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Vascular health risks and fMRI activation during a memory task in older adults

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Abstract

Vascular problems increase Alzheimer's disease (AD) risk, but the nature of this relationship remains unclear. Older adults having genetic risk for AD show regionally increased functional magnetic resonance imaging (fMRI) activity during memory, possibly representing compensation for a genetically induced neural deficit. We investigated whether vascular health risks, which similarly could lead to neuropsychological deficits, also showed increased fMRI activity during a memory task performed by 30 cognitively intact, primarily normotensive older adults (mean age = 61). Vascular risk measures included systolic blood pressure (sBP), body mass index (BMI), and total cholesterol. Higher sBP and BMI (but not total cholesterol) were significantly correlated with increased activation in posterior cingulate cortex and frontal, temporal, and parietal regions. In posterior cingulate and parietal cortices, these relationships were evident even within sBP and BMI ranges considered normal, and were independent of hippocampal volume. Our results are similar to those in prior AD risk research, and suggest that fMRI reveals an abnormal response to cognitive processes in cognitively intact older adults with increased vascular risk.

Keywords

fMRI; Cognitive aging; Memory; Blood pressure; Body mass index; Alzheimer's disease

1. Introduction

A growing body of evidence links vascular health risks to age-associated decreases in cognition (Muller et al., 2007; Singh-Manoux and Marmot, 2005; van den Kommer et al., 2007; Waldstein et al., 2005). High blood pressure (Kivipelto et al., 2002; Launer et al., 2000; Skoog et al., 1996; Whitmer et al., 2005b; Wu et al., 2003), body mass index (BMI) (Gustafson et al., 2003; Razay and Vreugdenhil, 2005; Rosengren et al., 2005; Whitmer et al., 2005a), and total cholesterol (Kivipelto et al., 2002; Whitmer et al., 2005b), even at midlife, have all been implicated in greater incidence of Alzheimer's disease (AD) or unspecified dementia later in life (Kivipelto et al., 2005). Links between vascular health and AD are controversial, however,

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with other studies showing no association (Li et al., 2005; Morris et al., 2001; Tan et al., 2003). Because vascular health factors may be associated with cognitive decline, we examined the influence of sBP, BMI, and total cholesterol levels on functional magnetic resonance imaging (fMRI) brain activation in middle-aged and older cognitively intact adults while they performed a verbal paired associates memory task.

Functional MRI may be a sensitive indicator of pre-symptomatic AD processes. Past studies have demonstrated fMRI activation differences between normal adults genetically at risk for AD and those lacking that known genetic risk (Bondi et al., 2005; Bookheimer et al., 2000; Wishart et al., 2006). These abnormalities in fMRI activation appear to predict future cognitive decline (Bookheimer et al., 2000). The mechanism is not definitively known, but one hypothesis is that this increased activation reflects a compensatory process in which additional cognitive resources are engaged to maintain performance (Bondi et al., 2005; Bookheimer et al., 2000; Wishart et al., 2006). Previous work examining the relationship between the $\epsilon 4$ allele of the apolipoprotein E gene (APOE4) and fMRI signal during a verbal paired associates task showed that APOE4+ adults preferentially activated posterior cingulate and parietal cortices (Bookheimer et al., 2000), regions known to show early hypometabolism with AD (Ishii et al., 1997; Johnson et al., 2005; Minoshima et al., 1997; Mosconi et al., 2004; Salmon et al., 2005). Because these regions were shown previously to be sensitive to increased challenge to cognition (in the form of genetic risk), they were a particular focus of this study. We hypothesized that the fMRI patterns associated with increased vascular risk would resemble those seen with higher genetic risk for AD using a similar task.

2. Methods

2.1. Participants

All 30 volunteers were right-handed, cognitively intact (mean age 61.0 ± 10.3), and were selected initially from a pool of 62 potential volunteers recruited through advertisements and seminars without regard to ethnicity or race. All potential participants received neurological and psychiatric evaluations. Each subject underwent a full neuropsychological battery that included several tests of memory including the Wechsler Memory Scale Logical Memory Test and Verbal Paired Associates II, the Buschke-Fuld Selective Reminding Test (total recall), and the Rey-Osterreich Complex Figure Recall Test (delayed recall). Age-adjusted scores were determined for each subject on these tests based on standard normative values. Subjects who scored worse than one standard deviation below the mean for their age on more than two of these tests were classified as having mild cognitive impairment (MCI) and were excluded from the study. Subjects in the current study additionally were required to have a Mini Mental State Exam (MMSE) score of at least 27. From the pool of potential participants, we also excluded those having illnesses that could affect cognition as well as those who were left-handed, were on cholinergic drugs, or for whom cholesterol and/or blood pressure information was not available within 6 months of the fMRI date.

