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A preliminary study of functional abnormalities in aMCI subjects during different episodic memory tasks

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Abstract

Functional MRI (fMRI) is an important imaging modality to understand the neurodegenerative course of mild cognitive impairment (MCI) and early Alzheimer's disease (AD) because the memory dysfunction may occur before structural degeneration is obvious. In this research, we investigated the functional abnormalities of subjects with amnesic MCI (aMCI) using three episodic memory paradigms that are relevant to different memory domains in both encoding and recognition phases. Both whole brain analysis and region-of-interest (ROI) analysis on the medial temporal lobes (MTL), which are central to the memory formation and retrieval, were used to compare the efficiency of the different memory paradigms and the functional difference between aMCI subjects and normal control subjects. We also investigated the impact of using different functional activation measurements in ROI analysis. This pilot study could facilitate the use of fMRI activations in MTL as a marker for early detection and monitoring progression of AD.

Keywords

amnesic mild cognitive impairment (aMCI); episodic memory; functional MRI; medial temporal lobe (MTL); ROI analysis

Introduction

Alzheimer's disease (AD) is an irreversible, degenerative brain disorder that affected 26.6 million people in 2006 and whose prevalence was estimated to quadruple by 2050 (Brookmeyer et al., 2007). It is characterized by progressive amnesia, executive and visuospatial dysfunction, as well as language and neuropsychiatric disturbances. A long prodromal phase during which a person has detectable cognitive deficits (mild cognitive

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impairment or MCI) but does not meet criteria for dementia usually precedes the diagnosis of AD and other dementias (Small et al., 2000; Palmer et al., 2003). The development of MCI with an amnesic component (or aMCI) has an annual rate of conversion to AD (or dementia) in the range of 6-25%, compared to only 0.5-4% for healthy subjects in similar age groups (Petersen et al 2001). Identification of neuropathological or functional changes of aMCI is a crucial step in finding treatments that prevent or slow the onset of dementia.

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 neurodegeneration at an early stage before structural changes are obvious, thus leading to an imaging marker for the early diagnosis of patients who are likely to develop AD. Several studies reported aberrant memory activations in aMCI subjects (Celone et al., 2006; Dickerson et al., 2005; Hämäläinen et al., 2007; Johnson et al., 2004; Machulda et al., 2003; O'Brien et al., 2010; Yassa et al., 2010). Variable results were obtained in these studies and may be caused by the different memory paradigms, the different analysis methods, and the heterogeneous spectrum of aMCI. In addition, most of these studies focused on the encoding process of memory in hippocampus and did not investigate activations in subregions of the MTL, which are critical for memory formation and retrieval.

Machulda et al (2003) found that MCI patients had less MTL activation during the memory encoding task of pictures than normal subjects and suggested that decreased MTL activation may be a specific marker of limbic dysfunction due to the neurodegenerative changes of AD, and fMRI is sufficiently sensitive to detect changes in MCI. Similarly, an analysis of the dynamic process of encoding novel repeating faces using functional MRI (fMRI) in non-demented elderly volunteers with and without diagnosed memory problems demonstrated greater MTL activity in healthy elderly than patients with compromised memory functioning on neuropsychological tests (Johnson et al., 2004). Dickerson et al (2005) used a face-name associative encoding task during fMRI scanning and found significantly greater hippocampal activation in the MCI group compared to controls, though there were no differences between these two groups in hippocampal or entorhinal volumes. They hypothesized that there is a phase of increased MTL activation early in the course of prodromal AD. Petrella et al. (2006) assessed abnormalities in brain activation patterns during encoding and retrieval of a face-name paradigm in subjects with MCI at field strength of 4 Tesla. They found that subjects with MCI showed decreased magnitude of activation in bilateral frontal cortex regions (during encoding and retrieval), the left hippocampus (during retrieval), and the left cerebellum (during encoding), and increased activation in the posterior frontal lobes (during retrieval) compared with magnitude of activation in control subjects. An independent component analysis (ICA) was used to analyze the hippocampal-based memory systems across the continuum of normal aging, MCI and mild AD (Celone et al., 2006). During an associative memory paradigm, paradoxical hyperactivation in the hippocampus was found in less impaired MCI, whereas significant hypoactivation was found in more impaired MCI subjects. Lately, increased fMRI activations during an associative encoding of novel picture-word pairs were also found in the posterior hippocampal, parahippocampal and fusiform regions for MCI subjects, accompanied by more atrophy in the anterior parts of the left hippocampus (Hämäläinen et al 2007). In addition, the negative correlation between the hippocampal volume and parahippocampal activation were discovered in the same study. The authors suggested that the increased fMRI activation in MCI in the posterior medial temporal and fusiform regions is compensatory due to the incipient atrophy in the anterior MTL.

