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Blood pressure is associated with higher brain amyloid burden and lower glucose metabolism in healthy late middle-age persons

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Abstract

Epidemiological studies suggest that elevated blood pressure (BP) in mid-life is associated with increased risk of Alzheimer's disease (AD) in late-life. In this preliminary study, we investigated the extent to which BP measurements are related to positron emission tomography (PET) measurements of fibrillar amyloid-beta burden using Pittsburgh Compound-B (PiB) and fluorodeoxyglucose (FDG) PET measures of cerebral metabolic rate for glucose metabolism (CMRgl) in cognitively normal, late-middle-aged to older adult apolipoprotein E (*APOE*) ε4 homozygotes, heterozygotes and non-carriers. PiB PET results revealed that systolic BP (SBP) and pulse pressure (PP) were each positively correlated with cerebral-to-cerebellar PiB distribution volume ratio (DVR) in frontal, temporal and posterior-cingulate/precuneus regions, whereas no significant positive correlations were found between PiB DVRs and diastolic BP

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(DBP). FDG PET results revealed significant inverse correlations between each of the BP measures and lower CMRgl in frontal and temporal brain regions. These preliminary findings provide additional evidence that higher BP, likely a reflection of arterial stiffness, during late-mid-life may be associated with increased risk of presymptomatic AD.

Keywords

APOE; blood pressure; arterial stiffness; brain imaging; PET; Alzheimer's disease; amyloid; PiB; Pittsburgh Compound-B

1. Introduction

Epidemiological studies have raised the possibility that cardiovascular risk factors such as elevated blood pressure (BP) in mid-life are associated with increased risk for Alzheimer's disease (AD) in late-life (Freitag et al., 2006; Launer et al., 2000; Skoog et al., 1996). However, cross-sectional and longitudinal studies in older adults have not confirmed this association (Morris et al., 2000; Morris et al., 2001; Petitti et al., 2005; Qiu et al., 2004; Verghese et al., 2003), instead suggesting that in late-life, lower BP is associated with increased risk of AD, with the decrease occurring perhaps as a secondary phenomenon in AD due to damage to brain regions important to BP regulation (Burke et al., 1994; Guo et al., 1996; Guo et al., 2001b). As a complement to traditional epidemiological studies we have proposed using brain imaging measurements as a quantitative presymptomatic endophenotype of AD, a feature more closely related to disease predisposition than the clinical syndrome itself (Reiman et al., 2001; Reiman et al., 2005). Utilizing established imaging measures that distinguish people with no copies, one copy and two copies of the apolipoprotein E (*APOE*) $\epsilon 4$ allele, the best established genetic risk factor for late-onset AD (Corder et al., 1993), we can evaluate the relationship between BP, amyloid pathology, brain function, and this well-established genetic risk factor in the predisposition to AD.

Examining fluorodeoxyglucose (FDG) positron emission tomography (PET) images from cognitively normal, late-middle-aged persons, we previously reported that compared to non-carriers (NC), *APOE* $\epsilon 4$ homozygotes (HM) and heterozygotes (HT) have significantly lower measures of the cerebral metabolic rate for glucose metabolism (CMRgl) in brain regions preferentially affected by AD (Reiman et al., 1996), and in fact, this reduction is correlated with gene dose (the number of $\epsilon 4$ alleles in a person's *APOE* genotype) (Reiman et al., 2005). Examining the relationship between cerebral hypometabolism, *APOE* $\epsilon 4$, and serum total cholesterol, another cardiovascular risk factor suggested to increase the risk of AD, we previously reported that increasing cholesterol levels are associated with lower CMRgl bilaterally AD-related brain regions and in additional frontal regions preferentially affected by normal aging, and these reductions are greater in *APOE* $\epsilon 4$ carriers compared to NC (Reiman et al., 2010a). Using another brain imaging measurement of preclinical AD, Pittsburgh Compound-B (PiB) PET (Klunk et al., 2004), which assesses fibrillar amyloid-beta ($A\beta$) *in vivo*, we previously reported that cognitively normal late-middle-age *APOE* $\epsilon 4$ carriers have greater fibrillar $A\beta$ burden compared to NC, and in fact, the fibrillar $A\beta$ measurements are correlated with *APOE* $\epsilon 4$ gene dose (Reiman et al., 2009).

