

# Combining CASL with Uni- and Multi-variate methods for early detection of Alzheimer's Disease

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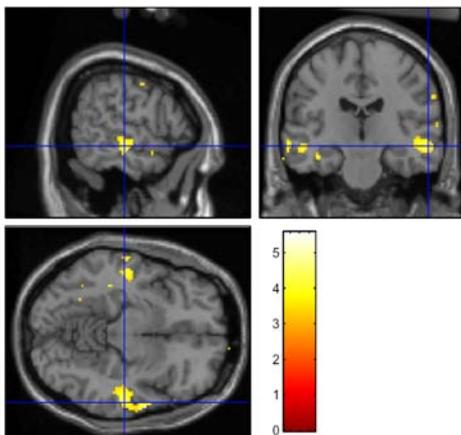
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**INTRODUCTION** There is an urgent need for biomarkers that can diagnose AD at its earliest stage as well as map its progression with time. PET and SPECT studies have suggested that there is a strong link between resting cerebral blood flow (CBF) and neuropathological changes of AD [1]. However, in addition to high cost and low availability, PET and SPECT are limited by their invasive nature, use of ionizing radiation, and low spatial resolution. Continuous Arterial Spin Labeling (CASL) is a non-invasive, feasible and cost-effective MRI technique that provides absolute quantification of CBF with reproducibility, resolution and contrast comparable with that obtained with PET or SPECT [2,3]. The main goal of this (ongoing) study is to develop a technique combining CASL with statistical methods capable of detecting an AD-related CBF pattern that contrasts AD subjects and healthy controls at baseline. Here we present results from both univariate and multivariate analysis of CASL data for detection of AD-related CBF changes. Multivariate techniques have been recently emerging due to certain advantages they can offer in comparison to the more commonly applied univariate methods. Multivariate approaches evaluate correlation/covariance of activation or CBF across brain regions, rather than proceeding on a region-by-region basis. Thus, their results can be more easily interpreted as a functional signature of neural networks [4].

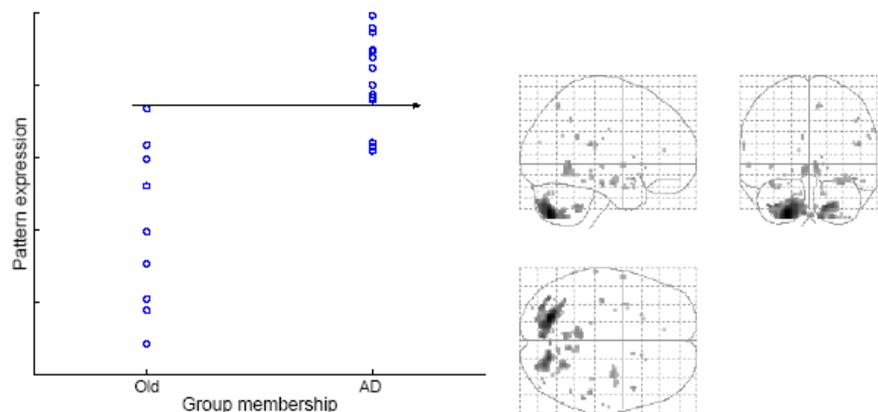
**METHODS** All images were acquired in a 1.5T scanner (Philips Medical Systems, Best, Netherlands) using a standard transmit-receive head coil. Single shot spin-echo EPI CASL perfusion images were acquired as described in [1] with: TR/TE/=4s/36ms,  $\theta=90^\circ$ ; FOV=220x198 mm<sup>2</sup>; acq.matrix=64 x 58; 15 slices, thickness/gap = 8mm/1mm; post-label delay=800ms; labeling time=2.0s. For all CASL images, the labeling plane was positioned 90mm beneath the center of the imaging volume. In addition, for each subject a high resolution, 3D, T<sub>1</sub> (SPGR) image was acquired with: TE/TR=3 ms/34 ms,  $\theta =45^\circ$ ; 100 slices; slice thickness/gap=1.5mm/1mm; FOV=240x240mm<sup>2</sup>; acq. matrix=256 x 256). All EPI images were motion corrected, co-registered with their corresponding SPGR image, and spatially normalized to Montreal Neurological Institute (MNI) standard brain space using SPM99. Each control-label pair yielded a CBF image in units of mL/100g×min, using the formula derived by Alsop *et al.*[1]. The resulting CBF images were averaged within subjects to yield a single average CBF image per subject. **Subjects:** CASL and SPGR images were acquired on 13 healthy elderly control and 17 early AD subjects. Only AD subjects rated as Clinical Dementia Rating (CDR)=1 [r] were used. Other causes of dementia were excluded with appropriate laboratory tests. The study was approved by the local IRB.

**RESULTS** *Voxel-wise analysis:* For the voxel-wise group contrast HEALTHY-AD, we computed statistical map (an SPM{t}) corresponding to the CBF difference at each voxel. The contrast showed areas of widespread CBF differences at the uncorrected false-positive rate,  $\alpha_{\text{uncorrected}}=0.001$ . The axial slice shown (Figure 1) indicates neuronally-mediated decrease in absolute CBF in bilateral medial temporal lobes.

*Covariance Analysis:* The same within-subjects average images that entered the voxel-wise analysis were subjected to covariance analysis. We found a significant discriminant pattern in the first 6 principal components whose subject expression distinguished healthy and AD subjects ( $p=0.03$ ). Specificity and sensitivity of the discrimination were 100% and 93%, respectively. These results are shown in Figure 2. Brain areas that were associated with the covariance pattern and showed decreased CBF in the AD subjects relative to controls were found in the bilateral temporal lobe (BA 13, 21, 22, 25), bilateral parietal lobe (BA 7, 40), cerebellum, as well as caudate and anterior cingulate gyrus (BA 24). There were also brain areas in the perceptual periphery that manifested increased flow in the AD subjects relative to the controls (not shown in figure): these areas were found in the bilateral occipital lobe (BA 17,19) and bilateral temporal lobe (BA 20, 21).



**Figure 1:** The SPM {T} map of the contrast: healthy-AD is overlaid on a high-resolution T1 template.



**Figure 2:** Left: subject expression values for the discriminant pattern constructed from the first principal components, obtained from a covariance analysis using the ASL data of 15 AD subjects and 9 healthy elderly controls. The horizontal line indicates a threshold value of specificity of 100% Right: areas associated with the discriminant pattern that show significantly decreased CBF ( $p<0.01$ ) in the AD subjects compared to the group discrimination.

**Discussion** The data we present here demonstrate the feasibility of a cross-sectional covariance approach for discriminating between AD subjects and healthy controls with ASL. Combining covariance analyses with CASL may prove useful in distinguishing between AD and controls even in very early AD where clinical reading and traditional univariate techniques fail. We are currently applying these techniques to a cohort which includes subjects with mild cognitive impairment (MCI) to determine if the same pattern which distinguishes healthy from AD will predict the conversion of the MCI to AD.

**References** [1] Scarmeas, N. *et al.*, *Neuroimage* **23**: 35-45 (2004)., [2] Alsop D.C., Detre J.A., *J Cereb Blood Flow Metab*, **16**(6):1236-1249 (1996), [3] Alsop D.C., *et al.*, *Annals of Neurology*, **47**(1): 93-100 (1999), [4] Habeck, C. *et al.*, *Neuroimage* **20**:1723-33 (2003).