To find the actual source of observed hyperactivity in the hippocampal region in MCI, Yassa et al (2010) conducted a higher-resolution fMRI study using a continuous recognition task designed to emphasize pattern separation, i.e. the ability to separate similar representations

into distinct, non-overlapping representations. They observed hyperactive BOLD signals in the CA3/dentate region and hypoactive signals in the entorhinal cortex during the separation condition. The high-resolution morphometric analysis of hippocampal subfields demonstrated that aMCI patients had smaller CA3/dentate and CA1 volumes. Their findings suggested that structural and functional changes in the CA3/dentate region of the hippocampus contribute to the deficits in episodic memory in aMCI and the functional hyperactivity may be evidence for a dysfunctional encoding mechanism. O'Brien et al (2010) hypothesized that subjects in early phases of prodromal AD may experience a period of hippocampal hyperactivation, followed by loss of hippocampal activation as the disease progresses. Their longitudinal fMRI study using a face-name associative memory paradigm revealed that subjects with more rapid decline showed both the highest hippocampal activation at baseline (hyperactivity), and the greatest loss of hippocampal activation subsequently.

More studies are needed to understand the course of the memory dysfunction of MCI and early AD and to investigate the most efficient way to use fMRI activations in MTL that would enable it as a marker for early detection of AD and for monitoring its progression. In this study, we examined eight subjects with aMCI and eight normal controls using three episodic memory paradigms that are relevant to different memory domains in both encoding and recognition phases. We used an MRI protocol that allows acquisition of oblique-coronal slices perpendicular to the long axis of the hippocampus to obtain more specific information for the MTL that is suitable for region-of-interest (ROI) analysis on both structural and functional data. Both whole brain analysis and ROI analysis were applied on fMRI data to compare the efficiency of the different memory paradigms and the functional difference between two groups. We also investigated the impact of using different functional activation measurements in ROI analysis.

Methods

Subjects

Eighteen subjects (ten with aMCI and eight normal controls) were consented and recruited from the community for participation in this study, which was approved by the Colorado Multiple Institution Review Board. Two subjects with aMCI were excluded from the study due to incidental imaging abnormalities (meningioma and arachnoid cyst). All subjects were right-handed and demographic information for those completing the study is shown in Table 1. Of the eight normal control subjects, four were women and four were men with an average age of 60.9 ± 8.3 years. Subjects with aMCI included three women and five men with an average age of 60.6 ± 3.2 years. Screening for vascular-based cognitive impairment (Modified Hachinski Ischemic Scale or HIS) and depression (Center for Epidemiologic Studies Depression Scale or CES-D) was performed to exclude potential stroke-related MCI (excluded for $HIS > 4$) and depression (excluded for $CES-D > 27$). Subjects with a past history of a major psychiatric illness (i.e. schizophrenia, bipolar illness), neurologic disorder (i.e. stroke, Parkinson's disease) or known structural central nervous system abnormality were excluded, as were those taking acetylcholinesterase inhibitors or medications with mood- or significant arousal-altering potential (e.g. benzodiazepines or stimulants). Diagnosis of amnesic MCI was made using Petersen Criteria (Petersen et al. 2001) following 1) a comprehensive neuropsychological evaluation, 2) a neurologic examination by a neurobehavioral neurologist or neuropsychiatrist, and 3) a diagnostic consensus by the neuropsychologist and the examining physicians. Neuropsychological battery included the mini-mental state examination (MMSE) (Folstein et al. 1975), Boston Naming Test (Mack et al. 1991), California Verbal Learning Test (CVLT) (Delis et al. 1987), Logical Memory I and II of the Wechsler Memory Scale-Revised (Hermann and Young 1987), Controlled Oral Word Association Task (Loonstra et al. 2001), Animal Naming (Tombaugh et al. 1999),

Trail Making A and B (Reitan 1958), Symbol Digit Test (Lezak et al. 2004), Block Design (Lezak 1995), and Benton Visual Retention test (Coman et al. 1999).

