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Age-related differences in memory-encoding fMRI responses after accounting for decline in vascular reactivity

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Abstract

BOLD fMRI has provided a wealth of information about the aging brain. A common finding is that posterior regions of the brain manifest an age-related decrease in activation while the anterior regions show an age-related increase. Several neurocognitive models have been proposed to interpret these findings. However, one issue that has not been sufficiently considered to date is that the BOLD signal is based on vascular responses secondary to neural activity. Thus the above findings could be in part due to a vascular change, especially in view of the expected decline of vascular health with age. In the present study, we aim to examine age-related differences in memory-encoding fMRI response in the context of vascular aging. One hundred and thirty healthy subjects ranging from 20 to 89 years old underwent a scene-viewing fMRI task and, in the same session, cerebrovascular reactivity (CVR) was measured in each subject using a CO₂-inhalation task. Without accounting for the influence of vascular changes, the task-activated fMRI signal showed the typical age-related decrease in visual cortex and medial temporal lobe (MTL), but manifested an increase in the right inferior frontal gyrus (IFG). In the same individuals, an age-related CVR reduction was observed in all of these regions. We then used a previously proposed normalization approach to calculate a CVR-corrected fMRI signal, which was defined as the uncorrected signal divided by CVR. Based on the CVR-corrected fMRI signal, an age-related increase is now seen in both the left and right side of IFG; and no brain regions showed a signal decrease with age. We additionally used a model-based approach to examine the fMRI data in the context of CVR, which again suggested an age-related change in the two frontal regions, but not in the visual and MTL regions.

Keywords

cognitive aging; age-related increase; age-related decrease; cerebral vascular reactivity (CVR); functional magnetic resonance imaging (fMRI); fMRI normalization

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INTRODUCTION

Cognitive aging studies using BOLD fMRI have revealed a wealth of information about the aging brain. While studies of cognitive performance and brain volumetrics usually show declines with age (Bartzokis et al., 2001; Park and Reuter-Lorenz, 2009; Raz et al., 2005), a common finding from the fMRI literature on aging is that older adults show heightened activation relative to young (Cabeza et al., 2004; Daselaar et al., 2003; Gutchess et al., 2005; Park et al., 2003). The frontal cortex, which plays a particularly important role in encoding and retrieval processes in memory (Stuss and Knight, 2002), has received the most attention in this regard. The increase in frontal activation in old adults is thought to represent a compensatory activation that occurs in the aging brain to accommodate the decreased volume of neural tissue and declining efficiency of neural circuitry (Cabeza et al., 2002; Park and Reuter-Lorenz, 2009). Furthermore, the present literature suggests that this effect could be lateralized depending on the type of fMRI task and the equivalence or nonequivalence of performance between the young and older groups (see (Spreng et al., 2010) for a review). In contrast to the pattern in the frontal regions, the findings in posterior brain regions such as visual areas (Buckner et al., 2000; Cabeza et al., 2004; Davis et al., 2008; Handwerker et al., 2007; Ross et al., 1997) and medial temporal lobe (Daselaar et al., 2003; Gutchess et al., 2005; Park et al., 2003) are typically represented by an age-related signal decrease, which is interpreted as a functional decline with age.

While these findings have been replicated reliably by many laboratories, an important but largely unaddressed point is that these BOLD fMRI signal patterns cannot be directly interpreted as neural activity changes in view of the notion that fMRI relies on dilation of blood vessels (Bandettini and Wong, 1997), yet this vasodilatory capacity is known to decline with age (Ito et al., 2002; Lu et al., 2011). Therefore, it is plausible that some of these age-related fMRI differences are simply a result of vascular alterations and that the true neural activity changes with age may manifest a different pattern from those observed previously.

It is therefore important to evaluate the fMRI signals in the context of vascular alterations with age, specifically the ability of vessels to react to vasoactive stimuli. With recent advances in physiological instrumentation and imaging technologies, this cerebrovascular reactivity (CVR) can now be measured conveniently and comfortably with the inhalation of CO₂-enriched gas mixture (Bright et al., 2009; Han et al., 2008; Lu et al., 2011; Mandell et al., 2008; Yezhuvath et al., 2009) or holding the breath (Di et al., 2012; Handwerker et al., 2007; Kannurpatti et al., 2011; Riecker et al., 2003; Thomason et al., 2007) while continuously monitoring the MRI signal. Compared to breath-hold, the CO₂-inhalation paradigm provides a measurable input function of end-tidal CO₂, thus is often considered a more accurate method for CVR evaluation.

In the present work, we applied an event-related, episodic memory (EM) fMRI task in 130 healthy individuals with an age range of 20 to 89 years old. To assess their vascular function and to use the vascular measure for the correction of fMRI signal, CVR was determined in each participant by inhalation of 5% CO₂, which allowed a quantitative mapping of vasodilatation capacity from the same voxels in which task-activated fMRI signals were measured. We then used a previously proposed normalization approach to calculate a CVR-corrected fMRI signal, which was defined as the uncorrected signal divided by CVR. Age-related differences in brain activation were examined using both uncorrected and CVR-corrected fMRI signals.

MATERIALS AND METHODS

Participants

A total of 130 participants were recruited in a large-scale lifespan study on cognitive function and neuroimaging, the Dallas Lifespan Brain Study (DLBS). Table 1 lists demographic information for the participants. All subjects underwent extensive health screening and had no contraindications to MRI scanning (pacemaker, implanted metallic objects, claustrophobia), and were generally of good health, with no serious or unstable medical conditions such as neurological disease, brain injury, uncontrollable shaking, history of by-pass surgery or chemotherapy, or use of medications that affect cognitive function. Twenty-four subjects who reported a diagnosis of hypertension were taking antihypertensive medications (mostly Angiotensin Converting Enzyme Inhibitors, Beta-blockers, and Angiotensin II Receptor Antagonists). All participants were highly right-handed, native English speakers with at least a high school education, and a Mini-Mental State Exam (MMSE) (Folstein et al., 1975) score of 26 or greater. Each subject gave informed written consent before participating in the study. The study protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center and the University of Texas at Dallas.

