Identifying Regional Patterns of Concordance and Dissociation between Gray Matter Loss and Hypoperfusion among Alzheimer's Disease Patients

S. Hayasaka[1,2], N. Schuff[1,2], J. Kornak[1,2], C. Studholme[1,2], V. Cardenas[1,2], A-T. Du[1,2], A. Duarte[1,2], G-H. Jahng[1,2], M. Weiner[1,2]

[1]Radiology, University of California San Francisco, San Francisco, California, United States, [2]Radiology, VA Medical Center, San Francisco, California, United States

Introduction: Loss of gray matter (GM) and reduction of brain perfusion in Alzheimer's disease (AD) patients have been observed in several neuroimaging studies. However, GM loss and hypoperfusion do not necessarily occur at the same locations [1]. Such lack of concordance between brain structure and function may be due to some underlying disease process, where one precedes independent of the other. In particular, regional hypoperfusion may occur without GM loss at the same location during an early stage of the disease. Thus, our goals are two-fold; first, to identify areas of concordance between GM loss and hypoperfusion, and second, to identify areas of dissociation where hypoperfusion can be observed without apparent GM loss.

Materials and Methods: 20 AD patients (mean age=72.9, mean MMSE=21) and 22 cognitive normal (CN) controls (mean age=73.6, mean MMSE=29.5) were scanned on a 1.5T Siemens Vision scanner. T1-weighted structural images were acquired using an MPRAGE sequence (TR/TE=9.7/4 ms, FA=15°, slice thickness=1.4 mm), and perfusion weighted images (PWI) were acquired using the DIPLOMA pulsed ASL method [2] (TR/TE/TI=2500/40/1500 ms, 5 slices of 8 mm thickness and 2 mm gap) covering the volume above the AC-PC line.

A study specific template was created by averaging T1 images of all the subjects. Both T1 and PWI images were spatially normalized to this template using SPM2. The normalized T1 images were segmented into different tissue types using the optimized VBM (voxel-based morphometry) protocol [3], and the normalized PWI images were corrected for the partial volume effect (PVE) using the Müller-Gärtner method [4]. From the resulting GM images, a T-statistic map was calculated comparing GM between AD and CN, adjusted for age and total intra-cranial volume. A T-statistic map for perfusion images, adjusted for age and the baseline perfusion measured at the motor cortex, was also calculated in order to compare AD and CN. The two T-statistic maps for the AD<CN comparison from the GM and perfusion images, T_{perf} and T_{GM}, respectively, were combined by calculating two combining functions, U and V, at each voxel [5]. The first combining function $U=T_{perf} \times T_{GM}$ was designed to identify areas of concordance where both perfusion and GM increase or decrease together (see Fig 1a). The second combining function $V= T_{perf} - (0.5\ T_{GM})^4$ was designed to identify areas of dissociation where hypoperfusion is observed without an apparent GM change (see Fig 1b). Since the distributions of U and V were unknown, a permutation test was used to assess significance level, using the cluster mass statistic [6].

Results: Fig 2 shows the critical region $U>8$ overlaid on the scatter plot of T_{perf} and T_{GM}, as well as the 3D rendering of the areas of significant concordance. The areas of concordance were found in the L/R posterior cingulate gyrus with some extension into the precuneus, as well as in the R angular gyrus. In all of these areas, a decrease in both GM and perfusion was observed (see Fig 2a). Fig 3 shows the critical region $V>3$ overlaid on the scatter plot of T_{perf} and T_{GM}, as well as the 3D rendering of the areas of significant dissociation, or hypoperfusion without GM change. The areas of dissociation were found in R precuneus and R middle frontal gyrus.