FMRI paradigms

Three memory paradigms involving encoding and recognition tasks were performed during fMRI. These memory paradigms are referred to as: 1) common outdoor pictures (“Pictures”), 2) pairing of faces and occupations (“Faces”), and 3) unrelated word pairs of objects and locations (“Words”). The structure of these paradigms was the same as shown in Figure 1 and described as follows. Each paradigm contained 6 periods of encoding (“E” in Figure 1), control (“C” in Figure 1), and recognition (“R” in Figure 1) tasks, as well as short instructions (“I” in Figure 1) where words on the screen reminded subjects of the task ahead. Behavioral data were collected using a conventional 2-button box using EPRIME (Psychology Software Tools, INC., Pittsburgh, PA). Specifically, the encoding task consisted of a series of novel stimuli (7 items displayed in sequential order for duration of 3 sec each and 21 sec total duration) that the subject must memorize. After the encoding task a control task occurred for 11 seconds where the subject saw the letter “Y” or “N”, which occurred in random order and random duration (0.5 to 2 sec). The subject was instructed to keep close attention to the “Y” and “N” and to press the right button whenever “Y” appeared and the left button whenever “N” appeared, as fast as possible. Reaction time and accuracy of the button presses were recorded. Besides serving as a distraction between encoding and recognition, due to its simplicity, this control condition functioned as an active control task that did not lead to any activation in regions associated with the memory circuit (hippocampal complex, posterior cingulate cortex, precuneus, fusiform gyrus). We found that an active distraction task is necessary as a null memory task because simple fixation or rest is known to induce activations in the default mode which has a large overlap with the memory circuit in the medial temporal lobes (Raichle and Snyder, 2007). Other active control tasks were used in episodic memory studies by Maguire et al. (2001) and Staresina & Davachi (2010). After the control task, the recognition task occurred consisting of 14 items – with half novel and half identical (in random order) to the items seen in the previous encoding task (each item is displayed for 3 sec). For the Faces and Words tasks that included pairs of items, new pairs always include two completely novel stimuli rather than re-paired studied items, as is sometimes done in associative recognition. The subject must press the right button if the item was seen in the previous encoding task and press the left button if the item was not seen (i.e. item is identified as novel to the subject). Reaction time and accuracy of the button presses were recorded. In each of the 6 periods, different items were used that the subject did not see before. The memory tasks were chosen to be not very challenging for aMCI subjects so that only on occasion (less than 2% of all items) subjects missed a response. Besides the 6 repeated runs, a 10-sec initial instruction (“I” in Figure 1) followed by an instruction and control period was included at the beginning of each paradigm and an instruction and control period was included at the end, as shown in Figure 1. For each paradigm, the scan duration was 9 min and 36 sec and 288 time frames were collected. The contrasts of interest in this work are “Encoding-Control” (E-C) and “Recognition-Control” (R

C).

MRI Data acquisition

Echo planar imaging (EPI) was performed in a 3.0T GE HDx MRI scanner (General Electric, Milwaukee, WI) equipped with an 8-channel head coil using the following parameters: ASSET=2, ramp sampling, TR/TE=2sec/30ms, FA= 70deg, FOV=22cm×22cm, thickness/gap=4mm/1mm, 25 oblique-coronal slices perpendicular to the long axis of the hippocampus, in-plane resolution 96×96 interpolated to 128×128, and 288 time points.

Besides three memory paradigms, a resting-state scan was also acquired where subjects were instructed to rest with eyes closed and not to think anything particular during the scan. Parallel imaging with ASSET=2 and sampling under the ramp with an echo-spacing of 0.69 msec for every two lines of k-space lead to less distortions and signal dropouts than conventional EPI acquisitions at 64×64 resolution. Furthermore, using the coronal oblique orientation, the cross section of hippocampal complex will be in the imaging plane with less susceptibility artifacts. The improvement over the conventional axial acquisition can be found in Jin et al. (2011, Fig. 1).

Standard high resolution T2-weighted structural images (0.43mm×0.43mm×2.5mm) aligned with the same orientation and coverage of the EPI scans and standard 3D SPGR T1-weighted high resolution (1mm × 1mm × 1mm) axial structural images were also collected.

MRI data analysis

Preprocessing—The first five echo planar volumes were excluded to avoid saturation artifacts. The remaining 283 volumes were pre-processed using SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>), including realignment to correct for motion artifacts, slice timing correction to correct for differences in image acquisition time between slices, and high-pass filtering using T=150 sec to remove low frequency components and signal drifts.

Whole brain group analysis—fMRI time series for each paradigm of each subject was analyzed using the general linear model (GLM) in SPM5 to generate contrast images and t maps of E-C and R-C. The classic two-gamma HRF was used to construct the design matrix for the first level GLM analysis. The contrast images were normalized to the Montreal Neurological Institute (MNI) space as follows: 1) a mean EPI image was used to co-register the contrast images to the high resolution T2-weighted image; 2) co-registered contrast images were further co-registered to the T1-weighted image using transformations determined by the T2-weighted image; 3) the high resolution T1-weighted anatomical image was used to determine parameters for spatial normalization of the contrast images to the MNI space. The normalized contrast images were spatially smoothed with a 6 mm FWHM Gaussian kernel and input into a second-level random effects analysis in SPM5. A one sample t-test for each individual group and a two sample t-test for group differences between normal control and aMCI were used. A cluster size (34 voxels for resliced images at 2mm×2mm×2mm resolution) was determined by AFNI using AlphaSim (Cox, 1996) to achieve a corrected statistical significance less than $p=0.05$ with an individual voxel threshold of $p<0.005$ for the activation maps. A neurological convention of display was used for the activation maps in this work, i.e. the left in the image corresponds to the left in the anatomy.

