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Structural Brain Alterations before Mild Cognitive Impairment in ADNI: Validation of Volume Loss in a Predefined Antero-Temporal Region

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Abstract

Volume losses in the medial temporal lobe, posterior cingulated, and orbitofrontal region have been observed in Alzheimer's disease (AD). Smaller reductions in similar regions have also been reported in amnestic mild cognitive impairment (aMCI), a canonical precursor to AD. We previously demonstrated that volume loss in bilateral anteromedial temporal lobe is present at baseline in longitudinally followed normal subjects who later developed MCI or AD. In this study we compared grey matter volumes within this predefined anteromedial temporal region (AMTR) at baseline between: 1) normal subjects enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) who subsequently developed cognitive complaints as reflected in a CDR memory box score of 0.5; and 2) normal subjects who remained normal over a median of 48 months of follow-up (CDR sum of boxes 0). We found significantly decreased volume within AMTR in the ADNI memory complainers. To relate AMTR results to those from conventional anatomy, we demonstrate that volumes extracted with the ICBM amygdala region had the best correspondence with AMTR volumes. In contrast, regions that have demonstrated volume loss in frank MCI and AD in ADNI, e.g., the posterior cingulate, did not show volume loss. These findings provide independent confirmation that volume changes preceding MCI occur in AMTR, a region of overlap between amygdala and anterior hippocampus.

Keywords

Alzheimer's Disease Neuroimaging Initiative; Alzheimer's disease risk; amygdala; brain aging; hippocampus; longitudinal studies; magnetic resonance imaging; medial temporal lobe; structural neuroimaging; voxel-based morphometry

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Introduction

Increasing attention is being directed toward the earliest stages of Alzheimer's disease (AD), particularly the prodromal period of cognitive normality in the presence of underlying AD pathology [1]. Imaging and other biomarkers of AD are likely to have complex dynamics over the course of the disease, and the role of each biomarker will likely change over this course, whether predictive, state-identifying, or indicative of intensity or rates of change in pathology [2]. Structural imaging studies using volume, shape, or cortical thickness measures have demonstrated clear differences between normal subjects and those with mild cognitive impairment (MCI) and AD (reviewed in [3, 4]).

An active area of investigation addresses the question of how early in the course of late-onset AD structural differences can be detected, and how useful they might be in predicting future cognitive impairment in normal aged persons. Most recent studies have been magnetic resonance imaging (MRI)-based, using 3-D images for processing and quantitation. Several studies have demonstrated a relationship between reduced brain volume, amyloid deposition measured using positron emission tomography (PET) ligands, and longitudinal declines on cognitive tests in normal subjects [5–7]. Longitudinal structural studies have shown that increased ventricular expansion [8] and increased regional [9, 10] or whole-brain [11] atrophy rates are associated with later cognitive decline in normal subjects. Decreased baseline amygdala, entorhinal, and hippocampal volume [12–18], regional cortical volume [19, 20] and cortical thickness [21] have been associated with subsequent decline on cognitive tests or diagnosis of MCI or AD in normal subjects. These studies include follow-up ranging from 2.3 to 10 years, most on the order of median 4–5 years (reviewed in [3]).

Overall, these studies show that MRI-based structural brain alterations can be detected in cognitively normal subjects, particularly in regions known to be affected by AD pathology early in the disease process (e.g., portions of the temporal and parietal lobes). However, these studies often use internal validation methods, and none of the regions identified as demonstrating decreased volume or thickness have been replicated on an independent longitudinal cohort of normal subjects. The purpose of the present study is to test a defined region demonstrating decreased volume in normal subjects who later developed MCI or AD [17] in an independent cohort of normal subjects enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Methods

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations, as a $60 million, 5-year public- private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California-San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and

subjects have been recruited from over 50 sites across the US.and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research, approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years." For up-to-date information, see http://www.adni-info.org.