Discussion: Using the combining function approach, we are able to identify areas of concordance between GM loss and hypoperfusion, as well as the areas of dissociation with hypoperfusion but no apparent GM loss. The patterns we found seem to follow the disease process of AD, progressing from the parietal lobe to the frontal lobe [7]. In the parietal lobe, both GM and perfusion show a decrease, consistent with advanced neuro-degeneration from the prolonged impact of the disease. In the frontal lobe, by contrast, only a perfusion change is observed, consistent with early neurodegeneration that does not involve massive neuron loss. These results are in agreement with a previous neuroimaging study of AD using MRI and SPECT [1], and suggest that hypoperfusion may be observed earlier than brain tissue loss. In conclusion, our method enables us to quantitatively assess changes in brain structure and function together, which should improve diagnosis and treatment monitoring of AD and other neurodegenerative diseases.

References: [1] Matsuda et al., *J Nuc Med* 43: 304-311 (2002). [2] Jahng et al., *MRM* 49: 307-314 (2003). [3] Good et al., *NeuroImage* 14: 21-36 (2001). [4] Quarantelli et al., *J Nuc Med* 45: 192-201 (2004). [5] Pesarin. *Multivariate Permutation Tests. Wiley* (2001). [6] Bullmore et al., *IEEE Trans Med Img* 18: 32-42 (1999). [7] Braak et al., *Eur Arch Psychi Clin Neurosci* 249(S3): 14-22 (1999).

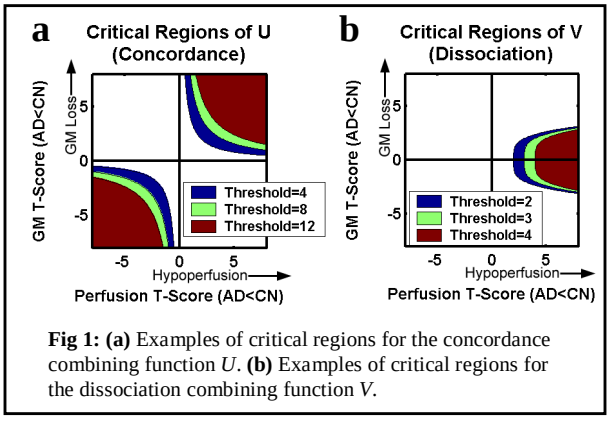

Fig 1: (a) Examples of critical regions for the concordance combining function U. **(b)** Examples of critical regions for the dissociation combining function V.

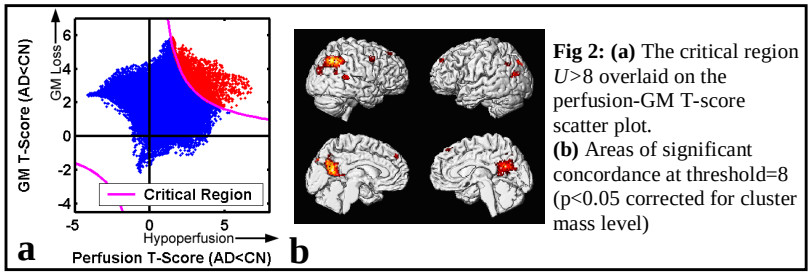

Fig 2: (a) The critical region $U>8$ overlaid on the perfusion-GM T-score scatter plot. **(b)** Areas of significant concordance at threshold=8 ($p<0.05$ corrected for cluster mass level)

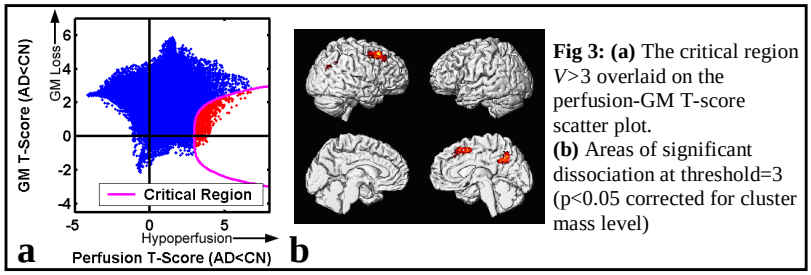

Fig 3: (a) The critical region $V>3$ overlaid on the perfusion-GM T-score scatter plot. **(b)** Areas of significant dissociation at threshold=3 ($p<0.05$ corrected for cluster mass level)