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Inverse Correspondence Between Hippocampal Perfusion and Verbal Memory Performance in Older Adults

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Abstract

Understanding physiological changes that precede irreversible tissue damage in age-related pathology is central to optimizing treatments that may prevent, or delay, cognitive decline. Cerebral perfusion is a tightly regulated physiological property, coupled to tissue metabolism and function, and abnormal (both elevated and reduced) hippocampal perfusion has been reported in a range of cognitive disorders. However, the size and location of the hippocampus complicates perfusion quantification, as many perfusion techniques acquire data with spatial resolution on the order of or beyond the size of the hippocampus, and are thus suboptimal in this region (especially in the presence of hippocampal atrophy and reduced flow scenarios). Here, the relationship between hippocampal perfusion and atrophy as a function of memory performance was examined in cognitively normal healthy older adults ($n = 20$; age = 67 ± 7 yr) with varying genetic risk for dementia using a custom arterial spin labeling acquisition and analysis procedure. When controlling for hippocampal volume, it was found that hippocampal perfusion correlated inversely ($P = 0.04$) with memory performance despite absent hippocampal tissue atrophy or white matter disease. The hippocampal flow asymmetry (left hippocampus perfusion–right hippocampus perfusion) was significantly ($P = 0.04$) increased in *APOE*- $\epsilon 4$ carriers relative to noncarriers. These findings demonstrate that perfusion correlates more strongly than tissue volume with memory performance in cognitively normal older adults, and furthermore that an inverse trend between these two parameters suggests that elevation of neuronal activity, possibly mediated by

neuroinflammation and/or excitation/inhibition imbalance, may be closely associated with minor changes in memory performance.

Keywords

cerebral blood flow; cortical volume; dementia; arterial spin labeling; magnetic resonance imaging

INTRODUCTION

Understanding physiological changes that precede irreversible tissue damage in disease is central to developing and optimizing treatments that may prevent, or delay, cognitive decline. It is well documented that the hippocampus is one of the first brain regions to be damaged in many disorders, including Alzheimer's disease (AD)-related dementia, epilepsy, and schizophrenia, and changes in hippocampal structure and function have been implicated to varying extents during the clinical progression of these conditions (Ishii et al., 1998; De Santi et al., 2001; Van Paesschen, 2004; Alsop et al., 2008). However, limited information is available on subtle changes in hippocampal function that may precede clinical disease and to what extent such functional aberrations are a cause, or a consequence, of disease.

More specifically, perfusion, or the rate of microvascular blood delivery to tissue, is a tightly regulated physiological parameter, responsible for delivery of glucose and oxygen to tissue and one of the key parameters (together with the cerebral metabolic rate of oxygen consumption, CMRO₂) that modulate contrast in commonly utilized blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI). Changes in perfusion, even within an anticipated healthy range, can, therefore, reflect the efficiency of very basic metabolic processes and potentially early stages of dysfunction. Even in the absence of direct relevance to pathology, changes in baseline perfusion can influence BOLD fMRI contrast (Buxton et al., 1998; Liu et al., 2004; Donahue et al., 2009), and therefore, understanding this parameter is of fundamental relevance to the majority of cognitive aging studies in humans that use BOLD fMRI to stratify participants (e.g., diseased vs. healthy).

Despite a large literature on cortical blood flow, quantification of perfusion in the hippocampus is relatively difficult. The main reason for this is that the gold-standard for quantitative perfusion imaging in vivo is H₂ ¹⁵O positron emission tomography (PET) (Raichle, 1981); while quantitative, PET perfusion imaging has generally been performed at a spatial resolution (or following spatial smoothing) of 5–10 mm, which introduces large partial volume effects in subcortical structures such as hippocampus, which tend to have a cross-sectional length of 4–8 mm. Other approaches using single photon emission computed tomography frequently suffer from similar spatial resolution limitations, as well as tracer uptake saturation effects (Tsuchida et al., 1996). These limitations are made more severe when applied to subjects where tissue atrophy may be implicated, and indeed, there is much disparity in the literature as to whether hippocampal hypoperfusion, or hyperperfusion, is present in memory-disordered patients (De Santi et al., 2001; Matsuda et al., 2002; Mevel et al., 2007). Importantly, both situations could exist to varying extents: hypoperfusion could be attributable to slight hypoxia and/or reduced tissue demand secondary to cell death, whereas hyperperfusion could be indicative of inefficient metabolic substrate processing or hippocampal hyperactivity, potentially instigated by excitation-inhibition imbalance, and requiring additional hemodynamic resources (Buzsaki et al., 2007; Filippini et al., 2009; Quiroz et al., 2010; Limon et al., 2012).