ADNI is a landmark multi-site study of biomarkers for MCI and AD that emphasizes MRI as a key modality [22]. A hallmark of this study is the availability of imaging and clinical data to the scientific community through an easily accessible set of web sites. Criteria for participation in ADNI as a normal control include age > 55 years, no clinical or imaging indicators of neurologic or psychiatric disease, absence of a memory complaint, normal basic and instrumental activities of daily living, and normal scores on the Mini-Mental Status Examination (MMSE; [23]), clinical dementia rating scale (CDR; [24]), and revised Wechsler memory scale [25]. Further protocol details are available on the ADNI web site: http://www.adni-info.org.

ADNI used a standardized 1.5-T MR imaging protocol across sites that included two T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE; [26]) imaging acquisitions, with TR 9 ms, TE 4 ms, 8° flip angle, 256^2 in-plane samples, and 192 sagittal slab partitions, with a spatial resolution of 0.94 × 0.94 × 1.2 mm. For full protocol see the LONI web site: http://www.loni.ucla.edu/ADNI/Research. Image data from 232 subjects labeled as normal were downloaded from the LONI web site on October 17, 2009. These images were B1-field corrected using the N3 algorithm [27], corrected for gradient distortion based on a standardized phantom scanned at each site, and scaled according to the ADNI protocol before being made available by the ADNI Mayo Clinic Imaging Core to LONI for download. Three of the image data sets were discarded because of poor quality, leaving scans from 229 ADNI normal control subjects for potential analysis.

Clinical data on these subjects were obtained from the ADCS web site on June 3, 2011, the cutoff date for follow-up in the current study. Criteria for inclusion in the present study were: 1) diagnosis of "Normal" at baseline, global Clinical Dementia Rating (CDR) score of 0, and CDR box score of 0 for both memory and orientation at the screening visit; 2) assessment at six months that included a CDR; and 3) follow-up for at least one year. These criteria were chosen because the goals of the study were to examine well-characterized normal subjects who were followed longitudinally with a minimum of at least two visits after the screening and baseline visits. Exclusions based on the above criteria (total n = 21) were made for the following reasons: follow-up less than a year (n=12), no 6-month evaluation (n=8), and CDR box score 0.5 for Orientation alone at month 6 visit (n=1).

Using both the baseline and follow-up data, comparison groups were defined as follows: 1) Normal Nonconverters (NN, n = 155) - Clinical diagnosis of "Normal", and both global CDR of 0 and CDR box scores for memory and orientation of 0 at baseline and at all follow-up visits; and 2) Memory Complainer (MC, n = 53) - Normal at baseline, but CDR box score for memory of 0.5 or greater at any time after the initial (screening) visit. MC is not equivalent to a diagnosis of MCI; 37 of these 53 subjects remained classified as clinically normal during follow-up (subgroup MC_N), and 16 were "converters" from normal at baseline to MCI or AD as diagnosed by the clinicians in ADNI (subgroup MC_C). Median time from baseline to conversion in MC_C subjects was 36 months (IQR 24–36 months). Table 1 lists the demographic characteristics of the NN and MC subjects. The median follow-up time was four years in both groups. Table 2 presents key results of the clinical and cognitive assessments in ADNI in all subjects at baseline and in the remaining subjects seen at the 48-month visit.

Validation Region

A pre-defined brain region mask for validation was developed in a prior study using images from an independent group of 136 normal aged subjects who did not participate in ADNI (Full details provided in [17]). All 136 subjects were normal at baseline; of these 113 remained normal throughout the period of longitudinal observation (5.4 years), and 23 subsequently developed cognitive impairment an average 4.0 years after baseline (MCI or AD). The brain region mask represents the region of significant volume difference between subjects who remained normal and those who converted to MCI or AD (Region illustrated on a single subject T1 axial image in Figure 1A). This region (called AMTR for short) mainly comprised the anteromedial temporal lobes bilaterally, with an additional small region within the left angular gyrus, and even smaller clusters of voxels in the anterolateral temporal lobes. The techniques for image analysis included optimized voxel-based morphometry using multi-channel MRI images for segmentation and custom templates for registration and analysis in SPM2 (Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/). The main question addressed in the current study was whether this region could be cross-validated, by demonstrating reduced volumes in an independent longitudinal sample of baseline-normal ADNI subjects who would later develop cognitive impairment.