Region-of-interest analysis of MTL—To better understand the functional changes in the medial temporal lobes (MTL), we conducted a region-of-interest (ROI) analysis using each subject's t maps. The ROIs were CA23DG (a combination of CA2, CA3, and dentate gyrus), CA1, subiculum (SUB), entorhinal cortex (ERC), perirhinal cortex (PRC), and parahippocampal cortex (PHC) on both left and right sides of the brain (i.e. total 12 subregions for each subject). These ROIs were delineated slice-by-slice in each subject's high resolution T2 image (see Figure 2) by a trained professional using methods developed at UCLA (Zeineh et al., 2000; Ekstrom et al., 2009). To avoid bias, the segmentation was done without knowledge of the group membership of the subjects. The volumes of the segmented MTL and its subregions were calculated using the delineated ROIs in T2 image. The t maps of E-C and R-C for each paradigm of each subject were co-registered to each subject's high resolution T2-weighted image using the subject's mean EPI image. Two fMRI

activation measurements of the subregions adapted from Dickerson et al. (2004) and Machulda et al. (2003) were calculated and compared. The gray matter in the 3D SPGR image of each subject was also segmented using SPM5 to calculate the gray matter volume for normalizing ROI volumetric measurements.

The first measurement is the relative activation extent (RAE) measurement proposed by Dickerson et al. (2004). An uncorrected p-value threshold was used to threshold t maps and the number of voxels that survived the thresholding was counted in each ROI. The RAE was defined as the ratio of the number of active voxels above threshold vs the total number of voxels in a ROI.

As proposed by Machulda et al. (2003), the second measurement is the area under receiver operating characteristic (ROC) curves for false positive fraction (FPF) less than a predefined threshold. The underlying assumption is that the certain neuroanatomic regions should activate at a high probability during a specific task, but only by chance during the null state. Rather than using a randomly permuted task fMRI time series as the null state (as in Machulda et al. (2003)), we utilized resampled resting-state fMRI data and performed the same first level GLM analysis to get the corresponding t maps for calculation of FPF (Nandy and Cordes, 2003).

Both RAE and area under ROC curves at certain FPF (A_{FPF}) were compared using a rank-sum test between the normal control and aMCI groups. We also addressed the multiple-comparison problem for 12 subregions for each contrast of a paradigm using the false discovery rate (FDR) (Benjamini and Hochberg, 1995). Analysis of co-variance (ANCOVA) was used to find the influence of subjects' age, education, and memory performance (accuracy and response time) on the fMRI activation.

Results

Age and education differences between normal control and aMCI subjects were not statistically significant, whereas MMSE differences were significant ($p=0.0041$). Assessment of memory performance, specifically for delayed recall (CVLT long delayed recall) and learning efficiency (CVLT Total), was significantly different between the two groups, but working memory (CVLT Trial 1) was not. Average Clinical Dementia Rating (CDR) score was 0.5 for the aMCI group and 0 for the normal control group (See Table 1).

In Table 2, we summarized the mean and standard deviation values of accuracy and response time (RT) of aMCI vs normal subjects. As can be seen, aMCI subjects generally spent more time and performed less accurately than normal subjects. The higher standard deviation values in the aMCI group indicate the greater variability of individual performance. But the only statistically significant difference ($p<0.05$) occurs in accuracy of the Faces paradigm.

Whole brain group analysis

In Figure 3, we showed the activation maps (corrected $p<0.05$, one sample t-test) of each group for contrast E-C and R-C for the three paradigms in coronal slices spanning the MTL. No activations due to motor responses of the control portion (C) were obtained in MTL regions in these slices. Thus, we chose to display only the positive activations for E-C and R-C contrasts. It can be seen that both encoding and recognition tasks of the three paradigms induced strong and robust activations at the MTL region in normal controls (the left column of Figure 3). Activations in the Pictures and Faces paradigms were bilateral, while the Words paradigm stimulated activation mainly on the left side. The aMCI subjects generally had less activations compared to normal controls in all paradigms (the right column of

Figure 3). The amount of decreased activation seemed to be greater in the recognition phase of memory than in the encoding phase of memory. For example, in the aMCI activation maps of the Words paradigm, the activation on the left side of MTL was present for contrast E-C, but not for contrast R-C (the bottom right blocks in Figure 3 (a) and (b)).

The statistical significant differences between normal control and aMCI subjects were shown in axial slices in Figure 4 (corrected $p < 0.05$, two sample t-test). The blue color represents greater activations of aMCI subjects vs normal control (NC) subjects; the red color means the opposite.

For the Pictures paradigm in Figure 4 (a), subjects with aMCI showed decreased activations in right MTL including hippocampus, parahippocampal gyrus, and fusiform gyrus and left middle temporal gyrus during encoding and decreased activations in right parahippocampal gyrus and fusiform gyrus during recognition. The increased activation for aMCI was observed in left precentral gyrus and superior motor area during recognition. These regions along with their peak locations, maximum t values, and cluster sizes were listed in Table 3.

For the Faces paradigm in Figure 4 (b), subjects with aMCI showed increased activation in the medial prefrontal cortex (MPFC) during encoding and decreased activation in the bilateral MTL including hippocampus, parahippocampal gyrus, and fusiform gyrus (more left in the anterior portion and more right in the posterior portion), left angular gyrus, and right cuneus/precuneus during recognition. These regions along with their peak locations, maximum t values, and cluster sizes were listed in Table 3.

