Differences of Functional Activation Patterns between Subjects with Mild Cognitive Impairment and Normal Subjects

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Introduction Alzheimer's disease (AD) is an irreversible, degenerative brain disorder that will affect up to 5.1 million Americans by 2010. It is the most common cause of dementia. The diagnosis of AD and other dementias is typically preceded by a long prodromal phase during which a person has detectable cognitive deficits (mild cognitive impairment or MCI) but does not meet criteria for dementia [1]. Functional MRI (fMRI) provides a non-invasive tool to reveal functional abnormalities of the brain and has the potential to detect functional changes due to neuro degeneration at an early stage before structural changes are obvious. FMRI can potential lead to an imaging marker for the early diagnosis of patients who are likely to develop AD. Though several fMRI studies have been conducted for MCI (a review can be found in [2]), this field is still in its infancy and more studies are needed to understand the dysfunction of MCI and early AD. In this work, we present fMRI results showing functional differences between MCI subjects and normal subjects for different memory paradigms.

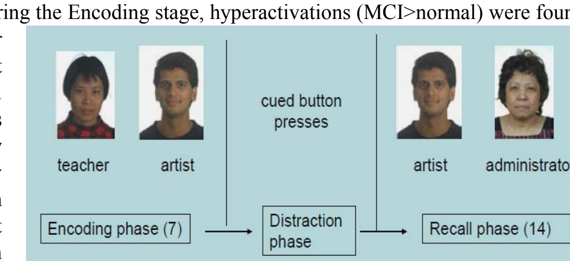
Methods Comprehensive neuropsychological tests (Memory Complaint, MMSE, Normal ADLS, and CES-D) and clinical tests (CDR and Modified Hachinski) were conducted by trained professionals and neurologists to screen subjects. Eight MCI subjects (3 females and 5 males, average age 60.9) and eight normal subjects (4 females and 4 males, average age 60.6) took part in an fMRI memory study. IRB approval was obtained according to institutional requirements.

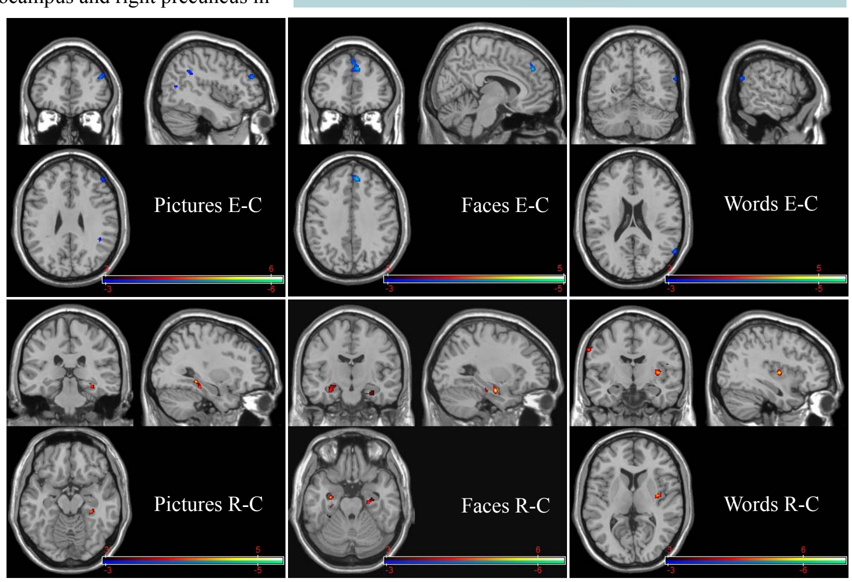
Three memory paradigms involving encoding and recognition tasks were performed during fMRI. These memory paradigms are referred to as: 1) common outdoor/indoor pictures ("Pictures"), 2) pairing of faces and occupations ("Faces"), and 3) unrelated word pairs of objects and locations ("Words"). For each of the three memory paradigms, there are four conditions. The first is an visual instruction condition to remind subjects of the task; the second is an encoding condition that consists of a series of novel stimuli for each paradigm that the subject must memorize; the third is an active control condition (distraction condition) where the subject sees the letter "Y" or "N" and presses the right button for "Y" or the left button for "N". Due to its simplicity, this control condition does not produce any activation in regions associated with the memory circuit (hippocampal complex, posterior cingulate cortex, precuneus, fusiform gyrus); the fourth is a recognition condition where the subject sees a series of stimuli – with half novel and half identical to the stimuli seen in the previous encoding condition, in a random design. The subject is instructed to press the right button if the stimulus is determined as seen in the previous encoding condition and to press the left button if the stimulus is identified as novel. Accuracy and reaction time (RT) of the button presses are recorded. The figure below shows an example of the face and occupation paradigm. Each of four conditions repeats six times for an overall duration of 10 minutes per paradigm.

