .42).

VBI AND PiB RELATIONSHIPS WITH COGNITION

All measures of cognition were normally distributed (*P* >.19 for all comparisons) and showed a similar range of performance (verbal memory: minimum score = 52.4, maximum score = 141.1; nonverbal memory: minimum = 46.8, maximum = 122.4; and executive function: minimum = 48.6, maximum = 123.6). To report the predictors of neuropsychological test performance, we provide standardized   values to allow for direct comparison of the strength of each variable's independent contribution (Table 3).

Verbal Memory—Demographic variables were not significant predictors of verbal memory performance in stage 1 (Table 3). In stage 2, presence of an infarct in subcortical gray matter was significantly related to memory performance (standardized   = −0.29; *P* = .02). Neither WMH volume nor PiB was a significant predictor of verbal memory. When all variables were included in the third stage (subcortical infarct from stage 2), the final equation explained 16.7% of the variance in verbal memory performance, and an infarct in the subcortical gray matter emerged as the only significant predictor after controlling for the effects of the other variables.

Nonverbal Memory—All demographic variables were significant predictors of nonverbal memory in stage 1; lower age, higher educational level, and female sex were associated with better performance (Table 3). In stage 2, an infarct in the subcortical gray matter again emerged as a significant predictor (standardized = −0.36; *P* = .007). White matter hyperintensity volume was not a significant predictor; however, PiB emerged as a significant predictor of performance (standardized = −0.27; *P* = .04). The stage 3 model included all variables (subcortical infarct from stage 2) and explained 48.0% of the variance in nonverbal memory performance. Age and educational level remained significant predictors, sex and an infarct in the subcortical gray matter were reduced to trends, and PiB was no longer a predictor, presumably because of its significant relationship with sex and age.

Executive Function—Educational level was a significant positive predictor of executive function in stage 1 (Table 3). In stage 2, when entered separately, infarcts in the cortical and subcortical gray matter were both significant predictors of executive function. When entered together, only cortical gray matter infarct emerged as a significant predictor (standardized = −0.41; *P* = .002). Therefore, only having a cortical gray matter infarct was retained for the stage 3 model. Neither WMH volume nor Global PiB Index was a significant predictor of performance. The stage 3 model explained 43.3% of the variance in executive function performance, with cortical gray matter infarct and educational level remaining as significant predictors.

All the cognitive analyses were rerun excluding the 6 individuals with CDR >0.5 to confirm that the findings were not driven by individuals with dementia. In stage 2, the Global PiB Index showed a trend toward predicting verbal memory performance (standardized = − 0.23; *P* = .09). The stage 3 models for all cognitive domains remained essentially unchanged.

COMMENT

The aim of this study was to determine the relative contributions of A and VBI to specific areas of cognition in a sample of clinically normal, cognitively impaired, and mildly demented individuals enriched for vascular risk factors. Vascular brain injury had the greatest influence across all measured cognitive domains and was not related to A. Dividing participants by cognitive status and regional location of the infarct (including the cortex) did not alter this finding. Approximately half the sample was classified as PiB-positive, and PiB was associated with both *APOE* genotype (with those having the e4 allele showing greater A deposition) and increasing age, which demonstrates that the effects of well-established risk factors for A were present and detectable in our sample. Thus, it may be that VBI and A, both individually prevalent, frequently converge in dementia, each affecting function but neither bearing a causal relationship to the other.[30–33]

In this study, infarct affected all cognitive domains.[34] Cortical gray matter infarcts influenced executive function, potentially because they predominantly encompassed the frontal lobe.[35] Subcortical gray matter infarction, all of which involved the basal ganglia with the majority affecting the striatum, influenced verbal and non-verbal memory.[36,37] There is suggestion that the striatum is involved in episodic memory learning,[38] and subcortical infarct has a significant association with amnestic MCI.[39] White matter hyperintensity burden was not related to any cognitive measure. The association between WMH and cognition (especially executive function) is generally small and most evident in cognitively normal samples.[35,36] We may not have found a significant influence of WMH because of the cognitive heterogeneity of the sample and also potentially because the effects of infarct surpassed those due to WMH.

Through the use of amyloid imaging, we measured the separate and combined influence of Aβ and vascular disease on cognition. In this sample of participants enriched for increased vascular risk, infarct was associated with both clinical status and cognition, whereas PiB was not. Also, we did not find an additive negative effect of Aβ on function in that there was no greater number of infarct-positive/PiB-positive individuals in the clinically impaired group. Thus, we found no evidence of a negative effect of PiB on cognition. Why?

First, it may be an issue of statistical power because subjects in our study ranged from cognitively normal to mildly impaired. This sample, in contrast to others,[15,37] may simply not be large enough to detect the modest effects of PiB within this somewhat restricted range of cognitive function. However, if this is the case, our results still say something about the relative strength of the effects of VBI and amyloid in normal to mildly impaired cognition.

