Quantitative Mapping of the Age-Dependence of Cerebral Blood Flow using Pulsed Arterial Spin Labeling

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Introduction

The relationship between aging and cerebral blood flow (CBF) in healthy adults remains a topic of debate [1-3]. Various quantitative perfusion-weighted imaging (PWI) techniques have been employed, including positron-emission tomography (PET) [1] and dynamic susceptibility contrast (DSC) MRI [2]. However, PET and DSC seem to disagree on whether CBF changes at all with age, an issue that may be partially derived from differential partial-volume effects across techniques [1]. Also, the invasiveness of both PET and DSC limit their research application. Arterial-spin labeling (ASL) is a versatile and noninvasive alternative, and continuous ASL (CASL) has shown sensitivity to differences in CBF between children and adults [3]. However, CASL requires specialized coils and is associated with higher power deposition, an impediment to high-field imaging. In this work, we assess the feasibility of pulsed ASL (PASL) in probing quantitative changes in resting CBF during aging in cognitively healthy adults, and evaluate the impact of partial-volume effects.

Methods

Fifty-eight healthy participants (26 men/32 women), aged 51.9±18.1 yrs (ranging from 22.6 to 87.2 yrs), were imaged using a Siemens Trio 3 T system. The scans employed 12-channel phased-array head coil reception and body-coil transmission. Two PWI datasets were obtained for each subject using FAIR QUIPSS II PASL [4] with ¾ partial Fourier EPI readout (matrix=64x64x, #slices=24, voxel size=3.4x3.4x5 mm^3), #frames=104, $TI_1/TI_2/TE/TR$ = 600 ms/1600 ms/12 ms/4 s. A slice-selective frequency-offset corrected inversion (FOCI) pulse was applied during tag and control, the latter scan acquired in the absence of slab-selective gradients. The tag and control labeling thicknesses were 140 mm and 340 mm, respectively, leaving 100 mm margins at either end of the imaging slab to ensure optimal inversion profile. The QUIPSS II saturation pulse was applied to a 100 mm slab inferior to the imaging region with a 10 mm gap between the adjacent edges of the saturation and imaging slabs. This PASL sequence was used in a calibration scan (TR =10 s) to estimate the equilibrium magnetization of arterial blood. A 3D anatomical scan (1x1x1 mm^3) was acquired using multi-echo MPRAGE [5]. The PWI data were motion- and drift-corrected, and the difference images calculated using surround subtraction, compensating for T_1-relaxation during transit delay. These volumes were then averaged across time and datasets to maximize signal-to-noise, following which quantitative CBF (qCBF) maps were obtained as per the Standard Kinetic Model using both cerebrospinal fluid (CSF)- and local tissue-based calibration, assuming a 95% labeling efficiency as well as proton density and T_2* values described by Çavuşoğlu et al. [6]; for the former, intensity non-uniformity correction was performed per Ref. [7]. The PWI data were registered to the anatomical images [8], and subsequently sampled into surface-space at a cortical depth of 50%, then registered to a surface-atlas using FreeSurfer. The correlation between cortical qCBF and age was obtained in considering the effect of cortical thickness, serving as a surrogate of potential partial-volume contamination. The statistical tests were performed post surface-smoothing (FWHM=10mm) and outlier removal, and corrected for multiple comparisons [9].

Results

The local-tissue calibration technique was found to produce lower local spatial variations in qCBF (data not shown), and intrinsically corrects intensity non-uniformities, which, if not normalized, could introduce artifactual spatial variations in qCBF. Based on this calibration method, the mean resting cortical grey matter qCBF in the young, middle-aged and old adult groups (mean age = 30.8±6.1, 50.0±5.8 and 72.6±8.3 yrs) were 51.1±10.8, 48.2±9.7, and 43.9±10.1 ml/100 g/min, respectively. Mean qCBF was higher in females than in males in the young and old groups ($p < 0.05$) but not in the middle-aged group, nor was the disparity significant when all ages were pooled; nonetheless, gender effects were adjusted for in the subsequent analyses. The corresponding data are shown on semi-inflated lateral (top) and medial (bottom) surface models in Fig. 1. Cortical thickness was regionally decreased with increasing age (shown in blue in Figure 1b), but its pattern did not completely overlap with that of qCBF (Figure 1a). Cortical thickness, hence the possibility of partial-volume effects, affected the qCBF-age relationship mainly in the superior frontal lobe, with minimal impact elsewhere. After the removal of cortical thickness effects, the most robust qCBF reductions (Figure 1c) remained in the medial-frontal, inferior-temporal, parietal, lateral-occipital and posterior-cingulate regions, irrespective of the calibration method. Averaging across all regions, linear regression revealed qCBF to decrease at ~0.19%/year ($p < 0.05$) (Figure 2). The most rapid reduction was observed in the superior parietal lobule, at ~0.36%/year.

Conclusion

Quantitative perfusion imaging using PASL is widely accessible, noninvasive and can be performed without additional hardware. Also, its lower power deposition is amenable to high-field applications. However, accurate qCBF mapping using PASL is beset by challenges such as transit-delay, image non-uniformity, and blood magnetization estimation. In this work, we have shown PASL to be feasible in studying cortical perfusion changes with age in spite of these challenges. Our qCBF estimates are consistent with the MRI and PET literature [6,10]. The qCBF reduction with age was robustly reproduced with both CSF and local-tissue calibration, with the localization in agreement with patterns of age-related oxygen metabolism decrease measured using PET [11]. Partial-volume effects were shown to modulate PASL-derived qCBF particularly in areas of significant cortical atrophy, and merits careful consideration. Future work will employ PASL to investigate sub-cortical CBF changes with age as well as perfusion alterations in Alzheimer's disease.

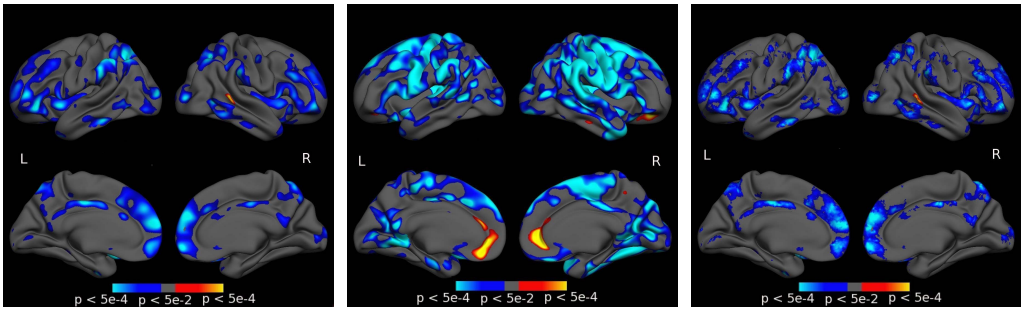

Figure 1. Significance maps: reductions in qCBF (a) and in cortical thickness (b) co-exist in aging, though affecting non-overlapping locations. CBF changes after regressing out cortical-thickness effects are shown in (c).

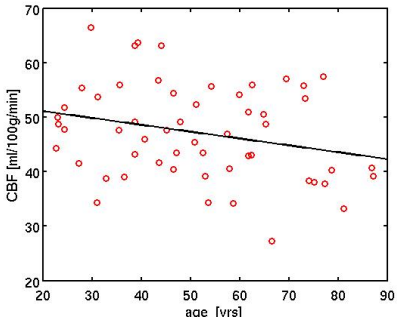

Figure 2. Cortical qCBF across subjects (circles) shows reduction with age.

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