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Evidence that volume of anterior medial temporal lobe is reduced in seniors destined for mild cognitive impairment

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Abstract

The present study sought to determine if volumes of specific brain structures could discriminate cognitively normal seniors destined to develop mild cognitive impairment (MCI) within a few years from those who will remain normal. Brain scans were collected from seventy-one cognitively normal seniors. Seventeen individuals later developed MCI (the presymptomatic MCI; pMCI group), while fifty-four remained normal. Whole brain volume (WBV) and volumes of the entorhinal cortex (ERC), hippocampus, and three subregions of the hippocampus (head; HH, body; HB and tail; HT) were compared. Results indicated that the pMCI group had smaller volumes than the normal group in the ERC, HH and HB, but not the HT or WBV. When HH/HB volumes and baseline memory test scores were included in a single logistic regression model, classification accuracy was very high (area under the curve = 0.93). These results show that smaller normalized volumes of anterior medial temporal lobe structures contribute to the development of MCI, a finding which may have implications for identifying seniors at risk for cognitive decline.

Keywords: MCI; Aging; Structural MRI; Hippocampus; ERC

1. Introduction

As the population over 65 increases, a growing number of individuals will be at risk for the development of Alzheimer's disease (AD). Early detection of neurobiological vulnerabilities in asymptomatic individuals has become a major research goal because emerging interventions are likely to be most successful prior to frank cognitive decline (Smith, 2007). Today, amnestic mild cognitive impairment (MCI) is generally accepted to represent early-stage AD. Amnestic MCI (hereafter referred to simply as MCI) is defined as a decline in memory performance below the age-adjusted normal range without significant impairment in daily living (Flicker et al., 1991; Petersen et al., 1999). In the majority of cases, MCI represents prodromal Alzheimer's disease at the clinical and pathological levels (Morris et al., 2001; Markesbery et al., 2006; Petersen et al., 2006).

However, neuropathological studies suggest that AD-related neurodegeneration begins even before the clinical stage of MCI (Davis et al., 1999; Bennett et al., 2006). This raises the question of whether brain vulnerabilities or changes associated with accumulating neuropathology can be detected in vivo, in individuals who are cognitively normal at the time of their scan but destined to develop MCI within a few years. If so, then it may be possible to predict which seniors are most likely to develop MCI, offering hope

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that cognitive decline could be delayed or even prevented by applying emerging treatments.

Neuroimaging studies have reported reduced whole brain volume (WBV) and reduced volume of medial temporal lobe (MTL) structures in AD and in MCI, with the entorhinal cortex (ERC) and hippocampus often affected (Jack et al., 1997; Convit et al., 1997; Killiany et al., 2002; de Leon et al., 2004). More recently, several studies have reported volumetric reduction in the ERC and hippocampus in individuals with subjective memory complaints compared to age-matched controls (Jessen et al., 2006; Saykin et al., 2006). However, the extent of volumetric reductions in cognitively normal individuals who do not yet show subjective memory complaints, but are destined to develop MCI within a few years, has been less studied.

The objectives of the present study were to (1) determine if regions known to show volumetric reduction in MCI/early AD (ERC, hippocampus and whole brain volume) are reduced in individuals who are presymptomatic at the time of their scan but later develop MCI (presymptomatic MCI; pMCI); and (2) assess the accuracy with which the volume of these structures can differentiate pMCI and normal individuals.

AD pathology is known to begin in anterior portions of the MTL (Braak and Braak, 1995), raising the possibility that volumetric reduction in pMCI, if present, may have a relative anterior-to-posterior gradient within the MTL. To explore this possibility, the accuracy of volumes of three principal anterior-to-posterior subregions of the hippocampus (head, body, and tail) in differentiating pMCI and normal individuals were explored in addition to the entire hippocampus, ERC and WBV.

2. Methods

2.1. Participants

Seventy-one healthy older adults between the ages of 63 and 94 participated. Informed written consent was provided in a manner approved by the local Institutional Review Board. Participants were recruited from the University of Kentucky AD Center (UK-ADC) longitudinal normal volunteer cohort. Inclusion criteria for this cohort are minimum 60 years of age, cognitive and neurological normality at enrollment, agreement to brain donation to the UK-ADC at death, a designated informant for structured interviews, willingness to undergo annual examinations. Participants were excluded from the cohort if they had a history of substance abuse (including alcohol), major head injury, major psychiatric illness, medical illnesses that are unstable, and/or that have an effect on the CNS, chronic infectious diseases, stroke or transient ischemic attack, encephalitis, meningitis, or epilepsy. The annual evaluation includes a comprehensive neuropsychological battery and general physical and neurological examinations that are detailed elsewhere (Schmitt et al., 2001).