MRI Experiment

All MR imaging experiments were conducted on 3 Tesla MR system (Philips Medical System, Best, The Netherlands). The experimental design is shown in Figure 1a. The BOLD fMRI experiment used an event-related, memory-encoding task, during which the subject viewed full-color photographs of outdoor scenes presented via a back-projection system (Park et al., 2012). Each subject received 3 fMRI runs with 32 photographs in each run. The paradigm started with a 20s fixation period, during which the subject looked at a small white cross at the center of the black screen. Then each photograph appeared for 3s followed by a fixation period with randomized duration from 4s to 17s (Figure 1b). The subject was instructed to determine if there was water in the scene and to press a button in their right hand accordingly. Tasks of similar type are widely used in cognitive aging studies (Gutchess et al., 2005; Park et al., 2003). Participants' vision was corrected using MR-compatible corrective lenses whenever necessary. The duration for each fMRI run was 5.75 minutes. Standard BOLD fMRI imaging parameters were used: TR/TE/flip angle=2000/25ms/80°, field-of-view (FOV) = 220x220 mm², matrix 64x64, voxel size 3.4x3.4x3.5mm³, 43 axial slices with whole brain coverage, 171 brain volumes in each run. A recognition test for the studied pictures was administered outside of the scanner approximately 20 minutes after the end of the fMRI task. Participants were presented with 96 presented photographs and 96 lure photographs matched to the studied pictures for content and judged whether they had studied each item earlier.

Cerebrovascular reactivity (CVR) was measured with hypercapnia, in which participants inhaled 5% CO₂ gas, while BOLD MR images were simultaneously acquired. The details of the CVR measurement has been described previously (Yezhuvath et al., 2009). Briefly, during the CVR scan, subjects were fitted with a nose clip, and breathed room air and the prepared gas in an interleaved fashion (switching every 1 min, Figure 1c) through a mouthpiece. The prepared gas was a mixture of 5% CO₂, 74% N₂ and 21% O₂ and contained within a Douglas bag through a two-way non-rebreathing valve and mouthpiece combination (Hans Rudolph, 2600 series, Shawnee, KS). A research assistant was inside the magnet room throughout the experiment to switch the valve and monitor the subject. BOLD MR images were acquired continuously during the entire experimental period. The end-tidal CO₂ (EtCO₂), the CO₂ concentration in the lung and thus arterial blood, was also recorded throughout the breathing task using a capnograph device (Capnogard, Model 1265,

Novamatrix Medical Systems, CT). The total duration for the CVR scan was 7 minutes. Other imaging parameters were identical to those of the memory-encoding fMRI.

Data Processing

Data analysis was conducted using the software Statistical Parametric Mapping (SPM2), University College London, UK) and in-house MATLAB (MathWorks, Natick, MA) scripts. Motion correction was performed by realigning the image volumes of memory-encoding fMRI and hypercapnia MRI to their respective first volume within each scan. Then the hypercapnia MRI images were co-registered with memory-encoding fMRI images by co-registering the mean image of hypercapnia MRI to the mean image of memory-encoding fMRI data, and applying the resulting transformation to each image volume in hypercapnia MRI. Next, all images were co-registered to the image template of Montreal Neurological Institute (MNI) via T1-weighted high-resolution anatomic image and were resampled to a voxel size of $2 \times 2 \times 2 \text{ mm}^3$. Finally, the memory-encoding fMRI and hypercapnia image volumes were smoothed using a Gaussian filter with a full-width-half-maximum (FWHM) of 8mm. For convenience, in the following text, fMRI specifically indicates the memory-encoding fMRI.

Single-subject-level fMRI analysis was conducted using a general linear analysis between the signal time course and the stimulus paradigm convoluted with a SPM-defined hemodynamic response. The group-level activation map was determined using a one-sample t-test performed on the contrast images comparing photograph viewing to fixation, with a threshold of $p < 0.001$ and cluster size of 200 voxels.

Hypercapnia MRI data were processed using a general linear model similar to a typical fMRI scan, except that the regressor was the EtCO₂ time-course rather than the fMRI paradigm. In-house MATLAB scripts were used to obtain EtCO₂ time-courses that were synchronized with MRI acquisitions. Since the hypercapnia-induced vasodilatation is mediated by CO₂ level changes, EtCO₂ time-course provides an input function to the vascular system. The BOLD timecourse is the output signal, and by comparing the input and output signals the vascular system property can be determined (Yezhuvath et al., 2009). Absolute CVR is expressed in units of %BOLD signal change per mmHg of EtCO₂ change (%BOLD/mmHg CO₂).

Age-related differences in brain activation were examined using both region-of-interest (ROI) and voxel-wise analyses. ROI analysis was performed in four regions that manifested the most robust activations in a memory-encoding task like ours where encoding activity was contrasted with baseline (Brewer et al., 1998; Kelley et al., 1998), specifically primary visual cortex (V1), medial temporal lobe (MTL), left inferior frontal gyrus (IFG), and right IFG. To allow for slight variations in brain anatomy across individuals, the final functional mask was determined on a subject-specific basis with a procedure described previously (Liu et al., 2012). Briefly, a preliminary mask was first defined using WFU PickAtlas Tool (Wake Forest University, <http://fmri.wfubmc.edu/cms/software>). Next, within the preliminary mask, the most activated voxels (2000, 1000, 500, and 500 most activated voxels for V1, MTL, left IFG and right IFG ROIs, which are approximately 15% of the total voxels in the preliminary masks) of each individual were identified as the final mask and were used for signal averaging for that individual. The fMRI signal in percentage change was calculated. The final mask was also applied to the hypercapnia MRI data to obtain an estimation of the regional CVR. The relationship between fMRI signal and age was evaluated by linear regression analysis with age of each individual as independent variable and individual fMRI signal as dependent variable. The age-dependence of CVR was assessed with a similar analysis. To evaluate the possible influence of hypertension, the

status of hypertension was added to the regression model as a categorical variable and tests were performed to see if there was a significant effect of hypertension.

Voxel-based analysis was performed using a regression analysis with age as the regressor. Voxels with a significant age-increase or age-decrease were identified with a threshold of $p < 0.001$ and cluster size of 200 voxels.

