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Entorhinal cortex volume is associated with episodic memory related brain activation in normal aging and amnesic mild cognitive impairment

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Abstract

The present study examined the relationship between entorhinal cortex and hippocampal volume with fMRI activation during episodic memory function in elderly controls with no cognitive impairment and individuals with amnesic mild cognitive impairment (aMCI). Both groups displayed limited evidence for a relationship between hippocampal volume and fMRI activation. Smaller right entorhinal cortex volume was correlated with reduced activation in left and right medial frontal cortex (BA 8) during incidental encoding for both aMCI and elderly controls. However, during recognition, smaller left entorhinal cortex volume correlated with reduced activation in right BA 8 for the control group, but greater activation for the aMCI group. There was no significant relationship between entorhinal cortex volume and activation during intentional encoding in either group. The recognition-related dissociation in structure/function relationships in aMCI paralleled our behavioral findings, where individuals with aMCI displayed poorer

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performance relative to controls during recognition, but not encoding. Taken together, these results suggest that the relationship between entorhinal cortex volume and fMRI activation during episodic memory function is altered in individuals with aMCI.

Keywords

recognition; medial temporal lobe; frontal cortex; intentional encoding; incidental encoding; fMRI

Introduction

Amnesic mild cognitive impairment (aMCI), a significant risk factor for Alzheimer's disease (AD), is characterized by impaired episodic memory function and is generally considered to represent a transitional state between normal aging and AD (Petersen, 2004). The memory deficits observed throughout the course of aMCI and AD are thought to be associated with pathophysiological changes (e.g., atrophy, reduced glucose metabolism, and increased amyloid deposition) in several key brain regions including medial temporal lobe, inferior/medial frontal cortices, and inferior parietal/posterior cingulate cortices (e.g., Barrio et al., 2008; Buckner et al., 2005; Chetelat and Baron, 2003; Mormino et al., 2009; Schonknecht et al., 2009; Tolboom et al., 2009). These brain regions comprise an episodic memory network (Dickerson and Eichenbaum, 2010) that is vulnerable to the pathophysiological changes associated with AD (Buckner et al., 2005; Sperling et al., 2010). Functional MRI (fMRI) studies in healthy adults have revealed that this network is also active during episodic memory function (see Cabeza and Nyberg, 2000 for review), and individuals with aMCI display altered fMRI activation patterns in this network during episodic memory tasks.

The encoding of episodic memories is a continually active process that occurs in a wide variety of settings. *Intentional encoding* refers to self-directed or controlled situations (e.g., word-list learning) where there is an explicit attempt to encode new episodic information. By contrast, *incidental encoding* (Craik and Tulving, 1975) refers to encoding that occurs in the absence of a deliberate intent to encode and is a secondary effect in many everyday situations. In fMRI experiments, incidental encoding has typically been examined using level of processing tasks, which involve deep (e.g., man-made versus natural animacy judgments) versus shallow (e.g., color judgments) encoding conditions where subjects are not instructed to remember the novel information (e.g., Mandzia et al., 2009). However, incidental encoding has also been examined using new/old item recognition tasks (e.g., words, scenes, line-drawings, or faces) where the incidental encoding of novel items during recognition is tested (Buckner et al., 2001; Habib et al., 2003; Tulving et al., 1996) or inferred based on the fact that novel items are encoded to a greater extent than old items (i.e., the novelty encoding hypothesis of Tulving and Kroll, 1995).

A variety of episodic memory paradigms have been used in previous fMRI studies in aMCI and a consistent pattern of increased (Dickerson et al., 2004; Dickerson et al., 2005; Hamalainen et al., 2006, 2007; Heun et al., 2007; Kircher et al., 2007; Lenzi et al., 2009; Yassa et al., 2010) or decreased (Dannhauser et al., 2008; Johnson et al., 2004; Johnson et al., 2006a; Machulda et al., 2009; Machulda et al., 2003; Mandzia et al., 2009; Petrella et al., 2006; Small et al., 1999; Xu et al., 2007) medial temporal or frontal cortex activation has yet to emerge. Certainly, heterogeneity in clinical (e.g., degree of functional impairment in aMCI, criterion used for aMCI diagnosis) and experimental (e.g., task difficulty, type of experimental stimuli, baseline conditions, and statistical methodology employed) variables contributes to the equivocal findings (Dickerson and Sperling, 2008; Stark and Squire, 2001; Trivedi et al., 2008).