In the present study, we used our proposed neuroimaging endophenotypes to test the hypothesis that elevated BP measurements of systolic BP (SBP), diastolic BP (DBP) and peripheral pulse pressure (PP) in cognitively normal, late middle-aged persons are associated with increased PiB burden and lower CMRgl in brain regions known to be preferentially affected by AD and normal aging and to examine the impact of *APOE* $\epsilon 4$ on these relationships.

2. Methods

2.1. Study population

Cognitively normal volunteers 47 to 68 years of age were enrolled into a longitudinal cohort study (Reiman et al., 1996, 2005). Participants provided informed consent, agreeing not to be given any information about their APOE genotype and were studied under guidelines approved by the human subjects committees at Banner Good Samaritan Medical Center and the Mayo Clinic. Venous blood samples were drawn and APOE $\epsilon 4$ genotypes characterized as previously described (Crook et al., 1994; Reiman et al., 1996). Originally, one APOE $\epsilon 4$ HT (with the $\epsilon 3/\epsilon 4$ genotype) and two $\epsilon 4$ NC were matched to a different $\epsilon 4$ HM for their gender, age (within 3 years), and educational level (within 2 years). All participants denied having an impairment in memory or other cognitive skills, had scores of at least 28 on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and less than 10 on the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), did not satisfy criteria for a current psychiatric disorder using a structured psychiatric interview, and had a normal neurological exam. Study participants have been assessed every two years using a medical examination, including collecting information on history of hypertension and use of blood pressure lowering medications, using clinical ratings, neuropsychological tests, volumetric MRI (to rule out gross clinical abnormalities and for analysis purposes) and FDG PET (Reiman et al., 1996; Reiman et al., 2001). Beginning in December 2007, study participants underwent PiB PET scans and BP measurements were acquired as part of their study visit. At the time of their PET scans, all returning subjects remained cognitively normal. For the current cross-sectional report, we analyzed the available BP, FDG PET and PiB PET data from our returning APOE $\epsilon 4$ HM, HT, and NC enrolled in our longitudinal cohort study. PiB and BP data were available for 32 participants whereas FDG PET data were available for 26 participants. Ten participants underwent both FDG PET and PiB PET as part of this study.

2.2 Measurement of blood pressure

Mean SBP and DBP was computed from three supine measurements using an automated cuff (GE Dinamap PRO 400) by a trained PET technician during the PET study visit as follows: 1) just prior to IV insertion, 2) during the transmission scan just prior to injection, and 3) immediately after the scan. PP was calculated as the difference between mean SPB and DBP. Participants were classified as hypertensive if their mean SBP or DBP measurements met JCN7 criteria for hypertension (SBP ≥ 140 and/or DBP ≥ 90 mm/Hg) (Chobanian et al., 2003).

2.3 Brain Imaging

Volumetric T₁-weighted MRI, PiB PET and FDG PET were performed as previously described (Reiman et al., 1996; Reiman et al., 2001; Reiman et al., 2009). Briefly, PiB PET was performed using the HR+ scanner (Siemens, Knoxville, TN) in the three-dimensional mode, a transmission scan, the intravenous injection of 15 mCi of ¹¹C-PiB, and a 90-min dynamic sequence of emission scans. Each person's PiB PET image was reconstructed using a filter back-projection method, correction for radiation scatter and attenuation, and a Hanning filter. The data were converted to cerebral-to-cerebellar PiB DVR, a measure of fibrillar A β burden, using images from the 40-to-90 min emission frames, an automatically labeled cerebellar reference region, and the Logan method. The Logan method was used to generate PiB DVR images in order to characterize and compare PiB DVR on a voxel-by-voxel basis (Reiman et al., 2009).