No subject had a known history of stroke or head trauma with loss of consciousness, or had evidence of a prior infarction or other abnormality on structural MRI except that seven participants had some evidence of white matter hyperintensities. Two of these had five or fewer unidentified hyperintensities of less than 5 mm each, one had neural loss and some demyelination without signs of ischemia, two had mild to moderate chronic small vessel ischemic changes, one had mild ischemic changes limited to the fronto-opercular region, and one had enlarged perivascular spaces with no sign of ischemia. Systolic blood pressure (sBP), but not BMI or total cholesterol, was significantly higher in participants in whom white matter hyperintensities were present (two-tailed t test; $p = 0.02$). No participant was diabetic.

Each potential subject underwent structural and functional MRI scanning, and an additional five were excluded from the study due to technically inadequate scans (total subject motion >2 mm or significantly correlated with task paradigm).

A registered nurse measured each subject's blood pressure after the subject had been supine or in a semi-fowler position for 10–15 min. Values recorded as high (greater than 140/90) or low (less than 100/60) were verified after a 10 min delay. Of the participants included in this study, two had stage I hypertension (140–159 mmHg), and the remainder were in the normotensive range. Three participants were considered obese (BMI > 29.9), and 14 had high total cholesterol (>200 mg/dL). Cholesterol was measured following a blood draw in the UCLA Clinical Research center. Blood was drawn at entry, but fasting was not required prior to the blood draws. Nearly half of the participants (14) were neither obese nor had sBP or total cholesterol outside the normal range. Systolic BP, total cholesterol level, and BMI were not significantly correlated with each other or with other variables that could potentially contribute to vascular risk or memory ability, such as gender, education, cognitive ability (as defined by MMSE score; Folstein et al., 1975), depression level (as defined by Hamilton Depression Battery; Hamilton, 1960), smoking status, or medication use (Table 1). Smoking status was defined as never smoked, light smoking for fewer than 10 years, or heavy smoking for greater than 10 years. Systolic BP was significantly correlated with diastolic BP ($r = 0.35$; $p = 0.05$). APOE genotype was available for 17 out of our 30 participants. Ten were APOE4+ (six with a known family history of AD) and seven were APOE4- (four with a known family history of AD). No scans from the current study were included in a previous study by Bookheimer et al. (2000), although three of the subjects included in the current study were also a part of the previous one.

The study was approved by the UCLA Human Subjects Protection Committee, and all participants gave written informed consent.

2.2. Imaging procedures

Whole brain fMRI scanning was administered using a gradient echo, echo planar scan sequence (Siemens Allegra 3T MRI) while the participants performed a verbal paired associates task (repetition time [TR] = 2500 ms; echo time [TE] = 35 ms; 3 mm slices/1 mm gap; 64×64 [3.1 mm $\times$ 3.1 mm] in-plane resolution; field of view [FOV] = 200×200 ; flip angle [FA] = 90°). We acquired high-resolution spin echo scans (TR = 5000 ms; TE = 33 ms; 128×128 [1.6 mm $\times$ 1.6 mm] in-plane resolution; FOV = 200×200 ; FA = 90° ; averages = 4) coplanar to the fMRI scans to aid in registration to a standard Montreal Neurological Institute (MNI) brain, allowing fMRI analysis to take place in standard space. We also performed whole brain structural Magnetization Prepared RAPid Gradient Echo (MPRAGE) T1 weighted volumetric scans (TR = 2300 ms; TE = 2.93 ms; 1 mm slices/0.5 mm gap; 256×256 [1.3 mm $\times$ 1.3 mm] in-plane resolution) for use in calculating hippocampal volumes, and a proton density/T2 weighted double echo structural scan for use in identifying white matter hyperintensities and other brain abnormalities.

2.3. Memory activation task

Subjects were tested using a verbal paired associates task shown to preferentially activate prefrontal, superior temporal, and inferior and superior parietal regions in those with a genetic risk for AD (Bookheimer et al., 2000). This task requires participants to learn pairs of words, and then to recall the second words in the pairs given the first as cues. The task was based on the Wechsler Memory Scale—revised verbal paired associates test (Wechsler, 1987). Because of scanner noise and a high percentage of older people with some degree of hearing loss, words were presented visually as well as auditorily.