Beside of this main analysis, fMRI analysis was also conducted to compare remembered versus forgotten photographs in the brain regions that showed significant age effect in the main analysis. Single-subject-level analysis was conducted using a general linear analysis and individual contrast images of remembered-forgotten photographs were calculated. The most activated 200 voxels of each individual within each anatomic ROI were selected and were used as the final mask. The fMRI signals of remember-forgotten contrast in the final masks were calculated. The averaged CVR was also calculated. The age-dependence of the uncorrected and CVR-corrected fMRI signals was assessed by linear regression analysis with age as the independent variable.

Integration of fMRI and CVR measurements

Two approaches were used to examine the fMRI data in the context of CVR. The first approach is based on the computation of a corrected fMRI signal. This approach was first proposed by Bandettini and Wong (Bandettini and Wong, 1997) and was adopted by a number of researchers (Biswal et al., 2007; Handwerker et al., 2007; Kannurpatti and Biswal, 2008; Kannurpatti et al., 2011; Thomason et al., 2007). Specifically:

$$S_{\text{fMRI,corr}} = S_{\text{fMRI,uncorr}} / \text{CVR} \quad [1]$$

where $S_{\text{fMRI,uncorr}}$ is the uncorrected fMRI signal and CVR is the vascular reactivity from the same ROI.

Previous studies have provided rationales for this computation. Briefly, uncorrected fMRI signal can be written as (Davis et al., 1998; Hoge et al., 1999):

$$S_{\text{fMRI,uncorr}} = M \cdot \left[1 - \left(1 + \frac{\Delta \text{CMRO2}}{\text{CMRO2}_0} \right)^{1.5} \times \left(1 + n \cdot \frac{\Delta \text{CMRO2}}{\text{CMRO2}_0} \right)^{-1.12} \right] \quad [2]$$

where $\frac{\Delta \text{CMRO2}}{\text{CMRO2}_0}$ is the activation-induced CMRO2 change and is the parameter related to neural activity; M is a parameter related to baseline physiologic state (e.g. venous oxygenation, venous blood volume, hematocrit); n is a parameter reflecting the capacity of the vessel to dilate to attract more blood flow given a unit fraction of CMRO2 increase,

specifically $n = \frac{\Delta \text{CBF}_{\text{fMRI}}}{\text{CBF}_0} \bigg/ \frac{\Delta \text{CMRO2}}{\text{CMRO2}_0}$, which is related to vessel property but other factors such as astrocyte-to-vessel pathway may also influence the value of n . Since M and n can be different across individuals, the measured BOLD signal will vary considerably even if CMRO2 change (i.e. neural activity) is identical.

CVR is related to the above parameters by (Davis et al., 1998; Hoge et al., 1999):

$$\text{CVR} = M \cdot \left[1 - \left(1 + \frac{\Delta \text{CMRO2}}{\text{CMRO2}_0} \right)^{1.5} \times (1 + p)^{-1.12} \right] \quad [3]$$

Note that Eq. [3] contains a new symbol p , which is percent blood flow increase per unit increase in end-tidal (Et) CO_2 , $\frac{\Delta \text{CBF}_{\text{CO}_2}}{\text{CBF}_0} / \Delta \text{EtCO}_2$. If one assumes that mild hypercapnia does not alter CMRO2 (Davis et al., 1998; Hoge et al., 1999), i.e., $\frac{\Delta \text{CMRO}_2}{\text{CMRO}_{20}} = 0$, Eq. [3] can be written as:

$$\text{CVR} = M \cdot [1 - (1+p)^{-1.12}] \quad [4]$$

The factors n (in Eq. [2]) and p (in Eq. [4]) are both related to vessel wall function, but each is influenced by other biochemical and cellular factors along the vasodilatory pathway. In the present study, we assume that age-related change in the common factor, i.e. vessel wall function, is the predominant factor in vascular aging. Thus, n and p is assumed to have a simple linear relationship, $p = cn$, where c is the ratio factor. One can then rewrite Eq. [4] as:

$$\text{CVR} = M \cdot [1 - (1+c \cdot n)^{-1.12}] \quad [5]$$

The corrected fMRI signal defined in Eq. [1] can then be written as:

$$S_{\text{fMRI,corr}} = \left[1 - \left(1 + \frac{\Delta \text{CMRO}_2}{\text{CMRO}_{20}} \right)^{1.5} \times (1+n \cdot \frac{\Delta \text{CMRO}_2}{\text{CMRO}_{20}})^{-1.12} \right] / [1 - (1+c \cdot n)^{-1.12}] \quad [6]$$

Comparing Eq. [6] to Eq. [2], one can see that the influence of M on fMRI is eliminated in the corrected signal. For the influence of n , Figure 2 shows simulation results of fMRI signal as a function of n , when $\Delta \text{CMRO}_2/\text{CMRO}_2$ is assumed to be 10% and c is assumed to be 0.01, 0.02 or 0.03. Note that the ideal situation would be that the signal is independent of n , i.e. a flat curve. As can be seen in Figure 2, the corrected fMRI signal is still sensitive to n , but the extent of the dependence is reduced.

Given that the direct division of fMRI by CVR does not completely remove the influence of the n factor, we have conducted exploratory analysis to use a semi-quantitative approach to examine the fMRI data in the context of CVR. In this approach, we start with a null hypothesis that $\Delta \text{CMRO}_2/\text{CMRO}_2$ does not change with age and we test whether we can reject the null hypothesis based on the fMRI and CVR data. Specifically, we assume an age-constant $\Delta \text{CMRO}_2/\text{CMRO}_2$ value of 30%, 20%, 6%, and 6% for V1, MTL, left IFG, and right IFG, respectively, based on a survey of the literature (Gauthier et al., 2012a; Mohtasib et al., 2012; Restom et al., 2007). Then, for each decade-averaged fMRI and CVR data, we can uniquely determine the n and M values based on Eqs. [2] and [5]. The exact procedure is as follows. We have two measurements, $S_{\text{fMRI,uncorr}}$ and CVR , and also two unknowns, n and M . Therefore, we have enough information to solve this equation group. Given the complexity of these equations, it is not feasible to solve them analytically. Instead, a numerical approach was used. For the ranges of n and M to be 1–10 and 0.01–0.20, respectively (Ances et al., 2009; Gauthier et al., 2012a; Gauthier et al., 2012b; Hutchison et al., 2012), we sampled the entire parameter space of (n, M) with a sampling interval of 0.0001 (for both parameters), and for each pair of (n, M) we obtain a estimated set of $\bar{S}_{\text{fMRI,uncorr}}$ and $\overline{\text{CVR}}$ using Eqs. [2] and [5]. The difference between the estimated set of $\bar{S}_{\text{fMRI,uncorr}}$ and $\overline{\text{CVR}}$, and the experimentally measured set of $S_{\text{fMRI,uncorr}}$ and CVR was calculated as $\text{Diff}_{(n,M)} = \sqrt{(\bar{S}_{\text{fMRI,uncorr}} - S_{\text{fMRI,uncorr}})^2 + (\overline{\text{CVR}} - \text{CVR})^2}$. For the group-averaged $S_{\text{fMRI,uncorr}}$ and CVR of each decade, we identified the set of (n, M) that yielded the minimal $\text{Diff}_{(n,M)}$. We can then examine how the identified n changes with age. Based on numerous histopathological and physiologic studies of vascular properties as a function of age (see D'Esposito et al., 2003 for a review), n should show an age-decrease or age-

