Cerebrovascular reactivity as a novel marker in assessing vascular dysfunction in Alzheimer's Disease

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INTRODUCTION: Vascular factors have been increasingly recognized as important in the clinical onset and progression of Alzheimer's disease (AD) [1]. Most previous reports on this topic have focused on cerebral blood flow (CBF). Despite consistent findings of temporoparietal hypoperfusion in patients with AD, there is a real possibility that reduction in CBF may not be an indication of vascular dysfunction, but may merely reflect a reduction in metabolic demand, a well-documented observation in the same brain regions in AD. Since flow and brain metabolism are tightly coupled [2], reduced metabolic demand (e.g. following neural loss) would result in reduced CBF, even with an intact vascular system. Here we seek to use a more direct approach to assess vascular function in AD. We applied BOLD MRI under hypercapnia (5% CO2 breathing) challenge to measure cerebrovascular reactivity (CVR) in a group of AD and normal subjects (NC). As a control measure, baseline CBF was also determined using a pseudo-continuous arterial spin labeling (PCASL) technique. Spatial patterns of CVR and CBF deficits were compared. The relevance of CVR to vascular integrity was confirmed by comparing to volume of FLAIR white matter hyperintensity (WMH), thought to reflect structural damage of vascular origin.

METHODS: A total of 13 AD patients (age: 69.2±9.3 years, MMSE:22.5±4) and 9 normal controls (age: 67.4±8.5 years, MMSE:29.6±0.5) were recruited and gave informed consent. Imaging was performed on 3T Philips scanner. For PCASL scan, 17 axial slices (thickness 7mm, resolution 3x3 mm^2) were used covering the entire cerebral cortex (TR/TE=4000/14ms, 30 control/label images, duration 4min). For CVR measurement, the subjects breathed room-air and 5% CO2 in an interleaved fashion (switching every minute), while BOLD MRI (resolution 1.8x1.8x6 mm^3, TR/TE=3000/30ms, duration 7min) were acquired similar to a typical fMRI scan. End-tidal CO2 which is the vasodilatory input function to brain vasculature was recorded throughout the scan. T1w MPRAGE (1x1x1mm^3) and FLAIR images were also acquired for structural assessment.

CBF map was obtained from the PCASL data using a model proposed by Alsop and Detre [3]. CVR data were processed using a general linear model (with SPM) similar to a typical fMRI scan, except that the regressor is the end-tidal CO2 trace rather than the "fMRI paradigm". The resulting CVR is in units of %BOLD/mmHg CO2. Inter-subject variations in global CBF and CVR were minimized by normalizing the maps to whole brain values, yielding relative CBF and CVR maps. These individual brain images were spatially normalized into MNI space using the T1w image. We recognize that AD is often accompanied by brain atrophy, which needs to be corrected in order to avoid partial volume effects on the CVR and CBF maps. We therefore used HAMMER software [4] for spatial normalization. The HAMMER algorithm also creates a deformation matrix containing atrophy information which can be used for atrophy mapping. Fig. 1 shows this result and we see clear atrophy in medial temporal lobe, consistent with numerous previous findings. FLAIR data were analyzed using a semi-automatic method [5] and the total volume of hyperintensity in the image was determined.

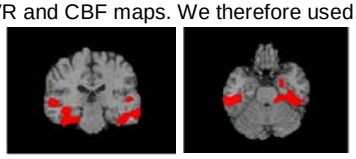

Fig 1. Temporal regions showing increased atrophy in AD compared to NC (2 sample t test, uncorrected p=0.01, k=1250)

RESULTS AND DISCUSSION: Members of both groups could perform CO2 task comfortably (n=8AD,8NC) and no adverse effect was observed. The left panel of Fig. 2 shows the averaged CVR maps for the AD (upper) and control (lower) groups. Reduced CVR in AD is evident in anterior brain regions (yellow arrows). Voxel-by-voxel group comparison between AD and controls shows that significant CVR deficits are observed in the frontal lobe, anterior cingulate cortex, and insular cortex (Fig. 3). Region-of-interest (ROI) analysis had similar results, identifying frontal lobe and insular cortex having reduced CVR ($p<0.05$). This spatial pattern is drastically different from the patterns of CBF deficit measured in the same groups (see CBF maps in Fig. 2 right panel, and voxel-based comparison results in Fig. 4), which shows predominantly temporoparietal regions. To further investigate whether these CBF deficit regions in AD showed any signs of CVR deficit (probably may not have reached significance threshold in the voxel-based analysis), we averaged the relative CVR within the voxels that showed CBF deficits (i.e. red voxels in Fig. 4). The CVR values were: AD 1.29±0.19; NC 1.14±0.12. There was not even a trend of reduction. If anything, the CVR in AD in these regions were slightly higher than controls. Given the discrepancy in the spatial locations of CVR and CBF deficit regions, we set out to determine if CVR or CBF is a better marker for vascular dysfunction. We compared these two markers to a measure of structural damage that is believed to be of vascular origin. White matter hyperintensities (WMH) in FLAIR images are thought to be related to microscopic ischemia and hypoxia [6]. We therefore studied the correlation between volume of WMH in the brain to the volume of white matter voxels that had a negative CVR value. We believe that voxels with negative CVR have lost their vascular reserve, so that their BOLD signal reduces during CO2 breathing (indicative of a steal effect from neighboring voxels). We found a significant positive correlation between these measures across subjects (for the whole group as well as for AD subjects only (Fig 5)), suggesting that subjects with lower CVR tend to have larger WMH volumes. Such correlation was not found when we compared WMH volume to CBF.

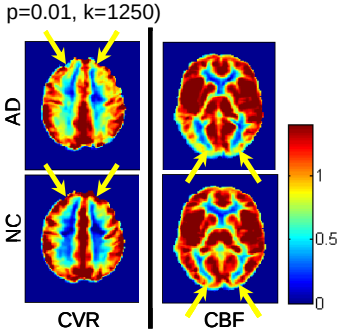

Fig 2: Averaged relative CVR (left) and CBF (right) maps for AD (top) and NC (bottom). AD showed CVR deficits in frontal and CBF deficits in parietal regions. These regions are indicated by yellow arrows.

In summary, our data suggest that cerebrovascular reactivity may be a better marker for vascular dysfunction in AD, compared to baseline CBF. Vascular deficits in AD were most pronounced in anterior regions in the brain, rather than the parietal/temporal lobes as proposed previously [7].

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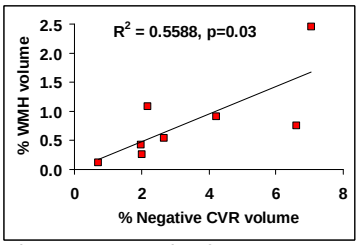

Fig 5. Scatter plot for FLAIR-CVR data for AD group (n=8). Both values are expressed as % of whole brain white matter volume to account for brain size differences.

Fig 4. Temporal and parietal regions showing CBF deficits in AD compared to NC (2 sample t test, uncorr p=0.01, k=200)

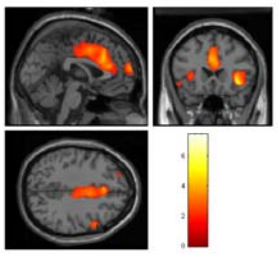

Fig 3. Brain regions showing CVR deficits in AD compared to NC (uncorrected p=0.05, k=200). Spatial locations correspond to anterior cingulate, insula and frontal cortex