We created alternate forms of the task using established normative data (Nelson et al., 2004) to match for average word frequency, length, and concreteness with the exception that no concreteness norms were available for two words in each list. Each list contained 4 two-syllable words and 10 one-syllable words combined into seven word pairs. Eleven of the 14 words in each list were nouns and 3 were adjectives. No word in any list was a free association norm of any other word in that list. One version of the task was used before scanning as a pretest designed to obtain behavioral data from each subject. Total correct retrievals for each subject were summed across their six trials to arrive at a total score out of a possible 42. During the scan, participants encoded seven pairs of unrelated words presented visually using MacStim presentation software (WhiteAnt Occasional Publishing). Each printed word was presented for 0.18 s followed by 0.82 s of blank screen. An additional 2 s separated the seven word pairs from one another. Each 30 s encoding block was followed by a 30 s distracter task (control task), included to discourage rehearsal, and involving a button press by the subject any time the symbol on the screen changed between a plus and a circle. In pilot scanning sessions this distracter task did not significantly change fMRI signal levels compared with viewing the fixation cross alone. During retrieval blocks, participants saw the first word of each word pair presented for 0.18 s. In the 3.82 s that followed, they attempted to recall the second word silently in order to avoid head motion associated with speaking aloud. Participants pressed buttons to indicate perceived success or failure at recalling the second word, and responses were recorded. After scanning, participants were tested verbally to assess learning of the stimuli. Word pair order was counterbalanced across trials. All visual word presentations were accompanied by simultaneous auditory presentations.

2.4. Functional data analysis

All functional data analyses were performed using the “Analysis Group at the Oxford Centre for Functional MRI of the Brain” (FMRIB) software library (FSL) tools. Skulls were first stripped automatically from each high-resolution spin echo coplanar scan using FSL’s Brain Extraction Tool (BET) (Smith, 2002). FSL’s FMRI Expert Analysis Tool (FEAT) was then used to perform individual preprocessing and statistical analysis of each participant’s fMRI scan as well as to perform group analyses. Preprocessing for each scan included brain extraction using BET and motion correction (Motion Correction using FMRIB’s Linear Image Registration Tool [MCFLIRT]) (Jenkinson et al., 2002) as well as registration of each functional scan to its corresponding coplanar high-resolution image using rigid body transformations, and to the MNI standard brain using linear transformation with 12 degrees of freedom. High-pass temporal filtering of 120 s was applied to the fMRI images, which were then spatially smoothed using a Gaussian smoothing kernel of 6 mm.

For aging studies in which the degree of brain atrophy is likely to be correlated with the variable of interest, as when older and younger groups are compared, it may not be appropriate to normalize scans to the MNI brain since fMRI results may be confounded by atrophy levels between groups. In order to determine whether brain atrophy among our cognitively intact older adults may have influenced our results, we ran statistical tests comparing our main variable of vascular health (sBP&BMI) (described in Section 2.5) with other variables related to brain atrophy. Specifically, we expected that those who are older, who have a family history of AD, or who have smaller hippocampal volumes relative to intracranial volume would have greater generalized brain atrophy. None of these measures was significantly correlated with sBP&BMI or fMRI activity in posterior cingulate and parietal cortex during encoding or retrieval (R^2 values ranged from 0.0006 to 0.08). Because of this, we have no reason to believe that atrophy levels unduly influenced our results. By using standard MNI space we have the additional benefit that we may report the standard coordinates of our peak activities, which may be useful to other researchers. We therefore chose to keep our results in standard MNI space.

2.5. Statistical comparisons

We performed statistical analyses on individual scans within FEAT using FMRIB's Improved Linear Model (FILM) (Woolrich et al., 2001), which applies the general linear model and uses non-parametric estimation of time series autocorrelation to remove estimated autocorrelation of noise between time points for each voxel. Analyses for fMRI contrasted activity during encoding (encoding blocks) and retrieval (retrieval blocks) of verbal paired associates with activity during control blocks. Using "FMRIB's Local Analysis of Mixed Effects" (FLAME) (Beckmann et al., 2003), we generated Z statistic images ($Z > 2.3$, cluster $p < 0.01$) of the combined individual fMRI activation results across participants. In order to establish which brain areas were active across subjects during encoding and retrieval, we obtained maps of statistically significant fMRI activation during those two processes. Next, we performed direct comparisons between encoding and retrieval blocks to ascertain whether these two processes were inherently different or could be grouped together in later contrasts. Finally, to test our primary hypothesis, we used three vascular risk factors (sBP, BMI, and total cholesterol) as covariates in the group analysis to investigate their possible correlations with the fMRI response. Because both higher sBP and BMI values were correlated with greater fMRI activation, we further investigated the effect on fMRI activation of these two variables together. To do this we correlated fMRI activity with a new covariate (sBP&BMI) equal to the sum of sBP and BMI together, with BMI normalized such that the normalized values were perfectly correlated with the unscaled BMI numbers ($R^2 = 1.0$), but shared the same range and similar variance as sBP (Brown-Forsythe test for equal variance $p = 0.54$). To calculate the normalized BMI numbers, we performed the following for each participant: BMI scaled = $((\text{BMI} - \text{BMI minimum}) \times (\text{sBP range}/\text{BMI range})) + \text{sBP minimum}$.