In a previous study, we found that individuals with aMCI displayed: 1) increased medial temporal, but reduced frontal cortex activation during the intentional encoding of items that were subsequently recognized, 2) reduced medial temporal and frontal cortex activation during the incidental encoding of new items during the recognition task, and 3) reduced medial temporal, but increased frontal cortex activation during successful recognition of old items (Trivedi et al., 2008). Taken together, these results suggest that the types of encoding (intentional versus incidental) and recognition examined are important variables that may contribute to the discrepant findings in the literature.

Another variable that may influence the results of fMRI studies of episodic memory function in AD, aMCI, or individuals with risk factors for AD is the volume of medial temporal lobe structures such as the hippocampus and entorhinal cortex. Atrophy in these structures among individuals with aMCI has been found to predict decline to AD (Chetelat and Baron, 2003; deToledo-Morrell et al., 2004; Jack et al., 2000; Risacher et al., 2010; Stoub et al., 2008). Previous studies have reported that medial temporal lobe volume correlates with fMRI activation in healthy older adults (Braskie et al., 2009; Rosen et al., 2005) and that this relationship is altered in individuals with AD (Garrido et al., 2002; Meulenbroek et al., 2010; Remy et al., 2005). However, similar structure/function relationships have not been extensively examined in individuals with aMCI.

In the present study, we examined the relationship between entorhinal and hippocampal volume and fMRI activation during intentional encoding success, incidental encoding of new items during recognition and recognition success in the same group of elderly controls with no cognitive impairment and individuals with aMCI as in Trivedi et al. (2008). These medial temporal lobe regions were chosen because they are pathologically involved very early during the course of AD prior to other cortical areas within the episodic memory network (Braak and Braak, 1991). We hypothesized that greater hippocampal and entorhinal cortex volume would be correlated with greater fMRI activation in the episodic memory network in elderly controls, whereas this relationship between volume and fMRI activation would be reduced in individuals with aMCI. This study provides important information about how volumetric changes to medial temporal lobe structures relates to altered fMRI activation patterns during episodic memory function in aMCI.

Methods

Participants

The present study included 38 of the 39 individuals who participated in the Trivedi et al. (2008) study and also received high-resolution structural MRI examinations. All participants were right handed based on the Edinburgh Inventory (Oldfield, 1971) and provided informed consent. The Rush University Medical Center Institutional Review Board approved this protocol. Participants were recruited from the Rush Alzheimer's Disease Center Memory Clinic Data Repository or the Memory and Aging Project (Bennett et al., 2005). All participants received yearly, detailed clinical evaluations that included a thorough medical history, informant interview, laboratory tests, and neurological and neuropsychological examinations that incorporate the procedures recommended by the Consortium to Establish a Registry for AD (CERAD; Morris et al., 1989) (see Bennett et al., 2006 for additional information). Exclusion criteria for all participants included evidence of any other neurological, psychiatric or systemic disorder, presence of contraindications for MRI scanning (e.g., cardiac pacemakers, claustrophobia), and age less than 65 years.

Elderly controls were required to have a normal neurological examination, Mini Mental Status Exam (MMSE) score ≥ 27 , and normal cognition as evidenced by neuropsychological examination. The Petersen et al. (2001; 1999) criteria for aMCI diagnosis were used. These

included memory complaints, normal activities of daily living, isolated episodic memory impairment (1.5 SD below the mean of age-matched controls), normal cognition in non-memory domains, and cognitive/functional status not consistent with dementia.

The high resolution MRI scans used for volumetric analyses of hippocampus and entorhinal cortex were performed on average 3.3 (\pm 3.2) months prior to the fMRI scanning session (range = -3.2 – 9.4 months prior to fMRI scanning). Although not ideal, this time delay was necessary to relieve the participants' discomfort from being in the scanner for an excessive duration. All but four of the participants had a 6-month or less time interval between scanning sessions. All participants were also required to have a stable clinical diagnosis within 6 months of either scanning session. One subject in the aMCI group was excluded because of questionable aMCI status during follow-up visits. The final sample size included in volume/fMRI activation regression analyses was 15 and 23 individuals in the aMCI and elderly control groups, respectively.