constant pattern. This notion is also supported by evidences from existing studies of calibrated fMRI. Thus, we would reject the null hypothesis that $\Delta\text{CMRO2}/\text{CMRO2}$ does not change with age, if n is observed to increase with age.

We also examined the sensitivity of these results to the assumptions on c and $\Delta\text{CMRO2}/\text{CMRO2}$. For sensitivity to c , we tested a range of values from 0.01–0.03 based on a literature survey (Ances et al., 2009; Gauthier et al., 2012a; Gauthier et al., 2012b). For sensitivity to $\Delta\text{CMRO2}/\text{CMRO2}$, we tested a range of $\Delta\text{CMRO2}/\text{CMRO2}$ values that are 50%- 150% of the nominal value described above. We examined whether the patterns of age-related changes in n are sensitive to these assumptions.

For voxel-wise fMRI correction, we divided the fMRI signal of each voxel by the smoothed (using 16mm full-width-half-maximum) CVR of the same voxel (to improve the reliability of CVR on a voxel level). The regression analysis was then repeated on the corrected fMRI signal map.

RESULTS

Behavioral data

The hit rate (correctly recognizing a picture as old) was 0.67 ± 0.21 and the false alarm rate (incorrectly recognizing a new picture as old) was 0.44 ± 0.17 across all subjects. Decade-by-decade hit rates and false alarm rates are shown in Table 1. To determine whether there was age-dependence in the hit rate and false alarm rate, we performed regression analysis on the hit rate and false alarm rate against age. Our results suggested that there is no age-dependence in the hit rate ($p=0.11$) or false alarm rate ($p=0.32$), congruent with findings from other studies (Gutchess et al., 2005).

Task activation data

As noted earlier, we were interested in neural activity across major brain regions, including visual areas. So our main fMRI data analyses focused on the picture-versus-fixation contrast. Figure 3a shows group-level activation maps of the memory-encoding task when using data from subjects of all ages ($N=130$). Consistent with reports in the literature (Brewer et al., 1998; Kelley et al., 1998), robust activations were detected in the visual areas, MTL, left IFG, and right IFG. Figure 3b shows anatomic locations of these regions (from WFU PickAtlas), which were further investigated in the ROI analysis.

CVR data

Figure 4a shows decade-by-decade CVR maps. It is evident from visual inspection that CVR decreased with age. Voxel-by-voxel regression analysis revealed that significant clusters of age-related CVR decline are observed throughout the brain (Figure 4b). Figure 4c plots CVR values in the four functional ROIs described above, showing a significant age effect in all regions examined. Comparing subjects in the 80s to those in the 20s, the averaged CVR decreased by 29%, 21%, 26%, and 36% in V1, MTL, left IFG, and right IFG, respectively. No significant age-related differences were found in the EtCO_2 levels of all subjects ($p > 0.12$). There was not a significant effect of hypertension on CVR ($p=0.89$).

Age-related differences in fMRI signal

Figure 5 shows decade-by-decade fMRI signals in each ROI before and after CVR correction. A significant interaction between age and region was observed for both uncorrected and corrected fMRI signals ($p < 0.005$), suggesting that the magnitude of the age effects was region-dependent. Before correction (blue curves), the results confirmed previously reported patterns of age-related differences in fMRI signals when using a

memory-encoding task (Daselaar et al., 2003; Gutchess et al., 2005). Specifically, in the visual cortex (Figure 5a) and MTL (Figure 5b), an age-related activation decrease was observed. In contrast, the frontal lobe showed evidence of an age-related increase. This effect was only present in the right IFG (Figure 5d), but not in its left counterpart (Figure 5c). In the CVR-corrected fMRI signal (red curves in Figure 5), the age-dependence pattern was considerably different. First, the signal decreases in the visual cortex and MTL were no longer present. Instead, the signal appeared to be constant across decades. Second, the age-related increase in the right IFG remained after the correction. Finally, the corrected fMRI signal also manifested an age-related increase in the left IFG, suggesting that frontal over-recruitment in cognitive aging was present in both hemispheres.

Voxel-based results of age dependence are illustrated in Figure 6. Consistent with the findings from the ROI analysis, the uncorrected fMRI signal showed an age-related decrease in posterior brain regions, while manifesting an increase in the right prefrontal regions (top panel of Figure 6). In the CVR-corrected fMRI data, on the other hand, no age-decreased clusters were detected. Instead, age-related increases were observed in bilateral prefrontal regions, bilateral thalamus, right visual association cortices, and in part of the brainstem (bottom panel of Figure 6). Additionally, both the corrected and uncorrected fMRI signal showed an age-related increase in superior temporal gyrus bilaterally. Details on areas revealing age differences in the uncorrected fMRI data and CVR-corrected fMRI data are shown in Table 2 and Table 3, respectively.

Since the left and right IFG showed significant age-related increase, further analysis using the contrast of remembered-versus-forgotten pictures was conducted in these two regions. The results showed significant age-related decrease in the uncorrected fMRI signal in both regions ($p=0.0026$ and 0.0008 for left and right IFG, respectively), but no significant age-effect was found in the CVR-corrected fMRI in either region ($p=0.12$ and 0.90 for left and right IFG, respectively).