If any of the following occurs, the subject is evaluated with a more detailed cognitive assessment and formal clinical assessment by study physicians: (i) the diagnosis from the examining physician changes to MCI or dementia, (ii) the supervising neuropsychologist suspects cognitive decline or the annual memory test scores drop below −1.5 S.D. cutoff from their prior annual assessment, (iii) a cholinesterase inhibitor, NMDA antagonist, or other treatment associated with the medical diagnosis of dementia by an outside physician is prescribed to the participant, (iv) evidence of functional impairment secondary to cognitive decline is elicited from the subject or informant. The UK-ADC consensus conference reviews this data and a diagnosis of normal, MCI (Winblad et al., 2004), or AD (McKhann et al., 1984) is assigned.

Eighty participants from the normal cohort volunteered for a brain imaging study in 1999. Data from nine participants were excluded due to poor scan quality, leaving 71 participants with usable images for the present study. Seventeen participants have since developed MCI, seven of whom have further progressed to AD. For the purposes of data analysis, the date of onset of MCI in all seventeen participants was assigned retrospectively by applying the following criteria: (1) a CDR score of 0.5, with a memory box score of at least 0.5; (2) a documented memory complaint; and (3) a score below −1.5 S.D. on one or both of the Weschler Memory Scale (WMS) total raw memory score or CERAD word list delayed recall. A total of fifty-four participants have remained 'normal' for an average of 5.1 years after their scan. Table 1 lists group demographic and key neuropsychological scores for the pMCI and normal groups.

2.2. MRI methods

Data were collected on a 1.5 T Siemens Vision scanner at the University of Kentucky's Magnetic Resonance Imaging and Spectroscopy Center. A 3-dimensional magnetization-prepared rapid gradient echo (MP-RAGE) image was collected: [repetition time (TR) = 15 ms, echo time (TE) = 7 ms, flip angle (FA) = 8°, resolution 1.25 mm × 0.94 mm × 1.5 mm].

Images were transferred to a Linux workstation running the Red Hat Enterprise operating system. Unless otherwise noted, all image pre-processing and analyses were conducted using Analyze software (Analyze Version 6.0, Mayo Clinic, Rochester, MN). Image processing was performed by a single rater (SM) who was blinded to participant information. Images were first 3D aligned to correct for minor head rotation. As a proxy for head size, intracranial area (ICA) was measured on a coronal section at the level of the anterior commissure (Insausti et al., 1998). Tracings surrounded the outline of the supratentorial compartment following the dural and tentorial surfaces, or the cerebral contour in regions where dura was not visible.

Images were then corrected for scanner-induced intensity inhomogeneity and skull-stripped using FSL's brain

Table 1
Group demographic characteristics and key neuropsychological scores

	Normal		pMCI	
	Normal (1999) $n = 54$, M/F = 21/33	Normal (2006) $n = 54$, M/F = 21/33	pMCI (1999) $n = 17$, M/F = 4/13	Transition to MCI $n = 17$, M/F = 4/13
Age (years)	78.1 (7.0)	83.16 (6.91)	80.5 (6.8)	84.4 (6.2)
Education	16.0 (2.0)	-	15.4 (2.5)	-
Scan to time point	-	5.1 (1.7)	-	3.9 (1.8)
MMSE	29.0 (1.1)	$28.7\ (1.5)_{53}$	28.6 (1.5)	27.7 (1.3)
Word list total	22.6 (4.0)	$21.4\ (5.0)_{41}$	21.4 (4.3)	$17.6\ (4.3)_{16}$[a]
Word list delayed	7.8 (1.7)	$7.0\ (2.2)_{40}$	6.2 (2.5)[b]	$4.4\ (2.5)_{16}$[a]
WMS	33.9 (6.1)	$30.3\ (7.4)_{52}$[a]	27.7 (6.0)[b]	$20.1\ (8.0)_{15}$[a]

Scores are given for normal and pMCI groups at baseline and at a second time point. Mean and standard deviation are given for each variable. If score values were missing, the number of participants used in the computation is shown as a subscript. *Note*: Normal; healthy control group, pMCI; presymptomatic mild cognitive impairment group.