2.6. Region of interest analysis

Because past positron emission tomography (PET) studies of glucose metabolism have shown that posterior cingulate and parietal cortices are among the first to be affected by AD (Ishii et al., 1997; Johnson et al., 2005; Minoshima et al., 1997; Mosconi et al., 2004; Salmon et al., 2005), we performed a region of interest (ROI) analysis in these regions alone. To do this, first we obtained maps of areas that were more active in participants who had higher sBP&BMI. Next we segmented those maps such that areas of increased activation within the parietal lobe and posterior cingulate were represented by distinct masks. This created separate ROI masks for encoding and retrieval that represented areas within parietal and posterior cingulate cortices regions whose increases in activation were significantly correlated with higher sBP&BMI during the memory task. FSL featquery applied these group ROIs to individual functional scans in order to calculate fMRI percent signal change for each scan within each region. Lastly, we created graphs of fMRI percent signal change in those ROIs versus sBP&BMI. In order to examine the possible effect that medications to reduce sBP or total cholesterol or both (five total participants), or the presence of white matter lesions (seven participants) might have on this relationship, we then recalculated the correlations, first removing participants on BP or cholesterol medications, and next removing those with white matter lesions.

2.7. Structural analysis

To investigate whether our results were influenced by hippocampal atrophy, we calculated hippocampal volumes as a percentage of intracranial volume and correlated that value with average fMRI activity in our functionally defined parietal and posterior cingulate ROIs. A mask of the MPRAGE scan brain matter was automatically created using BET (Smith, 2002). The masks were then manually refined using "FSL view," and the completed masks were applied to exclude non-brain matter. Hippocampal ROIs were defined by a single rater in native space, using a modification of guidelines outlined previously (Pruessner et al., 2000). Hippocampal head, body, and tail were all included in one ROI. Because in our older subjects, size of the

lateral ventricles varied considerably, we did not use the lateral ventricles as a landmark to exclude the Andreas-Retzius gyrus as described previously (Pruessner et al., 2000). Instead, we defined that boundary in the sagittal slice, by excluding the apparent hippocampal tail on all slices medial to the last slice in which the parahippocampal gyrus inferior to the hippocampus was unbroken. Intra-rater test–retest reliability of seven hippocampal volumes yielded a Pearson's R^2 of 0.91, and an average percent error of 2.5%.

3. Results

In comparison to the distracter control task, both encoding and retrieval blocks on average produced increased fMRI signal broadly across the cortex, including in sensory input areas, anterior and posterior language areas, and working memory regions including dorsolateral prefrontal cortex (DLPFC) and parietal cortex (Table 2).

Direct comparisons of encoding and retrieval blocks showed that encoding the word pairs resulted in more fMRI activity in auditory and visual cortex and visual association areas than retrieving them did. Conversely, retrieval blocks elicited more activity than encoding blocks in an extensive network of brain regions including motor regions (related to button press response) and regions important in working memory, such as prefrontal cortex and parietal regions. Because encoding and retrieval differently recruited brain regions, we continued to evaluate them separately for the remainder of the study.

We next examined the effects of sBP, BMI, and total cholesterol on fMRI response during the encoding and retrieval of verbal paired associates by using these variables as covariates. Both sBP and BMI correlated significantly with the magnitude of fMRI response, but total cholesterol did not. Specifically, during encoding, participants with higher sBP showed significantly increased activations in areas important in language processing and memory: posterior cingulate gyrus, parietal regions (including precuneus, angular gyrus, and supramarginal gyrus), occipital lobe (lingual gyrus), and left superior temporal gyrus (Wernicke's area). During retrieval, as in encoding, participants with higher sBP showed increased activations in parietal regions, including precuneus and angular gyrus. Additionally, they showed more activation in left frontal regions, including Broca's area and DLPFC, suggesting increased influence on speech production, possibly due to subvocal responses required during the retrieval period of the task.

