VESSEL-REACTIVITY-CORRECTED FMRI REVEALS NOVEL PATTERNS OF AGE-RELATED CHANGES IN BRAIN ACTIVITY

Peiying Liu[1], Andrew C. Hebrank[2], Karen M. Rodrigue[2], Kristen M. Kennedy[2], Denise C. Park[2], and Hanzhang Lu[1]

[1]*Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, Texas, United States,* [2]*Center for Vital Longevity, University of Texas at Dallas, Dallas, Texas, United States*

INTRODUCTION: Cognitive aging studies using BOLD fMRI have revealed a wealth of information about the aging brain. The findings are typically represented by an age-related signal decrease in posterior regions such as visual areas and medial temporal lobe, which is interpreted as an age-related degradation in neural circuitry (1). These findings are nicely complemented by observations of an increase in frontal activations especially in right dorsolateral prefrontal cortex (DLPFC), which is interpreted as compensatory activations using neural reserve (2,3). Despite this seemingly coherent model, an intuitive yet largely unaddressed issue is that brain vascular health also declines with age (4) and, since BOLD is a vascular-based signal, the above fMRI findings could be entirely or at least partly explained by an age-related change in vascular property (5,6). Few previous studies have considered this issue and no lifespan studies (not just two extreme age groups) have taken this factor into study design. Here, we conducted an fMRI study in 132 healthy subjects aged 20-89 years old using an episodic memory (EM) task. In the same session, cerebrovascular Reactivity (CVR) was measured via inhalation of CO2 gas mixture, allowing a quantitative mapping of vasodilatation capacity in the same voxels that fMRI signals were measured from. Reactivity-corrected fMRI signal revealed that no brain regions manifested age-related decline in neural activity (under similar task performance), not even in the occipital cortex. Instead, age-related fMRI signal increase was observed throughout the brain with the effect in frontal regions being most prominent. These findings shed novel insights on age-related changes in neural activity and provide an exemplary illustration that vascular decline should be considered in ALL aging studies using fMRI as a tool.

METHODS: A total of 132 subjects from 20-89 years old were recruited using criteria typical for cognitive aging studies. They have a minimal MMSE score of 26, at least a high school education, and corrected vision of 20/10. Their age and gender distributions are shown in Table 1. All MRI measurements were performed on a Philips 3T MRI scanner. For the EM fMRI task, each subject received 3 fMRI runs with 32 pictures in each run. Each picture appeared for 3s followed by a fixation period of 4-17s (randomized). The subjects were instructed to determine if there is water in the picture and to press buttons in their right hand accordingly. All subjects performed the task accurately. Tasks of similar type are widely used in previous aging studies (1). Standard BOLD fMRI imaging parameters were used: TR/TE=2000/25ms, voxel size 3.4x3.4x3.5mm^3, duration 5.75 min per run. CO2 is a potent vasodilator and, like acetozolamind (Diamox), it can be used to evaluate vascular elasticity and reserve. For the CO2 inhalation task, the subject breathed room-air and 5% CO2 (mixed with 21% O2 and 74% N2) in an interleaved fashion (switching every 1 min) while BOLD EPI images were acquired continuously. This short-duration breathing paradigm has previously been shown to improve subject comfort yet maintaining data quality (4,7). End-tidal CO2, the CO2 concentration in the lung and thus arterial blood, is recorded throughout the breathing task and a regression analysis between this signal and the MRI time course yields the Cerebrovascular Reactivity (CVR) map in the unit of %BOLD/mmHg. The CVR and fMRI data were of identical spatial resolutions, thus can be compared on a region-by-region basis. FMRI signal was calculated as the contrast between picture viewing and fixation. FMRI signal correction was based on a previous report and was simply scaling the signal using CVR, i.e. $fMRI_C$=fMRI/CVR (8,9).