For the Words paradigm in Figure 4 (c), subjects with aMCI showed decreased activation in right Rolandic operculum and right insula and increased activation in precentral and postcentral gyrus during recognition. No significant difference was found during encoding. These regions along with their peak locations, maximum t values, and cluster sizes were listed in Table 3.

Region-of-interest analysis of MTL

The average MTL volume and standard deviation were 8370.44 mm^3 and 1404.56 mm^3 for normal controls, and 8698.18 mm^3 and 1702.49 mm^3 for aMCI subjects, respectively. The difference between the two groups was not statistically significant ($p = 0.68$) using a two-sample t-test. A two sample t-test for each subregion of the MTL was also conducted but did not reveal any significant difference between the two groups. Furthermore, to avoid bias introduced by potentially different volumes of gray matter, we also segmented gray matter for each subject using SPM5. The average gray matter volume and standard deviation were $5.11 \times 10^5 \text{ mm}^3$ and $0.49 \times 10^5 \text{ mm}^3$ for normal controls, and $5.21 \times 10^5 \text{ mm}^3$ and $0.62 \times 10^5 \text{ mm}^3$ for aMCI subjects, respectively. There was no statistically significant difference in gray matter volumes between the two groups. Also, we normalized the volume of the MTL and subregions by the volume of the gray matter for each subject. A two-sample t-test on normalized quantities did not reveal any significant difference either.

The p threshold and the FPF threshold were chosen as 0.05 for calculating RAE and A_{FPF} , respectively, which are the same as that used in the original work by Dickerson et al. (2004) and Machulda et al. (2003). These results were summarized in Table 4 with each group's median values and p values of rank-sum test. The FDR was chosen as 0.1 serving an exploratory purpose in our study. Significant decreased activation measured by RAE for the aMCI group was found in: 1) Left CA23DG, Bilateral CA1, and Right SUB for R-C contrast of the Faces paradigm, and 2) in Left ERC for E-C contrast of the Words paradigm. The significant decreased activation measured by A_{FPF} for the aMCI groups was found in: 1) Left CA1 for R-C contrast of the Pictures paradigm, 2) Left CA23DG, Bilateral CA1, and

Bilateral SUB for R-C contrast of the Faces paradigm, and 3) Left CA1 and Right SUB for R-C contrast of the Words paradigm. If a more stringent number of 0.05 was used for FDR, there were no significant findings for RAE any more, but only the Left CA1 region for contrast R-C of the Pictures paradigm and the Left SUB region for contrast R-C of the Faces paradigm dropped from the list for significant A_{FPF} .

Using ANCOVA, subjects' age, education, recognition accuracy, and response time were modeled as covariates of a linear model of the RAE and A_{FPF} measurements. We corrected the measurements only if the beta weights of covariates were deemed significant through an ANCOVA test. At $p < 0.05$, we found that these covariates had significant influence on the RAE measurement in Left PHC for contrast E-C of the Pictures paradigm and in Left CA23DG and Left PHC for contrast E-C of the Words paradigm, and on the A_{FPF} measurement in Left CA23DG for contrast E-C of the Words paradigm. From Table 4, it can be seen that there was no significant group difference in these regions. Once we corrected the measurements for these covariates, the rank-sum test still remained insignificant in these subregions.

Discussion

All three paradigms in this study were able to induce strong BOLD fMRI activations in MTL during the encoding and recognition phases (see Figure 3). The lateralization of activations for E-C in the Words paradigm is consistent with the notion that encoding of verbal stimuli preferentially relies on left-hemispheric brain regions (Golby et al., 2001; Kelley et al., 1998; Powell et al., 2005; Weber et al., 2007). Our particular interest is subregions of the MTL (hippocampal complex, entorhinal cortex, perirhinal cortex, parahippocampal cortex, fusiform gyrus) and nearby regions involved in episodic memory (posterior cingulate cortex and precuneus). It is known that these areas are part of the default mode network, which engages in introspective modes of cognition including free thinking, remembering the past, envisioning the future, and mediating the perspectives of others (Andrews-Hanna et al., 2010; Buckner and Carroll 2007, Buckner et al., 2008; Mazoyer et al., 2001; Raichle et al. 2001; Shulman, et al. 1997). A simple fixation, like a resting state, used in the previous memory paradigms may not suppress the memory-related activation in these areas very well and be an inadequate control condition. Therefore, an active 'Control' task using cued button presses was used in our paradigms because it is very simple and does not lead to any activation in regions associated with episodic memory.

