Decrease in CMRO2 for Memory-Encoding Tasks in the Hippocampus of Mild Cognitive Impairment Subjects

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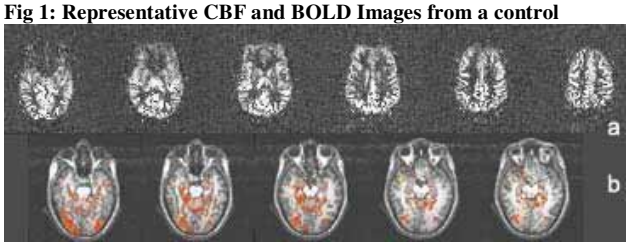
Introduction: Functional MRI studies have demonstrated that the early onset of Alzheimer's disease (AD) can be separately detected by blood oxygenation level dependent (BOLD) contrast [1] or regional cerebral blood flow (CBF) changes measured by arterial spin labeling techniques [2]. It is hypothesized that the combined methods of BOLD and CBF could provide a better index to mark early onset of AD, particularly in mild cognitive impairment (MCI) subjects. It has been shown that the cerebral metabolism rate of oxygenation ($CMRO_2$) changes could be derived from the combined measurements of BOLD and CBF changes [3]. Further, the $CMRO_2$ change could directly indicate localized neuronal activities. It is hypothesized that the $CMRO_2$ changes would be a better biomarker in distinguishing between normal elderly individuals and MCI subjects. In the present study, regional $CMRO_2$ changes induced by the memory-encoding task in the hippocampus were obtained. The $CMRO_2$ changes were significantly different between the normal elderly group and MCI group.

Method & Materials: Nine cognitively healthy elderly volunteers (72±4 years old) and 10 amnestic-type MCI patients (74±6 years old) participated in this study. Informed consents were obtained from all subjects for this IRB-approved study. All MRI data were acquired on a GE 3.0T scanner. fMRI- BOLD data were acquired with a single-shot gradient-echo EPI sequence (axial, 4mm thickness, 128×128, TE 25 ms, TR 2s). CBF data were acquired with QUIPSS-II method [4] with a PICORE tagging mode (axial, 8mm thickness, 64×64, TR 5s, TE 25ms, TI_1/TI_2 0.6/1.5s). A set of high-resolution anatomical images (SPGR) were acquired for image registration. The memory-encoding paradigm consisted of five blocks of 40 s on for novel scene encoding and 40 off for a luminance matched visual fixation image. All subjects were instructed to remember the scenes and took a recognition test 15 min after the scan. Data Analysis: The voxel time series data were processed with AFNI software [5]. After motion correction, data from one control and two MCIs were removed for further analysis due to excessive motion artifacts. Both BOLD and CBF changes were fitted with the block-designed task paradigm using *3dDeconvolve* program . All datasets were then converted to Talaraich image space and a predefined standardized hippocampus ROI was obtained. Activated voxels by the task in the hippocampus region from each individual was obtained with a threshold of goodness-of-fit (F-test, F>6.233, P<0.01). The degree of activation in the hippocampus was expressed as a percentage of activated voxels divided by the total voxels in the hippocampus. Voxel-based $CMRO_2$ changes were calculated by using the equation defined in Ref 3. Activation index was defined as a product between the degree of activation (%) and the ratio of mean $CMRO_2$ between activation and resting states.

Fig 1: Representative CBF and BOLD Images from a control



Results: Fig.1a shows the image qualities of a representative perfusion images from an elderly control. Fig.1b showed BOLD activation induced by a memory-encoding task from the same subject. The degree of activation in the hippocampus and the mean $CMRO_2$ changes from those voxels were shown in Table 1. The control group showed a significantly more activated voxels in the hippocampus than MCI group. The mean $CMRO_2$ changes didn't show significant difference between two groups. However, the activation index showed a statistically significant difference between the normal elderly control group and the MCI group. Fig. 2 shows a strong correlation between the activation index and RAVL score (R^2=0.4309, P<0.02) and the degree of activation and RAVL scores ((R^2=0.3834, P<0.04), but not between the activation index and MMSE score (R^2=0.2683, P<0.13).

Table 1. Comparisons in significance between activated voxels, $CMRO_2$ changes, and activation index.

	Normal Elderly Control (n=8)	MCI (n=8)
Degree of activation voxels (%)	23.06 % ± 4.48% * P<0.05	8.42 % ± 0.91% * P<0.05
Mean $CMRO_2$ changes (%)	63.81 % ± 219.16 % NS	-5.76 % ± 4.93 % NS
Activation Index	0.25 ± 0.03 Δ P<0.01	0.052 ± 0.005 Δ P<0.01

Discussion: Through the measurements of BOLD and CBF, the calculated total $CMRO_2$ changes expressed as activation index were significantly decreased in the MCI subjects than those of the controls during memory-encoding. **The activation index** was highly correlated to the cognitive memory function indicated by RAVL scores. The lower activation index for MCI subjects during the task suggests that MCI patients have decreased neuronal activities. Our result is consistent with other reported results measured by PET or MRS methods. With advantages of fMRI in high temporal and spatial resolution and with no radioactive tracer, detection of the early onset of AD or differentiation of AD from other dementia types could be feasible. In addition, the quantitative assessment for $CMRO_2$ changes could be applied to monitor disease progression or antidementia drug effect.

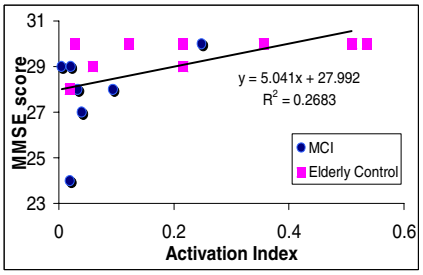


Fig. 2a Correlation between activation index and MMSE score.

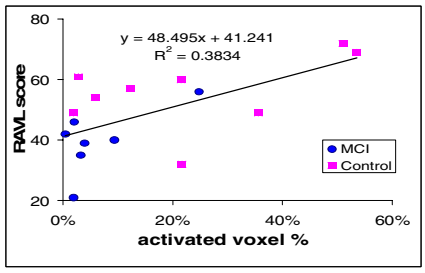


Fig. 2c Correlation between activated voxel and RAVL score.

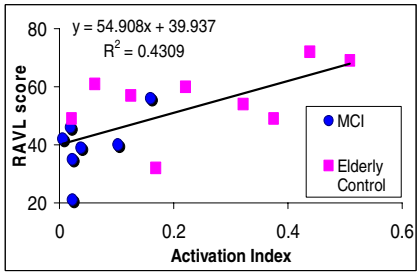


Fig. 2c Correlation between Activation index and RAVL score.

MMSE: Mini-Mental Status Examination. RAVL: Rey Auditory Verbal Learning Test

References: 1. Machulda, MM et al., Neurology 61:500-506 (2003). 2. Alsop, DC et al., Ann Neurol. 47(1):93-100 (2000). 3. Davis,TL et al., PNAS. 95:1834-1839 (1998). 4. Wong, EC et al., MRM 39:702-708 (1998). 5. Cox RW, Comput Biomed Res 29 :162-73 (1996).

Acknowledgments: This work was supported by NIH grants AG20279 and RR00058