Here, we more thoroughly investigated the relationships between hippocampal structure and perfusion, memory performance, and genetic dementia predisposition in healthy older

adults. To accomplish this, we used arterial spin labeling (ASL) (Detre et al., 1992; Williams et al., 1992; Buxton, 2005; Donahue et al., 2012), a noninvasive MRI approach capable of quantifying perfusion at a spatial resolution (3–4 mm) at or below the hippocampal cross-sectional length. We first ensured the reproducibility of this technique in hippocampus in healthy adults, after which we implemented this method as part of a multifaceted protocol including ASL MRI, T₁-weighted (T1w) and fluid attenuated inversion recovery (FLAIR) structural MRI, verbal memory evaluation, and genetic testing (apolipoprotein E- ϵ 4, *APOE*- ϵ 4 carrier status). The hypothesis to be investigated was that hippocampal perfusion will correlate more strongly with memory performance than anatomical features such as hippocampal volume and white matter lesions/hyperintensities. The findings report a careful perfusion experiment and analysis approach for reproducibly calculating hippocampal perfusion and extend recent results regarding hippocampal perfusion patterns in early AD patients (Alsop et al., 2008) to cognitively normal older adults more generally, which should be of use as an exemplar for identifying abnormal hippocampal perfusion patterns in more focused studies of age-related pathology.

MATERIALS AND METHODS

Subject Recruitment

The reproducibility of the ASL perfusion calculations was assessed first in young, healthy volunteers ($n = 7$; age = 29 ± 6 yr; M/F: 1/6), after which older healthy volunteers ($n = 20$, age = 67 ± 7 yr, M/F: 6/14) with no history of cerebrovascular disease or mental illness were enrolled in a study that included cognitive testing, genetic testing, and MRI. All participants provided informed, written consent as part of this HIPAA-compliant, IRB-approved study. Subject demographics are outlined in Table 1.

Cognitive Testing

Older volunteers underwent a neurocognitive battery including the Mini-Mental State Exam (MMSE) (Bleeker et al., 1988) and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Immediate (CERAD-I), Delay (CERAD-D), and Recognition (CERAD-R) exams (Morris et al., 1988). The CERAD (Morris et al., 1989; Mirra et al., 1991; Davis et al., 1992) has standardized procedures to evaluate memory performance with higher performance indicating better memory (Maximum scores for CERAD-I:30, CERAD-D and CERAD-R: 10). Encoding (CERAD-I) and retrieval (CERAD-D) rely on an intact cortical interaction between prefrontal regions and hippocampus. Although there are many memory measures to choose from, the CERAD was used because it is known to provide a large range of scores, even in volunteers with clinically normal memory performance, and it is not confounded by other cognitive domains such as executive functioning or semantic categorization strategies (e.g., California Verbal Learning Test). Additionally, we performed the MMSE (Folstein et al., 1975) to ensure that volunteers did not meet clinical criteria for dementia (defined by MMSE < 27).

Genetic Testing

Saliva samples were acquired from all older volunteers using Oragene DNA kits (DNA Genotek Inc., Ontario, Canada) and were processed at the Vanderbilt Center for Human Genetics Research. Genotyping was conducted using Taqman assays (rs7412 and rs429358) to identify carrier status for *APOE*- ϵ 2, - ϵ 3, and - ϵ 4 alleles. A total of 15 out of 20 volunteers agreed to provide this sample.

MRI

All participants underwent one MRI scanning session on a 3T Philips Achieva scanner (Philips Medical Systems, Best, The Netherlands) with body coil transmission and eight-channel SENSE array coil reception. For the young, healthy volunteers involved in the preliminary reproducibility study, the entire MRI protocol was repeated twice within the same scan session to assess within-subject reproducibility.

Structural imaging—Structural imaging consisted of both T_1 -weighted (T_1w) anatomical imaging for tissue volume quantification and coregistration, and T_2 -weighted (T_2w) FLAIR MRI for white matter hyperintensity classification. T_1w : 3D turbo field echo (TFE), spatial resolution = $1 \times 1 \times 1 \text{ mm}^3$, slices = 150, flip angle = 8° , TR/TE = 8.8/4.6 ms. FLAIR: 2D turbo spin echo (TSE; axial acquisition), spatial resolution = $0.9 \times 0.9 \times 1 \text{ mm}^3$, TR/TE = 11000/120 ms.