FDG PET was also performed using the HR+ scanner in the three-dimensional mode, a transmission scan, the intravenous injection of 5–8 mCi of [18F] fluorodeoxyglucose, and a 60-minute dynamic sequence of emission scans as the participants, who had fasted for at

least 4 hours, lay quietly with eyes closed in a darkened room. The reconstructed images consisted of 63 horizontal slices with a center-to-center slice separation of 2.46 mm, an axial field of view of 15.5 cm, an in-plane resolution of 4.2–5.1 mm full width at half-maximum (FWHM), and an axial resolution of 4.6–6.0 mm FWHM. Voxel-based analyses were performed using the PET images (counts relative to the whole brain uptake) acquired during the last 30 minutes.

2.4 Data analysis

For the PiB PET analyses, SPM5 (Wellcome Department of Cognitive Neurology, London, U.K.), and spatial information from the 3.5-to-10 min emission frames were used to automatically linearly and non-linearly deform the PiB distribution volume ratio (DVR) image according to the coordinates of a standard brain atlas (Talairach and Tournoux, 1988), smooth the images to 12 mm full width-at-half-maximum and generate statistical parametric maps of the association between BP measurements and PiB DVR on a voxel-by-voxel basis. Following the primary correlation analysis, several voxel-by-voxel post-hoc analyses were conducted, including 1) controlling for self-reported use of antihypertensive medication for treatment of hypertension and/or BP measurements that met JCN7 criteria for hypertension as described in Section 2.2 (using analysis of covariance), 2) examining the Pearson correlations between BP measures and PiB DVRs in the *APOE* $\epsilon 4$ carrier and NC groups, 3) examining the interactions between BP measures and PiB DVRs, and 4) a Monte-Carlo simulation (MCS) to examine the probability of observing the results of the present study. Specifically, MCS was used to examine the probability of observing at least N voxels in the hypothesized direction of the correlation (inverse correlation for PP and SBP with PiB DVR, positive correlation for DBP and PiB DVR) and at most n voxels in the opposite direction (where $N \gg n$). The assumption is that, if the hypothesis is not true (or the Null hypothesis of no correlation is true), then the N and n should not be significantly different (or observing the correlations in both directions should be random with equal chance). For each of the 1000 simulations, J (referring to the number of subjects in the study) Gaussian distributed random maps (within the whole brain mask used in the analysis) were generated, being independent to each other. Each map was then smoothed with the same FWHM used in the real analysis (also accounting for the reconstructed smoothness). The real PP, SBP or DBP were used in the simulation to compute the correlation with the random maps and to generate the corresponding t-score map for statistical significance. The number of voxels in the hypothesized direction of the correlation was recorded (referred to as dirN) as well as the number in the opposite direction (referred to as oppN). Over the 1000 simulations, we counted the number of occurrences (referred to as No), that $\text{dirN} \geq N$ and $\text{oppN} < n$ and then estimated the probability as $\text{Prob} = \text{No}/1000$.

For the FDG PET analyses, an automated algorithm (SPM5) was used to deform each person's FDG PET image linearly and non-linearly into the coordinates of a standard brain atlas, normalize the data for the variation in absolute whole-brain measurements using proportionate scaling, smooth the images using a three-dimensional Gaussian filter to a spatial resolution of 12 mm full-width-at-half-maximum, and generate statistical parametric maps of the Pearson correlations between BP measurements and lower regional CMRgl ($p < 0.005$, uncorrected for multiple comparisons). The statistical maps were superimposed onto a map of CMRgl reductions in previously studied probable AD patients and a spatially standardized, volume-rendered MRI (Alexander et al., 2002).

All non-imaging data, including demographics, neuropsychological scores, and blood pressure were examined using one-way analysis of variance (ANOVA) and chi-square tests with Stata 11.0 (StataCorp, College Station, TX).

3. Results

Participant characteristics, clinical ratings, neuropsychological scores, and BP measurements are shown in Table 1. Among PET PiB study participants, the *APOE* $\epsilon 4$ HM, HT, and NC groups did not differ in terms of their demographic features, BP measurements, use of antihypertensive medications, or cognitive functioning, with the exception that the HM had slightly higher mean HAM-D scores ($p = 0.03$), though all were within normal limits. Among FDG PET study participants, the *APOE* $\epsilon 4$ groups did not differ in regards to these same characteristics, with the exception that the HT were slightly older ($p = 0.04$). Comparing PET PiB study participants to FDG PET study participants (excluding the 10 participants who underwent both PET PiB and FDG PET), the two imaging groups did not differ, with the exception that the PET PiB participants were slightly older ($p = 0.02$) (data not displayed). Participants' MRIs were read by the radiologist and were found to be free of gross clinically significant abnormalities.