Results of alternative approach to combine fMRI and CVR data

Figure 7a and b show decade-by-decade changes in n and M under the null hypothesis that $\Delta\text{CMRO}_2/\text{CMRO}_2$ is constant across age. It can be seen that, in the two frontal regions, the flow-metabolism coupling ratio, n , increased with age ($p=0.0009$ and $p=0.0027$ for left and right IFG, respectively), which is not supported by existing literature (cross signs in Figure 7). In fact, it is expected that vascular function deteriorates with age (D'Esposito et al., 2003) and one previous study has shown that n decreases with age (Hutchison et al., 2012). Therefore, in these two regions, the null hypothesis that $\Delta\text{CMRO}_2/\text{CMRO}_2$ remains unchanged across age was rejected. This semi-quantitative analysis provides additional evidence that frontal $\Delta\text{CMRO}_2/\text{CMRO}_2$ changes with age in our data. In V1 and MTL, this analysis did not yield a significant correlation between n and age under the null hypothesis. Thus, there is no evidence to reject the null hypothesis of an age-constant $\Delta\text{CMRO}_2/\text{CMRO}_2$ in these two regions, which is consistent with the findings using the division correction approach.

Sensitivity analysis revealed that, within the range of $c=0.01$ to 0.03 , the factor n always showed an age-increase ($p<0.006$ for all values tested) in left and right IFG whereas V1 and MTL showed no age effect ($p>0.4$ for all values tested). For $\Delta\text{CMRO}_2/\text{CMRO}_2$, when the assumed $\Delta\text{CMRO}_2/\text{CMRO}_2$ is within 50–150% of the nominal value, the factor n always showed an age-increase ($p<0.05$ for all values tested) in left and right IFG whereas V1 and MTL showed no age effect ($p>0.4$ for all values tested). Therefore, the results are relatively insensitive to these assumptions.

DISCUSSION

The present study examined age-related differences in fMRI signal in the context of vascular function. In a memory-encoding task, the uncorrected fMRI responses showed an age-related decline in the occipital and medial temporal cortices while manifesting an age-related increase in the right frontal cortex. On the other hand, hypercapnia-based vascular assessment showed that vascular reactivity was reduced in all of these regions, suggesting that part of the fMRI observations could be attributed to an age effect on vascular function. CVR-corrected fMRI signal revealed that frontal over-recruitment in older individuals was still present, the extent of which now included bilateral frontal areas. Moreover, none of the brain regions manifested an age-related decrease in the CVR-corrected fMRI signal, which is distinctive from the vast majority of existing aging literature. Theoretical study of the CVR-corrected signal suggested that the correction (i.e. dividing fMRI signal by CVR) can account for variations in baseline physiologic state (i.e. the influence of M on fMRI signal) across individuals, but only partially correct for biases induced by the neurovascular coupling factor n . In particular, for individuals or brain regions with an n value of less than 4 (see Figure 2), the CVR-corrected signal may have still underestimated the true neural activation. Relevant for the interpretation of the data in the present study, if we assume that the neurovascular coupling factor, n , decreases with age due to arteriosclerotic changes (see D'Esposito et al. for a review (D'Esposito et al., 2003)), then it is likely that the true slope of age-related activation enhancement in the frontal regions is steeper than depicted in the present study. Similarly, it is possible that the true extent of activation enhancement includes more brain areas than those detected by the CVR-corrected fMRI.

Our findings based on the uncorrected fMRI signal were in good agreement with a large body of literature on cognitive aging. Ross et al. were the first to use fMRI to examine age-related differences in fMRI signal in the visual cortex and noted an attenuation in response amplitude (Ross et al., 1997), a finding widely reproduced by other researchers (Buckner et al., 2000; Cabeza et al., 2004; Handwerker et al., 2007). Medial temporal lobe activations in older individuals have been shown to be significantly lower compared to younger adults (Daselaar et al., 2003; Gutchess et al., 2005; Park et al., 2003). In the frontal lobe, scene encoding tasks like ours are known to activate both sides of the inferior frontal areas in young adults (Gutchess et al., 2005; Ofen et al., 2007), but the right IFG has the most pronounced age-increase effect (Gutchess et al., 2005).

The results demonstrated in the present study suggest that some of the fMRI findings in the cognitive aging literature may need to be re-interpreted in consideration of vascular changes with age. Since the early days of fMRI, researchers have become aware of the potential limitation of fMRI in the studies of brain aging (D'Esposito et al., 1999), as it is well known that a number of neurovascular changes take place with age including thickening of the vessel wall, necrosis of smooth muscle cells, and thickening of the basement membrane (D'Esposito et al., 2003). These structural changes will almost certainly affect the vessel's capacity to dilate, as confirmed by vascular reactivity studies in both humans and animal models (Ito et al., 2002; Lu et al., 2011; Tamaki et al., 1995; Yamamoto et al., 1980). However, in earlier days, the measurement of CVR was considered cumbersome and it was thought to be impractical to measure CVR in every individual who participates in an fMRI study. Recently, several categories of optimized hypercapnia equipment have become available (Han et al., 2008; Lu et al., 2011; Mandell et al., 2008; Yezhuvath et al., 2009), which can provide convenient and cost-effective measurement of CVR inside the MRI. Further improvement on the breathing paradigm suggested that the CO₂-inhalation duration can be shortened to less than 1 minute (thus no CO₂-induced discomfort) while maintaining the sensitivity of the MRI data (Yezhuvath et al., 2009). Therefore, it is now feasible to map

each subject's CVR in the same session that fMRI is performed, and to use the results to correct the fMRI signal.