Processing of ADNI Images

All 208 ADNI images were acquired at 1.5T; no 3T images were used. Images were segmented into six partitions (grey matter, white matter, cerebrospinal fluid, and three sets of non-brain tissues) using SPM8 prior probability maps (New Segment, unified segmentation; [28–30]). Segmentations were reviewed individually for quality and three images were deemed initially unsatisfactory; they were re-segmented after partially removing extracranial tissues using the Brain Extraction Tool (BET) in FSL v. 4.1.1 [31] and then included with the remaining images. A common template was created using an SPM8 iterative diffeomorphic registration algorithm on the segmented grey matter images. The common template was registered to MNI space. Modulated grey matter mages were normalized to the registered common template using the registration flow fields and then smoothed with an 8 mm kernel. Modulated images retain volume information from the original source images. An illustration of a representative segmented image registered to this template is shown in Figure 1B.

Volume within AMTR for each subject was extracted using the MNI space registered mask on each smoothed, registered, modulated grey matter image. This process is illustrated in Figure 2A. A similar process of region volume extraction was performed using anatomic regions defined in the LONI MNI/ICBM atlas template (http://www.loni.ucla.edu/ICBM; Figure 2B). The ICBM regions chosen were amygdala, entorhinal area, hippocampus, posterior cingulate, precuneus, superior and inferior parietal lobe, superior, middle and inferior temporal gyri and fusiform gyrus. Total intracranial volume (TIV) for each subject was calculated by summing the volumes from grey matter, white matter and cerebrospinal fluid segmented images with probability threshold set at >0.49 for each image.

Statistical Analysis

A standard least-squares model was developed in JMP 9.01 (SAS Institute, Cary, NC). The model examined the effect of group and of potential influential covariates on structure volumes separately. Extracted grey matter volume within AMTR was the dependent variable with the main effect of interest being group membership (NN, MC_N, MC_C), with additional covariates age at scan, gender, education, APOE allele status (ε4 allele present or absent), and TIV as independent variables (Table 3). The same grouping variable and

covariates were used in similar models with grey matter volumes extracted using standard template anatomic regions from the ICBM atlas as dependent variables (Table 3).

Receiver operator characteristic curves generated from a logistic regression model were then constructed contrasting MC_N versus NN and MC_C versus NN, with age at scan, gender, education, APOE allele status (ε4 allele present or absent), and AMTR volume as the regressors (Figure 3).

For analysis of demographic and clinical variables, one-way ANOVA with F-ratio test for significance was used for continuous variables, Pearson test on Chi Square for categorical variables, and Wilcoxon Rank Sums for nonparametric tests of potentially skewed variables. A p-value of less than 0.05 was considered significant.

Results

Baseline characteristics of the NN and MC groups were comparable in age, education, APOE allele status, duration of follow-up, and AVLT 30-minute delay score (Table 1). There was an increased representation of males in the MC group ($p = 0.04$). Performance on the ADAS word-list delay score was lower in the MC group at baseline ($p = 0.01$).

Follow-up characteristics are summarized in Table 2. After the median follow-up interval of 48 months, somewhat more than half of subjects in each group remained for analysis. Over this interval there was a significant decline in the MMSE and AVLT 30-minute delay scores in the MC group but not in the NN group (Table 2A). The subgroups MC_N (non-MCI) and MC_C (later-MCI) groups each differed from NN at 48 months. At 48 months the MC_N and MC_C groups also differed from each other on AVLT ($p=0.008$), unlike on MMSE ($p=0.38$).

The median CDR box score for memory *per visit* across all visits was 0.17 in the MC group, different from the NN group (Table 2B). The MC_N and MC_C subgroups individually differed from NN ($p< 0.0001$) and from each other ($p=0.002$). Memory box score per visit was calculated as the sum of all CDR box scores for memory, divided by the number of visits where a CDR was performed, for each subject. This is an imperfect metric but conveys a global sense of the clinical memory severity over time within each group despite differences in the timing and consistency of these scores between subjects followed for different intervals. In a group of baseline amnestic MCI subjects, for example, the value would be expected to be around 0.5; reversions would tend to lower this number, and progression would raise it. Thus, on average, clinical severity of memory impairment is quite low in the MC complainants, with later-MCI subjects (MC_C) scoring higher than the never-MCI subjects (MC_N), but lower than would be expected for other subjects classified as MCI at baseline.