3.1 PET PiB results

Statistical parametric maps of the relationship between BP measurements and PiB DVR measurements of fibrillar A β are shown in Figure 1 with the location and magnitude of the most significant correlations in Table 2. SBP was positively correlated with PiB DVRs bilaterally in the posterior cingulate-precuneus, frontal, temporal and parietal regions. In comparison, no significant positive correlations were observed between DBP and PiB DVRs, and in fact, upon inspection, DBP was found to be inversely correlated with PiB DVRs (lower DBP with higher PiB DVRs) bilaterally in the posterior cingulate-precuneus, frontal, temporal and parietal regions ($p < 0.05$, uncorrected for multiple comparisons, data not shown). Based on these observations and given that PP is the absolute difference between SBP and DBP, we then examined PP separately. Higher PP was positively associated with PiB DVRs in the precuneus, frontal and parietal regions ($p < 0.05$, uncorrected for multiple comparisons). The results from the post-hoc interaction analyses revealed that in fact, PP is associated with an increase in PiB DVRs compared to either SBP or DBP whereas no significant interactions were found in the opposite direction. Results from the post-hoc analyses examining the association between PP and PiB DVRs which controlled for participants' use of antihypertensive medication and/or meeting criteria for JCN7 hypertension were nearly identical to the primary Pearson correlation analysis. Similarly, post-hoc analyses controlling for *APOE* $\epsilon 4$ did not significantly alter the primary results.

Results from the MCS revealed that, over the 1000 simulations, for each of the PP, SBP, and DBP the probability for observing the results in the hypothesized direction of correlation (that is, positive correlation between SBP or PP and PiB DVR; inverse correlation between DBP and PiB DVR) was in fact greater than the probability of observing voxels in the opposite direction (PP $p = 0.005$; SBP $p < 0.001$; DBP $p < 0.001$). These results indicate that the BP and PiB DVR findings observed are in fact robust.

3.2 FDG PET results

Statistical parametric maps of the inverse association between BP measurements and lower CMRgl are displayed in Figure 2 and the location and magnitude of the most significant correlations between higher SBP, DBP and PP with lower CMRgl are shown in Table 3. Higher SBP, DBP, and PP levels were each correlated with lower CMRgl in frontal and temporal brain regions ($p < 0.005$, uncorrected for multiple comparisons). Correlations in the opposite direction (lower BP levels with higher CMRgl) were observed bilaterally in the cerebellum and medial temporal brain regions for SBP and PP, and in the left inferior

temporal brain region for DBP ($p < 0.005$, uncorrected for multiple comparisons) (data not displayed).

4. Discussion

This study in cognitively normal, late middle-aged to older adults demonstrates a positive association between measures of BP and fibrillar A β burden and an inverse association between the same BP measures and CMRgl. These brain imaging findings were not solely attributable to *APOE* $\epsilon 4$ status, self-reported use of antihypertensive medications or meeting criteria for hypertension. Indeed, these findings are in agreement with those from our larger cohort indicating that the presence of cerebrovascular risk factors is associated with preclinical memory decline in *APOE* $\epsilon 4$ homozygotes (Caselli et al., 2011). Taken together, these results suggest that incremental increases in BP measures, here likely reflecting increased arterial stiffness, may be associated with increased risk of presymptomatic AD.