Three previous studies have reported the correction of fMRI signal with hypercapnia results in the context of aging. Riecker et al. used a finger tapping motor task in six younger (age 22–31 years) and six older participants (age 54–82 years), and observed a lower fMRI signal in the older group (Riecker et al., 2003). The authors also performed hypercapnia with breath-hold challenge and noted a similar reduction in CVR signal. This was one of the first pieces of evidence that some of the age-related difference in fMRI signal may be due to vascular decline. Handwerker and colleagues used a visuomotor task in a group of younger (age 18–36 years) and a group of older (age 51–78 years) individuals, and both visual and motor areas showed an age-related reduction in fMRI (Handwerker et al., 2007). In the accompanying hypercapnia experiment, which was again performed with breath-hold, no CVR differences were observed comparing the two groups. The authors concluded that the fMRI age-effect was neural in origin. More recently, Kannurpatti et al. studied motor activation and breath-hold hypercapnia response in 12 younger (age 19–27 years) and 12 older (age 55–71 years) individuals (Kannurpatti et al., 2011). The data suggested that both the motor fMRI signal and the breath-hold response were greater in the older group.

The present work followed similar fMRI correction principles as those used in the previous studies (Handwerker et al., 2007; Kannurpatti et al., 2011; Riecker et al., 2003), but is different from them in several aspects. First, since memory decline is one of the most pervasive findings in cognitive aging, we have employed a scene-encoding task to understand age-related changes in brain regions associated with memory formation. Second, in our study, CVR was evaluated with a more accurate method, specifically by CO₂ inhalation, as opposed to breathhold. The advantage of CO₂-inhalation is that one can measure both the input (EtCO₂) and output (BOLD MRI signal) of the vascular system precisely during the experiment, thereby allowing a more definitive determination of the vasoreactive property. Breath-hold challenge, on the other hand, does not permit the recording of the input, because the EtCO₂ value is not measurable when the individual does not produce any exhaled air. This is particularly relevant for the accuracy of CVR estimation in view of the large heterogeneity in the ability and extent of different subjects in holding their breath. This variability in CO₂ concentration may have contributed to the discrepancy in breath-hold results in the literature. For example, in motor cortex studies as described above, age-related increase (Kannurpatti et al., 2011), decrease (Riecker et al., 2003), and preservation (Handwerker et al., 2007) have all been reported. Third, the present study used a relatively large sample (N=130) and the participants represented the whole age range across the adult lifespan, instead of just extreme age groups.

While the main analyses of the present study used an fMRI contrast of photograph viewing versus fixation, we have also conducted analyses to compare remembered versus forgotten photographs. Although the SNR of this contrast is lower, this allows the control of subject performance and permits the study of neural activity underlying successful memory. To limit the number of comparisons, we have focused on the two frontal regions that showed an age-increase in the main analyses. It was found that before CVR correction, the fMRI signals in both left and right IFG showed a significant age-related decrease. The uncorrected fMRI data would suggest that, to successfully complete the same task, the older group requires less neural activity, which is somewhat counter-intuitive and difficult to explain. In the CVR-corrected fMRI signal, there was no significant age-effect in either region. These CVR corrected data lead to a different conclusion from the uncorrected data, suggesting that to successfully complete the same task, the older group requires the same amount of neural activity as the young group, which is within expectation. Together with findings from the main analyses that the older group has a greater fMRI signal when comparing photograph

viewing to fixation, these data suggest that the older group had a stronger signal when viewing the pictures, but this signal was stronger for both remembered and forgotten pictures.

In the present study, the corrected fMRI signal was calculated by computing the ratio between the uncorrected fMRI signal and CVR (Eq. [1]). While this calculation is supported by some theoretical and experimental evidence and was widely adopted by a number of researchers (Bandettini and Wong, 1997; Handwerker et al., 2007; Kannurpatti et al., 2011; Liu et al., 2012; Thomason et al., 2007), recent work by Liau and Liu (2009) showed that there are caveats in this index too. Specifically, because the relationship between fMRI and CVR is not truly linear and the intercept between them is not zero, the ratio index is still sensitive to certain aspects of the vascular variability (Liau and Liu, 2009). As shown in Eq. [6], while the corrected fMRI signal is immune to inter-subject variability in M , the influence of n is still present. As can be seen in Figure 2, the ratio calculation between fMRI and CVR did not fully correct the effect of n . In the context of aging in which n is expected and has been shown to decrease with age (Hutchison et al., 2012), Figure 2 shows that even with the corrected fMRI signal, the evoked neural activity is still slightly under-estimated for the older groups. That is, the real age-related increase in bilateral frontal activation may be even more prominent than depicted in Figure 5. It is also possible that there is an age-related increase in the V1 area and MTL.

The work of Liau and Liu (Liau and Liu, 2009) also demonstrated in a young group of subjects that the use of CVR as a covariate (rather than as a scaling factor) is more effective in reducing inter-subject variability in fMRI signals. The covariate approach, however, is not feasible in the present study of cognitive aging, because CVR itself is also strongly correlated with age and a correlation between independent variables would make the regression model illconditioned. We therefore used a semi-quantitative approach in which we examined how n would have to behave with age in order for an age-constant $\Delta CMRO_2/CMRO_2$. Then, if the pattern of n clearly contradicts the established knowledge of vascular changes with age, we can reject the null hypothesis and suggest that $\Delta CMRO_2/CMRO_2$ is indeed age-dependent. The results of this analysis were found to support those of the ratio calculation approach.

It is important to note that the separation of neural from vascular alterations in aging can also be performed with a model-based, quantitative approach called calibrated fMRI. The calibrated fMRI approach uses a hypercapnia or hyperoxia challenge in a separate scan to estimate M and, in the fMRI experiment, simultaneous BOLD and CBF images are acquired to allow computation of $\Delta CMRO_2/CMRO_2$ in a definitive manner. Compared to the CVR method used in the present study, the advantage of calibrated fMRI is that $\Delta CBF/CBF$ is also measured in the experiment, which is crucial for the estimation of $\Delta CMRO_2/CMRO_2$. A potential limitation of the method is that the overall SNR of data are relatively noisy due to additional noise contributions from CBF and M measurements. Several studies have used calibrated fMRI to study various brain regions in the context of cognitive aging (Ances et al., 2009; Gauthier et al., 2012b; Hutchison et al., 2012; Mohtasib et al., 2012; Restom et al., 2007), but their results are variable in terms of how $\Delta CMRO_2/CMRO_2$ changes with age. In the visual cortex, Ances et al. observed an age-constant $\Delta CMRO_2/CMRO_2$ (Ances et al., 2009), but Hutchison et al. noted a slight increase with age (Hutchison et al., 2012). In MTL, Restom et al. observed a greater $\Delta CMRO_2/CMRO_2$ in the older group, but the authors did not perform the actual calibration experiments but instead assumed an age-constant M value (Restom et al., 2007). Frontal fMRI signals are generally weaker. A recent study by Gauthier et al. showed no significant differences in $\Delta CMRO_2/CMRO_2$ between young and older groups, and the author attributed this to a low SNR of the data (Gauthier et al., 2012b). Mohtasib et al. studied frontal activation and an age-dependence of $\Delta CMRO_2/CMRO_2$ was

only found when comparing young subjects to a subgroup of older subjects whose performance was poor (Mohtasib et al., 2012). A complete summary of existing studies using calibrated fMRI and CVR-correction in aging is shown in Table 4.

