Assessing Arterial Spin Labeled Perfusion MRI as an Early-Alzheimer's Disease Marker using the ADNI 2 data

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Introduction. Cerebral blood flow (CBF) measured by arterial spin labeled (ASL) perfusion MRI provides a quantitative measure of brain function similar to FDG-PET [1], but at a lower cost and without ionizing radiation. ASL is being included in the Alzheimer's Disease Neuroimaging Initiative (ADNI), providing an opportunity to assess CBF variations across different AD disease stages. We assessed CBF difference within a PET-derived metaROI, which has proven sensitive to early AD-related change, across a spectrum of elderly controls (EC), patients with either "early" or "late" Mild Cognitive Impairment (MCI) as defined by ADNI, and patients with AD from the ADNI cohort. For comparison, we also examined differences in hippocampal volumetry (HIPPVOL), a standard structural biomarker of AD.

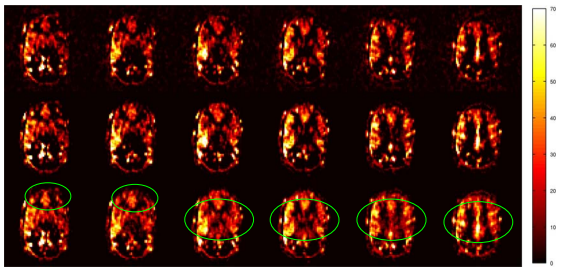

Fig. 1. One representative subject's CBF map generated using different processing strategies.

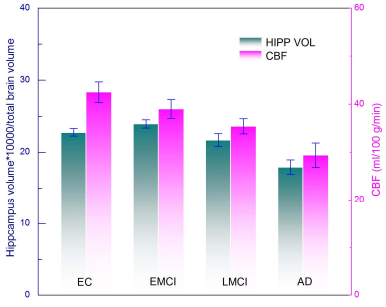

Fig. 2 Hippocampus volume and metaROI CBF of all four subgroups. Hippocampus volume was a relative number in proportion to the total intracranial brain volume. Error bars mean standard errors.

Materials and Methods. Data from 46 elderly controls (EC) (age: 72.9±7.0 yrs, MMSE: 28.9±0.19), 15 AD patients (age: 75.6±8.8 yrs, MMSE: 22.4±1.6), 31 early MCI patients (EMCI; age: 68.73±7.2, MMSE: 28.55±1.36), and 36 late MCI (LMCI; age: 72.21±7.26, MMSE: 27.44±2.03) were analyzed. ASL data were acquired using a Siemens product Q2TIPS PICORE [2] with TR/TE=3400/12 ms, TI1/TI2=700/1900 ms, FOV=256 mm, 24 sequential 4 mm thick slices with a 25% gap between the adjacent slices, partial Fourier factor= 6/8, imaging matrix=64x64. MPRAGE obtained at 1 mm isotropic resolution were also used. 10 subjects had unusable ASL data due to poor coverage and image quality.

ASL images were preprocessed using ASLtbx with standard procedures [3,4] and global nuisance cleaning [3]. CBF was calculated using the Buxton model[5]. Outlier CBF maps were further cleaned using an adaptive procedure in which initial outliers were identified using head motion time courses and the whole-brain CBF time series as described previously[4], then CBF volumes with a CC <0.15 (p<1e-6) or CC>2*SD from the remaining mean were identified as new outliers and were also excluded. This was repeated until no new outliers were identified. Most subjects converged with one iteration, only 3 subjects took 2 iterations. Fig. 1 shows the effects of outlier cleaning (AOC) for a representative subject. As compared to no outlier cleaning (NOC), both the basic outlier cleaning (BOC) and AOC gradually improved CBF image quality. As compared to both NOC and BOC, AOC also improved CBF signal in the central brain regions of each slices. Partial volume effects were corrected using the method proposed in[6]. An in-house software package [7] was used to automatically extract HIPPVOL from MPRAGE data. SPM DARTEL [8] was used to map each individual brain into the MNI space and mean CBF from the PET-derived meta-ROI (ROI) described by Landau et al. [9] was extracted for all subjects. A series of 2-sample t-tests were performed on the HIPPVOL and the Landau ROI CBFs to assess their difference between different sub-groups.

Results and Discussion. CBF and HIPPVOL were related to MMSE (across 4-groups with cc=0.21, 0.37, and p=0.014, 3.1e-5, respectively). ASL CBF in the metaROI appeared to decrease inversely with degree of impairment (EC to AD; Fig. 2, p=0.0018, ANOVA). Hippocampal volume also decreased with impairment, with the exception of the EMCI group (p=4.44e-5, ANOVA). Both hippocampal volume and ASL CBF significantly (Table 1) differentiated AD patients from the other 3 groups: ECs, EMCIs, and LMCIs. Neither measure revealed significant differences between EC and EMCI patients, however while ASL CBF significantly differentiated LMCI from EC, hippocampal volumes did not. Our results are the first to demonstrate the sensitivity of CBF to prodromal and early AD in a multi-site context. While the pathoetiology of MCI is heterogeneous, ASL MRI appears to track disease severity consistent with prior work with FDG PET. These findings support the potential utility of ASL MRI as an AD biomarker in clinical research and practice.

Table 1. p values of cross-population differences of age, MMSE, (HIPPVOL), and metaROI CBF

	AGE	MMSE	HIPPVOL	CBF
EC vs LMCI	0.648744	0.000163	0.252813	0.016064
EC vs EMCI	0.012593	0.242929	0.138071	0.267138
EC vs AD	0.235616	1.07E-22	3.84E-05	0.002124
EMCI vs LMCI	0.05405	0.012639	0.02983	0.15555
EMCI vs AD	0.007356	3.65E-17	7.57E-07	0.007576
LMCI vs AD	0.161632	3.26E-11	0.010993	0.042573

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Reference [1] chen et al, Neurology, 2011, 77:1977-85. [2] Wong et al., NMR in biomedicine, 1977, 237-49. [3] Wang, Z., et al, Mag Res Img, 26, 261-269, 2008. [4]. Wang MRI, 2012, in press, [5] Buxton et al, MRM, 1998, 40(3): 383-96. [6] Du et al, Neurology, 2006, 67: 1215-1220. [7] Wang et al, Neuroimage, 2011, 55(3), 968-85. [8] Ashburner, Neuroimage, 2007, 38(1), 95-113. [9] Landau et al, Neurobiology of aging, 2011, 32(7), 1207-18.