Perfusion imaging with ASL—A pseudo-continuous ASL (pCASL) protocol was implemented with optimized labeling duration ($\tau = 1650 \text{ ms}$) and postlabeling delay ($w = 1650 \text{ ms}$). Other imaging parameters: single-shot 2D echo planar imaging readout, spatial resolution = $3.5 \times 3.5 \times 7 \text{ mm}^3$, slices = 15, vascular crusher gradients, and averages = 15. The labeling slice was placed 83 mm proximal (inferior) to the center of the imaging volume, and background suppression was not used to avoid the postlabeling delay varying with the slice number in the 2D readout.

Analysis

Structural quantification—For cortical gray matter volume calculations, FreeSurfer (Athinoula A. Martinos Center, Boston, MA, USA) was applied to the T_1w data, and the calculated hippocampal volume was normalized by the intracranial volume (ICV) on a subject-by-subject basis (Fischl and Dale, 2000). White matter lesion count was recorded from the FLAIR data, which was quantified visually by a neuroradiologist.

Perfusion quantification—All ASL data were corrected for motion using standard affine registration routines. Subsequently, the difference between Control and Label ASL acquisitions was calculated after which the mean difference image ($\Delta M = \text{Control} - \text{Label}$) was recorded. Next, perfusion (f ; ml/g/s) was calculated from the ΔM images using (Wang et al., 2002),

$$f = \frac{\Delta M \lambda}{2M_0 \alpha \left[\frac{e^{-\delta R_{1,a}}}{R_{1,app}} \left(e^{(\delta-w)R_{1,app}} - e^{(\delta-\tau-w)R_{1,app}} \right) \right]} \quad (1)$$

where, M_0 is the equilibrium brain tissue magnetization, $\alpha = 0.85$ is the labeling efficiency (Wu et al., 2007), $\lambda = 0.9 \text{ (ml/g)}$ is the blood/tissue water partition coefficient (Herscovitch and Raichle, 1985), $\delta \approx 1.5 \text{ s}$ is the transit time from the labeling region to the tissue compartment (MacIntosh et al., 2010), $R_{1,a} \approx 0.59 \text{ s}^{-1}$ is the longitudinal relaxation rate of blood water at 3.0T (Lu et al., 2004), $\tau = 1.65 \text{ s}$ is the labeling duration, $w = 1.65 \text{ s}$ is the postlabeling delay, and $R_{1,app} = R_1 + f/\lambda$ where $R_1 \approx 0.83 \text{ s}^{-1}$ is the longitudinal relaxation rate of hippocampal brain tissue (in the absence of perfusion).

Following perfusion quantification, ASL data were coregistered to the subject's native T_1 space (Jenkinson et al., 2002), and the subject-specific hippocampal masks from the FreeSurfer output were applied to enable perfusion quantification only within these regions, separately for right and left hippocampi. This procedure was chosen rather than coregistration to standard brain atlases to account for differences in hippocampal sizes

between subjects, which could bias the perfusion calculation as is the case when a single standard brain atlas is used.

Statistical Approach

For the reproducibility study, the primary statistical objective was to assess the voxel-wise correlation of hippocampal perfusion measures between each of the scan sessions. To achieve this, we calculated standard descriptive statistics, including means and standard deviations for each of the scan sessions, as well as the intraclass correlation coefficient (ICC) for each of the seven subjects and associated P -value. $P < 0.05$ was required for the measurement to be deemed sufficiently reproducible.

The primary statistical objective of the memory study in the older adults was to assess the correlation between hippocampal perfusion and memory performance, as calculated using the CERAD-I exam. A secondary objective was to assess the correlation between hippocampal volume and the CERAD-I exam, separately in left and right hippocampi. The Pearson correlation coefficient and corresponding P -value (one-tail) was calculated to test the above hypotheses, with the requirement $P < 0.05$ for significance. For group comparisons, an unpaired Student's t -test accounting for unequal variances was used with the requirement $P < 0.05$ for significance. Finally, a contingency aim was to assess whether any trends in the above hypotheses differed for volunteers who were carriers of the *APOE*- $\epsilon 4$ allele. Therefore, subjects for which *APOE*- $\epsilon 4$ status was available were grouped as noncarriers, and carriers of the *APOE*- $\epsilon 4$ allele.

RESULTS

Reproducibility Study

In young, healthy volunteers hippocampal perfusion was found to be 35.6 ± 5.6 ml/100 g/min. The average standard deviation between all two measurements in the same scan for each volunteer was 4.0 ml/100 g/min. The ICC between sequential scans = 0.80 ($P = 0.03$), demonstrating that the ASL perfusion measurement in the hippocampus provided acceptable reproducibility.

Hippocampal Perfusion in Older Adults

Figure 1 shows (a) representative slices from the T_1w structural image, along with (b) the perfusion maps from the same slices, and (c) axial perfusion data for all slices for a representative subject (61 yr/F).