Anatomical Imaging

High resolution, structural MRI scans were acquired on a 1.5T General Electric Signa scanner (Milwaukee, WI) using a 3D spoiled gradient recalled echo pulse sequence (SPGR). The scanning parameters included: 124 contiguous, coronal sections, 1.6-mm-thick, acquisition matrix = 256 \times 192, field of view = 22 cm, TR (repetition time) = 33.3 ms, TE (echo time) = 7 ms, 35° flip angle, signals averaged = 1.

The Analyze software package (Mayo Clinic Foundation, Rochester, MN) was used to calculate hippocampal and entorhinal cortex volumes. All volumes were traced on coronal slices reformatted to be perpendicular to the long axis of the hippocampus. To correct for individual differences in brain size, the volume of each region of interest was divided by total intracranial volume (TICV) using the formula: absolute volume (mm³)/TICV (mm³) \times 1,000. TICV was computed by tracing the inner table of the cranium on consecutive, 5mm thick, sagittal sections across the entire brain.

The protocol and validation procedures used for quantifying hippocampal and entorhinal cortex volume have been published previously (deToledo-Morrell et al., 1997; Goncharova et al., 2001). Briefly, hippocampal and entorhinal cortex volumes were derived separately for right and left hemispheres. Hippocampal tracings included the fimbria, dentate gyrus, hippocampus proper, and subiculum, and began at the first section where the hippocampus could be clearly differentiated from the amygdala by the alveus and continued on each image until the slice before the full appearance of the fornix. Entorhinal cortex tracings began with the first section where the gyrus ambiens, amygdala, and parahippocampal white matter were visible. In rostral sections, the superomedial border was the sulcus semiannularis and in caudal sections, the subiculum. The lateral border was the shoulder of the collateral sulcus, which was constructed by drawing a straight line from the most inferior point of the white matter to the most inferior tip of the gray matter. Tracings were continued until three sections rostral to the first appearance of the lateral geniculate nucleus. All tracings were completed by one of two authors (TRS and SG) with an inter-rater reliability of 95% or greater who were blinded to clinical status.

Functional imaging

The fMRI task consisted of an encoding and recognition phase. Total scanning time was 11 minutes and 20 seconds for encoding and 15 minutes and 5 seconds for recognition. For each participant, a total of 300 functional volumes were acquired during encoding and 400 functional volumes were acquired during recognition. The first two volumes at the beginning of each session were discarded. Head movement was minimized using foam

padding around the participant's head. Magnet compatible vision correction lenses were used when appropriate. Functional images were obtained using a T2*-weighted 2D gradient-echo spiral pulse sequence with higher order shimming. The scanning parameters included: TR = 2250 ms; TE = 40 ms; 24 cm field of view; 84° flip angle; slice thickness = 6 mm with 0 mm gap; inplane resolution = 3.75 mm; 30 slices, signals averaged = 1.

A 3D Fourier transform spoiled gradient recalled (SPGR) pulse sequence structural scan was acquired after the functional imaging scans. The scanning parameters included: 124 contiguous, axial slices, 1.6-mm-thick, acquisition matrix = 256 × 128, TR = 34 ms, TE = 7 ms, 22 cm field of view, 35° flip angle, in-plane resolution = 0.9375 mm, signals averaged = 1. These SPGR images were not used for the volumetric tracings since the pulse sequence was not ideal for the hippocampal and entorhinal cortex volumetric protocol.

Experimental fMRI Task

The fMRI task used in this study is described in greater detail in Trivedi et al. (2008). Stimuli consisted of black and white line drawings of nameable objects from the Snodgrass and Vanderwart (1980) training set and the word “push” for the baseline condition. The PsyScope software (Cohen et al., 1993), run on a Macintosh Powerbook G4 (Cupertino, CA), was used to generate the visual stimuli and record behavioral responses and reaction times (RT). The computer images were back-projected onto a screen mounted in the bore of the magnet by a magnet-compatible projector (Resonance Technology, Inc., Van Nuys, CA). Participants viewed the screen images via a mirror mounted on the head coil. Behavioral responses were recorded with a magnet-compatible button-press device.