RESULTS and DISCUSSION: Fig. 1 shows fMRI activation maps. Robust activation is seen in early visual areas, medial temporal lobe (MTL), right inferior frontal gyrus (IFG) and left IFG. These four regions were therefore used in the ROI analysis. Fig. 2a (blue) shows age-related differences in the *uncorrected* fMRI signals. Consistent with previous reports, visual area (p=0.05) and MTL (p=0.02) showed age-related decrease (1). Previous reports also suggested that age-related over-recruitment or compensatory responses are more pronounced in the right frontal region (p=0.002) than that on the left side (2,3). This pattern was also observed in our results (Fig. 2a). These data, however, have not accounted for vascular changes in aging. Decade-by-decade CVR maps are shown in Fig. 3 and ROI values are shown in Fig. 2b. As can be seen, an age-related reactivity decline is evident in all regions examined. Therefore, the loss of vascular reactivity itself could result in fMRI signal decrease independent of any true neural differences. For regions manifesting age-related fMRI decrease such as visual areas and MTL, the observations could be partly or entirely due to vascular effect rather than neuronal effect. A false negative error could also occur when age-related neural over-recruitment is offset by the reactivity decline, resulting in no apparent changes in the measured fMRI signal. Using adjustment method described in the Method section, one can correct the fMRI signal using CVR. The corrected fMRI signal is shown in Fig. 2a (red). It can be seen that age-related over-recruitment is now seen in both left and right frontal regions (both p<0.001). Importantly, none of the regions examined showed a signal increase with age. Voxel-wise analysis revealed patterns of similar nature (Fig. 4).

To our knowledge, the present report is the first cognitive aging study that interpreted fMRI findings in the context of vascular changes. Our observations provide strong evidence of a need to re-examine previous fMRI aging literature and suggest that previous studies may have over-estimated age-related decline while under-estimating the extent of compensatory over-recruitment. The reactivity-corrected fMRI data suggested no evidence of age-related decline in neural activity (under similar task performance).

REFERENCES: 1) Gutchess et al, J Cogn Neurosci 17:84, 2005; 2) Cabeza et al, Neuroimage 17:1394, 2002; 3) Park and Reuter-Lorenz, Annu Rev Psychol 60:173, 2009; 4) Lu et al, JCBFM 21:1426, 2011; 5) D'Esposito et al, Nat Rev Neurosci, 4:863, 2003; 6) Riecker et al, JCBFM, 23:565, 2003; 7) Yezhuvath et al, NMR Biomed, 22:779, 2009; 8) Handwerker et al, HBM 28:846, 2007; 9) Kannurpatti et al, HBM, 32:1125, 2011.

Table 1. Subject information

Decade	Num. of subjects	Gender
20's	26	17/9
30's	19	13/6
40's	20	14/6
50's	20	13/7
60's	18	12/6
>70	29	15/14

Fig. 1 Activation map from group level one-sample t test (N=132). Uncorrected p<0.001, k>200.

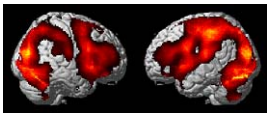

Fig. 2 Scatter plots of the ROI analysis. (a) fMRI signal changes with age. Red color indicates uncorrected fMRI signal. Blue color indicates CVR corrected fMRI signal. (b) Regional CVR changes with age. Each dot represents the mean value of each decade. Error bars are standard deviation. p<0.05 is considered significant.

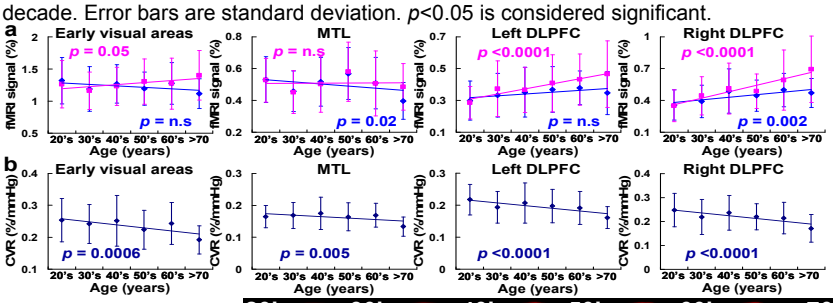

Fig. 3 Decade-by-decade CVR maps.

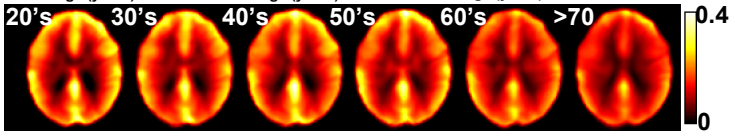

Fig. 4 Voxel-based analysis of age-related increase (warm color) and decrease (cold color). Uncorrected p<0.005, cluster size k>200.