Grey matter differences within AMTR and anatomic regions from the ICBM atlas were tested in the models detailed in Table 3, comparing volumes between the MC_N, MC_C, and NN groups. AMTR, amygdala, entorhinal area, and hippocampus volumes were different between groups in descending order of significance (Table 3A). AMTR and amygdala showed significant differences comparing MC_N and MC_C subgroups to NN, but not between MC_N and MC_C (post-hoc Tukey's HSD). Entorhinal volume was significant only in the MC_C to NN comparison, whereas hippocampus, although significant in the least squares model overall, did not demonstrate individual paired group differences. In contrast there were no volume differences between groups, either paired or overall, in posterior cingulate, precuneus, superior and inferior parietal lobe, superior, middle, and inferior temporal gyrus, or fusiform gyrus (Table 3B). Gender and TIV were significant in the model as expected.

The ROC curve for the MC_C versus NN comparison using AMTR had an area under the curve (AUC) of 84%, with an optimum sensitivity of 75% and specificity of 88%. The curve for MC_N versus NN had an AUC of 67% and optimum sensitivity 84% of but specificity of only 45% (Figure 3). Adding baseline ADAS word list performance increased the AUC from 84% to 88% for the MC_C versus NN comparison (sensitivity 94%, specificity 78%), but only increased AUC from 67% to 69% for the MC_N versus NN comparison (sensitivity 70%, specificity 57%). Logistic regressions using the ICBM region volumes gave results with a pattern parallel to the results in Table 3. For example, ICBM amygdala gave an AUC of 82% for MC_C versuss NN, and 66% for MC_N versuss NN, slightly lower than for AMTR. Age, gender, education, and APOE were not significant in the logistic regressions underlying these curves.

Discussion

The main finding of the study is independent validation of an anteromedial temporal brain region where volume is reduced in initially normal subjects judged by ADNI clinicians as newly memory impaired during follow-up. This region we term AMTR was defined empirically in a separate group of normal subjects who were imaged using MRI and then followed carefully for subsequent memory impairment. Grey matter volume was compared between subjects who developed MCI and those who remained normal over five-plus years of follow-up using voxel-based morphometry. The region of statistically significant difference defined AMTR and comprised mainly the anteromedial temporal lobe (amygdala and head of hippocampus/subiculum). The subjects, imaging methods, and analysis techniques used to determine AMTR were completely independent of ADNI; nonetheless, this region demonstrated decreased volume when applied to normal ADNI subjects. This confirms that volume in AMTR is decreased in normal subjects destined to develop memory impairment. Both studies had at least four years follow-up, and therefore the scope of the study is not dominated by early declines following baseline evaluation.

A salient comparison with recent preliminary results from a subset of baseline normal ADNI subjects demonstrates overlaps and differences. In the comparison study, a priori regions based on the literature were selected from the FreeSurfer atlas labeling (http://surfer.nmr.mgh.harvard.edu), and volumes in these regions and their paired interactions were then used to predict decline on AVLT-30-minute delay and Logical Memory paragraph recall tests [19]. In contrast, AMTR was based on empirical differences found in a previous VBM analysis with no a priori assumptions regarding where differences would be found, and validation was thus independent using a separate test data set rather than internal based on the original training data. Our study defined memory decline clinically based on CDR memory box score rather than psychometric test scores. Nonetheless, there was overlap between regions included in the best fitting model from the comparison study (hippocampus, amygdala, parietal lobe, inferior and middle temporal gyri) and the current study. Other regions not included even partially in AMTR were superior temporal gyrus, posterior cingulated, and cingulate isthmus; specific regions tended to trade places in different models of multiple regions, likely because paired interactions were included [19]. We used ICBM template regions and did not find differences in neocortex with this method (Table 3B).

Prediction accuracy cannot be safely compared since definitions of memory decline were different between studies, and follow-up was shorter (2 years) in the comparison study [19]. This could mean early decliners at two years had lower volumes at baseline compared to those who might decline after further follow-up. With those caveats in mind, the cross-validation accuracy for the comparison study was 81%, whereas in the current study overall accuracy was 84% for converters to MCI, and 71% overall for the MC group (Figure 3). Notwithstanding noted differences, the overlap in regions whose volumes are identified as

predictive of decline in normal subjects, despite differing clinical definitions of decline, follow-up periods and analysis methods, strengthens the fundamental finding that these differences are significant.