Figure 2 shows the coronal, sagittal, and axial slices depicting the left and right hippocampus for a representative subject. The subject specific hippocampus mask is overlaid on the T_1w scan, and the hippocampal perfusion map is shown. Note that in this procedure, the hippocampus mask is calculated on a subject-specific basis and differences in hippocampal size are, therefore, taken into account.

The mean MMSE and CERAD scores for all 20 subjects were 29.6 ± 0.7 and 21.2 ± 3.9 , respectively (Table 1). As expected, the MMSE results showed little variability in this population, and therefore, the CERAD-I results, which showed a much larger range of variability (min = 14; max = 28), were the subject of the correlative study.

Figure 3 shows the results from the hippocampal perfusion and CERAD-I analysis. CERAD-I was found to be negatively correlated with baseline hippocampal perfusion ($R = -0.41$; $P = 0.04$) in the absence of any statistically significant correlation with total hippocampal volume ($R = 0.24$; $P = 0.15$). Therefore, hippocampal perfusion was more

strongly (inversely) correlated with memory performance than was hippocampal volume. A trend for a positive correlation between left hippocampal volume and CERAD-I was found, which was not preserved when the right hippocampal volume was considered (left: $R = 0.34$, $P = 0.07$, right: $R = 0.02$, $P = 0.46$). Perfusion in both the left ($R = -0.35$; $P = 0.07$) and right ($R = -0.36$; $P = 0.06$) hippocampus considered separately showed a strong trend for a correlation with CERAD-I.

Carriers vs. Noncarriers

The CERAD-I scores between the *APOE*- $\epsilon 4$ carriers and noncarriers were found to be significantly different (carriers: 23.3 ± 3.3 , noncarriers: 19.3 ± 4.2 , $P = 0.03$), but the MMSE scores were not different (carriers: 29.4 ± 1.0 , noncarriers: 29.1 ± 0.9 , $P = 0.24$). Additionally, the hippocampal flow asymmetry (left hippocampus perfusion–right hippocampus perfusion) was significantly ($P = 0.04$) different between the two groups (Fig. 4), with elevated left hippocampal perfusion being modestly associated with improved CERAD-I performance. There was no significant difference ($P = 0.31$) between the total hippocampal volumes (normalized by ICV) of carriers (0.77 ± 0.05) and noncarriers (0.76 ± 0.04) nor between the individual hippocampi (right hippocampal volume in *APOE*- $\epsilon 4$ carriers, noncarriers = 0.38 ± 0.02 , $P = 0.49$), left hippocampal volume in *APOE*- $\epsilon 4$ carriers = 0.39 ± 0.04 , *APOE*- $\epsilon 4$ noncarriers = 0.38 ± 0.02 , $P = 0.25$)

FLAIR White Matter Hyperintensities

The white matter hyperintensities as quantified from the FLAIR data showed a large range of variability between subjects (min count = 1; max count = 44) and did not correlate with the CERAD I scores. There was no significant trend for a relationship between the number of white matter hyperintensities and hippocampal perfusion ($R = -0.22$, $P = 0.19$) nor hippocampal volume ($R = 0.06$, $P = 0.41$). The hyperintensities were categorized based on their location into periventricular hyperintensities (PVH) and temporal lobe hyperintensities (TLH). The number of PVH and TLH correlated strongly (PVH: $P < 0.01$, TLH: $P = 0.01$) with the total hippocampal volume asymmetry, while hippocampal perfusion asymmetry showed a strong trend for a correlation with PVH ($P = 0.07$) and TLH ($P = 0.05$). When the subjects were categorized into carriers and noncarriers, all subjects that exhibited PVH and TLH were carriers of the *APOE*- $\epsilon 4$ allele.

DISCUSSION

The major finding of this study is that in older adults with no history of cerebrovascular disease, cognitive impairment, or mental illness, hippocampal perfusion was found to be inversely correlated with memory performance as assessed using the CERAD-I exam. A secondary finding of this work is that the effect size between memory (CERAD-I) and hippocampal perfusion, measured as Pearson's correlation coefficient, was stronger ($r = -0.41$) than the effect size between memory and hippocampal size ($r = 0.24$). This suggests that perfusion, rather than structure, may be a more sensitive indicator of memory performance and early stages of memory decline. These findings are particularly intriguing because elevated hippocampal perfusion was associated with poorer memory performance, whereas the opposite trend might have been expected. However, recent work in early stage AD has demonstrated similar hyperperfusion in hippocampus and other medial temporal structures (Alsop et al., 2008). Our work is an extension of this study in which volunteers only at-risk for memory disorders and cognitive decline were considered, yet similar findings were observed. While speculative, these findings could be explained in terms of inefficient hippocampal processing and thereby the requirement for more hemodynamic and metabolic resources to meet demand. Alternatively, elevation of neuronal activity could be attributed to minor excitation-inhibition imbalance (Dickerson, 2006; Buzsaki et al., 2007).

