Quantitative Hippocampal Perfusion Response to a Memory Encoding Task: A Comparison Between Healthy Young and Elderly Adults

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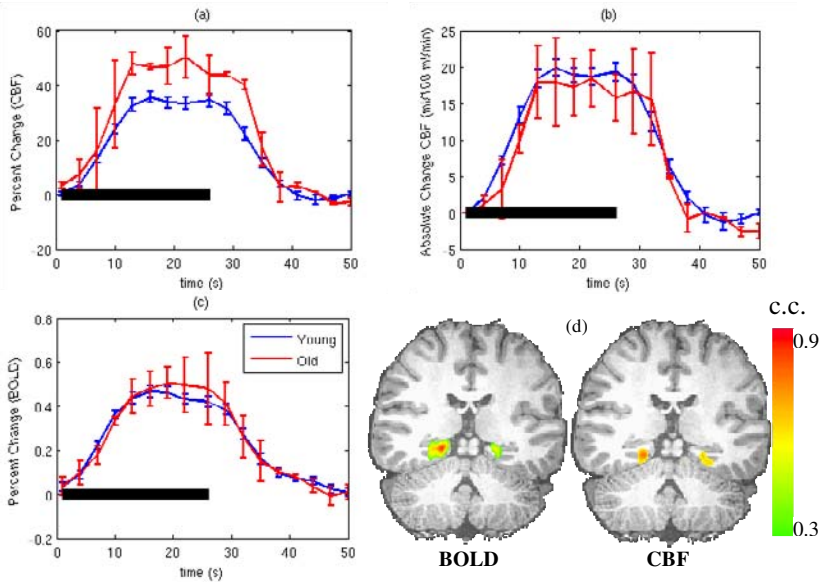
Introduction

Perfusion-based functional magnetic resonance imaging (fMRI) with arterial spin labeling (ASL) has several potential advantages over traditional blood oxygenation level-dependent (BOLD) fMRI for the study of cognitive function. These benefits include the possibility of a more linear relationship between neural activity and cerebral blood flow (CBF) [1], more precise localization of neural activity [2], and an inherent insensitivity to low frequency drifts. In addition, ASL techniques are compatible with acquisition methods, such as a spin-echo readout, that are useful for reducing magnetic susceptibility-related artifacts in brain structures such as the hippocampus. Despite these potential advantages, the application of ASL to the investigation of cognitive function has been rather limited due to the lower inherent sensitivity of ASL as compared BOLD. In addition, there has been relatively little application of functional ASL to studies examining the effects of aging or disease. In this study, we demonstrate that ASL can be used to obtain robust quantitative measures of functional increases in hippocampal perfusion in healthy young and elderly adult subjects.

Methods

Eleven healthy young (age range 23-31) and three healthy elderly (age 65,68,75 yrs) subjects participated in the study. None had any history of cognitive impairment. Imaging was performed on a 3T GE Signa whole body system, where simultaneous perfusion and BOLD data were acquired using a dual echo PICORE QUIPSS 2 sequence with spiral readout [3]. Subjects viewed a series of novel and familiar landscape scenes, presented in a block design. Each block consisted of 10 familiar or novel images, with 2s per image and a 0.5s gap between images. A total of 5 blocks of each type were presented per run (250s), with 3 runs per subject. Subjects maintained attention by using a button box to indicate whether images were horizontally or vertically oriented. Data were also acquired at rest for quantification of baseline CBF. Imaging parameters were: TR=3s, TI1/TI2=700/1400ms, TE1=2.8ms, TE2=24 ms, flip angle 90, FOV 240mm, 64x64 matrix. Five 6mm slices aligned with the hippocampus were acquired. Data from one of the elderly subjects (age 68yrs) could not be used due to severe motion artifacts.

Perfusion and BOLD time series were acquired from the running difference and average of tag and control images, respectively. Cardiac and respiratory confounds were removed from the data using an extension of RETROICOR for perfusion-based fMRI [4,5]. For each subject, a hippocampal region of interest (ROI) that included both the hippocampus and para-hippocampal gray matter was defined using a high resolution anatomic T1-weighted image. BOLD and ASL data were averaged over runs and correlated with a smoothed boxcar reference function. Correlation coefficient thresholds were set at 0.3, with nearest neighbor clustering. CBF was quantified for each of the resting scans, using CSF as a signal intensity reference [6]. Average CBF values of activated voxels from the perfusion functional runs within the hippocampal ROI were used to calculate baseline CBF values, and absolute change in CBF during activation.



Results

Reliable and robust activation was seen in all subjects. The figure shows mean group responses for (a) percent change in CBF, (b) absolute change in CBF and (c) percent BOLD signal change The mean percent CBF change in young subjects was significantly lower (two-sided t-test, $p<0.022$) than that in the elderly subjects (means 34% vs. 47%). However, the mean absolute CBF change was not significantly different between groups (18.8 and 17.4 ml/100ml/min for young and old, respectively ($p=0.74$)). Mean baseline CBF was significantly lower in the elderly (42.5 ± 19.7ml/100ml/min) than the young (56.3 ± 4.8ml/100ml/min) subjects ($p<0.015$)). The mean BOLD % change was not significantly different between groups (0.43% and 0.48%) ($p=0.26$). An example correlation map showing BOLD and perfusion activation for a young subject is shown in (d). Physiological noise correction of the functional perfusion data was critical. As compared to the analysis of the data without noise correction, the removal of physiological components resulted in a significantly larger ($p<0.0001$) number of activated voxels in the young subjects (average number of voxels per subject before correction= 82, after correction = 210, 2.5 fold improvement) and an even larger increase ($p<0.0001$) in the elderly subjects (average number of voxels per subject before correction= 15, after correction = 121, 8 fold improvement).

Discussion

Robust measures of hippocampal perfusion changes were obtained in both young and older subjects, with physiological noise correction playing a critical role. The preliminary data suggest that elderly subjects have a lower resting CBF, with an increased percent change in CBF during functional activation. However, the response in absolute units of CBF is comparable to that of the young subjects. As compared to a previous study reporting perfusion-based fMRI of hippocampal activation [7] in a small sample size (N=3) of young healthy adults, the functional CBF increases obtained in the present study show significantly less variation (31% ± 17.2 (previous) vs. 34% ± 6.3 (present)) across a larger sample size, due in large part to the use of physiological noise correction. In addition, the use of physiological noise correction enabled us to detect functional CBF activation in elderly subjects. The results of this study support the feasibility of measuring functional hippocampal perfusion in healthy older subjects and lay the groundwork for further studies aimed at examining the effects of aging and disease, such as Alzheimer's disease, on hippocampal perfusion.

References

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