[a] Significant differences between time points within the same participant group.

[b] Significant between-group differences (pMCI vs. Normal) at baseline.

extraction technique (www.fmrib.ox.ac.uk/fsl). Volumetric computation of regions of interest (ROIs) were conducted on the intensity corrected, skull-stripped images. The first ROI, whole brain volume was computed automatically in Analyze, as previously described (Martin et al., 2007) (Fig. 1).

Volumetric measurements of medial temporal lobe ROIs were obtained through manual tracing. The procedures and boundaries used for tracing these ROIs are described below. Prior to ROI measurement, video display images were magnified by a factor of two to enable precise tracing. The boundaries of each ROI were traced for each slice sequentially from anterior to posterior. The number of voxels within the ROI was computed automatically using the Analyze ROI summing function. The total volume within each ROI was then computed by multiplying the number of voxels within the ROI by voxel volume in cubic millimeters. Intrarater reliability measurements were established by having the rater re-trace the boundaries for each ROI on 10 randomly selected data sets (Gold et al., 2008). Intrarater reliability was demonstrated via uniformly high intraclass correlations for all manually traced structures ($\geq$0.93).

2.3. Hippocampal measurement

The procedure and boundaries used to trace the entire hippocampus were those established by Jack et al. (1997), and used in recent work from our lab (Martin et al., 2007). First, images were resliced at an angle perpendicular to the long axis of the hippocampal formation to optimize the identification of hippocampal boundaries. Hippocampal anatomic boundaries included the CA-1 through CA-4 sectors of the hippocampus proper, the dentate gyrus, and the subiculum. Boundaries used to trace the hippocampus are shown in Fig. 2 and described in its legend.

After the entire hippocampus was traced it was partitioned into three segments in order to explore the possibility of an anterior-to-posterior gradient of MTL volumetric reduction in pMCI. Specifically, the hippocampus was segmented

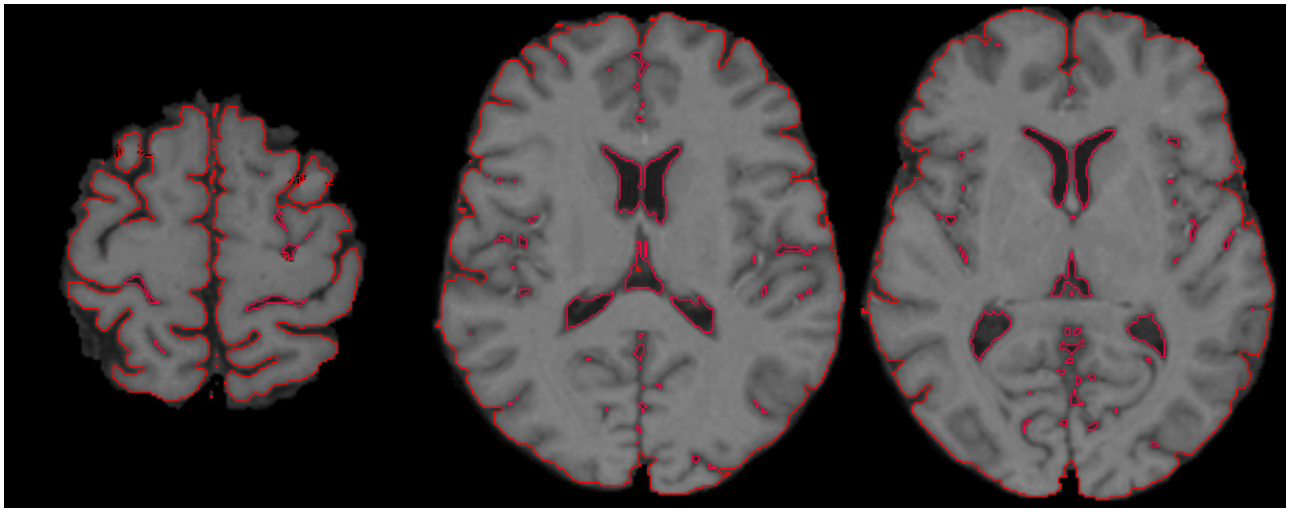

Fig. 1. Example of whole brain volume measurement on three axial slices. Thresholding was set to include parenchema and exclude ventricular compartments and CSF in sulci, as indicated by the boundary between the red contour lines.