There were differences within the current study between MC subjects who later developed MCI or AD (MC_C), and those who had at least one post-baseline visit with a CDR memory box score of 0.5 but no MCI diagnosis (MC_N). In general the MC_N group was milder than MC_C on all measures of cognitive impairment: MMSE decline over 48 months (−.85 versus −1.29), AVLT_30 minute delay score decline at 48 months (−0.92 versus −6.43), overall CDR memory score per visit (0.13 versus 0.25), and ADAS word list delay at baseline (7.0 versus 6.5). Nonethelessm baseline AMTR volume was lower in both MC_N (4.34 ±0.04 cc) and MC_C groups (4.21 ±0.06 cc) than in NN (4.46 ±0.02 cc). The AMTR was not different between MC_N and MC_C (Tukey's HSD, model in Table 3A). The interpretation if these findings that we favor is that at least some subjects in the milder MC_N group remain at risk for conversion to MCI, and may be in the earliest stages of atrophy within AMTR at baseline. However, this represents a long-range prediction over approximately four years that needs further study. Since the volume decrease at baseline is less in MC_N than MC_C, and cognitive performance at baseline adds more to prediction of memory decline in MC_C than MC_N, these findings suggest that detection of atrophy within AMTR begins shortly before or contemporaneous with memory alterations, perhaps within a few years of each other. These anatomic measures together appear to have a useful predictive range of about 2 to 4 years for decline from cognitive normality, although group differences could well extend beyond this interval. Alterations in molecular biomarkers are likely to precede these changes, perhaps by many more years [2, 4].

A further caveat is that atrophy or volume loss is specific in its regional distribution, but as a biomarker it has limits because it is only indirectly attributable to synaptic or neuronal losses, or to underlying pathologies and mechanisms of disease. Furthermore In this study we compared results of baseline MRI with clinical testing, specifically a change in CDR box score for memory from a baseline score of zero during longitudinal follow-up. We chose the CDR measure because it captures the judgment of memory alterations according to experienced examiners using a standardized, validated methodology. We do not exclude the possibility that other more sensitive cognitive tests might detect changes earlier than the ones used at baseline in ADNI. If so, future comparisons between these tests and neuroimaging would be warranted.

In summary, AMTR volume at baseline in normal subjects is shown to be a valid predictor of future memory decline in the ADNI study. The AMTR region is simply defined and template based, and could easily be applied to other similar populations by incorporation into an automated image-processing pipeline.

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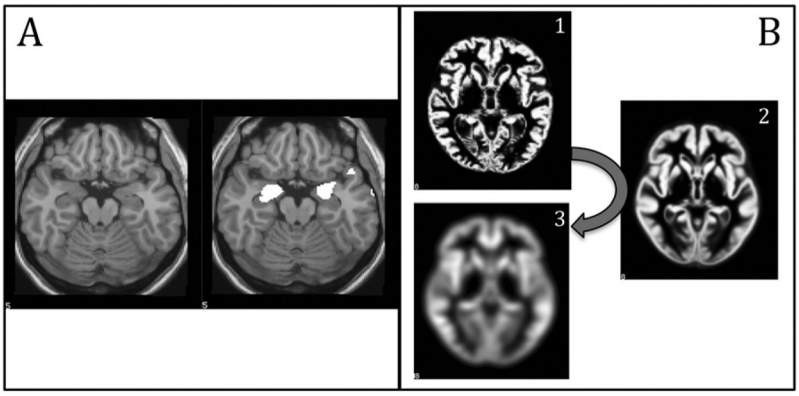

Figure 1.

A) AMTR Region. Illustration of AMTR showing ICBM single subject T1 axial image without (left) and with (right) overlay of AMTR for this slice level. The AMTR comprises mainly amygdala and hippocampus. B) Processing steps for image normalization. Grey matter segmented images from all 208 subjects were non-linearly co-registered to create a common template (image 2). Individual grey matter segmented images from each subject (image 1) were registered to the template and smoothed with an 8 mm kernel (image 3). Registration preserved grey matter volume in each voxel by incorporating the Jacobian determinant from each individual registration flow field.