The findings from the present study should be interpreted in view of a few limitations. First, this study used a cross-sectional design. It has been previously shown that a cross-sectional study may contain sampling bias and its results could be considerably different from a longitudinal design (Nyberg et al., 2010). We are currently performing a four-year follow-up in these participants and the results will be presented in a future report. Second, our ROI analysis was based on voxel numbers chosen empirically (2000, 1000, 500, and 500 most activated voxels in V1, MTL, left IFG, and right IFG, respectively). These numbers were chosen to ensure that enough voxels were included in each region for spatial averaging but not too many to include voxels in the noise level. To test whether the choice of these numbers would affect our results, we performed two additional analyses in which the voxel numbers were changed to half or twice the numbers used above. These analyses were consistent with our initial conclusions. Finally, in the voxel-wise fMRI correction (Figure 6), the CVR map was further smoothed with an empirically determined FWHM of 16mm to improve the robustness of the voxel-wise CVR value. This was because CVR is used as the denominator in the fMRI correction, which tends to be more sensitive to noise (e.g. divide by zero problem). Thus, further improvement in the CVR mapping technique is desirable.

CONCLUSIONS

The observations from the CVR-corrected fMRI data suggested that, during a memoryencoding task, older individuals showed a bilateral enhancement in frontal activation compared to younger subjects. There was no evidence of age-related decline in evoked neural activation in the brain, even for the occipital lobe. Further analysis using a different approach also confirmed an age-related difference in frontal neural activity independent of vascular changes.

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Highlights

- Examined age-related changes in fMRI response in the context of vascular aging
- An age-related reduction in cerebral vascular reactivity was observed
- Corrected fMRI signal showed age increase in both left and right frontal lobe
- No age-related decrease was observed in corrected fMRI signal

Figure 1.

Experimental design. (a) Schematic diagram of the MRI experiment. Each subject underwent a memory-encoding fMRI scan followed by a recognition test for the studied pictures outside the MRI scanner. Cerebral vascular reactivity (CVR) was measured with a CO₂-inhalation task. (b) FMRI paradigm. Each photograph was displayed for 3 seconds followed by a fixation period with pseudo-randomized duration of 4 to 17 seconds. The subject was instructed to determine if there is water in the scene and to press buttons in their right hand accordingly. (c) Timing of the CVR scan. Subjects were fitted with a nose clip, and breathed room air and 5% CO₂ gas (mixed with 74% N₂ and 21% O₂) in an interleaved fashion (switching every 1 min) through a mouthpiece.

Figure 2.

Simulation results of fMRI signal as a function of n . The following assumptions were used:

$M=0.08$ (Davis et al., 1998), $\frac{\Delta CMRO_2}{CMRO_{2_0}}=10\%$ (Liau and Liu 2009), $c=0.01, 0.02, \text{ or } 0.03$.

Figure 3.

Brain regions activated by the memory-encoding task. (a) Group-level activation maps comparing photograph viewing to fixation. $N=130$. Threshold: p value < 0.001 , cluster > 200 voxels. The results are shown in rendered views. The activated brain regions included occipital lobe, medial temporal lobe (MTL), left inferior frontal gyrus (IFG), right IFG, left pre/postcentral gyrus, insula, and anterior cingulate gyrus. (b) Anatomic masks defined in PickAtlas encompassing the four regions of interest (ROIs) examined in this study. For each individual, the final mask used for signal averaging consists of the most activated voxels in these ROIs.

Figure 4.

Decade-by-decade results of cerebrovascular reactivity (CVR). (a) Averaged CVR maps for each decade. CVR is written in units of percent signal change per mmHg change in end-tidal CO₂. Slice numbers are relative to the total of 91 slices in MNI space. (b) Voxels showing significant CVR decrease with age. $p < 0.005$ and cluster size > 200 . (c) CVR values in each ROI. Error bar indicates standard deviation across individuals. Voxels in the ROI included for spatial averaging were identical to those used for fMRI signal averaging. The p values and trend lines are based on linear regression of individual data.

Figure 5.

Decade-by-decade results of fMRI responses. Data for different ROIs are plotted in separate panels. Within each panel, blue and red symbols represent uncorrected and CVR-corrected fMRI results, respectively. p value associated with the age dependence are also shown in respective color. Error bar indicates standard deviation across individuals. To display uncorrected and corrected data in the same scale, the fMRI signals have been converted to z scores in the plots. The p values and trend lines are based on linear regression of individual data.

Figure 6.

Voxel-wise results of the age dependence of fMRI signal before (top) and after (bottom) CVR correction. Red clusters indicate voxels with an age-related increase. Blue clusters indicate voxels with an age-related decrease. N=130. Threshold: p value < 0.001 , cluster > 200 voxels. Labels were added to the images to indicate the brain regions involved. MTL – medial temporal lobe; STG – superior temporal gyrus; IFG – inferior frontal gyrus.

Figure 7.

Decade-by-decade changes in n and M when assuming an age-constant $\frac{\Delta \text{CMRO2}}{\text{CMRO2}_0}$ value of 30%, 20%, 6%, and 6% for V1, MTL, left IFG, and right IFG, respectively. The cross signs indicate the averaged literature values of n and M (Ances et al., 2009; Hutchison et al., 2012; Restom et al., 2007).

Table 1

Subject demographic and behavioral performance information.