Both the encoding and recognition phases utilized an event-related design. Each event consisted of a stimulus presented for 4500 ms followed by a 500 ms interstimulus interval. The stimuli were presented in a pseudorandomized order such that none of the event types were displayed more than three times in a row.

During encoding, participants viewed 150 events, including 50 man-made objects and 50 naturally occurring objects intermixed with 50 presentations of the push baseline condition. Participants determined whether the picture was man-made or naturally occurring and were explicitly instructed to remember each picture for recognition. During recognition, participants were presented with a total of 200 events, which included an average of 104 old (all 100 pictures from encoding were shown plus 4 repeats) items, 52 new (not shown during encoding) items, and 44 null events. The unbalanced number of presentations for the different event types was used to maximize exposure to the old items. There were no specific instructions given to the participants to encode the new items presented during recognition. RT and behavioral responses during encoding and recognition were recorded with button presses in left, right, or with both hands for man-made/old, natural/new, and the push baseline conditions, respectively.

fMRI Image Processing

After image reconstruction, all T2*-weighted images were realigned to correct for motion using SPM2 (Wellcome Department of Cognitive Neurology, London, UK). Signal artifacts and excessive motion were examined using a software package (<http://web.mit.edu/swg/software.htm>) that interfaced with SPM2. Functional images with signal intensity values greater than 3 SD above the overall whole brain mean signal intensity were excluded from each subject's functional volumes (see also Ofen et al., 2007). All of the subjects included in this study displayed less than 3 mm of movement in any plane.

The structural T1-weighted 3D SPGR volumes obtained after fMRI scanning were spatially normalized to the SPM2 standard brain template using a 12 parameter affine normalization

and nonlinear adjustments with $7 \times 8 \times 7$ basis functions. The normalized T2* volumes were smoothed using an 8 mm full width at half maximum (FWHM) isotropic Gaussian kernel. The time-series (at each voxel) was then regressed on a reference waveform and the significance of this regression was used to construct an SPM (T-statistic) map. The reference waveform was calculated by convolving a square wave representing the event (man-made/natural/push for encoding condition; old/new/push for recognition condition) with the estimated hemodynamic response function. A high pass filter of 128 was used to remove low-frequency drifts in the fMRI signal. Temporal autocorrelation was estimated using the first-order autoregressive (AR1) method on supra-threshold voxels. A customized general linear model (GLM) masking procedure (<http://web.mit.edu/swg/software.htm>) was employed to insure that the signal from all voxels was represented within each participant's functional volumes.

The functional volumes from encoding and recognition were separated into trial types based on the accuracy data collected during recognition (see also Buckner et al., 2001; Heun et al., 2000, 2004; Trivedi et al., 2008) collapsed across man-made and natural items to maintain consistency with previous fMRI studies in the literature. These trial types included: “hits” (i.e., items presented during encoding that were correctly identified as old during recognition), “misses” (i.e., old items presented during encoding that were identified as new during recognition), “correct rejections” (i.e., items correctly identified as new during recognition), and false alarms” (i.e., items incorrectly identified as old during recognition). Items that were not responded to were excluded from the statistical analyses.

Intentional encoding success was evaluated with a contrast of “hits > misses” using the encoding functional volumes (Buckner et al., 2001; Heun et al., 2000, 2004). Successful recognition was evaluated with a “hits > misses” contrast using the recognition functional volumes. Incidental encoding was defined using a new > old contrast of “correct rejections > hits” using the recognition functional volumes. While this contrast is not identical to the hits > misses contrast that was used to examine intentional encoding and recognition success, previous studies have employed similar contrasts of incidental encoding to examine new versus old effects (Bondi et al., 2005; Johnson et al., 2006a; Sperling et al., 2003). Although a post-scan recognition test was not performed to verify encoding of the new items presented during recognition, incidental encoding of novel items during recognition can be inferred because 1) there were no instructions to encode the new items during recognition and 2) new items are encoded to a greater extent than old items during recognition tasks (Habib et al., 2003; Tulving et al., 1996).