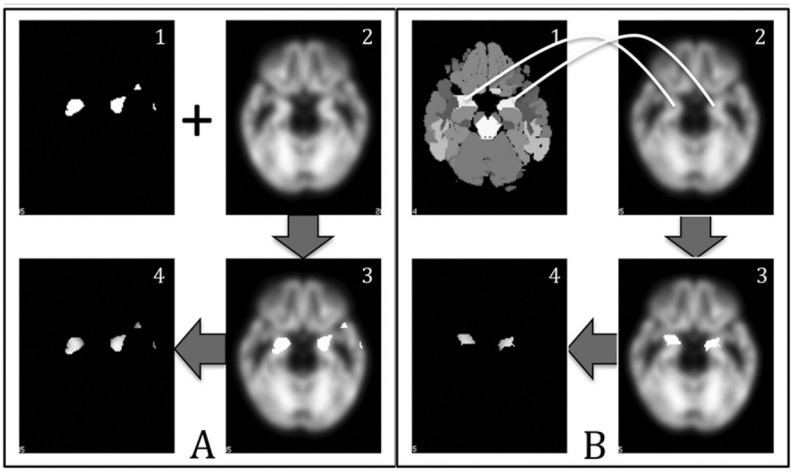

Figure 2.

A) Extraction of volumes from subject images. The AMTR mask region (image 1) was used to extract voxel values representing grey matter volume from each subject image (images 2 & 3) by isolating only the voxels underlying the mask (image 4). Total extracted volume was the sum of the voxel values scaled by the modulation factor of the image. B) A procedure similar to that used for AMTR (A; above) used masks of registered labeled regions from the ICBM atlas template to extract volumes. The amygdala region is shown in the same sequence of steps as A. This procedure was repeated for each region to calculate volumes (cf. Table 3).

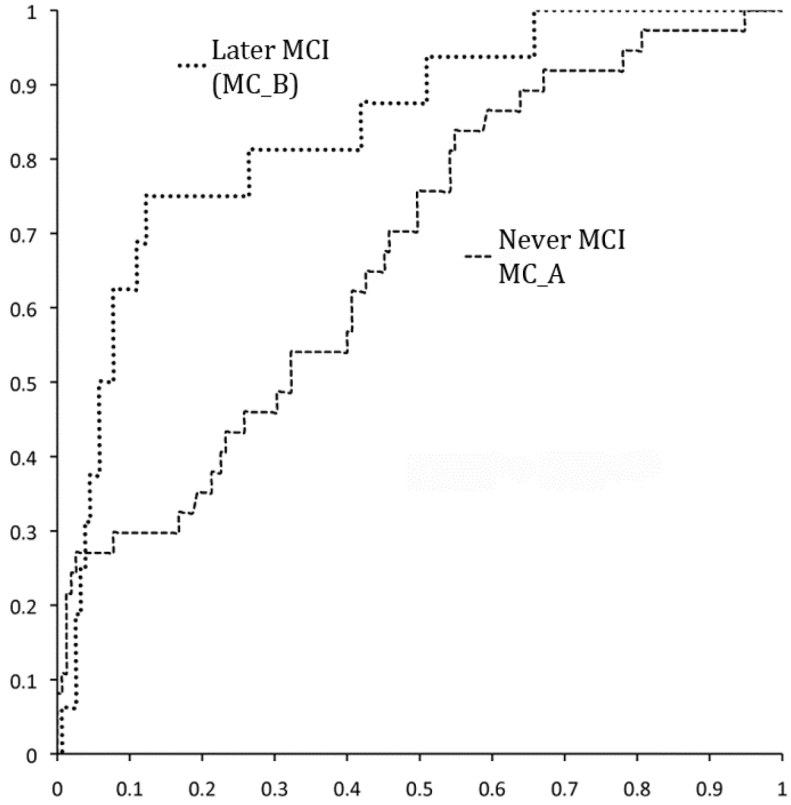

Figure 3.
Volume within AMTR is predictive of a later classification of MCI in baseline normal subjects in ADNI with 84% overall accuracy (Later MCI; MC_C). Accuracy was 71% for the entire MC group combined.

