Perfusion and Diffusion Imaging in a Mouse Model of Alzheimer's Disease

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INTRODUCTION Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a decline in memory and cognitive function. Recent evidence suggests that cerebrovascular dysfunction could emerge as an early predictor of AD (1,2,3). Transgenic mouse models of AD are available for study, however due to their small size, cerebral blood flow studies (CBF) have been largely limited to destructive or invasive methods (1,2). Continuous arterial spin labeling MRI with a separate neck labeling coil provides a non-invasive means to image CBF. In mice, however, this has not been possible because the proximity of the neck coil to the brain significantly saturates the brain signal. To overcome this limitation, we recently developed the cardiac spin labeling (CSL) technique (5) in which the labeling coil is placed at the heart position. In this study, we used CSL to image basal CBF and hypoxia-induced blood oxygen level dependent (BOLD) and CBF changes in a presenilin-1/amyloid precursor protein (PS/APP) transgenic mouse model of AD. Additionally, diffusion tensor imaging was performed to image apparent diffusion coefficient (ADC) and fractional anisotropy (FA) in PS/APP and control mice.

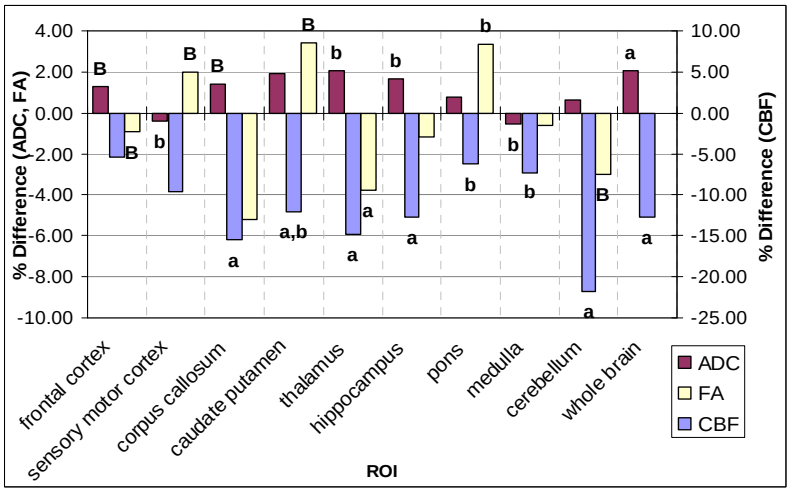
METHODS Twelve mice (6 control, 6 PS/APP, 20-29 months, 25-40 g) were imaged under ~1.1% isoflurane and spontaneous breathing conditions. Each animal was imaged twice separated by ~1 week. Respiration rate and rectal temperature were maintained within normal physiological ranges. PS/APP mice were double transgenic with APPswe mutation and mutant human PS1 with the exon 9 deletion (PS1ΔE9). Control mice were wild-type littermates. After MRI, brains were fixed and stained with 6E10 β-amyloid antibody to confirm the presence of amyloid plaques in the PS/APP brains.

MRI was performed on a 7T/30cm Bruker scanner with a 150 G/cm gradient (6 cm ID) using a small surface brain coil with active decoupling (ID = 1.1 cm) and a small circular heart coil (ID = 0.9 cm) for spin labeling placed in the heart position (5). All images were acquired using single shot EPI with a 1.28x1.28 cm FOV, 64x64 matrix, and 11 1-mm slices. CBF MRI used a 2.1 s labeling pulse, 2.6 s TR, 9 ms TE. Imaging under physiological challenge had the same parameters except with 6 slices and 18 ms TE. DTI was acquired using spin echo EPI with 2.2 s TR, 24 ms TE, 0 and 1200 s/mm^2 b values, and diffusion gradients in 30 directions. Hypoxic challenges involved 3.5 min of 30% O_2 in air and 3.5 min of 10% O_2 in nitrogen. CBF maps (ml/g/min) and ADC maps (mm^2/s) were calculated as in (6). Regions of interest (ROI) were drawn on images for regional analysis of CBF, ADC and FA. Statistical analysis was performed using analysis of covariance with age as a covariate. Data are given as mean ± SD.

RESULTS Quantitative blood flow images showed a decrease in all regions in PS/APP mice, although not all changes were significant (**Figure**). Average whole brain CBF was 0.94 ± 0.09 ml/g/min (n=6) in control animals compared to 0.82 ± 0.17 ml/g/min (n=6) in PS/APP mice. ADC tended to increase in most regions, although it was significant only in the whole brain. FA also did not show significant difference between groups. In general, our age range did not have a significant effect on CBF, but age had a strong significance on both ADC and FA in many of the ROIs. The hypoxia-induced CBF changes were -46 ± 7% in controls (n=4) and -42 ± 16% in PS/APP (n=4) (p=0.6 between control and PS/APP). The hypoxia-induced BOLD changes were -9.6 ± 1.8 % in controls and -12.3 ± 3.0 % in PS/APP (p<0.05 between control and PS/APP). Histologically, PS/APP mice were loaded with plaques throughout the brain, including the cerebellum, whereas control mice did not show any plaques (data not shown).

DISCUSSION CBF was consistently lower in all regions of the PS/APP mouse brain, as expected. Interestingly, the ROI with the largest CBF decrease was the cerebellum, in contrast to (1) where the cerebellum was found to have a relatively small and non-significant decrease. Although the cerebellum in AD has less Aβ-pathology than do many forebrain regions, the cerebellum in this PS/APP mouse is heavily laden with Aβ deposits. The brain stem had only a small change in CBF, consistent with most other studies (1,3). ADC tended to increase as expected, but was statistically non-significant. FA also did not show significant differences. There are conflicting results in the literature regarding diffusion imaging, as some reports have found no changes in ADC and FA in AD, but other reports have found changes. The most commonly reported alterations in diffusion occur in regions of white matter, and while the increased ADC and decreased FA we found in the corpus callosum are similar to reported differences in AD (4), our changes were not statistically significant. A possible explanation for this is a loss in sensitivity due to partial volume effects in the thin corpus callosum of mice. Previous reports have found significant attenuation of changes in relative CBF (2) and relative cerebral blood volume (7) during physiological stimulation. However, our CBF fMRI showed only a slight attenuation of the response to hypoxia in PS/APP mice.

This study demonstrates that quantitative CBF and CBF fMRI can be measured in mice and could provide a useful, and possibly early, marker for AD. Future studies will image different animals at different stages of pathogenesis at higher spatial resolution.



	PS/APP	Control	% Diff
ΔBOLD	-12.3 ± 3.0	-9.6 ± 1.8	27.7
ΔCBF	-41.8 ± 16.1	-45.9 ± 7.3	-9.0

Table. CBF and BOLD % changes in PS/APP and control mice responding to 10% O_2. The difference in ΔBOLD between PS/APP and control was significant at p<0.05.

Figure. Regional % differences in CBF, ADC, and FA between control and PS/APP mice. a: significance between PS/APP and control p<0.05, b: significance between ages p<0.05, B: significance between ages p<0.005.

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