Statistical analyses of demographic, performance, and volumetric data

The demographic, fMRI behavioral performance, and RT data were analyzed using two-sample between-groups t-tests (two-tailed). A Chi-square test was used to examine group differences in gender distributions. The volumetric data were analyzed using a 2×2 repeated measures ANOVA with hemisphere as the within-subjects factor and group as the between-subjects factor. The significance level for all statistical analyses was set at $p < 0.05$.

fMRI regression analysis with hippocampal and entorhinal cortex volume

We conducted two-way ANCOVAs for fMRI activation during intentional encoding, incidental encoding, and recognition with group as a between-subjects factor and volume as a within-subjects factor. Age was included as a covariate to account for possible age-related effects on volume or fMRI activation and a statistical trend for the aMCI group to be older than elderly controls (see results section below).

All fMRI statistical analyses were conducted across the whole brain using a false discovery rate (FDR) corrected p value of 0.05. Follow-up, region of interest (ROI) analyses were restricted to the episodic memory network (Buckner et al., 2005; Dickerson and Eichenbaum, 2010): bilateral inferior and medial frontal cortices, bilateral medial temporal lobes (hippocampus and parahippocampal gyrus including entorhinal cortex), bilateral posterior cingulate cortex (posterior cingulate/retrosplenial cortices), and bilateral inferior parietal cortex. The ROIs were obtained from Wake-Forest Pick automated anatomical labeling atlas (Maldjian et al., 2003). The statistical threshold for the ROI analyses was a voxel-level, uncorrected threshold of $p = 0.001$, with a cluster correction for spatial extent ($p = 0.05$) (Poline et al., 1997). The cluster size (k) for all analyses was 20 voxels.

We examined the main effects of volume and group \times volume interactions to determine whether the relationship between volume and fMRI activation differed between the two groups. In a second step, we extracted percent signal change values (3mm radius spheres) from clusters that displayed significant interactions or main effects in the SPM2 regression analysis. These values were then entered into SPSS 16 (SPSS Inc., Chicago, IL), and the Spearman's rank correlation coefficient was used to determine if the correlations were significant using a statistical threshold of $p = 0.05$.

Results

Demographic, fMRI task performance, and volumetric data

Table 1 provides the mean demographic, volumetric and behavioral performance data (i.e., accuracy and RT) for the elderly control ($n = 23$) and aMCI ($n = 15$) groups. Briefly, there were no significant differences between the elderly control group and aMCI groups in terms of age ($p = 0.08$), education ($p = 0.31$) or gender distributions ($p = 0.34$). However, the aMCI group had significantly lower MMSE scores compared to elderly controls ($t = 4.66$, $p < 0.0001$).

There were no significant differences in behavioral performance between the two groups during encoding ($p = 0.31$). The aMCI group performed significantly worse than the elderly control group during recognition of the old items ($t = 3.91$, $p < 0.001$) and a trend towards significantly worse performance for the new items presented during recognition ($t = 1.95$, $p = 0.06$). The aMCI group also had significantly longer RTs than the elderly control group during both encoding ($t = 3.35$, $p = 0.001$) and recognition of new ($t = 2.44$, $p = 0.02$) and old ($t = 2.00$, $p = 0.05$) items.

The repeated measures analysis of the entorhinal cortex volumes did not reveal a significant group \times hemisphere interaction ($p = 0.24$) or main effect of hemisphere ($p = 0.11$). However, there was a significant main effect of group ($F = 11.24$, $p = 0.002$) in which the aMCI group displayed significantly smaller total entorhinal cortex volume relative to the elderly control group. For hippocampal volume, there was no significant group \times hemisphere interaction ($p = 0.52$). However, there was a significant main effect of hemisphere ($F = 4.68$, $p = 0.04$) with right hippocampal volume being significantly larger than left hippocampal volume across both groups and a trend for a significant main effect of group ($p = .07$) with the aMCI group having smaller total hippocampal volume relative to the elderly control group.

Entorhinal and hippocampal volume correlations with fMRI activation

Entorhinal cortex volume—Whole brain analyses did not reveal any significant group \times entorhinal cortex volume interactions or main effects of entorhinal cortex volume ($p_{FDR} = 0.05$). In contrast, the follow-up ROI analyses for the entorhinal cortex volume/fMRI activation analyses revealed several interesting findings. The intentional encoding regression

analysis failed to reveal any significant main effects of entorhinal cortex volume or group \times entorhinal cortex volume interactions. However, the incidental encoding regression analysis revealed a significant main effect of volume, which reflected a significant positive correlation between right entorhinal cortex volume and activation in midline (both left and right) medial frontal cortices (BA 8) ($x, y, z = 0, 42, 46$; $t = 4.44, p < 0.0001$; $k = 205$) (see Fig. 1, panel A) in both the aMCI (R^2 's $> 0.37, p$'s ≤ 0.05) and elderly control (R^2 's $> 0.28, p$'s < 0.01) groups. There were no significant group \times entorhinal cortex volume interactions for incidental encoding.

