Characterization of CMRO2, resting CBF, and cerebrovascular reactivity in patients with very early stage of Alzheimer's Disease

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INTRODUCTION: With the disappointing negative outcomes of several clinical trials of amyloid vaccine, there is a strong emphasis in Alzheimer disease research for early detection, with the notion that amyloid treatment in these patients will be more beneficial. At present, the earliest stage that can be defined clinically is called early Mild Cognitive Impairment (MCI), which is a clinical diagnosis that includes a cognitive complaint in the context of generally intact everyday functional abilities. In research settings, MCI is characterized by a clinical dementia rating (CDR) score of 0.5, typically associated with a mild memory impairment of 0.5-1.5 standard deviations below average on a standardized neuropsychological memory test. A clear clinical diagnosis in the early stage of MCI can be challenging, and it is not yet entirely clear which biomarker(s) might already show an abnormality in these patients. In this study, we used several MRI modalities to characterize the neurobiology in early MCI. We first used a novel technique to detect abnormalities in the brain's energy "budget" denoted by cerebral metabolic rate of oxygen ($CMRO_2$). Next, given that the $CMRO_2$ measure was a whole-brain index only, we further used regional CBF as a surrogate marker to probe which regions showed the most pronounced abnormality. Finally, we are cognizant that CBF reduction can have at least two explanations: 1) neural dysfunction, i.e. neurons are metabolically less active thus they receive less blood supply; 2) vascular dysfunction, i.e. cerebrovasculature has degraded capacity thus cannot deliver sufficient blood flow. To differentiate these two possibilities, we measured a more specific vascular marker, Cerebrovascular Reactivity (CVR) to CO_2 inhalation, in the same subject cohort.

METHODS: EXPERIMENT A total of 34 early-MCI patients (age 66.3±7.1), diagnosed based on standard Petersen criteria as modified by the ADNI project, and 22 elderly controls (age 66.2±6.5) were studied on a 3T system (Philips). Three MRI biomarkers were measured. *Global $CMRO_2$* was measured using a recently described method (1). Briefly, $CMRO_2$ (in unit of μmol O_2/min/100g brain tissue) was quantified based on arterio-venous difference in oxygen content (known as the Fick principle), i.e., $CMRO_2=CBF\times(Y_a-Y_v)\times C_a$, where CBF was measured by phase-contrast MRI at the feeding arteries of the brain (Fig. 1a), Y_a is the arterial blood oxygenation from pulse oximetry, Y_v is the venous oxygenation and was determined using a novel TRUST MRI technique (Fig. 1b) (2), and C_a is a constant representing the capacity of blood to carry O_2 and was assumed to be 7.96 μmol O_2/100ml blood. The scan duration of a complete set of $CMRO_2$ measurement was 4 min. *Resting CBF* was measured with a pseudo-continuous ASL (PCASL) sequence with following parameters: TR/TE=4300/14ms, label duration=1650ms, post label delay=1525ms, 29, 5mm thick axial slices, duration 5 min 40s. *CVR* was measured with a CO_2-inhalation procedure (3), in which the subject breathed 1-min of room air and 1-min of 5% CO_2 (mixed with 21% O2 and 74% N2) in an interleaved fashion while BOLD images were continuously acquired (scan duration = 7 min). DATA ANALYSIS: The data were processed with previously established procedures to obtain global CMRO2 (1), CBF map (4), and CVR map (4), respectively (not detailed here due to space limitations). Global $CMRO_2$ values were compared across subject groups using two-sample t tests. CBF maps were compared across groups using voxel-wise analysis tool in SPM to identify any clusters with a significant difference. The CBF-detected significant clusters were saved as a mask and were applied to the CVR map of each subject. Two-sample t test was used to compare the resulting regional CVR values across groups.