For example, while glutamatergic (GLUergic) neurons are largely expected to control perfusion through a proportionally larger energy budget relative to γ -aminobutyric acid (GABA)-ergic interneurons (as well as GABAergic interneurons being supported more significantly by oxidative phosphorylation), increased GLUergic activity relative to GABAergic activity could provide an explanation for this finding, and indeed GABAergic activity has been found to be suppressed in memory disorder patients (Limon et al., 2012).

When volunteers were grouped on the basis of *APOE*- ϵ 4 status, even in the relatively small volunteer population studied, the CERAD-I scores were found to be higher in noncarriers, relative to carriers. White matter hyperintensities especially, the PVH and TLH were present only in the carrier group and correlated strongly to the hippocampal volume and perfusion asymmetry but not with the CERAD scores. Furthermore, hippocampal perfusion, not volume, was significantly different between these two groups. The carrier group showed hyperperfusion of the right hippocampus (41.8 ± 10.4 ml/g/min) compared to the left hippocampus (35.0 ± 7.1 ml/g/min, noncarriers: right hippocampus = 34.1 ± 9.5 ml/g/min, left hippocampus = 34.4 ± 7.2 ml/g/min). These findings are consistent with recent work using BOLD fMRI as a surrogate for neuronal activity, in which *APOE*- ϵ 4 carriers were found to have increased connectivity in key brain regions of default mode network decades before symptoms of memory impairment would be expected to commence (Dickerson and Sperling, 2008; Filippini et al., 2009; Wolk and Dickerson, 2011).

H_2 ^{15}O PET and MRI (Whatmough and Chertkow, 2007; Heo et al., 2010) measurements during memory tasks have found similar negative correlations in healthy older adults between verbal and spatial memory performance and baseline hippocampal perfusion. Although cognitively normal older adults have generally lower baseline perfusion compared to young adults (Leenders et al., 1990; Marchal et al., 1992; Matsuda et al., 2003), they exhibit a larger change in perfusion during memory encoding tasks (Restom et al., 2007). By contrast, conflicting evidence is available for determining the relationship between cognition and hippocampal volume. Although most studies that evaluate hippocampal volume in relation to dementia related memory performance find negative correlations (Barber et al., 2001; Dickerson et al., 2001; de Toledo-Morrell et al., 2004), other studies report less conclusive findings (van Petten, 2004; van Petten et al., 2004), and there is less available information on how these relationship manifest in cognitively normal older adults who transition to memory disorders.

CONCLUSIONS

We applied a noninvasive ASL MRI approach to assess the relationship between hippocampal perfusion and memory performance in cognitively normal older adults. These findings demonstrate that perfusion, rather than tissue volume, correlate most strongly with memory performance in this population, suggesting the changes in hippocampal volume that are reported in dementia patients may arise secondary to changes in hemodynamics.