In contrast, the recognition success analysis revealed a significant group \times left entorhinal cortex interaction in the right medial frontal cortex (BA 8) ($x, y, z: 8, 46, 52$; cluster size = 55; $F = 30.39$, voxel-level $p < 0.0001$, uncorrected). Post-hoc t-tests revealed a significant positive correlation between left entorhinal cortex volume and fMRI activation in right BA 8 ($x, y, z: 8, 46, 52$; cluster size = 55; $t = 5.98$, voxel-level $p < 0.0001$, uncorrected) in the elderly control group ($R^2 = 0.48, p < 0.0001$) and a significant negative correlation ($R^2 = 0.53, p = 0.002$) in the aMCI group (see Fig. 1, panel B). The correlations remained significant even after removing two subjects who demonstrated extreme percent signal change values (R^2 's $> 0.27, p$'s ≤ 0.05). There were no other interactions or main effects of volume for recognition.

Hippocampal volume—Whole brain analyses did not reveal any significant main effects or group \times hippocampal volume interactions ($p_{FDR} = 0.05$). Likewise, the follow-up ROI analyses failed to reveal any significant right or left hippocampal volume correlations with fMRI activation for intentional encoding success, incidental encoding, or recognition success. The hippocampal volume statistical analyses were re-examined after removing the cluster correction threshold requirement (i.e., a voxel level threshold set at $p = 0.001$). These analyses revealed a significant direct relationship between right hippocampal volume and fMRI activation in midline medial frontal cortex (BA 6/8) ($x, y, z = 0, 36, 44$; $t = 4.17, p < 0.0001$; $k = 69$) during intentional encoding for both aMCI and elderly controls. Furthermore, there was a direct relationship between left hippocampal volume and fMRI activation in left medial frontal cortex (BA 10) ($x, y, z = -16, 58, 2$; $t = 3.90, p < 0.0001$; $k = 20$) during incidental encoding for both groups. Additional analyses using the more liberal threshold did not reveal significant group \times hippocampal volume interactions or main effects of hippocampal volume for any of the remaining contrasts.

Discussion

It is well known that medial temporal lobe structures such as the hippocampus and entorhinal cortex are critical for normal episodic memory function (Squire, 1992). Recent evidence suggests that inferior/medial frontal, inferior parietal, and posterior cingulate cortices are also critical for different aspects of episodic memory function (Cabeza and Nyberg, 2000; Stebbins et al., 2002; Wagner et al., 2005). Many of these brain regions are anatomically connected to each other via white matter pathways and are thought to form an episodic memory network that is preferentially vulnerable to pathophysiological changes indicative of AD (Buckner et al., 2005). However, few previous studies have examined the relationship between medial temporal lobe volume and fMRI activation in this network during episodic memory function (e.g., Braskie et al., 2009; Rosen et al., 2005; Sandstrom et al., 2006).

In the present study, we found that smaller right entorhinal cortex volume was associated with reduced activation bilaterally in medial frontal cortex (BA 6/8) during incidental encoding for both elderly controls and aMCI. No such relationships were observed during intentional encoding. In contrast, during recognition, left entorhinal cortex volume was

differentially associated with fMRI activation in right medial frontal cortex (BA 8) during recognition for individuals with aMCI compared to elderly controls. Specifically, smaller left entorhinal cortex volume was associated with reduced fMRI activation in right BA 8 in the elderly control group and increased fMRI activation in right BA 8 in the aMCI group. However, these medial frontal cortical areas did not overlap with the medial frontal or medial temporal regions where we previously observed altered task-related activation in aMCI (Trivedi et al., 2008). These results suggest that alterations in structure/function relationships in aMCI are independent from functional alterations alone.

