Regional correlation between pCASL perfusion and PiB-PET in familial Alzheimer's disease

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TARGET AUDIENCE: Neuroimaging scientists and clinicians

INTRODUCTION: Biomarkers for pre-symptomatic stages of Alzheimer's disease (AD) have become increasingly important for the development of preventative interventions. [^{11}C]Pittsburgh compound B ([^{11}C]PiB) PET amyloid imaging has been widely used for monitoring amyloid-β deposition, and for evaluating anti-amyloid and other therapies of AD. In particular, tracer kinetic modeling of PiB-PET can yield multiple parameters including R1 (related to tracer delivery or relative perfusion), binding potential (BP) and distribution volume ratio (DVR=BP+1) of PiB[1]. Arterial spin labeling (ASL) is a noninvasive MRI technique to measure cerebral blood flow (CBF), and has shown promises as an imaging marker of AD[2]. The purpose of the present study was to systematically compare ASL perfusion MRI with PiB PET in 25 familial AD (fAD) related subjects who are either carriers of *PSEN1*, *PSEN2*, or *APP* mutations or their non-mutation carrying family members.

METHODS: Twenty-five fAD related subjects (age 38+/-12 years, 15 females) participated in this study. Dynamic ^{11}C-PIB PET/CT scans were acquired on each subject in list-mode for 70 mins. Raw PET data were rebinned into 6 x 30s, 4 x 180s, and 11 x 300s, and were reconstructed using ordered subset expectation maximization algorithm (6 iterations, 16 subsets) with a post-reconstruction 3D Gaussian smoothing (FWHM: isotropic 3mm). A retrospective image-based movement correction procedure was applied to correct for possible misalignment between CT and PET scans and between PET image frames.

All subjects also underwent MRI scans on a Siemens Tim Trio 3T scanner. Pseudo-continuous ASL (pCASL) with 3D background suppressed GRASE sequence was applied for perfusion measurement with the following imaging parameters: FOV=220mm, matrix=64×64, TR=4s, TE=22ms, labeling duration=1.5s, post delay time=1.5s, 26 5mm slices, 40 pairs of label and control measurements. A T1-weighted structural scan MPRAGE was also acquired.

Both ASL and PET images were coregistered to the subject's MPRAGE images, which were warped to MNI single-subject brain template using the symmetric image normalization method implemented in ANTS[3]. The normalized CBF images were further smoothed with a 3mm FWHM kernel, and then scaled by dividing the CBF of each voxel by the mean CBF in cerebellum for each subject, thereby generating relative CBF (rCBF) images. Using the combined transformation from template to PET space, tissue time-activity curve was generated for cerebellar gray matter (reference region) and parametric images of relative perfusion (R1) and distribution volume ratio (DVR) were constructed by simplified reference tissue model (SRTM)[4] and Logan graphical method[5], respectively.

RESULTS: Figure 1 shows the mean rCBF, R1 and DVR images over the 25 subjects studied. R1 and rCBF images show high consistency with each other with high contrast between gray and white matter. DVR images show more uniform spatial distribution between cortical gray and white matter. Voxel-by-voxel correlations between the mean rCBF and mean R1 maps of 25 subjects were calculated separately for 9 ROIs. The scatter plots of rCBF to R1 in each ROI are shown in Figure 2. Significant correlations between rCBF and R1 were observed in each ROI with an overall mean correlation coefficient of r=0.65. The highest correlation was seen for cingulum (r=0.80) with the lowest correlation seen in hippocampus (r=0.30). A reduced correlation with the mean correlation coefficient of 0.4 was found between rCBF and DVR. The correlation between the mean ROI values of rCBF and R1 values across 25 subjects in the 9 ROIs was also calculated. The overall correlation was intermediate (mean r=0.19) with the highest correlation in parietal cortex (r=0.45) and lowest correlation in amygdala (r=-0.05). The cross-subject correlation between the mean rCBF and DVR ROI values was also calculated in the 9 ROIs, which showed negative correlations with a mean correlation coefficient of r=-0.18.

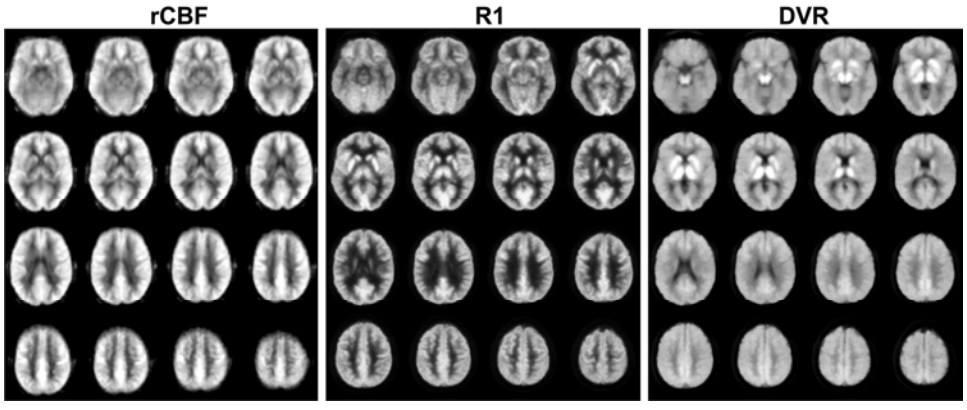

Figure 1 Averaged rCBF, R1 and DVR images across 25 subjects

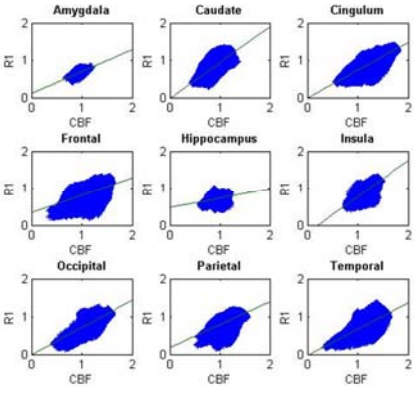

Figure 2 Pixel-wise scatter plots between mean rCBF and R1 maps in 9 ROIs

DISCUSSION: To the best of our knowledge, this is the first study to systematically compare ASL perfusion with PiB PET. The similar spatial pattern and significant voxel-wise correlations between rCBF and R1 are expected since both parameters reflect brain perfusion. The negative cross-subject correlation between rCBF and DVR suggest that brain regions with high DVR values may be associated with hypoperfusion. This is consistent with the vascular hypothesis of AD, that cerebrovascular dysfunctions, such as hypoperfusion, likely precede and may even cause vascular and parenchymal amyloid deposition[6]. Our data suggest that ASL and PiB PET, in direct comparison, can provide valuable diagnostic information for AD.

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