Functional MRI (fMRI) was performed in a 3.0T GE HDx MRI scanner equipped with an 8-channel head coil using the following parameters: ASSET=2, ramp sampling, TR/TE=2sec/30ms, FA= 70deg, FOV=22cmx22cm, thickness/gap=4mm/1mm, 25 oblique-coronal slices perpendicular to the long axis of the hippocampus, in-plane resolution 96x96 interpolated to 128x128, and 288 time points. The fMRI time series were motion corrected and smoothed (3D Gaussian FWHM=6mm). Contrast images were calculated for each subject using the general lineal model in SPM5 [3] with a block design. The regressors for all conditions were specified using the classical HRF. A second level two-sample t-test was used to infer group difference on the normalized contrast images. A cluster size >272mm^3 was determined by AFNI using AlphaSim [4] to achieve statistical significance less than $p=0.05$ with an individual voxel threshold of $p<0.005$.

Results In Table 1, we summarize accuracy and response time (RT) of MCI (in the left) vs normal subjects (in the right). As can be seen, MCI subjects generally spent more time and performed less accurate than normal subjects. The biggest difference occurs in the face and occupation paradigm.

In the bottom figure, we show the most prominent functional differences between MCI and normal subjects for the contrasts of Encoding vs. Control ("E-C") and Recognition vs Control ("R-C") tasks. The blue color represents greater activations of MCI subjects vs normal subjects, the red color means the opposite. A neurology convention of display was used, i.e. the left in the image corresponds to the left in the anatomy. During the Encoding stage, hyperactivations (MCI>normal) were found in the follow regions: 1) right middle frontal and angular gyrus in "Pictures"; 2) frontal superior medial gyrus and middle cingulate cortex in "Faces"; and 3) the right middle temporal, right superior temporal and right angular gyrus in "Words". No significant difference in the medial temporal lobe (MTL) was found. One possible explanation of these findings is that when subjects tried to memorize the novel stimuli, both MCI and normal subjects use MTL to consolidate memory function in a similar intensity, while impaired MTL function in MCI subjects was partially compensated by recruiting other brain regions to perform memorization. During the Recognition stage, MCI subjects showed hypoactivation (MCI<normal) in the following regions: 1) the right hippocampus in "Pictures"; 2) bilateral hippocampi proper, parahippocampus and right precuneus in "Faces"; and 3) bilateral posterior central sulcus, right insula, right Rolandic operculum, and left cerebellum in "Words". The only notable region with increased activation during Recognition in MCI subjects is left precentral gyrus in "Pictures". The biggest difference in MTL activation is in the face and occupation paradigm and correlates well with the biggest difference in memory task performance. There is no difference in MTL activation for "Words".





Conclusions The current study suggests that MCI subjects may utilize brain regions other than MTL to facilitate encoding of new information. The MTL is hypoactive during the recognition task of "Pictures" and "Faces" and indicates that MCI subjects may have impaired retrieval function.

	Pictures	Faces	Words
Accuracy	89.3% vs 95.7%	83.9% vs 94.2%	89.2% vs 95.0%
RT (sec)	1.12 vs 1.00	1.61 vs 1.40	1.40 vs 1.22

Table 1. Memory task performance of MCI vs normal groups.

References [1]. Peterson RC et al., 2001. *Arch Neurol* 58, pp 1985-. [2] Dickerson BC and Sperling RA, 2008. *Neuropsy* 46, pp 1624-. [3] Worsley K and Friston K, 1995. NeuroImage 2, pp 173-. [4] Cox RW, 1996. Comput. Biomed. Res. 29, pp 162-. *This work is partially supported by the NIH (1R21AG026635).*