As in participants with higher sBP, those with greater BMI had significantly greater fMRI activation in posterior cingulate, precuneus, DLPFC, inferior frontal gyrus (Broca's area), and temporal cortex (Wernicke's area) during retrieval. In addition, participants with higher BMI showed more activation in anterior cingulate, inferior temporal lobe, middle occipital gyrus, and in midbrain (tectum), suggesting greater influence on the attentional and sensory processing systems than found with increased sBP.

In order to investigate a possible additive effect of higher sBP and BMI, we created a combined risk variable, sBP&BMI (see Section 2.5), which we used as a covariate in the group analysis (Table 3; Figs. 1 and 2). All of the regions showing increased activation during encoding or retrieval with higher sBP or BMI also did so with a higher sBP&BMI covariate except for inferior temporal gyrus and midbrain (whose activity had correlated only with increased BMI). In addition, greater fMRI signal was seen with increased sBP&BMI in certain other regions, most notably (during retrieval) in the hippocampus and parahippocampal gyrus, which are areas important in memory processes and known to be affected early by incipient AD. Because of the additive effect of sBP and BMI together and the similarities of the relationships between fMRI activations and both sBP and BMI, for the remainder of this paper, all mention of

correlations between vascular factors and fMRI activations will use the combined variable sBP&BMI, unless otherwise noted.

All brain regions that were preferentially activated with higher sBP&BMI during encoding were also preferentially active during retrieval. Several additional regions also were activated preferentially during retrieval, including hippocampus, parahippocampal gyrus, fusiform gyrus, and anterior cingulate gyrus. The increased activation during memory retrieval as compared to encoding is consistent with greater activity required to perform a more challenging task (Bookheimer et al., 2000).

Finally, because the posterior cingulate and parietal lobe are affected early in incipient AD, we examined the relationships between sBP&BMI and fMRI signal in those regions separately. The relationship between higher sBP&BMI and fMRI signal was evident in several regions (Table 3). However, we focused specifically on these two areas both to demonstrate an overlap in the area that shows functional changes both in early AD and with increased cardiovascular risk, and to show that our results were not being driven by outlying data points. The relationships were consistent across the range of values, holding true for participants at vascular risk as well as for those in the healthy range of sBP&BMI (Fig. 3). Age, performance on the scanner task, and hippocampal volumes were not significantly correlated with sBP&BMI or with fMRI activity in posterior cingulate and parietal cortex. Multiple regressions showed that the individual contribution of sBP&BMI to fMRI activity in this region remained significant during retrieval after controlling for age ($p = 0.002$) and performance ($p = 0.001$), but our omnibus F significances were reduced to trends when age and performance modified our weaker results during encoding. After controlling for hippocampal volumes, the individual contribution of sBP&BMI remained significant during both encoding ($p = 0.000048$) and retrieval ($p = 0.000051$).

We next used ANCOVA to evaluate the influence of AD risk on our results by investigating the interactions between known family history of AD or APOE genotype and sBP&BMI while predicting fMRI activity in posterior cingulate and parietal cortex. The relationships between sBP&BMI and fMRI activity were not significantly different in those with or without a known family history of AD (interaction $p = 0.07$ for encoding; $p = 0.98$ for retrieval). The same was true when we controlled for possession of the APOE4 allele in the 17 subjects for whom genotype was known (interaction $p = 0.91$ for encoding; $p = 0.73$ for retrieval).

As discussed in Section 2.6, we performed the ROI analysis again, first excluding participants who were taking drugs to treat high blood pressure or cholesterol. Our R^2 values remained significant ($R^2 = 0.57$, $p = 0.00001$ for both encoding and retrieval) without the medicated participants included in the analysis.

Next, we repeated the ROI analysis, excluding those who had any white matter lesions. Without those participants included, the relationship between sBP&BMI and fMRI activation in the parietal and posterior cingulate cortices remained significant ($R^2 = 0.48$, $p = 0.0002$ for encoding; $R^2 = 0.39$, $p = 0.001$ for retrieval).

4. Discussion

We found that in older, cognitively intact adults, fMRI activation during a verbal memory task was higher in several task-related brain regions in participants who had higher sBP&BMI, even within the normal ranges of these variables. These regions included frontal lobe, temporal lobe, precuneus, and posterior cingulate cortex. Our whole brain results are in keeping with a recent study focusing solely on medial temporal lobe that similarly found increased fMRI signal in older adults having increased risk for stroke (Bangen et al., 2007).