A more substantive explanation is that, because amyloid deposition is an initiating event, the strength of association between PiB and cognition may depend on the cognitive syndrome studied. In cognitively normal persons, the downstream consequences (eg, neuronal death and synaptic loss) of amyloid have not yet occurred and the relationship of PiB to cognition is weak. In dementia, the downstream events have nearly always occurred to a degree, but Aβ may have already reached a plateau[38]; consequently, the relationship is only modest. In MCI, sometimes the downstream events have occurred but sometimes they have not, other causes of impairment (such as VBI) may be present, and the amyloid-cognition association is weak. Thus, across a wide range of disease severity, as Aβ levels increase, clinical function declines[15,39]; however, if the range of disease severity is limited, as it was here, amyloid effects may be difficult to detect.

In contrast to Aβ, VBI represents end-stage pathologic consequences of the vascular pathogenic process. Thus, in a sample such as this one that is restricted with regard to the range of cognitive impairment, it is perhaps not surprising that end-organ damage (VBI) has greater impact than do precipitating pathogenic events (Aβ). These results suggest that VBI, specifically infarction, warrants consideration when examining causes of MCI. Although our sampling does not permit generalizing the frequency of VBI to the aged population, other studies clearly show a high prevalence of this disorder.[40]

The literature suggests a link between vascular risk factors (eg, hypertension and diabetes mellitus) and Aβ aggregation,[41–43] and indeed an association between elevated coronary risk and Aβ deposition has been reported recently[41] (however, see Chui et al[44]). While it is tempting to conclude that the high rate of vascular risk in our sample accounts for the relatively high proportion of PiB-positive cases, more basic factors, such as the mean age of 78 years, might also account for this. In addition, half the participants were cognitively impaired or demented, groups in which the prevalence of cerebral Aβ exceeds 50%.[45]

If there is an association between vascular risk and Aβ, it does not appear to be mediated by VBI—at least as defined by MRI-measured infarcts and WMH. This does not exclude the possibility that more subtle types of vascular disease, such as microvascular damage or blood-brain barrier dysfunction, contribute to Aβ deposition.[46]

Cerebrovascular disease is highly prevalent in the elderly population. In this study of clinically normal to mildly demented individuals, we found that VBI negatively affected cognition. Although MCI is clearly a significant risk factor for AD, the present data suggest that the impact of VBI should be considered when defining the etiology of MCI. Reductions in cerebrovascular disease may be important in preventing MCI.

Acknowledgments

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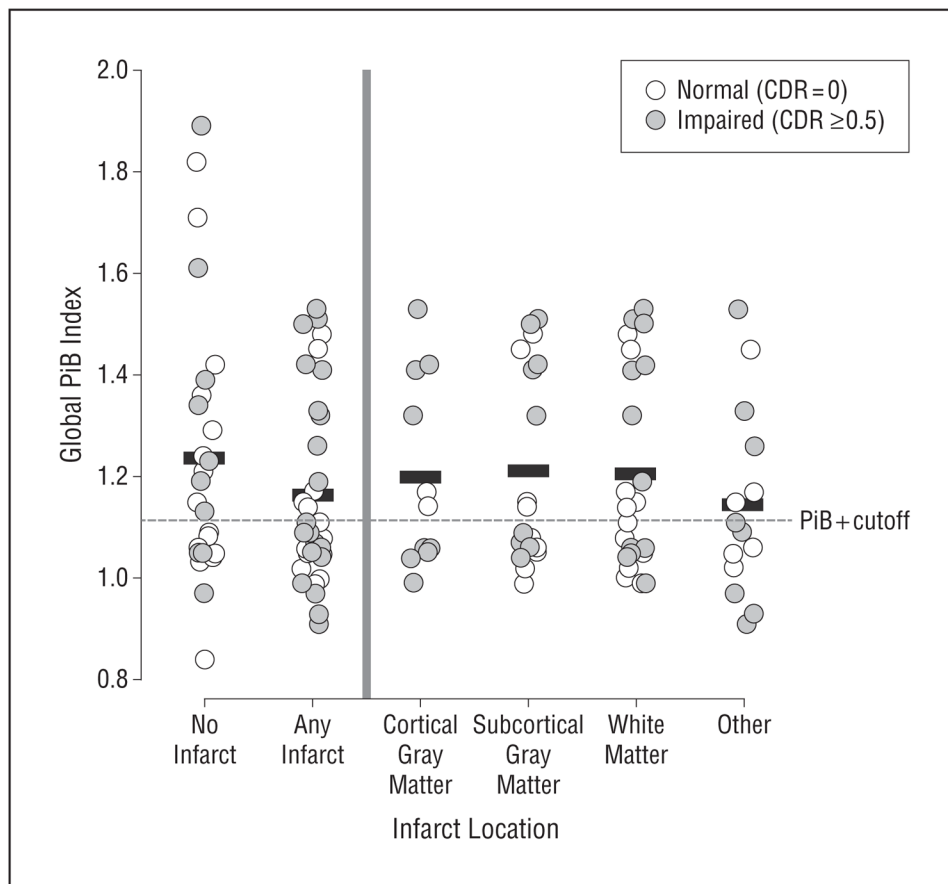**Figure.**
Scatterplot of Global Pittsburgh Compound B (PiB) Index volume stratified by infarct presence and location. Black bars represent mean Global PiB Index for infarct groups. The dichotomous categorization of Global PiB Index (PiB+/−) is shown by the dashed line. Circles represent clinical status of individuals: white, normal (Clinical Dementia Rating [CDR] = 0); gray, impaired (CDR ≥ 0.5).