The findings from the present study support those from previous neuroimaging and neuropathology studies on the negative impact of elevated BP and increased arterial stiffness on brain function and structure. Findings from MRI studies suggest that hypertension exacerbates brain aging (Raz and Rodrigue, 2006), is associated with greater ventricular volume (Salerno et al., 1992; Strassburger et al., 1997) and reduced overall brain volume (Wiseman et al., 2004), while increases in SBP are associated with reduced grey matter volume (Gianaros et al., 2006). Moreover, untreated hypertension in mid-life is associated with hippocampal atrophy in late-life (Korf et al., 2004). Findings from FDG PET studies suggest that even those with medically-controlled hypertension have reduced cerebral glucose metabolism in brain regions related to AD and aging (Beason-Held et al., 2007; Salerno et al., 1995). Autopsy studies have reported that elevated BP is associated with the hallmark neuropathological markers of AD, including increased neurofibrillary tangles, amyloid plaques, and brain atrophy compared to age-matched normotensive individuals (Petrovitch et al., 2000; Sparks et al., 1995; Sparks et al., 1996).

The pathophysiological mechanism by which elevated BP or increased arterial stiffness influences the development of AD has not been elucidated. Moreover, which BP component is most predictive of presymptomatic AD and clinical AD is uncertain, as findings from our study suggest that PP, a measure of arterial stiffness, may be the most sensitive, though other studies suggest SBP may be most informative (Freitag et al., 2006). It is plausible that PP, which is a pulsatile component that is an indicator of large artery stiffness, is a better predictor of presymptomatic AD, whereas SBP is a better predictor in older adults closer to the median age of onset of dementia symptoms. Results from recent molecular studies suggest that circulatory defects, such as those caused by stiffening of the vasculature system, may result in failure of clearance of A β from the brain (Bell et al., 2009). Another possibility is that white matter lesions due to increases in BP may reduce cerebral blood flow thus contributing to AD or operate in an additive fashion with AD neuropathology to worsen cognition function resulting in dementia (a “critical threshold” hypothesis) (Petrovitch et al., 2000). Alternatively, increasing BP levels or arterial stiffness in mid-life could have a direct effect on the development of neuropathological features of AD or brain atrophy (Petrovitch et al., 2000), potentially due to the reduction in the blood-brain barrier caused by hypertension, resulting in amyloid deposition (Gentile et al., 2009). On the other hand, increases in BP may alter the responsiveness of the cerebrovasculature to neuronal activation, resulting in reduced cognitive functioning (Jennings et al., 1998).

Several observational studies have suggested that use of antihypertensive medications may be associated with a lower prevalence and incidence of dementia and AD and preserved cognitive function (Guo et al., 1999; Haag et al., 2009; Hajjar et al., 2005; Hanon et al.,

2008; in't Veld et al., 2001; Khachaturian et al., 2006). However, the findings from randomized clinical trials have been mixed, with some trials finding a protective effect against cognitive decline or incident dementia (Forette et al., 1998; Forette et al., 2002), with others finding no beneficial effects (Diener et al., 2008; Lithell et al., 2003). The inconsistent findings may be due to several factors, including duration of treatment (Haag et al., 2009; Peila et al., 2006) and age in which treatment was started (Haag et al., 2009), particularly because findings from some studies suggest that treatment may be most effective in reducing incident AD in those younger than 75 years of age. Moreover, there is some evidence that only *APOE* ϵ 4 carriers experience the protective effect of antihypertensive medications (Guo et al., 2001a; Hestad and Engedal, 2006), potentially due to an interaction between cerebrovascular disease and ϵ 4 (Caselli et al., in press). Inconsistent findings may also be due to type of medication, as there is some evidence to suggest that only angiotensin receptor blockers and angiotensin converting enzyme (ACE) inhibitors, and not other blood pressure-lowering medications, are associated with a reduced risk of AD (Li et al., 2010). Findings from the study of AD-model transgenic mice (Wang et al., 2007) and expired brain donors (Hoffman et al., 2009) suggest that antihypertensive treatments may protect against AD neuropathology, potentially by reducing vascular and arterial stiffness, thereby increasing blood flow to the brain and aiding in the removal of amyloid (Bell et al., 2009). *In vitro* studies suggest that ACE may play a role in the metabolism of A β , and while this is somewhat paradoxical in light of clinical studies which report a beneficial effect of ACE inhibitors on development of AD, it is possible that the beneficial effect is due to their ability to reduce the renin angiotensin system (Takeda et al., 2008).