The majority of the previous work on functional changes in aMCI (Celone et al., 2006; Dickerson et al., 2005; Hämäläinen et al. 2007; Johnson et al., 2004; Machulda et al., 2003; Miller et al., 2008; O'Brien et al. 2010) was focused on the encoding process of episodic memory. In our study, we found more significant difference between normal control and aMCI subjects during the recognition phase either in the whole brain analysis or in the ROI based analysis. The decreased activation in left hippocampus of aMCI subjects during retrieval in the Faces paradigm was found to be consistent with previous results reported by Petrella et al. (2006). Our finding may indicate that compared to the encoding phase of our task, the recognition phase may rely on regions within the memory circuit that are affected more by aMCI than by normal aging. Thus, using our tasks with analysis of the recognition phase may improve our ability to differentiate normal aging and aMCI subjects than using encoding tasks. Although the additional recognition task introduces extra challenge for the subjects and prolongs the scanning time (about 10 min in our study), the increased power of discriminating abnormal memory functions from normal ones may lead to an fMRI imaging marker for predicting the onset of AD.

In our whole brain analysis, the aMCI group showed decreased activation in memory relevant areas such as MTL and cuneus/precuneus. These findings are consistent with results from Machulda et al. (2003) and Johnson et al. (2004). Although the “paradoxically” increased activation was not observed in our study, it has been reported for the subjects at risk for AD, by virtue of their genetics (APOE4 status) (Bookheimer et al., 2000) or evidence of MCI (Celone et al., 2006; Dickerson et al., 2005; Hämäläinen et al., 2007; O'Brien et al., 2010; Yassa et al., 2010). A study on the relationship between fMRI activation and cognitive test scores has shown that greater hippocampal activation in MCI subjects predicted a greater degree and rate of subsequent cognitive decline (Miller et al., 2008). However, it may be that this hyperactivation occurs only in the earliest stage of prodromal AD and hypoactivation will eventually occur. One explanation for not finding the paradoxical “hyperactivation” in MTL is because our patient group may be at the more severe stage of MCI according to MMSE scores. The mean MMSE score (28.1) in our study is close to that (28.4) in Machulda et al. (2003) and is lower than that (29.6) in Dickerson et al. (2005). The mean MMSE score was 29.3 for less-impaired MCI and was 28.6 for more-impaired MCI in Celone et al. (2006). To fully understand the patterns of functional changes in the memory network and their relationship to AD pathology, a longitudinal study and cross-modality studies (combining structural MRI, PET amyloid beta peptide imaging, and cerebrospinal and serum fluid examinations) seems to be necessary. It is inspiring to see an attempt to use fMRI in a longitudinal study (O'Brien et al., 2010), although the two time points used in that study may not be sufficient to track a functional pattern that reveals increasing activation (compensation) followed by decreasing activation (loss of function).

Although prefrontal cortex plays a more important role in executive function and working memory (Banich 2004), it has connections with the MTL through pathways involving the retrosplenial cortex and posterior cingulate cortex (Greicius et al., 2009). Thus, compensation effects are likely to involve the prefrontal cortex when subregions of the MTL lose its function. Several studies have reported that healthy older adults or AD patients recruited various regions within the frontal and parietal lobes to maintain normal memory function otherwise affected by normal aging or pathological degenerations (Anderson et al. 2000, Cabeze et al. 2002, Gould et al. 2006, Grady et al. 2002, Logan et al. 2002, Pariente et al. 2005). We suspect that increased activation in MPFC (Figure 4 (b)) in the aMCI group might represent such a compensatory effect due to the disrupted encoding function in MTL and that other elevated aMCI activation in precentral gyrus and superior motor area was more likely caused by the (active) control state (which is not memory relevant). The compensatory postulation has to be carefully scrutinized since the BOLD signal is not a direct measure of neural activity, but depends on local changes in cerebral blood flow, cerebral blood volume and cerebral metabolic rate of oxygen consumption (Buxton et al., 2004). In our study, we used Modified Hachinski Ischemic Scale or HIS to exclude vascular-based cognitive impairment and the volumetric measurements in MTL to avoid the confounding factor caused by the cerebrovascular disease. The problem of interpretation of compensatory neural recruitment can be addressed more systematically by the region-activation performance model (Han et al. 2009).

In this study, we used three paradigms, which span three different domains of memory. The Pictures paradigm contained only a single domain stimulus of outdoor scenes. The Faces paradigm combined both face images with text describing people's occupations (verbal stimuli). The combination of two nouns needs to be memorized in the Words paradigm. The latter two paradigms required associative memory and were more difficult than the first one. For subjects who participated in our study, the worst performance occurred in the Faces paradigm while similar performance was achieved in the Pictures and Words paradigms (see Table 2). The results from the whole brain analysis and the ROI based analysis on the subregions in MTL also revealed that more significant differences (i.e. more significant

voxels in whole brain analysis and more significant subregions in ROI analysis) between aMCI and normal controls were found in the Faces paradigm. Most previous studies also adapted the face-name or picture-name scheme to study encoding differences (e.g. Dickerson et al., 2005, O'Brien et al., 2010) or encoding and retrieval differences (Petrella et al. 2006) between healthy elderly and elderly patients with memory deficits. The use of paired stimuli is presumably better because recognizing face-occupation pairs requires the hippocampus to associate different types of information (Mayes et al., 2007). These results also imply that to get detectable functional difference a certain level of difficulty has to be reached. Our Faces paradigm seems to be a good candidate for further investigating the functional predictor for onset of AD and progression.

