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 brain vasculature; 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 CO2 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 CMRO2 was measured using a recently described method (1). Briefly, CMRO2 (in unit of μmol O2/min/100g brain tissue) was quantified based on arterio-venous difference in oxygen content (known as the Fick principle), i.e., CMRO2=CBF(Vo2)max/CVB, where CBF was measured by phase-contrast MRI at the feeding arteries of the brain (Fig. 1a), Yo2 is the arterial blood oxygenation from pulse oximetry, Yo4 is the venous oxygenation and was determined using a novel TRUST MRI technique (Fig. 1b) (2), and C0 is a constant representing the capacity of blood to carry O2 and was assumed to be 7.96 μmol O2/100ml blood. The scan duration of a complete set of CMRO2 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 CO2-inhalation procedure (3), in which the subject breathed 1-min of room air and 1-min of 5% CO2 (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 CMRO2 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 CMRO2 of the MCI patients were 152.4±24.6 μmol/min/100g, which was 12.7% lower (p=0.068) than the values (174.5±27.2 μmol/min/100g) of the control group. We emphasize that in these regions appears to be intact, and that the CMRO2 rate of the control brain is normal (60 μmol/min/100g). Next, when CBF reduction was due to a concomitant decrease in both CBF (by 6.0%) and Y0-Y0′ (also known as the oxygen extraction fraction, by 6.3%).

Although the global CMRO2 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 CMRO2 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 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 CO2, 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 precuneus/posterior cingulate region.