Age-dependence of hemodynamic response characteristics in human fMRI

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Introduction: Functional MRI studies of cognitive aging have generally compared the amplitude and extent of BOLD signal increases evoked by a task in older and younger groups. BOLD is thus used as a direct index of neuronal activation and it is assumed that the relationship between neuronal activity and the hemodynamic response is unchanged across the lifespan. However, one of the main sources of potential confounds in functional MRI studies of aging stems from the ambiguous nature of the BOLD signal, which makes it difficult to draw physiologically specific conclusions from the amplitude and spatial extent of observed changes. The increases in BOLD signal observed during tasks arise from concomitant local changes in blood flow, blood volume and oxidative metabolism. This complicates the direct, quantitative comparison of BOLD signal changes between groups, especially when changes in hemodynamic function across groups are suspected [1]. Even in healthy aging, differences in vascular and metabolic function have been observed that could affect the coupling between neuronal activity and the BOLD signal [2]. Here we use a calibrated fMRI method [3] to explore vascular and metabolic changes that may bias such BOLD comparisons.

Methods: Acquisitions were conducted in 31 young (10 female, mean age of 24 ± 3 years) and 31 older (14 female, mean age of 64 ± 5 years) healthy participants on a 3T MRI system. Sessions included an anatomical, 1mm^3 MPRAGE acquisition (TR/TE/flip angle = 2300ms/3ms/90°, 256x240 matrix) and two pseudo-continuous arterial spin labeling (pCASL) runs, providing simultaneous BOLD contrast using dual-echo readouts (TR/TE1/TE2/flip angle = 2000ms/10ms/30ms/90° with 4x4x7mm voxels, 64x64 matrix and 11 slices, post-label delay=900ms, tag duration=1.5s, with a 100mm gap) during a modified Stroop and a hypercapnia challenge (5mmHg end-tidal CO_2 change, iso-oxic during two, 2min blocks). Older participants had an additional FLAIR acquisition to estimate the presence and severity of white-matter lesions (TR/TE/flip angle =9000ms/107ms/120, inversion time = 2500 ms, 512x512 matrix with 0.43x0.43x4.8mm voxels) and all included participants had no or few lesions. The Stroop task consisted of two 60s blocks each of control and Stroop conditions, separated by 60s rest blocks for a total acquisition of 9min. ROIs were determined from the intersection of each group's significant BOLD and CBF change to the Stroop task. The grey matter ROI was obtained by automatic tissue segmentation. BOLD and CBF percent effects were determined by averaging over each ROI and *M* was obtained using the generalized calibration model [3].

Results: This study explores the hemodynamic and vascular changes in regions thought to be associated with age-related changes. Reaction times (RT) to a Stroop task were found do be significantly higher in the older group than in the younger group ($p < 0.0001$) (Figure 1). Group analysis of the Stroop task activation maps revealed significant BOLD and ASL signal increases in similar areas for both groups. Significant BOLD and ASL increases (Figure 1) were found in several regions over cortex including anterior cingulate, part of the frontal, parietal and occipital lobes, as well as some sub-cortical structures covering mainly the putamen. Percent BOLD and CBF responses to the Stroop task were similar between the two groups over all ROIs. In contrast to the BOLD and CBF responses to the Stroop task, other hemodynamic signals were found to be generally decreased in the older group. More specifically, BOLD and CBF responses to hypercapnia were found to be significantly lower in pooled ROIs ($p < 0.0001$) (Figure 2 and 3) in the older group as compared to the young. Baseline CBF and the calibration parameter *M* were also found to be lower in the older group over pooled ROIs ($p \leq 0.003$) (Figure 3).