RESULTS AND DISCUSSION: All MCI patients had a CDR of 0.5 and all controls had a CDR of 0 (by definition). The Mini-Mental-State-Exam (MMSE) scores did not differ between groups (Control 29.1±1.0; MCI 28.6±1.6; p=0.29), again confirming the very early stage of their condition. Global $CMRO_2$ of the MCI patients were 152.4±24.6 μmol/min/100g, which was 12.7% lower (p=0.008) than the values (174.5±27.2 μmol/min/100g) of the control group. We emphasize that the observed metabolic deficit in MCI could not be attributed to brain atrophy, as the $CMRO_2$ calculation accounts for brain volume. In fact, whole-brain volume was not different between groups (1122.1±117.4 ml in MCI and 1139 ±107 ml in control, p=0.64). Further investigation of the experimental measures revealed that the $CMRO_2$ reduction was due to a concomitant decrease in both CBF (by 6.0%) and Y_a-Y_v (also known as the oxygen extraction fraction, by 6.3%).

Although the global $CMRO_2$ measure provided evidence of abnormality in early MCI, no spatial information is available in this technique. Thus it is not clear which brain region(s) may have contributed to this global observation. Unfortunately, no $CMRO_2$ mapping technique is currently available using MRI. Thus, we used CBF as a surrogate marker for region-specific assessment. Voxel-wise comparison of CBF between MCI and control groups revealed a single cluster with a significant reduction in MCI (Fig. 2). This cluster is located in the precuneus/posterior cingulate region, which is a key area of the Default-Mode-Network (DMN) and is well known to be implicated in Alzheimer Disease. CBF in this region decreased by 10.9% in the MCI group compared to the controls.

As noted, interpretation of CBF reduction is not trivial in that it can be either attributed to neural dysfunction or vascular dysfunction. Therefore, to gain a better insight into the mechanism of the CBF reduction in the precuneus/posterior cingulate region, we measured another vascular marker, reactivity to CO_2, which is an index more specific to vascular function. Fig. 3 shows group-averaged CVR maps. When investigating CVR in the CBF-deficit regions, we found no difference (p=0.67) between MCI (0.21±0.06 %BOLD/mmHg) and control (0.20±0.06 %BOLD/mmHg) groups, suggesting that vascular function in these regions appears to be intact and that the CBF reduction noted is most likely attributed to underlying neural dysfunction.

In summary, the present work suggests that a reduction in brain metabolic rate appears to be an early change that can be detected in the early MCI stage. This deficit was found to be most prominent in the precuneus/posterior cingulate region based on a CBF marker, which could be attributed to either neural or vascular dysfunction. Further experiment suggested that vascular reactivity to CO_2 in this region was intact, therefore suggesting that the CBF deficit most likely had a neural/metabolic cause.

REFERENCES: 1) Xu et al. MRM, 62, 141, (2009); 2) Lu et al. MRM, 60, 357 (2008); 3) Yezhuvath et al. NMR Biomed., 22, 779 (2009); 4) Yezhuvath et al. Neurobiol. of Aging, 33, 75 (2012)

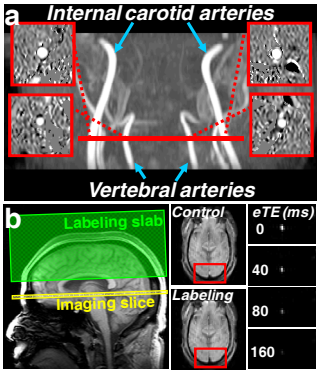

Fig. 1. CMRO2 technique. a) Phase contrast MRI for the measurement of global CBF; b) TRUST MRI for the measurement of global Yv.

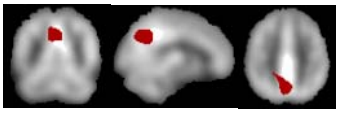

Fig. 2. Regions in red color show lower CBF in early-MCI patients compared to elderly controls. The background image is the averaged CBF map.

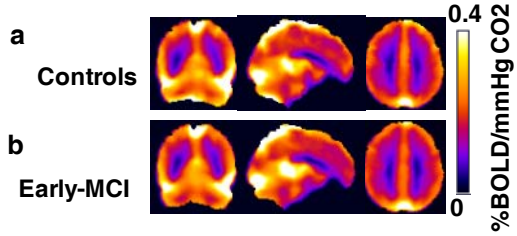

Fig. 3. Averaged CVR maps for a) Elderly control group and b) early-MCI group. The locations of the displayed section views are the same as those in Fig. 2.