Age range	20's	30's	40's	50's	60's	70's	80's
Total number of subjects	25	19	20	20	18	19	9
Gender (male/female)	9/16	6/13	6/14	7/13	6/12	9/10	4/5
Education (years, mean $\pm$ SD)	15.6 $\pm$ 2.6	17.7 $\pm$ 2.0	16.6 $\pm$ 3.1	16.9 $\pm$ 2.5	16.3 $\pm$ 2.1	16.7 $\pm$ 3.3	16.8 $\pm$ 1.1
MMSE (mean $\pm$ SD)	28.7 $\pm$ 1.5	28.3 $\pm$ 1.4	28.7 $\pm$ 1.4	28.7 $\pm$ 1.3	27.9 $\pm$ 1.3	27.6 $\pm$ 1.5	27.6 $\pm$ 1.4
Number of hypertensive subjects	0	0	1	3	8	9	3
Hit Rate (mean $\pm$ SD)	0.64 $\pm$ 0.15	0.63 $\pm$ 0.14	0.69 $\pm$ 0.10	0.69 $\pm$ 0.12	0.66 $\pm$ 0.12	0.71 $\pm$ 0.08	0.67 $\pm$ 0.11
False Alarm Rate (mean $\pm$ SD)	0.45 $\pm$ 0.15	0.39 $\pm$ 0.14	0.48 $\pm$ 0.15	0.42 $\pm$ 0.15	0.39 $\pm$ 0.13	0.50 $\pm$ 0.14	0.48 $\pm$ 0.12

Table 2

Brain regions showing age-related differences in uncorrected fMRI signal.

Coordinates (x y z)	# of voxels	Regions	Age-related change
38 -16 50	14841	R precentral gyrus (BA4/6) L precentral gyrus (BA4/6) R supplementary motor area (BA6) L supplementary motor area (BA6) L postcentral gyrus (BA4) R postcentral gyrus R inferior parietal gyrus (BA40) L inferior parietal gyrus (BA40) R superior frontal gyrus R superior parietal gyrus L Precuneus (BA 7) R inferior frontal gyrus R middle frontal gyrus (BA8)	Increase
-6 -56 -12	3522	R cerebellum L cerebellum	Increase
-60 -38 10	827	L middle temporal gyrus (BA22)	Increase
60 -30 8	453	R superior temporal gyrus	Increase
30 -44 -6	1010	R parahippocampal gyrus (BA19) R fusiform gyrus (BA32)	Decrease
-24 -80 -8	733	L fusiform gyrus (BA32)	Decrease
6 -92 10	474	R calcarine gyrus L calcarine gyrus	Decrease

Table 3

Brain regions showing age-related differences in corrected fMRI signal.

Coordinates (x y z)	# of voxels	Regions	Age-related change
34 -20 56	26202	R precentral gyrus (BA4/6) L precentral gyrus (BA4/6) R supplementary motor area (BA6) L supplementary motor area (BA6) L postcentral gyrus R postcentral gyrus L Precuneus R cuneus (BA7) R superior frontal gyrus R superior parietal gyrus L inferior parietal gyrus (BA40) R inferior parietal gyrus (BA40) R inferior frontal gyrus (BA44/47)	Increase
27 -45 -12	6585	R cerebellum L cerebellum R lingual gyrus (BA17) L lingual gyrus (BA17)	Increase
12 -18 0	294	R thalamus	Increase
56 -30 10	713	R middle temporal gyrus R superior temporal gyrus (BA42) R supramarginal gyrus (BA40)	Increase
38 -86 1	445	R middle occipital gyrus (BA18/19) R middle temporal gyrus R inferior temporal gyrus	Increase

Table 4

Age-related changes in neural activation as determined from the calibrated fMRI and CVR-correction methods.

Study	Task	Region**	$\frac{\Delta \text{BOLD}_{\text{fMRI}}}{\text{BOLD}_0} (\%)$	CVR	n	$\frac{\Delta \text{CMRO2}}{\text{CMRO2}_0} (\%)$
Calibrated fMRI studies						
Restom et al. 2007	Picture encoding	MTL	Y > O	-	No change	No change
Ances et al. 2009	Flickering checkerboard	VC	Y > O	No change	No change	No change
Hutchison et al. 2012	Flashing sinusoidal	VC	Y > O	-	Y > O	Y < O
Mohitashib et al. 2012	grating annuli Stroop task	LMFG	Y < O	-	No change	Y > O
		RMFG	Y < O	-	No change	No change
Gauthier et al. 2012b	Stroop task	M1	Y < O	-	No change	Y > O
		LFC	No change	Y > O	No change	No change
		RFC	No change	Y > O	No change	No change
		PC	No change	Y > O	No change	No change
CVR normalization studies*						
Riecher et al. 2003	Button pressing	LSMC	Y > O	Y > O	-	No change
Handwerker et al. 2007	Visumotor saccade task	FEF	Y > O	No change	-	No change
		M1	No change	No change	-	No change
		SEF	Y > O	No change	-	No change
		VC	Y > O	No change	-	Y > O
Kannurpatti et al. 2011	Bilateral finger tapping	SMC	No change	-	-	No change
		VC, PC	No change	-	-	No change
This study	Scene viewing	VC	Y > O	Y > O	-	No change
		MTL	Y > O	Y > O	-	No change
		LIFG	No change	Y > O	-	Y < O

Study	Task	Region**	$\frac{\Delta \text{BOLD}_{\text{fMRI}}}{\text{BOLD}_0} (\%)$	CVR	n	$\frac{\Delta \text{CMRO2}}{\text{CMRO2}_0} (\%)$
		RIFG	Y < 0	Y > 0	-	Y < 0

$\frac{\Delta \text{CMRO2}}{\text{CMRO2}_0} (\%)$ is estimated by $\frac{\Delta \text{BOLD}_{\text{fMRI}}}{\text{BOLD}_0} / \text{CVR}$

** MTL=medial temporal lobe, VC=visual cortex, LMFC=left middle frontal gyrus, RMFG=right middle frontal gyrus, M1=primary motor cortex, LFC=left frontal cortex, RFC=right frontal cortex, PC=parietal cortex, LSMC=left primary sensorimotor cortex, FEF=frontal eye field, SEF=supplementary eye field, SMC=primary sensorimotor cortex, LIFG=left inferior frontal gyrus, RIFG=right inferior frontal gyrus.