Table 1

Participant Characteristics Stratified by PiB Status[a]

	PiB− (n = 32)	PiB+ (n = 29)	t	χ²	P Value
Age, mean (SD), y	76.6 (7.5)	79 (6.3)	$t_{59}=1.4$		.17
Male sex	19 (59)	24 (83)		$\chi^2_1=4.00$	.046
Educational level, mean (SD), y	13.8 (2.9)	14.1 (2.5)	$t_{59}=0.5$		.64
APOE ε4 allele[b]	3 (12)	10 (40)		$\chi^2_1=5.09$	.02
MMSE score, mean (SD)	28 (2.2)	27.4 (2.3)	$t_{59}=1.0$		.32
GDS score, mean (SD)	1.5 (1.7)	2.4 (2.6)	$t_{57}=1.5$		.14
Infarct+	20 (62)	14 (48)		$\chi^2_1=1.25$	.26
CDR 0.5	15 (47)	16 (55)		$\chi^2_1=0.42$	.52

Abbreviations: APOE, apolipoprotein E; CDR, Clinical Dementia Rating; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; PiB, Pittsburgh Compound B; −, negative;+, positive.

[a]Data are presented as raw count (percentage) unless otherwise indicated. Group comparisons used independent t tests for continuous variables and χ² tests for categorical variables.

[b]Data concerning APOE allele status were not available for 11 participants.

Table 2

Participant Characteristics Stratified by Infarct Status[a]

	Infarct− (n = 27)	Infarct+ (n = 34)	t	χ^2	P Value
Age, mean (SD), y	79.3 (7.5)	76.6 (6.4)	$t_{59} = 1.5$		.13
Male sex	20 (74)	23 (68)		$\chi_1^2 = 0.30$	.59
Educational level, mean (SD), y	13.9 (2.8)	14 (2.7)	$t_{59} = 0.1$		.92
APOE 4 allele[b]	4 (17)	9 (33)		$\chi_1^2 = 1.64$	.20
MMSE score, mean (SD)	28.2 (2.1)	27.3 (2.4)	$t_{59} = 1.6$		.12
GDS score, mean (SD)	1.6 (1.7)	2.2 (2.6)	$t_{57} = 1.0$		.33
PiB+	15 (56)	14 (41)		$\chi_1^2 = 1.25$	.26
CDR 0.5	10 (37)	21 (62)		$\chi_1^2 = 3.68$	.055

Abbreviations: *APOE*, apolipoprotein E; CDR, Clinical Dementia Rating; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; PiB, Pittsburgh Compound B; −, negative;+, positive.

[a]Data are presented as raw count (percentage) unless otherwise indicated. Group comparisons used independent *t* tests for continuous variables and χ^2 tests for categorical variables.

[b]Data concerning *APOE* allele status were not available for 11 participants.

Table 3

Variance in Composite Cognitive Test Performance Explained by Demographics and Neuroimaging Markers of Pathologic Change[a]

| | Demographic Characteristic | | | Neuroimaging Marker of Pathologic Change | | | | | | |
| | | | | Infarct | | | | | WMH Volume | Aβ, Global PiB Index |
Stage	Age	Female Sex	Educational Level	Cortical Gray Matter	Subcortical Gray Matter	White Matter	Other	Number (0, 1, or >1)		
Verbal Memory										
1	−.11	.06	.24							
2				−.06	−.29[b]	−.06	−.02	−.19	.02	−.18
3	−.24	−.02	.16		−.34[b]				.19	−.08
Nonverbal Memory										
1	−.27[b]	.28[b]	.36[c]							
2				.06	−.36[c]	.05	−.05	−.13	−.08	−.27[b]
3	−.31[b]	−.21	.45[d]		−.23				.02	−.12
Executive Function										
1	−.01	.08	.51[d]							
2				−.47[d]	−.33[b]	−.17	−.20	−.14	−.21	−.15
3	−.08	−.19	.38[c]	−.54[c]					.05	−.04

Abbreviations: Aβ, β-amyloid; PiB, Pittsburgh Compound B; WMH, white matter hyperintensity.

[a] Standardized β values are displayed to allow for direct comparison of each variable's contribution. Stage 1 includes the demographic variables: age and sex. Stage 2 evaluates the contribution of infarct location (cortical, subcortical, cortical white matter, or other [cerebellum, medulla, midbrain, or pons]), WMH volume, and PiB, each considered separately. Stage 3 includes demographic variables, the best infarct predictor identified in stage 2, WMH volume, and PiB.

[b] $P<.05$.

[c] $P<.01$.

[d] $P<.001$.