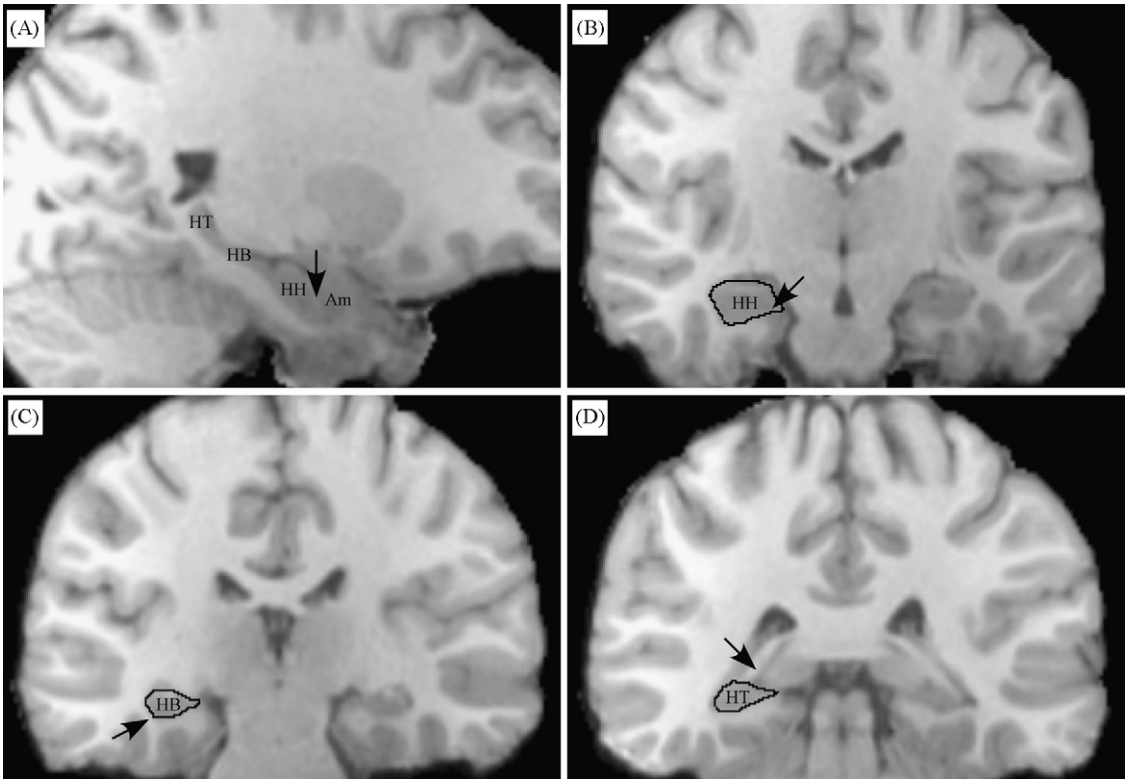

Fig. 2. Anatomic boundaries used for manual tracing of the hippocampus and its subregions. (A) Approximate locations of the hippocampal head (HH), hippocampal body (HB), and hippocampal tail (HT) in a sagittal plane. The boundary between the amygdala (Am) and HH was demarcated in the sagittal plane where the alveus (denoted by the arrow) can be seen to clearly divide the two structures. Panels (B–D) show examples of one anterior slice of each hippocampal subregion in the coronal-oblique plane in which tracing was performed. (B) The anterior boundary of the HH was demarcated through automatic transfer of the alveus position from the sagittal plane (see panel (A)) to the coronal-oblique plane. The uncus (denoted by arrow) demarcates the HH from the HB. (C) The anterior boundary of the HB was demarcated as the first slice in which the uncus is no longer visible. The white matter of the parahippocampal gyrus (denoted by arrow) represents the inferior hippocampal boundary. (D) The anterior boundary of the HT was demarcated as the first slice in which the crus of the fornix (denoted by arrow) is in view.

into three principal anterior-to-posterior subregions using the Duvernoy (2005) guidelines: (1) an anterior segment, the hippocampal head (HH; Fig. 2B), (2) a middle segment, the hippocampal body (HB; Fig. 2C), and (3) a posterior segment, the hippocampal tail (HT; Fig. 2D). The transition between HH to HB was demarcated by the first slice in which the uncus is no longer visible. The transition between HB to HT was demarcated by the first slice in which the crus of the fornix becomes visible.

