Prediction of Conversion from Mild Cognitive Impairment to Alzheimer's Disease Based on Regional Brain Volume Measured on MRI and MRI-Guided Perfusion Measured by SPECT

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Purpose:

Neuroimaging research conducted over the last two decades has generated a wealth of knowledge about brain aging and AD. It has been shown that hippocampal atrophy is one of the earliest pathological signs of AD, and the amount of atrophy is correlated with the severity of the patient's memory impairment. Given the unprecedented growth of scientific knowledge, particularly in imaging markers and biomarkers, Dubois and Feldman proposed revisions of the long-standing NINCDS-ADRDA diagnostic criteria that were first published in 1984 [1]. More specifically, it is recommended that imaging measures be included as supportive features for the diagnosis of AD. The purpose of this study was to quantify volume and perfusion in the medial-temporal-lobe (MTL) structures and cortical brain areas in MCI patients and healthy age-matched normal controls (NC). The volume and perfusion measures were correlated with each individual's scores on tests of episodic memory. The differences in brain volume, perfusion, and memory-function scores between MCI and NC groups were investigated. In addition, after 3-years of longitudinal follow-up, those MCI patients who had converted to AD were identified along with those who remained stable. The differences between MCI-AD converters and stable MCI were compared to find which imaging measures can be used to differentiate between them to predict conversion.

Methods:

Thirteen individuals (9 men, 4 women) diagnosed with amnestic MCI (12 single domain, 1 multiple domain) with a mean age 74 (±6) years old, and 12 (6 men, 6 women) age-matched healthy elderly controls with a mean age of 75(±4) years old were recruited. The MRI studies were performed on a 1.5 Tesla MRI scanner using 3D-SPGR sequence with the pixel size of 0.86 x 0.86 x 1.5 mm. On a different day each subject received a SPECT (Tc-ECD) scan. The regions of interest (ROIs) for the MTL structures, including left and right hippocampus, parahippocampal gyrus, and amygdala, were manually outlined on the high-spatial resolution structural MRI. The volumes of these structures, normalized to the intracranial volume, were measured as the normalized percent volume (NPV). Each ROI was then mapped onto the SPECT images using the transformation matrix obtained from co-registration between structural MRI and SPECT (Fig. 1). The perfusion intensity for each structure was measured, and then normalized to that of cerebellum to obtain the cerebral perfusion ratio (CPR). In addition to the MTL, the SPECT perfusion in the gray matter of the frontal, lateral temporal, parietal, and occipital lobes was studied using ROI defined on high-spatial-resolution structural MRI. These regional ROIs were obtained using algorithm-based gray matter segmentation combined with atlas-based lobar masking in each individual subject. All subjects were evaluated using a comprehensive battery of neuropsychological tests. The memory scores on the 5- and 30-minute delayed-recall test from the 10-item CERAD word list, and the immediate and 30-minute recall of two stories from the WMS-III Logical Memory subtests were obtained. A composite memory score (CMS), defined as the sum of the 4 memory scores, each normalized to its mean, was used in the analysis.

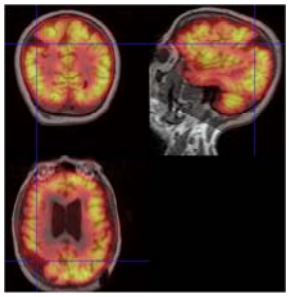

Fig.1 The color SPECT perfusion images co-registered and overlaid on the MR images.