Using volumetric procedures identical to the present study, Rosen et al. (2005) found that smaller volume of the left entorhinal cortex was associated with reduced fMRI activation in the right inferior frontal cortex in healthy older adults during incidental encoding of words. However, there were no correlations between left or right hippocampal and right entorhinal cortex volumes and fMRI activation. In addition, Braskie et al. (2009) found that greater thickness of the left entorhinal cortex in healthy older adults was associated with greater activation in medial frontal cortex during retrieval, but not during encoding, of word-paired associates. Four additional studies (3 in individuals with AD and 1 in individuals with aMCI) did not report hemispheric differences in the pattern of volume/fMRI activation correlations, therefore limiting our ability to compare the results of the present study (Garrido et al., 2002; Hamalainen et al., 2007; Meulenbroek et al., 2010; Remy et al., 2005).

To our knowledge, Sandstrom et al (2006) were the first to examine differences in the relationship between hippocampal volume and fMRI activation in elderly controls relative to individuals with aMCI. These authors found that smaller volume of the right hippocampus was associated with greater extent (i.e. % of activated voxels within the anatomical ROI of the hippocampus) of fMRI activation during retrieval of face-name paired associates in aMCI, but not in elderly controls using a template-based method (similar to the methods used in the present study). Conversely, hippocampal volume was not associated with extent of fMRI activation during intentional encoding or recognition in aMCI or elderly controls when the correlations were done in native space within manually traced ROIs of the hippocampus. These authors suggested that hippocampal atrophy in individuals with aMCI might confound template based analytic methods that are commonly used for analysis of fMRI data. However, Sandstrom et al. (2006) did not examine the relationship between hippocampal or entorhinal cortex volume and the *magnitude* of fMRI activation in template or native space nor did they examine the relationship between fMRI activation and entorhinal cortex volume.

The structure/function relationships observed in the present study may be mediated by anatomical connections between entorhinal and medial frontal cortices (Insausti et al., 1987). Canto et al. (2008) suggested that the efferent and afferent anatomical connectivity of the entorhinal cortex are indicative of a prominent role in both encoding and recognition processes. For example, entorhinal cortex volume correlates with performance on neuropsychological tests of encoding and recognition in normal aging (e.g., Rosen et al., 2003; Yonelinas et al., 2007), and many fMRI studies have revealed that medial temporal and frontal lobe regions are active during both encoding and recognition/retrieval processes (see Cabeza and Nyberg, 2000 for review).

Perhaps AD-related neuropathology in the entorhinal cortex of individuals with aMCI disrupts these structure/function relationships during recognition, but not during encoding. The behavioral results and volume/fMRI activation correlations observed in the present study support this interpretation. That is, individuals with aMCI displayed similar structure/function relationships and behavioral performance to the elderly controls during encoding, but altered structure/function relationships and poorer behavioral performance during

recognition. The altered relationship between entorhinal cortex volume and medial frontal cortex activation in aMCI during recognition may represent a compensatory response, where increased activation compensates for disease-related cognitive or neuropathological changes (e.g., Cabeza et al., 1997) or de-differentiation, where increased activation is associated with a greater difficulty in engaging a specific neural mechanism for successful recognition performance (e.g., Dennis and Cabeza, 2010; Li and Lindenberger, 1999). Regardless of the specific mechanisms associated with this dissociation, our findings highlight the importance of assessing structure-function relationships in normal aging and aMCI. The use of both template-based and native space methods (Dickerson et al., 2004; Dickerson et al., 2005; Sandstrom et al., 2006; Vandembroucke et al., 2004) and/or including some measure of medial temporal lobe volume as a covariate could perhaps clarify some of the conflicting findings in the fMRI literature in aMCI.

These results also highlight the importance of incorporating volumetric analysis and potentially other neuroimaging indices to better understand how neurodegenerative diseases such as AD impact specialized neural networks. As an example, several recent studies have found that combining different neuroimaging modalities with or without other AD markers more accurately distinguishes individuals with aMCI that convert to AD (Devanand et al., 2008; Jhoo et al., 2010; Landau et al., 2010; Walhovd et al., 2009; Walhovd et al., 2010), although volumetrics or morphometry appear to have more diagnostic sensitivity than other neuroimaging measures alone (e.g., Karow et al., 2010; Walhovd et al., 2009).