2.4. Entorhinal cortex measurement

The procedure and boundaries used to trace the entorhinal cortex were those validated by Killiany et al. (2002), which involve tracing the ERC on three consecutive coronal images centered at the level of the mammillary bodies. Outlining this mid-region of the ERC was performed due to established difficulties defining anterior and posterior sections of the ERC. Stereologic data from human brain tissue indicates that neuron count within a single section of this mid-region of the ERC is an excellent predictor of total ERC neuron count (Gomez-Isla et al., 1996). If more than one image contained the mammillary bodies, the first image (in the anterior-to-posterior direction) was used as the center image for measurement of the ERC. The slice immediately preceding the presence of the mammillary bodies was the first slice in which the ERC was traced. Boundaries used to trace the ERC are shown in Fig. 3 and described in its legend.

2.5. Statistical analysis

Comparisons of age, and neuropsychological scores were tested by analysis of variance (ANOVA), using a Dunnett's post hoc analysis. The between-group comparison of education level was tested with the Wilcoxon rank sum test.

Potential group differences in ROI volumes were explored via analysis of covariance (ANCOVA) with age, sex, education, and ICA as nuisance covariates. Separate mixed ANCOVAs were run for whole brain volume and MTL ROI (ERC, HH, HB, HT, and hippocampus total). Post hoc comparisons were conducted for each MTL ROI, using the Sidak procedure to correct for multiple comparisons.

For data presentation purposes, ROI volumes normalized to ICA are reported: (ROI volume/ICA) × 100. The per-

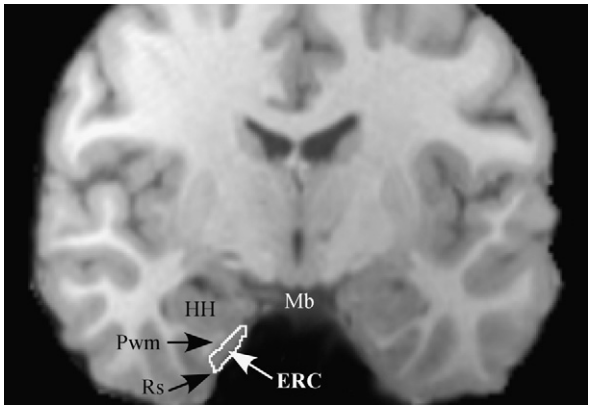

Fig. 3. Anatomic boundaries used for manual tracing of the entorhinal cortex (ERC). The ERC was traced on three consecutive coronal images centered at the level of the mammillary bodies (Mb). The rhinal sulcus (Rs) demarcated the inferior boundary. The lateral boundary was demarcated by parahippocampal white matter (Pwm) on the inferior-medial surface of the hippocampal head (HH). Tracing began at the angle formed by the junction of the rhinal sulcus and the surface of the brain. The outline then transected the angle formed by the rhinal sulcus and the inferior-medial surface of the brain, proceeding across the gray matter to the white matter. Tracing then proceeded along the gray-white boundary to the inferior surface of the hippocampus. Finally, the outline followed the lateral surface of the brain back to the starting point.

centage of normalized volumetric reduction in each ROI in the pMCI group was then estimated: (normal mean − pMCI mean/normal mean) × 100.

Receiver operating characteristic (ROC) curves were generated from logistic regression models by calculating the sensitivity and specificity of ROI volumes in predicting pMCI. The area under the curve (AUC) was used to assess the diagnostic accuracy of ROI volumes in classifying pMCI and normal individuals. All curves controlled for age, sex, education level and ICA. Separate curves were generated for those ROIs (HH, HB, ERC) and neuropsychological scores (WMS total and CERAD word list delayed) that showed a significant between-group effect in the analyses described above. A final ROC curve was generated that incorporated both significant ROIs and neuropsychological scores.