Though the findings in the present study were obtained in a cohort of cognitively normal, predominately normotensive individuals, demonstrating that even small incremental increases in BP reflecting arterial stiffness may be associated with presymptomatic AD, there are some potential limitations. For instance, the sample size was small and requires validation in a larger cohort, which may help clarify the FDG PET results and lack of positive correlation between DBP and PiB burden. In addition, the PET PiB DVR analyses used a lenient statistical threshold, though the findings were restricted to brain regions that are relevant to AD, reducing the false positive rate, and were supported by the MCS findings. Moreover, in contrast to previous epidemiological studies (Haan et al., 1999; Peila et al., 2001; Qiu et al., 2003), as well as our own clinical study (Caselli et al., 2011), the results from the present study did not indicate an *APOE* ϵ 4 effect. Also, participants in our study have a reported family history of probable AD and are generally in good health, thereby potentially reducing the generalizability of our findings to other populations. That said, our findings, which should be viewed as hypothesis generating and are likely applicable to individuals who would enroll in a presymptomatic AD trial (Reiman et al. 2011; Reiman et al., 2010b). Future studies will examine the additive effect of having multiple cerebrovascular risk factors on these neuroimaging measures of presymptomatic AD, the impact of white matter hyperintensity burden on the association between BP and our neuroimaging measures of presymptomatic AD, the longitudinal relationship between BP and our presymptomatic endophenotypes, and whether other, more sensitive measures of arterial stiffness, such as central PP, are better suited to detect an effect compared to standard brachial BP measures. In addition, future studies will examine the relationship between these brain imaging measures and volumetric MRI, by utilizing a multimodal multivariate network analysis approach (Chen et al., 2009) to characterize the linkage between the patterns of information from the same subject's complementary MRI, FDG PET and PET PiB images to fully characterize the relationship between BP and these brain imaging measurements.

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Figure 1. Statistical brain maps showing correlations between higher Pittsburgh Compound-B PET measurements of fibrillar amyloid-β burden and (A) higher systolic blood pressure, (B) higher pulse pressure ($p < 0.05$, uncorrected for multiple comparisons) in cognitively normal adults. No significant positive correlations were found between PiB measurements and higher diastolic blood pressure.

Figure 2.

Statistical brain maps showing the correlations between lower CMRgl and (A) higher systolic blood pressure, (B) higher diastolic blood pressure, and (C) higher pulse pressure and ($p < 0.005$, uncorrected for multiple comparisons) are shown in dark and light blue. These statistical maps are projected onto the lateral and medial surfaces of the left and right cerebral hemispheres and shown in relationship to brain regions preferentially affected by AD (Alexander et al., 2002), which are shown in dark blue and purple. The dark blue areas thus reflect significant correlations between higher blood pressure measurements and lower CMRgl in the brain regions that are preferentially affected by AD.

Table 1
Participant characteristics, clinical ratings, neuropsychological scores and blood pressure measurements