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REFERENCES

- Alsop DC, Casement M, de Bazelaire C, Fong T, Press DZ. Hippocampal hyperperfusion in Alzheimer's disease. *Neuroimage*. 2008; 42:1267–1274. [PubMed: 18602481]
- Barber R, McKeith IG, Ballard C, Gholkar A, O'Brien JT. A comparison of medial and lateral temporal lobe atrophy in dementia with Lewy bodies and Alzheimer's disease: Magnetic resonance imaging volumetric study. *Dement Geriatr Cogn Disord*. 2001; 12:198–205. [PubMed: 11244213]
- Bleecker ML, Bolla-Wilson K, Kawas C, Agnew J. Age-specific norms for the Mini-Mental State Exam. *Neurology*. 1988; 38:1565–1568. [PubMed: 3419600]
- Buxton RB. Quantifying CBF with arterial spin labeling. *J Magn Reson Imag*. 2005; 22:723–726.
- Buxton RB, Wong EC, Frank LR. Dynamics of blood flow and oxygenation changes during brain activation: The balloon model. *Magn Reson Med*. 1998; 39:855–864. [PubMed: 9621908]
- Buzsaki G, Kaila K, Raichle M. Inhibition and brain work. *Neuron*. 2007; 56:13.
- Davis PC, Gray L, Albert M, Wilkinson W, Hughes JP, Heyman A, Gado M, Kumar AJ, Destian S, Lee C, Duvall E, Kido D, Nelson MJ, Bello J, Weathers S, Jolesz F, Kikinis R, Brooks M. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). III. Reliability of a standardized MRI evaluation of Alzheimer's disease. *Neurology*. 1992; 42:1676–1680. [PubMed: 1513454]
- De Santi S, de Leon MJ, Rusinek H, Convit A, Tarshish CY, Roche A, Tsui WH, Kandil E, Boppana M, Daisley K, Wang GJ, Schlyer D, Fowler J. Hippocampal formation glucose metabolism and volume losses in MCI and AD. *Neurobiol Aging*. 2001; 22:529–539. [PubMed: 11445252]
- de Toledo-Morrell L, Stoub TR, Bulgakova M, Wilson RS, Bennett DA, Leurgans S, Wu J, Turner DA. MRI-derived entorhinal volume is a good predictor of conversion from MCI to AD. *Neurobiol Aging*. 2004; 25:1197–1203. [PubMed: 15312965]
- Detre J, Leigh J, Williams D, Koretsky W. Perfusion imaging. *Magn Reson Med*. 1992; 23:37–45. [PubMed: 1734182]
- Dickerson BC. Functional magnetic resonance imaging of cholinergic modulation in mild cognitive impairment. *Curr Opin Psychiatry*. 2006; 19:8.
- Dickerson BC, Sperling RA. Functional abnormalities of the medial temporal lobe memory system in mild cognitive impairment and Alzheimer's disease: Insights from functional MRI studies. *Neuropsychologia*. 2008; 46:12. [PubMed: 17897685]
- Dickerson BC, Goncharova I, Sullivan MP, Forchetti C, Wilson RS, Bennett DA, Beckett LA, de Toledo-Morrell L. MRI-derived entorhinal and hippocampal atrophy in incipient and very mild Alzheimer's disease. *Neurobiol Aging*. 2001; 22:747–754. [PubMed: 11705634]
- Donahue MJ, Blicher JU, Ostergaard L, Feinberg DA, MacIntosh BJ, Miller KL, Gunther M, Jezzard P. Cerebral blood flow, blood volume, and oxygen metabolism dynamics in human visual and motor cortex as measured by whole-brain multi-modal magnetic resonance imaging. *J Cereb Blood Flow Metab*. 2009; 29:1856–1866. [PubMed: 19654592]
- Donahue MJ, Strother MK, Hendrikse J. Novel MRI approaches for assessing cerebral hemodynamics in ischemic cerebrovascular disease. *Stroke*. 2012; 43:903–915. [PubMed: 22343644]
- Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith S, Mathews PM, Beckmann CF, Mackay CE. Distinct patterns of brain activity in young carriers of the APOE-ε4 allele. *Proc Natl Acad Sci USA*. 2009; 106:6. [PubMed: 19118201]
- Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci USA*. 2000; 97:11050–11055. [PubMed: 10984517]
- Folstein MF, Folstein SE, McHugh PR. Mini-mental state: A practical method for grading the cognitive state of patients for the clinician". *J Psych Res*. 1975; 12:189–198.
- Heo S, Prakash RS, Voss MW, Erickson KI, Ouyang C, Sutton BP, Kramer AF. Resting hippocampal blood flow, spatial memory and aging. *Brain Res*. 2010; 1315:119–127. [PubMed: 20026320]
- Herscovitch P, Raichle ME. What is the correct value for the brain—Blood partition coefficient for water? *J Cereb Blood Flow Metab*. 1985; 5:65–69. [PubMed: 3871783]
- Ishii K, Sasaki M, Yamaji S, Sakamoto S, Kitagaki H, Mori E. Paradoxical hippocampus perfusion in mild-to-moderate Alzheimer's disease. *J Nuclear Med*. 1998; 39:293–298.

- Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002; 17:825–841. [PubMed: 12377157]
- Leenders KL, Perani D, Lammertsma AA, Heather JD, Buckingham P, Healy MJ, Gibbs JM, Wise RJ, Hatazawa J, Herold S, Beaney RP, Brooks DJ, Spinks T, Rhodes C, Frackowiak RSJ. Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age. *Brain Res*. 1990; 113:27–47.
- Limon A, Reyes-Ruiz JM, Miledi R. Loss of functional GABA(A) receptors in the Alzheimer diseased brain. *PNAS*. 2012; 109:6.
- Liu TT, Behzadi Y, Restom K, Uludag K, Lu K, Buracas GT, Dubowitz DJ, Buxton RB. Caffeine alters the temporal dynamics of the visual BOLD response. *Neuroimage*. 2004; 23:1402–1413. [PubMed: 15589104]
- Lu H, Clingman C, Golay X, van Zijl PC. Determining the longitudinal relaxation time (T1) of blood at 3.0 Tesla. *Magn Reson Med*. 2004; 52:679–682. [PubMed: 15334591]
- MacIntosh BJ, Filippini N, Chappell MA, Woolrich MW, Mackay CE, Jezzard P. Assessment of arterial arrival times derived from multiple inversion time pulsed arterial spin labeling MRI. *Magn Reson Med*. 2010; 63:641–647. [PubMed: 20146233]
- Marchal G, Rioux P, Petit-Taboué MC, Sette G, Travère JM, Le Poec C, Courtheoux P, Derlon JM, Baron JC. Regional cerebral oxygen consumption, blood flow, and blood volume in healthy human aging. *Arch Neurol*. 1992; 49:1013–1020. [PubMed: 1417508]
- Matsuda H, Kanetaka H, Ohnishi T, Asada T, Imabayashi E, Nakano S, Katoh A, Tanaka F. Brain SPET abnormalities in Alzheimer's disease before and after atrophy correction. *Eur J Nuclear Med Mol Imaging*. 2002; 29:1502–1505.
- Matsuda H, Ohnishi T, Asada T, Li ZJ, Kanetaka H, Imabayashi E, Tanaka F, Nakano S. Correction for partial-volume effects on brain perfusion SPECT in healthy men. *J Nucl Med*. 2003; 44:1243–1252. [PubMed: 12902414]
- Mevel K, Desgranges B, Baron JC, Landeau B, De la Sayette V, Viader F, Eustache F, Chetelat G. Detecting hippocampal hypometabolism in Mild Cognitive Impairment using automatic voxel-based approaches. *Neuroimage*. 2007; 37:18–25. [PubMed: 17566762]
- Mirra S, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, Vogel FS, Hughes JP, Van Belle G, Berg L. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology*. 1991; 41:479–486. [PubMed: 2011243]
- Morris JC, Mohs RC, Rogers H, Fillenbaum G, Heyman A. Consortium to establish a registry for Alzheimer's disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. *Psychopharmacol Bull*. 1988; 24:641–652. [PubMed: 3249766]
- Morris JC, Heyman A, Mohs RC, Hughes JP, CanBelle G, Fillenbaum G, Mellitis ED, Clark C. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*. 1989; 39:1159–1165. [PubMed: 2771064]
- van Petten C. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: Review and meta-analysis. *Neuropsychologia*. 2004; 42:1394–1413. [PubMed: 15193947]
- Quiroz YT, Budson AE, Celone K, Ruiz A, Newmark R, Castrillón G, Lopera F, Stern CE. Hippocampal hyperactivation in presymptomatic familial Alzheimer's disease. *Ann Neurol*. 2010; 68:11.
- Raichle ME. Measurement of local cerebral blood flow and metabolism in man with positron emission tomography. *Federat Proc*. 1981; 40:2331–2334.
- Restom K, Bangen K, Bondi M, Perthen JE, Liu TT. Cerebral blood flow and BOLD responses to a memory encoding task: A comparison between healthy young and elderly adults. *Neuroimage*. 2007; 37:430–439. [PubMed: 17590353]
- Tsuchida T, Yonekura Y, Nishizawa S, Sadato N, Tamaki N, Fujita T, Magata Y, Konishi J. Nonlinearity correction of brain perfusion SPECT based on permeability-surface area product model. *J Nuclear Med*. 1996; 37:1237–1241.

- Van Paesschen W. Qualitative and quantitative imaging of the hippocampus in mesial temporal lobe epilepsy with hippocampal sclerosis. *Neuroimaging Clin N Am*. 2004; 14:373–400. vii. [PubMed: 15324854]
- van Petten C, Plante E, Davidson PS, Kuo TY, Bajuscak L, Glisky EL. Memory and executive function in older adults: Relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities. *Neuropsychologia*. 2004; 42:1313–1335. [PubMed: 15193940]
- Wang J, Alsop DC, Li L, Listerud J, Gonzalez-At JB, Schnall MD, Detre JA. Comparison of quantitative perfusion imaging using arterial spin labeling at 1.5 and 4.0 Tesla. *Magn Reson Med*. 2002; 48:242–254. [PubMed: 12210932]
- Whatmough C, Chertkow H. rCBF to the hippocampal complex covaries with superior semantic memory retrieval. *Behav Brain Res*. 2007; 181:262–269. [PubMed: 17544157]
- Williams DS, Detre JA, Leigh JS, Koretsky AP. Magnetic resonance imaging of perfusion using spin inversion of arterial water. *Proc Natl Acad Sci USA*. 1992; 89:212–216. [PubMed: 1729691]
- Wolk DA, Dickerson BC. Fractionating verbal episodic memory in Alzheimer's disease. *Neuroimage*. 2011; 54:10. [PubMed: 20643213]
- Wu WC, Fernandez-Seara M, Detre JA, Wehrli FW, Wang J. A theoretical and experimental investigation of the tagging efficiency of pseudocontinuous arterial spin labeling. *Magn Reson Med*. 2007; 58:1020–1027. [PubMed: 17969096]

FIGURE 1.