3. Results

Table 1 presents group demographic and key neuropsychological data. There were no baseline group differences in mean age, education, MMSE or CERAD's word list total, but the pMCI group had lower mean scores on the CERAD word list delayed and WMS total. At follow-up an average of 5.1 years later, the group that remained normal had lower scores compared to their baseline on the WMS total. The average follow-up time of 3.9 years for the pMCI group (the time of MCI diagnosis) was shorter than that of the normal group [$t(69) = 2.56$, $p < 0.05$]. Despite this earlier follow-up time, the MCI group had lower scores compared to their own baseline on the CERAD word list delayed and word list total, and the WMS total. However, the average MMSE at the time of MCI diagnosis was 27.7, indicating that this diagnosis was made at an early stage. The normal and pMCI groups did not differ in their proportions of *APOE4* carriers (10/54 or 19% in the normal group versus 4/17 or 24% in the pMCI group), χ^2 (1) = 0.175, $p = 0.68$.

Table 2
Percentage of normalized volumetric reduction in each ROI in the pMCI group compared to the group that remained normal

ROI	Normal mean	pMCI mean	% Difference
WBV	111.87 (6.98)	109.51 (8.12)	2.11
ERC	0.85 (0.21)	0.71 (0.28)	16.47
HH	12.98 (2.29)	9.74 (2.72)	24.96
HB	9.89 (1.74)	8.26 (1.86)	16.48
HT	3.58 (0.97)	3.55 (1.06)	0.84
Hipp. total	26.46 (3.85)	21.56 (5.01)	18.52

Normalized means of each group are given for whole brain volume (WBV) the volumes of the entorhinal cortex (ERC), hippocampus head (HH), hippocampus body (HB) hippocampus tail (HT) and total hippocampus (Hipp. total). Normalized mean volumes refer to average left–right volume in mm^3 divided by ICA in mm^2, multiplied by 100. The percent difference is with respect to the mean value of the normal group. *Note*: Normal; healthy control group, pMCI; presymptomatic mild cognitive impairment group.

Table 2 lists the percentage of volumetric reduction in each ROI in the pMCI group. WBV was not different between groups, $F(1, 69) = 0.29$, $p = 0.59$. Because there were no hemisphere by group interactions in any of the MTL ROI volumes (all F's < 1.0), the average left–right volume in each MTL ROI was used in all analyses. There was a significant ROI by group interaction, $F(4, 62) = 7.53$, $p < 0.001$. The ERC was significantly larger in the normal group than the pMCI group, $F(1, 65) = 6.29$, $p = 0.015$, as was the total hippocampus volume, $F(1,65) = 20.85$, $p < 0.001$. In terms of hippocampal subregions, the HH was significantly larger in the normal than the pMCI group $F(1, 65) = 16.04$, $p < 0.001$, as was the HB, $F(1,65) = 12.79$, $p = 0.001$. However, HT volumes did not differ between groups, $F(1, 65) = 0.16$, $p = 0.69$.

3.1. Classification of individuals using MRI and neuropsychological measures

The area under the curve was 0.87 for the HH, 0.84 for the HB, and 0.79 for the ERC. When the curve incorporated both the HH and HB, the AUC improved to 0.90 (Fig. 4; panel A). The AUC was 0.81 for the model including WMS total and CERAD word list delayed (Fig. 4; panel B). When scores from these memory tests were added to the model including HH and HB, the AUC improved to 0.93 (Fig. 4; panel C). This volumetric-neuropsychological model yielded a sensitivity of 94% and a specificity of 83%.

4. Discussion

Results demonstrate reduced volume of anterior MTL structures in presymptomatic mild cognitive impairment