In order to conduct the ROI based analysis, we manually segmented subregions in MTL on high resolution T2 slices perpendicular to the long axis of hippocampus following the segmentation procedure in Zeineh et al. (2000) and Ekstrom et al. (2009). The segmentation procedure was followed by a 3D to 2D cortical unfolding technique that has been reported to have high intra-rater reliability (>0.9) as measured by an intra-class correlation coefficient (Burggren et al. 2008). In this study, test-retest reliability was larger than 90% as measured by repeating the segmentation procedure for 3 randomly picked subjects two weeks apart from the original segmentation. Although automatic segmentation would be desired (Chupin et al., 2009), due to the complexity of the problem, the development of algorithms for automatically segmenting subregions of the MTL is still a daunting task and has not been solved yet.

To reduce error during co-registration and normalization to the MNI atlas, the EPI images were acquired co-planar to the T2 images for easier co-registration. The RAE and A_{FPF} measurements were subsequently calculated in each subregion of co-registered functional images. Different measurements used in previous studies might be one reason that contradictory results have been reported. For example, the increased MTL activation for MCI subjects was reported by using RAE (Dickerson et al., 2005), while dissimilar results were reported by using A_{FPF} (Machulda et al., 2003). However, our study showed that the results based on these two measurements for the same set of data were largely in agreement (Table 4), thus, this discrepancy between Machulda et al. (2003) and Dickerson et al. (2005) is more likely caused by the heterogeneity of aMCI population instead of different measurements used. In this study, both measurements demonstrated that aMCI subjects had only decreased activation in certain subregions of MTL, while no significant increased activation was found. Meanwhile, the A_{FPF} measurement seemed to be more sensitive because more significant subregions were discovered. Indeed, when we lowered FDR to 0.05, there were no significant findings for RAE any more, but only the Left CA1 region for contrast R-C of the Pictures paradigm and the Left SUB region for contrast RC of the Faces paradigm dropped from the list for significant A_{FPF} . The computation for A_{FPF} is more complex than for RAE so its increased sensitivity is at the expense of more computation.

We did not find that the volume of a single subregion or of the whole MTL, either normalized by the gray matter volume or not, was significantly different between normal control and aMCI subjects, whereas the functional activations were in several subregions (Table 4). Thus, in our study, there is evidence that functional changes occur in the absence of structural atrophy, which is consistent with the previous report that the functional abnormalities were found without abnormalities of hippocampal or entorhinal volumes (Dickerson et al. 2005).

It is also interesting to note that the severity of memory deficit reflected by neuropsychological test scores may not be directly evident by structural atrophy, at least at the early stage of prodromal AD. In this case, fMRI may be a useful tool to reveal alterations

in memory regions very early for pathological aging, especially in the MTL. Early detection is important for intervention, because by the time structural changes are obvious, it may be too late to achieve satisfactory intervention outcomes.

One limitation of this study is the small sample size. As a preliminary study to investigate the effects of three different memory paradigms and two ROI measurements used in fMRI on detecting functional abnormalities of subjects with aMCI, the results are consistent with previous reports and thus may represent reliable findings, while further experiments using more subjects in each group are needed to generalize those new findings or to reveal more subtle abnormalities of aMCI subjects. Nevertheless, these results are important and meaningful for pilot data suggesting that some effects may be possible in a larger sample study.

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Figure 1.

Memory paradigms used in the fMRI study (shown as Faces). The structure is the same for all three paradigms except that the stimuli are outdoor scenes for Pictures, face and occupation pairs for Faces, and word pairs for Words. “II” is initial instruction (10 sec), “I” is instruction reminding subjects what to do next (5 sec), “C” is control condition of cued button press (11 sec), “E” is encoding of 7 stimuli (21 sec), “R” is recognition of 14 stimuli (42 sec). The memory tasks repeat 6 times with novel stimuli. Scan time for each paradigm was 9 min and 36 sec.

Figure 2. Delineated subfields of MTL in one anterior slice (upper) and one posterior slice (bottom) (radiological convention). CA23DG: CA2, CA3 fields and dentate gyrus; CA1: CA1 field; SUB: subiculum; ERC: entorhinal cortex; PRC: Perirhinal cortex; PHC: parahippocampal cortex.

Figure 3.

Group t-maps for E-C (a) and R-C (b) contrasts of normal controls (NC) and aMCI for the Pictures, Faces, and Words paradigms with corrected $p < 0.05$. Coronal views spanning the MTL are shown in a 2×4 block for each subject group and memory paradigm combination (separated by white lines). The Left column is for NC and the right column is for aMCI. From the top to the bottom, the three rows in both (a) and (b) are for the Pictures, Faces, and Words paradigms, respectively.

Figure 4.

