Study of Cerebral Venous Density in Alzheimer's Disease using Susceptibility Weighted Magnetic Resonance Imaging

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Target Audience: This research could benefit clinicians and researchers that are examining the causes and effects of Alzheimer's Disease on the cerebral venous system.

Purpose: The goal of this work was to assess whether the cerebral venous system changes as a result of Alzheimer's Disease (AD), the most common form of dementia. The most common indication of AD is brain atrophy, which behaviourally is related to impairment of short term memory, mood and overall brain function. It currently has no known cause and no cure. This study was performed because we hypothesized that cerebral venous density differed between suspected AD patients and healthy aged-matched controls. If the aetiology of AD has a vascular component, the venous density may be expected to be lower in AD subjects. Venous density was assessed through novel segmentation of susceptibility weighted imaging (SWI) data.

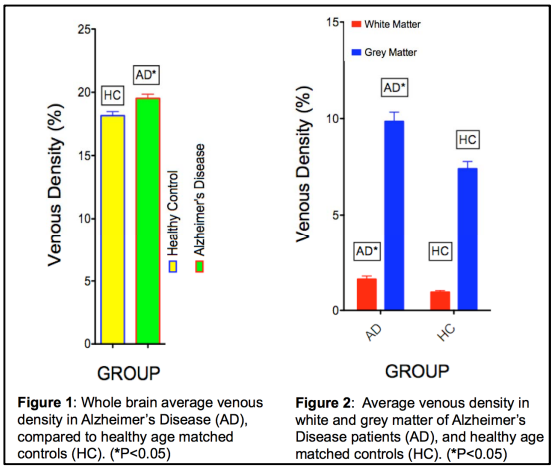

Figure 1: Whole brain average venous density in Alzheimer's Disease (AD), compared to healthy age matched controls (HC). (*P<0.05)

Figure 2: Average venous density in white and grey matter of Alzheimer's Disease patients (AD), and healthy age matched controls (HC). (*P<0.05)

Methods: In a study approved by our institutional research ethics board, 37 early stage [suspected] AD subjects and 16 healthy age-matched controls were evaluated. Scanning was performed with a 3Tesla HD Signa MRI (GE Healthcare, Milwaukee, WI) and 8 channel phased array RF coil. Each subject was scanned with a 3D IR-prepped fSPGR sequence (TI/TR/TE=450/7.5/2.1ms, 12° flip angle, FOV=24cm, 320x192matrix, 90 slices 2mm thick, interpolated to 1 mm thick) and a home written SWI sequence with full flow compensation (spoiled gradient echo, TR/TE=30/20ms, flip=15°, 512x256 matrix, 24cm FOV, 2mm thick). Phase and magnitude images were reconstructed and SWI data was calculated based on Haacke *et al.* **[1]**. Vessel segmentation to give 'vesselness' images was performed using the Vessels Segmentation Toolbox developed with SPM8 (Wellcome Dept. of Imaging and Neuroscience, University College London) and MATLAB (Mathworks, Natick MA) by Vigneau-Roy and based on Descoteaux *et al.* **[2]**. Vein density was calculated for each subject from number of voxels in vesselness images and number of voxels in images of the whole brain. Brains were segmented into grey and white matter, and cerebrospinal fluid (CSF). Outputs were binarized and multiplied by vesselness images to create segmented venous images for each subject, and vein density was determined for both white and grey matter. Healthy controls and AD subjects were registered to the LONI atlas **[3]** made for AD with the FSL 'FLIRT' **[4]** utility using an affine 12 parameter method. The registration transformation matrix generated was applied to the venous volumes. Each volume was blurred with a 5mm FWHM Gaussian kernel. Using AFNI, a 3D unpaired Student's T-test was performed to determine voxel-wise differences between groups.

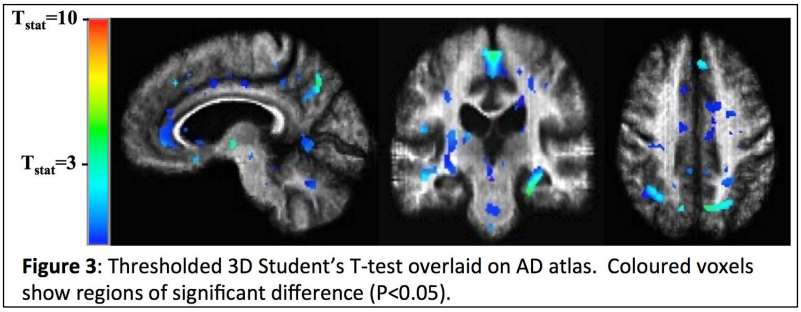

Figure 3: Thresholded 3D Student's T-test overlaid on AD atlas. Coloured voxels show regions of significant difference (P<0.05).

Results: Subjects with AD had an overall statistically greater cerebral venous density than healthy aged-matched controls (HC) (**Fig.1**). Furthermore, the AD group had statistically significantly higher venous density, in both white and grey matter, compared to the HC group (**Fig.2**). Based on voxel-wise whole brain assessment the most significant change in venous density for AD subjects was in the grey matter, most specifically in the hippocampus and the entorhinal cortex (EC) (**Fig.3**).

Discussion: It is well understood the brain atrophies in AD. We hypothesize, because of the non-rigid nature of veins, reduced brain volume could allow the veins to expand. A recent study has proposed that amyloidogenesis contributes to an increase in neoangiogenesis causing hypervascularization in subjects with AD. In the study it was found that immunization with Aβ caused a reversal of the hypervascularization **[5]**. This provides another possible explanation for the increase in venous density that we found in AD subjects. The hippocampus and the EC are regions known to be impacted by AD **[6]**, and our results reflect this.

References: **[1]** Haacke EM, *et al.* (2004) MRM 52(3):612-618. **[2]** Descoteaux M, *et al.* (2008) Med. Imag. Analysis 12(4):497-513. **[3]** Alzheimer's Disease Template. (2008) LONI | Atlases | Atlas Details. Web. 20 Feb. 2013. www.loni.ucla.edu/Atlases/Atlas_Detail.jsp?atlas_id=8 **[4]** Jenkinson M, *et al.* (2002) NeuroImage 17(2):825-841. **[5]** Biron KE, *et al.* (2013) Sci. Rep. 3:1354. **[6]** De Leon MJ, *et al.* (2004) J Int Med. 256:205–223.