There are several limitations to the present study. First, the structural MRI scans used for volumetric analyses were acquired on average 3 months prior to the fMRI scans. Therefore, we cannot entirely rule out the possibility that entorhinal cortex or hippocampal volumes changed between scanning sessions particularly in individuals with aMCI. We tried to reduce this possibility by only including participants whose clinical status did not change between scanning sessions. Second, there is a wide degree of functional impairment across the entire spectrum of aMCI, and not all individuals with aMCI convert to AD (Petersen, 2004). Therefore, we cannot completely rule out the possibility that some of the individuals in the aMCI group may not convert to AD. Third, we did not include a post-scan recognition task to verify whether subjects encoded the novel items that were presented during recognition. However, previous fMRI studies that have used similar “new > old” contrasts as proxy measures of incidental encoding and have reported robust activation in parts of the episodic memory network (Buckner et al., 2001; Johnson et al., 2006b). In addition, we have recently found that healthy young adults activate episodic memory network regions and display a similar level of accuracy during the successful encoding of items under intentional (82%) and incidental (86%) conditions (Trivedi et al., 2010). Despite these findings, we can only infer that the novel information was being encoded during recognition (Tulving and Kroll, 1995) in the present study.

Even with these limitations, our findings are consistent with the results of previous studies, indicating that medial temporal lobe volume is associated with fMRI activation in medial frontal regions during different stages of episodic memory function. The dissociation in volume/fMRI activation relationships between elderly controls and individuals with aMCI that paralleled our behavioral results is a novel contribution of this study. More studies investigating the influence of AD risk factors on cross-sectional and longitudinal changes in the relationships of volumetrics with other measures of brain structure and function are necessary if neuroimaging techniques are to become useful AD biomarkers (Perrin et al., 2009).

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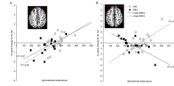
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**Fig 1.**

Panel A depicts a scatter plot of midline medial frontal cortex (BA 6/8) regions where smaller volume of the right entorhinal cortex was associated with reduced activation during incidental encoding in both groups. Panel B depicts a scatter plot of right medial frontal cortex (BA 8) regions where there was a group \times left entorhinal cortex volume interaction during successful recognition. Percent signal change from the local maxima in right BA 8 is displayed on the y-axis, and left entorhinal cortex volume is displayed on the x-axis. The crosshairs on the brain image represents the local maxima from the cluster from which signal change was extracted. The dashed line and white circles display the data for the ONC group, whereas the data for the aMCI group is displayed by the full line and black boxes. The brain image is oriented in neurological view with the right hemisphere displayed on the right side, and left hemisphere on the left side of the brain image.

Table 1
Demographic, volumetric, and fMRI task performance data

Variables	ONC (n = 23)	aMCI (n = 15)	p-value
Age (years)	73.1 (5.5)	77.1 (8.7)	0.10
Education (years)	16.2 (3.0)	14.9 (3.3)	0.21
Gender (M/F)	11/12	5/10	0.34
MMSE	28.8 (1.2)	26.2 (2.2)*	< 0.0001
R Hippocampal Volume	1981.2 (402.4)	1835.6 (300.5)	0.24
L Hippocampal Volume	1917.4 (230.4)	1716.9 (244.3)*	0.01
R Entorhinal Cortex Volume	546.1 (81.7)	412.7 (118.9)*	< 0.001
L Entorhinal Cortex Volume	504.8 (116.6)	406.1 (141.2)*	< 0.001
fMRI task performance			
Encoding – total correct (%)	88.2 (14.1)	82.3 (16.4)	0.24
Encoding RT – total (ms)	1194.7 (213.4)	1455.5 (263.9)*	0.001
Recognition – novel items % correct	77.2 (14.2)	66.6 (19.5)	0.06
Recognition – old items % correct	79.8 (12.9)	61.2 (16.4)*	< 0.001
Recognition RT – novel items only (ms)	1583.6 (314.6)	1840.4 (321.4)*	0.02
Recognition RT – old items only (ms)	1588.4 (274.6)	1789.1 (340.9)*	0.05

Notes: The hippocampal and entorhinal cortex volumes are normalized to total intracranial volume. MMSE = Mini Mental Status Exam, RT = reaction time, ms = milliseconds, L = left, R = right. The p-values represent the results of the two group t-tests.

* denotes comparisons where the ONC group was significantly different relative to the aMCI group.