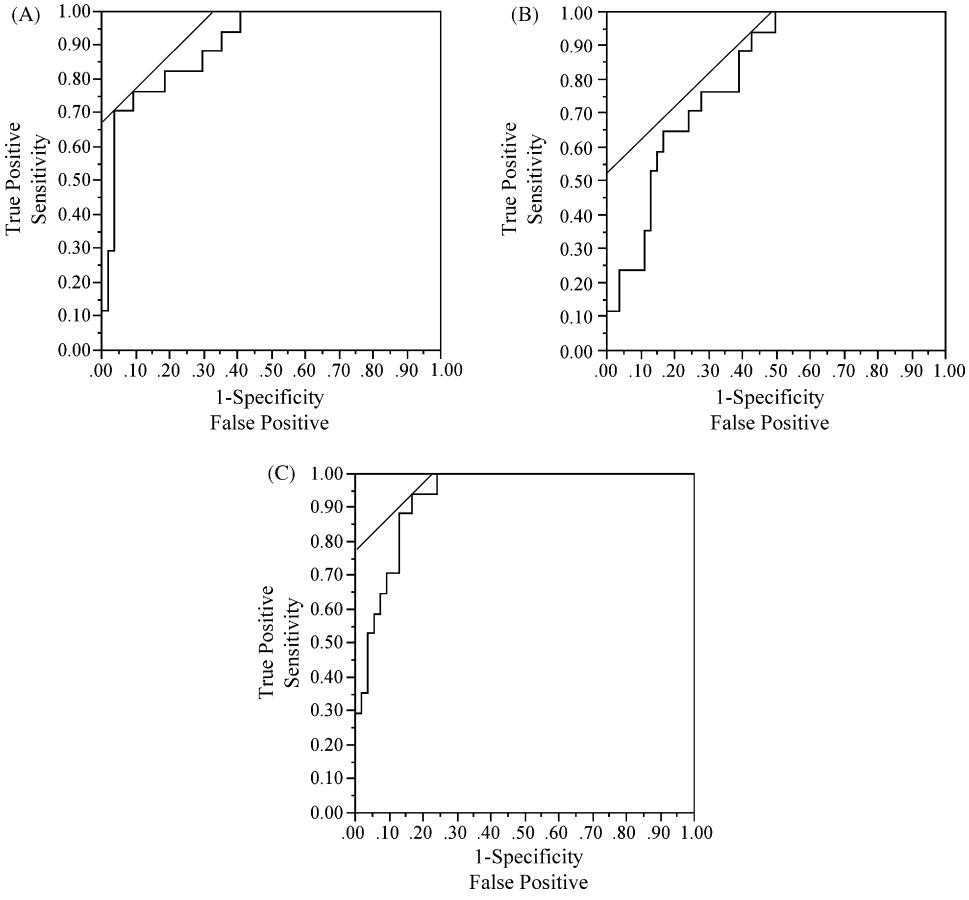

Fig. 4. Receiver operator characteristic (ROC) curves. The area under the curve (AUC) was 0.90 for the volume of HH and HB (panel (A)), and 0.81 for the word list delayed, and WMS total (panel (B)). Combining the HH and HB volumes and memory scores into one model improved the AUC to 0.93 (panel (C)).

(pMCI), approximately 4 years prior to MCI diagnosis. Previous studies have reported volumetric reduction of the ERC and hippocampus in MCI compared to normals and in AD compared to MCI (Jack et al., 1997; Convit et al., 1997; Killiany et al., 2002; de Leon et al., 2004). Some studies have indicated more widespread volumetric reduction in MCI and mild AD, affecting neocortical regions (Chetelat et al., 2002; Gold et al., 2005; Pennanen et al., 2005) and whole brain volume (Jack et al., 2004, 2005; Fotenos et al., 2005), suggesting tissue loss may already be occurring in a widespread manner throughout the brain in MCI.

In contrast, the present pMCI group had relatively small WBV reduction (2%) but considerable reduction in some MTL structures (19% in the hippocampus and 16% in the ERC). The pMCI reductions observed in the hippocampus and ERC are smaller than the range of reductions of approximately 30–50% reported in mild to moderate AD compared to normal groups (Killiany et al., 2002; Pennanen et al., 2004), consistent with reports that these structures undergo accelerated reduction in AD (Jack et al., 2000; Pennanen et al., 2004). In a study of 5 middle-aged adults who developed familial AD within 3 years, an average of 16% volume decrease in MTL structures was observed compared to controls (Schott et al., 2003), which is comparable to the reductions we observed in seniors who developed the prodromal stage (MCI) of late-onset AD within 4 years.