	PET PiB Study				FDG PET Study			
	APOE ε4 non-carriers (n=13)	APOE ε4 heterozygotes (n=11)	APOE ε4 homozygotes (n=8)	P-value	APOE ε4 non-carriers (n=8)	APOE ε4 heterozygotes (n=12)	APOE ε4 homozygotes (n=6)	P-value
Age (years)	64.1 ± 3.8	65.5 ± 4.4	61.4 ± 5.4	0.14	58.9 ± 6.7	64.1 ± 5.9	56.2 ± 5.6	0.04
Sex (F/M)	9/4	8/3	5/3	0.89	6/2	8/4	4/2	0.91
Education (years)	16 ± 2.5	17.4 ± 2.7	15.0 ± 1.4	0.11	14.5 ± 2.1	17.3 ± 3.5	14.8 ± 1.3	0.06
Blood Pressure								
SBP (mm/Hg)	129 ± 16.9	123.4 ± 11.1	124.8 ± 14.3	0.62	127.9 ± 19.4	128.0 ± 20.7	116.6 ± 14.3	0.45
DBP (mm/Hg)	72.6 ± 8.4	63.5 ± 6.9	68.5 ± 13.2	0.08	71.8 ± 10.4	72.2 ± 10.4	63.4 ± 9.3	0.22
PP (mm/Hg)	56.4 ± 13.4	59.9 ± 12.1	56.3 ± 5.8	0.71	56.1 ± 15.7	55.8 ± 14.7	53.1 ± 8.5	0.91
Hypertensive, %	23.1	9.1	25.0	0.59	25.0	41.7	16.7	0.51
Antihypertensive medication use, %	15.4	54.5	37.5	0.13	0	41.7	50	0.07
Body Mass Index	28.1 ± 6.1	26.5 ± 3.6	29.0 ± 5.0	0.54	24.9 ± 3.2	26.9 ± 5.8	27.6 ± 4.8	0.55
MMSE	29.6 ± 0.65	29.6 ± 0.92	29.6 ± 0.74	0.99	29.8 ± 0.5	29.2 ± 1.5	29.5 ± 0.8	0.52
HAM-D	1.1 ± 1.3	1.4 ± 1.7	3.1 ± 2.2	0.03	2.0 ± 2.2	1.3 ± 1.4	3.0 ± 2.4	0.21
AVLT								
Total Learning	49.8 ± 7.9	50.6 ± 11.5	42.3 ± 10.7	0.16	51.3 ± 8.2	48.9 ± 11.6	50.3 ± 7.8	0.87
Short Term Memory	9.6 ± 2.5	9.8 ± 4.4	8.3 ± 4.0	0.61	10.5 ± 2.8	10.1 ± 2.9	10.5 ± 2.5	0.93
Long Term Memory	9.3 ± 2.9	10.0 ± 4.2	7.3 ± 3.9	0.47	9.6 ± 3.2	9.4 ± 3.7	8.8 ± 2.8	0.91
Complex Figure Test								
Copy	34.1 ± 2.2	33.5 ± 3.7	35.3 ± 1.5	0.37	32.3 ± 4.8	33.2 ± 3.6	33.5 ± 4.8	0.86
Recall	20.1 ± 7.7	21.7 ± 9.0	16.4 ± 5.7	0.31	17.1 ± 7.6	19.6 ± 7.6	15.8 ± 5.3	0.53
Boston Naming Test	56.9 ± 2.6	57.0 ± 3.6	57.1 ± 2.4	0.99	56.5 ± 3.0	55.9 ± 3.8	57.2 ± 2.8	0.76
WAIS-R								
Information	14.6 ± 6.7	13.1 ± 2.5	12.1 ± 1.7	0.47	12.3 ± 2.1	12.7 ± 2.4	12.2 ± 1.6	0.86
Digit Span	11.5 ± 2.8	12.5 ± 3.1	12.3 ± 2.3	0.63	11.1 ± 3.6	12.2 ± 3.0	11.7 ± 1.6	0.75
Block Design	12.5 ± 2.6	12.9 ± 2.6	13.0 ± 2.9	0.88	11.1 ± 2.1	13.3 ± 3.2	13.3 ± 3.2	0.24
Arithmetic	12.5 ± 2.1	13.1 ± 3.5	12.6 ± 2.9	0.86	11.6 ± 2.6	12.5 ± 2.7	13.7 ± 2.5	0.37
Similarities	12.8 ± 2.2	13.0 ± 2.8	13.1 ± 1.5	0.94	11.5 ± 2.6	12.8 ± 1.4	13.0 ± 1.9	0.26

	PET PiB Study			FDG PET Study				
	APOE ε4 non-carriers (n=13)	APOE ε4 heterozygotes (n=11)	APOE ε4 homozygotes (n=8)	P-value	APOE ε4 non-carriers (n=8)	APOE ε4 heterozygotes (n=12)	APOE ε4 homozygotes (n=6)	P-value
COWAT	48.1 ± 12.5	52.2 ± 9.6	46.3 ± 8.1	0.45	50.3 ± 8.4	50.8 ± 14.6	47.7 ± 5.4	0.85
WMS-R Orientation	14.0 ± 0.0	13.9 ± 0.3	13.8 ± 0.5	0.18	13.9 ± 0.4	13.9 ± 0.3	13.8 ± 0.4	0.88