In our study, the frontal regions that correlated with sBP&BMI were left-lateralized during encoding, in keeping with the well-known hemispheric encoding/retrieval asymmetry (HERA) model (Tulving et al., 1994). Unlike during encoding, the correlated activations we saw in the frontal lobe during retrieval were bilateral, and so did not display the typical lateralized pattern described by the HERA model. However, the frontal activation bilaterality during retrieval is consistent with the hemispheric asymmetry reduction in older adults (HAROLD) model, which describes reduced frontal asymmetry of activation in older adults (Cabeza et al., 1997; Cabeza, 2002). Similarly, in our study, sBP&BMI was correlated with medial temporal activation during retrieval, but not during encoding, although memory encoding has reliably elicited medial temporal lobe (MTL) activity previously (Wagner et al., 2005). In aging populations, however, lack of MTL activation during encoding has been documented (Grady et al., 1995), as found in the current study.

Our results suggest that increased cardiovascular risk is associated with changes in brain function during a memory task even within the normal ranges of sBP and BMI, before memory ability is altered, and independent of hippocampal volume. These findings raise interesting questions about what are acceptable levels of cardiovascular risk and to what extent such related changes to brain activation are reversible.

Various studies in past years have examined brain function at rest by performing meta-analyses across PET or fMRI studies and comparing regions that deactivate during the active condition across a number of tasks. As a result of these studies, a network of brain regions has emerged that is more active during the resting state than during the test condition. This network has reliably included precuneus, posterior cingulate, inferior parietal lobule, anterior cingulate, DLPFC, and medial frontal regions (Mazoyer et al., 2001; McKiernan et al., 2003; Shulman et al., 1997), regions that in the current study all showed more activity during the memory task than during the control task in participants with higher sBP&BMI. Therefore, it is possible that the perceived increases in activation we found with higher sBP&BMI actually relate to greater reduction of activity during the control task, in other words, a reduced resting state in those areas.

Hypertension and obesity are both risk factors for coronary artery disease, and possibly cerebrovascular disease as well (Isozumi, 2004). Additionally, hypertension has been associated with reduced regional cerebral blood flow in healthy adults at rest (Meyer et al., 1985; Sinha et al., 2005). One previous study that used ^{15}O -water tracer PET to measure regional cerebral blood flow found that hypertensive participants had reduced overall cerebral blood flow compared with normotensive participants (Jennings, 2003). However, unlike in the current study, the authors of that study found that during a memory task, blood flow in posterior parietal cortex was depressed compared with normotensive participants who activated readily in that area (Jennings, 2003). The current study, however, largely includes normotensive and non-obese participants, while the previous study compared hypertensive and normotensive participants. One possible model that would accommodate both studies involves a linear regional decrease in blood flow at rest due to mild arterial changes as sBP increases through a normal range, but a compensatory increase in blood velocity during the task such that available oxygen then mirrors that seen in participants having lower sBP&BMI. The result would be an overall apparent increase in regional activity in those with more cardiovascular risk. Such compensatory effects have been proposed in cognitive aging literature previously (Bondi et al., 2005; Bookheimer et al., 2000; Dickerson et al., 2004; Garrido et al., 2002; Johnson et al., 2000). With further increases in sBP, however, the arterial changes frequently associated with hypertension (such as hardening and plaque deposits) might decrease regional blood flow to the extent that compensation can no longer occur in those same regions, even during the task, and net signal change appears small, as shown previously (Jennings, 2003).

Parietal and posterior cingulate cortices are among the first regions to show signs of hypometabolism or hypoperfusion in AD (Ishii et al., 1997; Johnson et al., 2005; Minoshima et al., 1997; Mosconi et al., 2004; Salmon et al., 2005). In normal, healthy older adults, genetic risk for AD is also associated with blood flow and glucose metabolism changes in these same brain regions, suggesting that changes occur prior to onset of the disease (Drzezga et al., 2005; Reiman et al., 2004, 2005; Small, 1996). We have no way of knowing which, if any, of our subjects will eventually decline cognitively, but the overlap in areas of differential activation in both vascular risk and AD risk suggests a possible vehicle by which the two types of risk might interact in some older adults, as shown in many studies between high midlife sBP or BMI and later AD risk (Gustafson et al., 2003; Kivipelto et al., 2002, 2005; Launer et al., 2000; Skoog et al., 1996; Swan et al., 1998; Wu et al., 2003; Yamada et al., 2003). If a decreased resting state does indeed underlie our results, the link between vascular health and risk for AD found in some past studies may be explained by an overlap of areas associated with AD risk and vascular health risk. Vascular health-related decreases in resting state activity occurring in regions that are later depressed by AD could compound AD effects, perhaps making symptoms evident at an earlier age. The task we used in the current study includes control activity and the task activity, but no true “resting state” periods. Because any activity during our control task is necessarily compared with activity during the memory task, it is not possible to separate the effects of each in order to determine whether resting state activity was, in fact, correlated with vascular risk factors.