Conclusions: Neuroimaging studies of cognition typically use the BOLD signal to localize brain regions involved in the performance of a task. Cognitive studies of aging often compare the BOLD signal changes in groups of young and older adults in the context of tasks known to be associated with significant behavioral age-related differences. The assumption made in such studies is that the BOLD signal can be taken as a direct index of neuronal activity. However, there is reason to believe that this simplifying assumption may not be valid when comparing groups of widely different age, given that significant vascular changes are known to occur during adult life [1,2]. The results of the present study indicate that caution must be exercised when making these direct comparisons and that there are in fact profound vascular biases associated with age. Age-related vascular changes may mask some metabolic differences and lead to erroneous conclusions when only BOLD results are taken into account to make inferences about the neuronal resources used during performance of a task.

References: [1] Ances B.M. et al. Effects of aging on cerebral blood flow, oxygen metabolism, and blood oxygenation level dependent responses to visual stimulation. 2009; Hum Brain Mapp 30: 1120-1132; [2] Brown W. R. et al. Review: cerebral microvascular pathology in ageing and neurodegeneration. 2011; Neuropathol Appl Neurobiol 37: 56-74; [3] Gauthier C. J. et al. A generalized procedure for calibrated MRI incorporating hyperoxia and hypercapnia. 2012; Hum Brain Mapp In press.

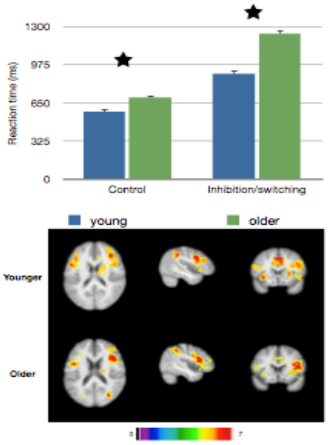

Figure 1. Stroop responses
Maps of significant BOLD responses to the Stroop task were not different between groups, while behavioral responses showed older adults to be slower than younger adults ($p < 0.0001$).

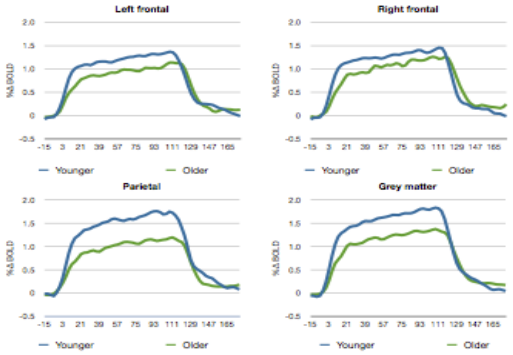

Figure 2. BOLD hypercapnia time courses
Time courses of percent BOLD signal change in response to hypercapnia over all functionally determined ROIs (left frontal, right frontal, parietal) and over all grey matter. BOLD responses to hypercapnia were lower in all ROIs in the older group ($p < 0.0001$).

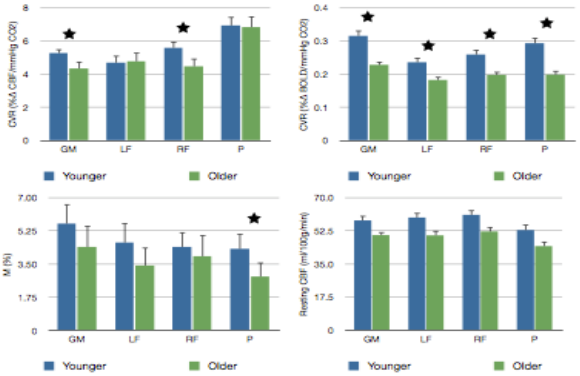

Figure 3 Baseline CBF, CVR and M
This figure shows baseline CBF values in ml/100g/min, CBF CVR in percent CBF change per mmHg end-tidal PCO2 increase, BOLD CVR in percent BOLD signal change per mmHg end-tidal PCO2 increase and M in percent for all ROIs, where GM is grey matter, LF is left frontal, RF is right frontal and P is parietal. Baseline CBF showed a trend towards a lower baseline flow in the older group over pooled ROIs ($p < 0.0001$), while only BOLD CVR differed significantly over all ROIs ($p < 0.002$). Significance at the individual ROI level is indicated by a star.