(a) T_1 -weighted structural images with (b) overlaid perfusion maps as quantified from the arterial spin labeling method for a representative subject (61 yr/F). (c) Axial perfusion images overlaid on the T_1 -weighted image for the same subject. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FIGURE 2.

(a, d, g) depict the coronal, sagittal, and axial views of the hippocampus in a representative subject. (b, e, h) The individualized hippocampal masks. (c, f, i) Baseline hippocampal perfusion (ml/100 gm/min) overlaid on the T_1 -weighted images in only the region defined from the hippocampus mask. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FIGURE 3.

Correlation of CERAD-I to (a) hippocampal perfusion and (b) volume. CERAD-I (maximum score = 30 indicating best memory performance) scores are negatively correlated to baseline hippocampal perfusion, yet exhibit no statistically significant relationship with hippocampal volume.

FIGURE 4.

Hippocampal perfusion asymmetry (left hippocampal perfusion–right hippocampal perfusion) of the left and right hippocampus in noncarriers ($n = 8$) and carriers ($n = 7$) of *APOE*- $\epsilon 4$ allele. The results demonstrate that in healthy older *APOE*- $\epsilon 4$ carriers, perfusion is reduced in left hippocampus relative to right hippocampus.

TABLE 1

Subject Demographics

Subject	Sex	Age (yr)	APOE-ε4	CERAD-I	MMSE	Left HC Perfusion (ml/100 g/min)	Right HC Perfusion (ml/100 g/min)	Left HC volume	Right HC volume
1	M	77	N	21	29	35.7	33.5	0.35	0.36
2	F	65	N	24	30	31.7	41.1	0.38	0.37
3	F	64	N	21	30	45.2	35.6	0.35	0.41
4	F	76	N	28	30	24.5	21.0	0.39	0.37
5	F	63	N	24	29	38.6	35.7	0.39	0.39
6	F	65	N	28	30	29.8	33.2	0.42	0.39
7	M	68	N	19	29	27.7	22.1	0.42	0.39
8	F	61	N	21	30	42.1	50.6	0.39	0.40
Mean		67		23	30	34.4	34.1	0.39	0.38
STD		6		3	1	7.2	9.6	0.02	0.02
9	F	70	Y	14	28	44.4	54.6	0.43	0.40
10	F	78	Y	22	28	27.7	33.1	0.40	0.39
11	M	77	Y	14	29	31.0	50.0	0.32	0.37
12	M	78	Y	22	30	29.3	41.0	0.43	0.39
13	M	64	Y	18	30	32.0	29.7	0.38	0.39
14	F	62	Y	20	29	35.5	32.4	0.36	0.34
15	F	60	Y	25	30	45.3	52.4	0.40	0.37
Mean		70		19	29	35.0	41.9	0.39	0.38
STD		8		4	1	7.1	10.4	0.04	0.02
16	F	61	N/A	22	30	38.3	42.7	0.42	0.42
17	F	64	N/A	25	30	35.0	40.7	0.37	0.38
18	F	61	N/A	19	30	43.8	46.8	0.38	0.41
19	M	62	N/A	18	30	47.5	40.0	0.35	0.38
20	F	62	N/A	18	30	50.5	39.3	0.38	0.36
Mean		62		20	30	43.0	41.9	0.38	0.39
STD		1		3	0	6.4	3.0	0.02	0.03
All Subject Mean		66		21	30	36.8	39.0	0.39	0.38

Subject	Sex	Age (yr)	APOE-ε4	CERAD-I	MMSE	Left HC Perfusion	Right HC Perfusion	Left HC volume	Right HC volume
All Subject STD		7		4	1	7.6	9.2	0.03	0.02

Sex. M, male; F, female; APOE-ε4. N, noncarrier; Y, one or more copy; N/A did not provide genetic sample. Cognitive testing. CERAD-I, Consortium to establish a registry for Alzheimer's disease Immediate Recall Exam (max score = 30). MMSE, Mini-mental state exam (max score = 30). Imaging. HC, Hippocampal complex; ICV, Intracranial volume.