The present results concur with several recent findings of reduced MTL volume in pMCI (den Heijer et al., 2006; Smith et al., 2007). Our results concerning the extent of hippocampal reduction are similar to those of den Heijer et al. (2006), who observed an average of 17% hippocampal reduction in seniors destined to develop dementia (AD and vascular dementia types) within 2–3 years (den Heijer et al., 2006). However, this study did not compute volumes of hippocampus subregions, ERC, or WBV. By computing the volume of these structures, and parcellating the hippocampus into anterior (hippocampus head; HH), middle (hippocampus body; HB) and posterior (hippocampus tail; HT) regions, the present study demonstrated a gradient of MTL volumetric reduction in pMCI. In addition to the substantial ERC reductions noted above, the pMCI group had considerable reductions in the HH (25%) and HB (16%), but minimal reduction in the HT (1%) or WBV (2%). The exact reductions observed in hippocampal subregions should not be taken literally because they are likely to vary somewhat depending upon the specific boundaries used for segmentation. Nevertheless, the general finding of an anterior-to-posterior gradient of hippocampal reductions is in-line with pathology data showing

that AD begins in anterior portions of the MTL before affecting posterior MTL and neocortex (Braak and Braak, 1995).

Results from the present study also demonstrate that normalized anterior MTL volume can differentiate individuals destined to develop MCI within a few years from those who will remain cognitive normal with a high degree of accuracy. After controlling for age, sex, education level, and ICA, volumes of anterior portions of the hippocampus (HH and HB) differentiated the pMCI and normal groups with 90% accuracy. The volumes of these structures were more accurate in differentiating the pMCI and normal groups than memory tests known to be sensitive to amnestic MCI (the WMS and CERAD word list delayed), which were 80% accurate. However, the highest discriminatory accuracy (93%) was observed when these memory scores were included in a model with anterior hippocampal volumes.

Although pMCI participants had lower average WMS and CERAD word list delayed scores than the normal group at baseline, there are several reasons for which they were unlikely to have had undetected MCI. First, the baseline cognitive scores of all pMCI participants were within the age- and education-adjusted normal range and none of the participants had either diagnostic criteria necessary for MCI diagnosis: a documented memory complaint, and a CDR box score of 0.5 for memory. Second, it is not uncommon for normal individuals who later develop AD to have lower average cognitive test scores than their age-matched peers who remain normal, sometimes extending back to childhood (Linn et al., 1995; Elias et al., 2000; Whalley et al., 2000). Finally, the average MMSE score for the pMCI group at MCI diagnosis was 27.7, a near-normal average score approximately 4 years after their baseline scan.

Noninvasive in vivo probes are needed to identify seniors at risk for cognitive decline because emerging interventions may be most successful prior to MCI (Smith, 2007). Baseline measures are likely to contribute to this process due to the time-sensitive need to establish diagnosis. The present results suggest that baseline volumetric measurement can help identify individuals at future risk for MCI. In particular, results suggest that anterior MTL structures may be of particular diagnostic relevance because reduction of these structures was observable in pMCI participants compared to normal participants who had a longer average follow-up time from scan to diagnosis. The observation that volumetric declines were relatively confined to anterior MTL structures in pMCI offers hope that potential therapies could protect the brain from reductions of posterior MTL and WBV associated with the onset of MCI.

This study had several limitations that highlight open questions and may help guide future research. First, like most other normal control volunteer groups at AD centers, participants were highly educated. High education may buffer effects of brain pathology on cognition (Stern, 2002), which could lengthen the presymptomatic period relative to groups with lower education. Future studies will be required to determine the extent to which the present and similar findings generalize to cohorts with lower levels of education. Our ADC is currently in the process of attempting to recruit lower education volunteers in the normal control cohort to address this question. Second, the cross-sectional nature of the study does not enable us to determine the relationship between cognitive decline and volumetric reductions in various ROIs over time. We are in the process of following pMCI participants longitudinally to address this issue. Third, as with most studies of this kind, the sample size of the presymptomatic group was relatively small and pathological diagnosis cannot yet be confirmed. Although most individuals given a clinical diagnosis of MCI at our center show AD pathology (Markesbery et al., 2006), it is not yet possible to know what percentage of the present MCI or normal samples harbor significant AD pathology. Some misclassification of participants (according to the neuropathology gold standard) is thus possible. This issue should be addressable in the future because participants in the longitudinal normal cohort study at our ADRC have agreed to brain donation at death.

Conflict of interest statement

The authors have no actual or potential conflicts of interest associated with this research.

Acknowledgments

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