All values are mean ± standard deviation (SD) unless otherwise noted.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MMSE, Mini-Mental State Exam; HAM-D, Hamilton Depression Rating Scale; AVLT, Auditory Verbal Learning Test; WAIS-R, Wechsler Adult Intelligence Scale-Revised; COWAT, Controlled Oral Word Association Test; WMS-R, Wechsler Memory Scale-Revised

Table 2

Location and magnitude of maximally significant relationships between higher blood pressure measurements and fibrillar A β burden

Brain region	Atlas coordinates (mm) ^a			Correlation coefficient	p-value ^b	
	X	Y	Z			
Systolic BP						
Precuneus	Left	2	-81	48	0.35	2.45×10^{-2}
	Right	30	-22	64	0.56	5.9×10^{-3}
Frontal	Left	-30	-20	64	0.37	2.0×10^{-2}
	Right	20	-29	-2	0.34	2.6×10^{-2}
Pulse Pressure						
Precuneus	Left	2	-81	48	0.36	2.11×10^{-2}
	Right	4	-75	55	0.33	3.3×10^{-2}
Frontal	Right	30	-22	64	0.45	4.8×10^{-3}
	Left	-30	-20	64	0.37	1.8×10^{-2}
Medial Temporal	Right	20	-29	-2	0.37	2.1×10^{-2}

The data were extracted from voxels associated with maximally significant cerebral-to-cerebellar PiB DVR increases correlated with increasing systolic BP or pulse pressure in cognitively normal *APOE* $\epsilon 4$ homozygotes, heterozygotes and non-carriers. No significant positive correlations were observed between PiB DVRs and diastolic BP.

^a Atlas coordinates were obtained from Talairach and Tournoux (Talairach and Tournoux, 1988). X is the distance to the right (+) or left (-) of the midline, Y is the distance anterior (+) or posterior (-) to the anterior commissure, and Z is the distance superior (+) or inferior (-) to a horizontal plane through the anterior and posterior commissures.

^b P-values are one-tailed and uncorrected for multiple comparisons.

Table 3

Location and magnitude of the most significant correlations between higher blood pressure measurements and lower regional-to-whole brain CMRgl

Brain region	Atlas coordinates ^a			Correlation coefficient	p-value ^b	
	X	Y	Z			
<i>Systolic BP</i>						
Frontal	Right	16	70	1	0.57	1.2×10^{-3}
	Left	-16	49	42	0.54	2.0×10^{-3}
Temporal	Right	50	-75	12	0.59	7.2×10^{-4}
Anterior Cingulate	Right	4	42	-2	0.54	2.0×10^{-3}
<i>Diastolic BP</i>						
Frontal	Right	34	54	27	0.58	8.5×10^{-4}
Temporal	Right	50	-38	13	0.64	2.0×10^{-4}
	Left	-48	-44	21	0.55	1.9×10^{-3}
Precuneus	Right	20	-55	32	0.55	1.6×10^{-3}
<i>Pulse Pressure</i>						
Frontal	Right	2	36	-9	0.61	4.7×10^{-4}
	Left	0	34	-12	0.64	1.9×10^{-4}
Temporal	Right	50	-73	11	0.65	1.6×10^{-4}
Anterior Cingulate	Right	4	39	-2	0.60	5.3×10^{-4}
	Left	2	35	10	0.58	3.5×10^{-4}

The data were extracted from voxels associated with maximally significant CMRgl reductions correlated with increasing systolic BP, diastolic BP, or pulse pressure in cognitively normal *APOE* ε4 homozygotes, heterozygotes and non-carriers.

^a Atlas coordinates were obtained from Talairach and Tournoux (Talairach and Tournoux, 1988). X is the distance to the right (+) or left (-) of the midline, Y is the distance anterior (+) or posterior (-) to the anterior commissure, and Z is the distance superior (+) or inferior (-) to a horizontal plane through the anterior and posterior commissures.

^b p-values are one-tailed and uncorrected for multiple comparisons.