Finally, it is possible that rather than being specific to cardiovascular risk or to AD risk, the overlapping patterns of fMRI activation seen with cardiovascular risk in this study and previously with genetic risk for AD (Bondi et al., 2005; Bookheimer et al., 2000) are indicators of compensation for challenges to the memory processes in general, which may or may not be progressive. Such compensation for cognitive decline may be characterized initially by increased recruitment of brain regions to augment cognitive resources. Only future longitudinal study will help to elucidate these relationships.

Our participants were recruited by UCLA’s Memory and Aging Clinic. Volunteers having a family history of dementia are naturally drawn to these studies, and in this current group of thirty participants, only ten had no known direct family history of AD (parent, grandparent, or sibling). Because of this, our results may be generalizable only to those with an increased risk for AD. However, a recent study including subjects who largely were not known to have increased AD risk found increased fMRI activity in medial temporal lobe with increased stroke risk (Bangen et al., 2007), suggesting that, in that region at least, the results are not specific to those with increased AD risk. Future whole brain studies having AD risk that is more representative of the general population than the current study are necessary to determine whether all of these results apply to the population at large.

We did not find a significant correlation between sBP&BMI and fMRI activity in primary sensory cortex, such as auditory or primary visual cortices, although both regions were engaged during the task. We did, however, see correlations between this measure and fMRI activity in motor cortex. It is therefore unclear how specific our results were to memory processes. Future studies that covary vascular health measures with fMRI activity using motor and sensory processing tasks would test this question more directly.

One goal of this study was to examine the relationships between vascular health risks and fMRI activity during a memory task across a mostly healthy range of vascular risk factors. We found that the correlations between sBP&BMI and fMRI activity were not driven solely by vascularly at risk outliers, but were evident across participants in the healthy ranges of sBP and BMI as well. This suggests that in these brain regions, sBP and BMI interact with fMRI activity as continuous variables. Therefore, separating participants into vascular risk versus no risk may

mask such effects, as participants on either side of this somewhat arbitrary boundary would almost certainly be similar to one another.

We did not find a significant correlation between total cholesterol and fMRI activity during the memory task. It is possible that the effect of cholesterol is not distributed continuously as are the effects of sBP and BMI. Alternately, the brain response may have been more sensitive to the individual components of total cholesterol (HDL and LDL), which were not available to us. Lastly, caution must be taken in interpreting our cholesterol results since some of our subjects had their cholesterol tested without first having fasted, which may have affected the results.

Our results demonstrate that even within the normal range, certain vascular health risks in older, cognitively intact adults are correlated with increased fMRI activity during a memory task in regions similar to those showing greater activity in adults having increased AD risk. This study raises the question of how vascular risk and cognition may be associated, and provides a starting point for future studies aimed at investigating these relationships further.

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Fig. 1. Correlation of fMRI activity with sBP&BMI during encoding, shown in (A) axial and (B) sagittal. During encoding, those with higher sBP&BMI had more activation in a number of posterior cingulate, parietal, frontal, and temporal lobe regions important in memory processes, and known to be affected by Alzheimer's disease. Images are shown in radiological convention (left = right).

Fig. 2. Correlation of fMRI activity with sBP&BMI during retrieval, shown in (A) axial and (B) sagittal. During retrieval blocks, those with higher sBP&BMI had increased activation in the same areas that showed increased activity during encoding, and notably, in additional areas important to memory, such as hippocampus, parahippocampal gyrus, and fusiform gyrus. Images are shown in radiological convention (left = right).

Fig. 3.

Correlation of sBP&BMI with fMRI percent signal change in posterior cingulate and parietal regions. Graphs depict the relationships between sBP&BMI and fMRI percent signal change in posterior cingulate and parietal regions during (A) encoding and (B) retrieval. The region of interest was selected by including only posterior cingulate and parietal regions identified as being significantly correlated with sBP&BMI. Only those whose sBP&BMI variable exceeds 270 are either obese or hypertensive (five subjects).