Results:

The volumes of 4 MTL structures were significantly smaller in the MCI than the NC patients; including right parahippocampal gyrus, left parahippocampal gyrus, right hippocampus, and right amygdala. The perfusion of 4 MTL structures were smaller in the MCI patients, including right hippocampus, right parahippocampal gyrus, right amygdala, and left hippocampus. The volumes of 6 medial temporal lobe structures were added as NPV_MTL, and their volume-weighted perfusion was calculated as CPR_MTL. Fig. 2 shows the scatter plot between CPR and NPV(a), CMS vs. NPV (b), and CMS vs. CPR(c). The three figures clearly demonstrate that MCI patients have lower MTL volume, lower MTL perfusion, and worse memory scores than their age-matched healthy peers. During the follow-up period, 4 MCI patients converted to AD, and the values for these individuals are circled in each of the figures. Interestingly, the 4 converters had lower volume and perfusion (in the lower left quadrant of Fig.2), suggesting the potential of using imaging measures in the medial temporal lobe to predict MCI-AD conversion. Perfusion measured from the gray matter of the frontal, temporal, parietal, and occipital brain lobes did not differentiate between NC and MRI, or between stable MCI and MCI-AD converters.

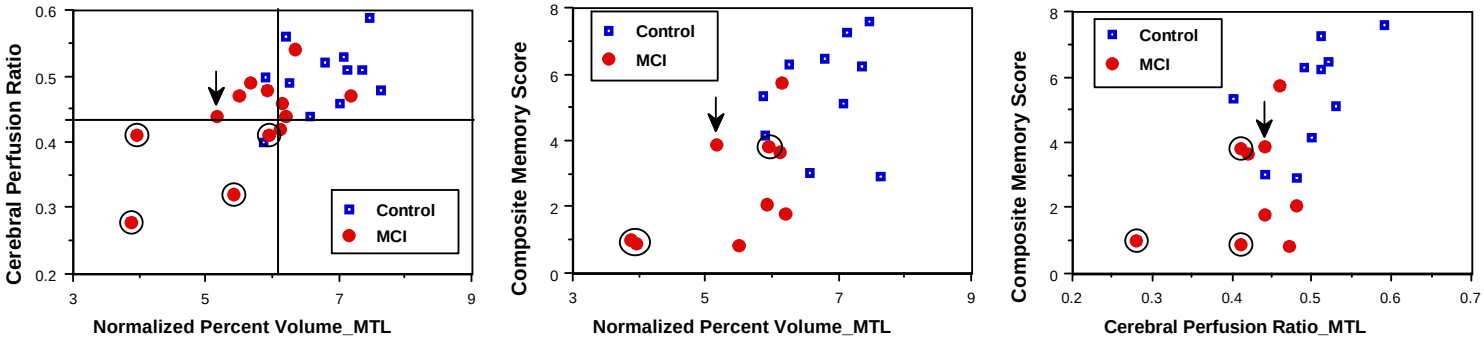

Fig. 2. The correlation between the volume and perfusion of medial temporal lobe structures, and composite memory score (CMS). MCI patients have lower volume (NPV_MTL), perfusion (CPR_MTL), and lower CMS. The multiple-domain MCI patient is indicated by an arrow, and the 4 MCI-AD converters are indicated by circles. The converters are located in the lower left quadrant in (a), with lower volume & perfusion compared to stable MCI.

Discussion:

Our study demonstrates that perfusion measured with SPECT in the medial temporal lobe structures and the gray matter in other brain regions can be quantified with MRI-guided regional analysis. We observe volume reductions and hypoperfusion mainly confined within the medial temporal lobe of MCI patients. Perfusion in the corpus callosum, or in the gray matter of frontal, lateral temporal, parietal or occipital lobe is not significantly affected in MCI. Incorporating the imaging findings of medial temporal lobe volume loss and hypoperfusion, with deficits on neuropsychological measures, may provide early markers to identify MCI patients who are suffering from prodromal or preclinical AD. Our results support including imaging markers as supportive features as part of the diagnostic criteria for AD [1]. Refining diagnostic criteria is urgently needed to help in selecting patients who have underlying AD pathology to participate in drug trials. They are more likely than the general MCI population to benefit from the interventions designed to slow the progression to AD, allowing for more accurate evaluation of therapeutic efficacy.

[1] Dubois B, Feldman HH, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 2007; 6:734-746.