Group difference between aMCI and normal controls for the Pictures (a), Faces (b), and Words (c) memory paradigms (corrected $p < 0.05$). The left column is for contrast E-C and the right column is for contrast R-C. No significant difference was found for E-C of the Words paradigm (thus no figure). The blue color represents greater activations of aMCI subjects vs normal control (NC) subjects, the red color means the opposite. For the Pictures paradigm (a), subjects with aMCI showed decreased activations in right medial temporal lobe including hippocampus, parahippocampal gyrus, and fusiform gyrus and left middle temporal gyrus during encoding, and decreased activations in right parahippocampal gyrus and fusiform gyrus during recognition. Increased activation for aMCI was observed in left precentral gyrus and superior motor area during recognition. For the Faces paradigms (b), subjects with aMCI showed increased activation in the medial prefrontal cortex (MPFC)

during encoding, and decreased activation in the bilateral medial temporal lobe including hippocampus, parahippocampal gyrus, and fusiform gyrus (more left in the anterior portion and more right in the posterior portion), left angular gyrus, and right cuneus/precuneus during recognition. For the Words paradigm (c), subjects with aMCI showed decreased activation in right Rolandic operculum and right insula and increased activation in precentral and postcentral gyrus during recognition.

Table 1

Demographic and neuropsychological test data for subjects

	Normal Control	aMCI
Number of subjects	8	8
Female	4 (50%)	3 (37.5%)
Age (years)	60.6±8.3	60.9±3.2
Education (years)	16.9±2.1	16.9±1.9
MMSE *	29.6±0.5	28.1±1.1
CDR *	0±0	0.5±0
Working Memory	0.5±1.3	-0.4±1.7
Delayed Recall *	0.8±0.8	-0.7±1.5
Learning Efficiency *	62.0±9.8	50.5±11.5

MMSE=mini mental state examination.

* p<0.05 statistical significance between aMCI subjects and normal controls for Mini Mental State Exam or MMSE (p=0.0041), Clinical Dementia Rating or CDR (p=0), Delayed Recall (CVLT Long Delayed Recall) (p=0.0233), and Learning Efficiency (CVLT Total) (p=0.0488).

Table 2

Memory tasks performance using the mean values (and standard deviations in parentheses) of accuracy and response time (RT) - aMCI vs. normal control

	Pictures	Faces	Words
Accuracy	89.3%(10.0%) vs 95.7%(2.4%)	83.9%(9.0%) vs 94.2%(3.1%) *	89.2%(7.5%) vs 95.0%(4.5%)
RT (sec)	1.12(0.18) vs 1.00(0.08)	1.61(0.29) vs 1.40(0.12)	1.40(0.23) vs 1.22(0.13)

* Statistically significant difference between two groups ($p < 0.05$).

Table 3

Significant difference (corrected $p < 0.05$) between aMCI and normal controls for the Pictures, Faces, and Words paradigms.

	Area	Peak MNI (mm)	Max t	Cluster size
E-C				
aMCI<NC				
Pictures	Right HC/PHG/FG	32,-36,-8	6.2516	109(5/64/40)
	Left Middle Temporal Gyrus	-62,-50,0	4.8789	108
aMCI>NC				
Faces	Superior MPFC	6,42,44	2.9898	117
R-C				
aMCI<NC				
Pictures	Right PHG/FG	32,-36,-8	4.7355	74(42/32)
Faces	Left HC/PHG/FG	-30,-12,-22	6.4737	174(67/53/54)
	Right HC/PHG	20,-30,-6	4.8119	127(30/97)
	Right Cuneus/Precuneus	10,-66,36	4.3249	194(58/136)
	Left Angular Gyrus	-46,-68,28	3.7474	35
Words	Right Rolandic Operculum	52,-4,14	4.0589	74
	Right Insula	38,-8,4	6.3204	35
	Left Postcentral Gyrus	-62,-10, 36	5.0160	34
aMCI>NC				
Pictures	Left Precentral Gyrus	-38,0,48	2.9818	48
	Superior Motor Area	-6,10,52 (L) 6,24,60 (R)	2.9921 (L) 2.9825 (R)	96 112
Words	Left Precentral Gyrus	-36, -2, 46	3.0055	38

Table 4

Subregions with significant difference between normal controls and aMCI using “relative activation extent” (RAE) and area under ROC curves (A_{FPP}) for false discovery rate less than 0.1.

	RAE Median (NC)	RAE Median (aMCI)	p
Faces R-C, Left CA23DG	0.372	0.161	0.025
Right CA1	0.219	0.006	0.010
Left CA1	0.307	0.039	0.025
Right SUB	0.214	0.013	0.032
Words E-C, Left ERC	0.056	0	0.003

	ROC Median (NC)	ROC Median (aMCI)	p
Pictures R-C, left CA1	0.032	0.010	0.005
Faces R-C, Left CA23DG	0.037	0.011	0.010
Right CA1	0.025	0.004	0.007
Left CA1	0.030	0.006	0.001
Right SUB	0.027	0.009	0.010
Left SUB	0.009	0.004	0.033
Words R-C, Left CA1	0.026	0.007	0.005
Right SUB	0.017	0.003	0.005