Table 1

Demographic and clinical characteristics of the participants

# Participants	30
Men/women	10/20
Age	61.0 ± 10.3 (42–77) ^a
Education (years)	16.5 ± 3.0 (12–24) ^a
# Having family history of AD	20 ^b
Mini Mental State Exam (MMSE) (Folstein et al., 1975)	29.1 ± 9.0 (27–30) ^a
National Adult Reading Test (NART full IQ) (Nelson and Willison, 1991)	114.5 ± 7.4 (93–123) ^a
Hamilton Depression Battery (HAM-D) 21 item (Hamilton, 1960)	2.9 ± 3.4 (0–13) ^a
fMRI task score (verbal paired associates) (42 possible score)	30.0 ± 8.9 (13–42) ^a
BMI	23.5 ± 3.8 (16.2–31.1) ^a
Systolic BP (mmHg)	120.6 ± 16.6 (91–159) ^a
Total cholesterol (mg/dL)	198.0 ± 38.0 (126–277) ^a
# Users of anti-depressive drugs	2 ^c
# Users of anti-hypertensive drugs	3 ^d
# Users of statin drugs	4 ^d
# Regular users of non-steroidal anti-inflammatory drugs	9

^aDemographic and clinical features are listed as mean ± standard deviation (range).

^bIncludes parents, grandparents, or siblings.

^cFor mild depression, stable at the time of scanning.

^dTwo participants were taking both anti-hypertensive drugs and statins.

Table 2

Average fMRI activations during memory task

	Sample MNI coordinates encoding	Maximum Z scores encoding	Sample MNI coordinates retrieval	Maximum Z scores retrieval
Cingulate				
Anterior cingulate cortex	-6, 16, 38	5.42	12, 26, 28	6.52
Posterior cingulate cortex	-6, -46, 12	3.48	-2, -38, 24	4.84
Parietal				
Precuneus	-24, -78, 44	4.43	-10, -74, 50	4.70
Inferior parietal lobule	-30, -54, 36	6.57	-30, -54, 36	6.58
Temporal				
Superior temporal g.	-46, -34, 6	7.16	-46, -34, 6	6.22
Middle temporal g.	-62, -36, 6	7.58	-60, -38, -2	6.43
Parahippocampal g.	-30, -30, -22	5.27	-30, -28, -26	4.02
Hippocampus	-36, -24, -12	4.54	-30, -20, -8	4.36
Frontal				
DLPFC	-46, 6, 24	7.30	-48, 6, 24	7.18
Inferior frontal g.	-42, 14, 22	7.84	-38, 18, -10	6.48
Precentral g.	-48, -2, 44	7.09	-48, -2, 38	7.79
Occipital	26, -88, 12	5.70	-10, -76, 6	5.77
Brainstem			-2, -32, -18	6.20
Striatum			-14, 0, 20	5.98
Thalamus			-4, -16, 12	5.62
Cerebellum			-6, -58, -18	5.32

Functional MRI activity during encoding and retrieval blocks was compared with activity during control blocks. Regions with statistically significant activity increases ($Z = 2.3$; cluster $p < 0.01$) were identified based on the MNI atlas.

Table 3

Increased activation associated with larger sBP&BMI covariate during encoding and retrieval

	Brodman area	Sample MNI coordinates encoding	Maximum Z score encoding	Sample MNI coordinates retrieval	Maximum Z score retrieval
Cingulate					
Anterior cingulate cortex	32			-8, 30, 30	3.87 ^a
Posterior cingulate cortex	30, 31	22, -56, 20	3.47	-10, -44, 30	4.08 ^b
Parietal					
Precuneus	7, 31	-14, -62, 22	4.06	12, -60, 32	3.75 ^b
Supramarginal g.	40	-52, -54, 46	3.10	-46, -56, 38	2.35 ^c
Superior parietal cortex	7	24, -72, 58	4.93	22, -68, 58	3.19
Temporal					
Superior temporal g.	22, 39	-68, -50, 10	3.80	-46, -50, 28	3.03 ^c
Middle temporal g.	21, 37	-60, -32, 0	3.85	-40, -56, 6	4.04 ^a
Parahippocampal g.	36			-16, -28, -18	2.50
Hippocampus				-26, -22, -10	3.55
Fusiform g.	37			-24, -40, -18	3.55
Frontal					
DLPFC	9	-46, 12, 24	4.23	-8, 32, 32	4.26 ^b
Middle frontal g.	6, 8	-44, 22, 38	3.08	0, 18, 44	3.47
Inferior frontal g.	44, 45, 47	-54, 8, 18	3.23	-54, 12, 20	3.62
Precentral g.	4			20, -16, 50	3.71 ^a
Occipital	7	-10, -72, 30	3.57	-8, -70, 30	4.14 ^b
Pons				-2, -28, -26	4.26
Cerebellum				-10, -40, -26	2.98

^aRegion also showed increased activation for higher BMI alone, but not for higher sBP.^bRegion also showed increased activation for higher sBP and BMI considered separately.^cRegion also showed increased activation for higher sBP alone, but not for higher BMI.