Association between Cerebral Blood Flow and Age-Related Changes in White Matter Microstructure

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Introduction

White matter (WM) degeneration occurs as part of normal aging [1] and in age-associated degenerative diseases such as Alzheimer's dementia [2] and cerebral amyloid angiopathy [3]. WM integrity is strongly influenced by cerebrovascular status [4,5]. Recently, arterial spin labeling (ASL) magnetic resonance imaging (MRI) has been used to characterize cerebral blood flow (CBF), a metric of vascular and metabolic health that has been applied in the study of aging [6,7], but it is unclear whether changes in CBF are associated with the described WM deterioration. In this work, we use diffusion tensor imaging (DTI) in conjunction with pulsed ASL perfusion imaging to probe this connection.

Methods

Seventy eight cognitively healthy participants were imaged using a Siemens Trio 3 Tesla system (34 men/44 women, 23 to 88 years). The sample was comprised of 10 young (<40 years), 37 middle-aged (<60 years) and 31 older (>60 years) adults. The scans employed 12-channel phased-array head coil reception and body-coil transmission. The diffusion-weighted images were obtained using twice-refocused spin echo [8], 64 slices, TR/TE = 7920/83 ms, b =700s/mm^2, 2x2x2 mm^3 voxels, 60 directions, 10 b=0 volumes. Two perfusion datasets were obtained for each subject using FAIR QUIPSS II PASL [9] with ¾ partial Fourier EPI readout, 24 slices, matrix=64x64, voxel size=3.4x3.4x5 mm^3, 104 frames, TI_1/TI_2/TE/TR = 600 ms/1600 ms/12 ms/4 s, tag = 140 mm, control label = 340 mm, saturation gap = 100 mm. Calibration scan: EPI with TR = 10 s. A 3D anatomical scan (1x1x1 mm^3) was acquired using multi-echo MPRAGE [10]. Quantitative CBF maps were computed from the mean control-tag difference using surround subtraction, compensating for transit delay, using the Standard Kinetic Model with local-tissue calibration [11]. Fractional anisotropy (FA), mean (MD), axial (L1) and radial (LR) diffusivity were computed using the FSL Diffusion Toolbox, with motion and eddy-current correction. The ASL and DTI data were co-registered using boundary-based registration [12]. Voxelwise DTI group-analysis was performed using TBSS (Tract-Based Spatial Statistics [13]), whereby all subjects were aligned based on FA, and a common skeleton obtained, from which all DTI parameters were sampled (threshold = 0.2). General linear model-based statistical analyses were performed using cortical CBF and age as regressors.

Results

Mean cortical CBF decreased in aging at a rate of 0.38%/year ($p < 0.05$), controlled for concurrent cortical atrophy. The peak age-related CBF reductions were in the superior frontal and parietal, mid-inferior temporal, insular, precuneus and cingulate regions. Age-associated decrease in FA and increase in MD overlapped in the anterior WM, with most the MD effects accounted for by increasing LR, while L1 dropped in the posterior tracts (Figure 1). Correlations with CBF alone were weaker, but mirrored the correlations with age. Interestingly, unlike the age effects, which were mainly observed in FA, MD and LR (Figure 1), the CBF effects (independent of age) were strongest in the MD, L1 and LR (p<0.05 for all results), and was more evenly distributed instead of being more weighted towards tine anterior part of the brain. The genu and body of the corpus callosum were most affected by both age and CBF. Scatter plots for select ROIs are shown in Figure 3. To isolate the effect of natural CBF variations in DTI parameters, the effect age was regressed out of the DTI parameters. However, this had negligible effect on the observed correlations.

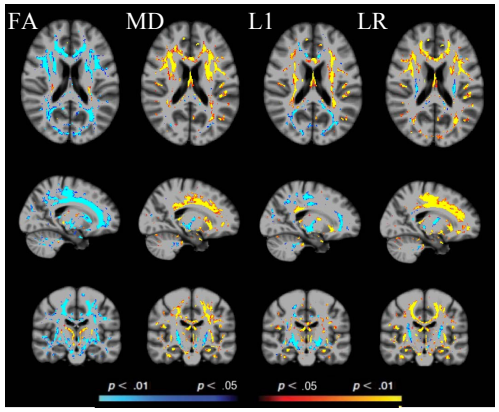

Figure 1. Correlation between anisotropy (FA), mean diffusivity (MD), axial (L1) and radial (LR) diffusivity and age – aging induces global decline in FA, the spatial distribution of which is mirrored by changes in L1.

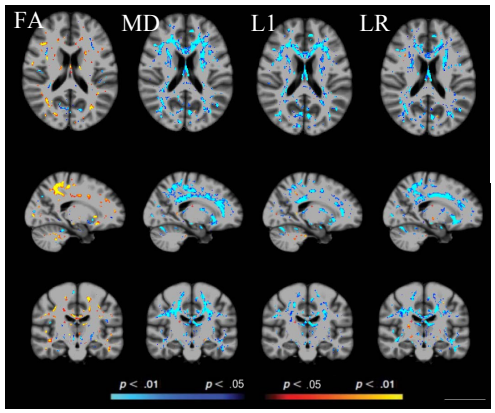

Figure 2. Correlation between FA, MD, L1 and LR and mean cortical CBF (regressing out the effect of age) – aging induces global decline in FA, the spatial distribution of which is mirrored by changes in L1.

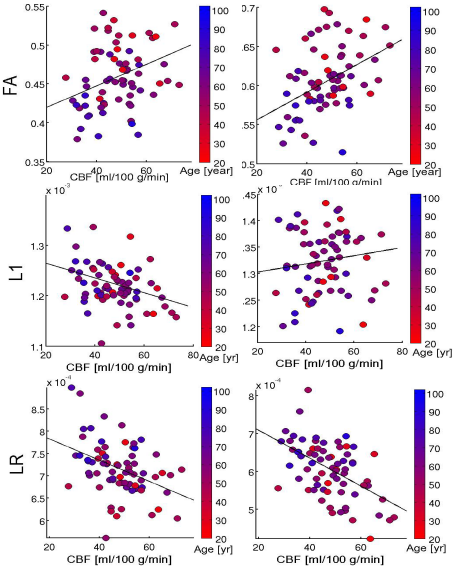

Figure 3. Anisotropy, axial and radial diffusivity vs. CBF in the anterior corona radiata (left) and cingulum (right).

Conclusion

This study is the first to examine the relationship between CBF and regional diffusion parameters in aging. CBF is significantly associated with DTI-measures of WM integrity, demonstrating a definitive link between neurovascular factors and WM health even within each age group. Our findings also suggest a spatial correspondence between the influences of cortical perfusion and aging on underlying WM structure in aging. Interestingly, the spatial influence of age on WM integrity also differs somewhat from that of CBF alone. Future work will examine the connection between structural, perfusion and cognitive health measures.

References

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