Table 1

Baseline characteristics of study subjects. MC subgroups: MC_N = MC subjects who remained normal and did not convert to MCI during the observation period; MC_C = MC subjects classified as normal at baseline but who converted to MCI during longitudinal follow-up. Values provided are mean ±SD or median [IQR]. Performance on the ADAS word-list delay score was lower in MC at baseline.

Group	n	Age years	Education years	Gender M:F	Any APOE4	Follow-up Months	MMSE	AV Delay 30 min	ADAS WL Delay
NN	155	75.9 ±5.3	16.1 ±2.8	76:79	27%	48 [36–48]	29 [29–30]	7 [5–10]	8 [6–9]
MC	53	76.2 ±4.4	16.3 ±2.6	34:19	26%	48 [36–48]	29 [29–30]	7 [4–10]	7* [5–8]
MC_N	37	75.9 ±4.1	16.7 ±2.5	25:12	19%	48 [36–48]	29 [29–30]	7 [4–10]	7 [6–8]
MC_C	16	76.7 ±5.1	15.6 ±2.9	9:7	44%	36 [36–48]	29 [28.3–29.8]	6.5 [2.5–11.3]	6.5* [4.3–8]

Any APOE4: Presence of one or two apolipoprotein E ε4 alleles; MMSE: Mini-Mental Status Examination score (Range 0–30); AV Delay 30 min: Rey Auditory Verbal Learning Test 30-minute delay score (Range 0–15; [32]); ADAS WL Delay: Alzheimer's Disease Assessment Scale word list delay score (Range 0–10; [33]). MMSE, AV Delay 30 min, and ADAS WL Delay did not show proper goodness of fit for the normal distribution, so non-parametric statistics were used.

Table 2

ADNI Assessment Results. The median follow-up, 48 months, was chosen for longitudinal comparison to preserve statistical power lost to subject attrition over time.

Table 2A. Time-point and longitudinal test performance in NN and MC groups at baseline and 48 months.

Time Point	*Base*	*M48*	*Base*	*M48*		*Base*	*M48*	
Group	**n**	**n**	**MMSE**	**MMSE**	**MMSE (Diff.)**	**AVLT 30 Min**	**AVLT 30 Min**	**AV Delay (Diff.)**
NN	155	82	29.2	29.3	0.10	7.6	8.4	0.73
MC	53	33	29.1	28.2††	−0.94*	7.0	4.9††	−2.09*
MC_N	37	26	29.1	28.3††	−0.85*	6.7	5.8†	−0.92
MC_C	16	7	29.1	27.9††	−1.29*	8.1	1.7††	−6.43*

Table 2B. CDR memory box score per visit across all visits by group and by subgroup.

Group	n	Median CDR Memory per Visit
NN	155	0.0 [0 – 0]
MC	53	0.17†† [0.1 – 0.28]
MC_N	37	0.13†† [0.1 – 0.13]
MC_C	16	0.25†† [0.18 – 0.48]

Values are means.

Dagger (†) indicates significant difference in paired Wicoxon comparisons *versus* NN at each time point (vertically).

Double daggar (††) indicates p< 0.001.

Asterisk (*) indicates significant difference comparing baseline (Base) and 48 month (M48) values in paired t-tests (horizontally).

Values are medians [IQR].

Dagger (†) indicates significant difference in paired Wicoxon comparisons versus NN at each time point (vertically).

Double daggar (††) indicates p< 0.001.

Table 3

Regional grey matter volumes in ADNI subjects who were normal at study entry.

Table 3A. Grey matter volumes in defined medial temporal regions. AMTR represents the region to be validated (see text). Amygdala, Entorhinal and Hippocampus regions are defined anatomically from the ICBM atlas template.

	AMTR		Amygdala		Entorhinal		Hippocampus	
	F ratio	p-value	F ratio	p-value	F ratio	p-value	F ratio	p-value
Group	8.2	0.0004	7.3	0.0008	6.6	0.002	4.4	0.01
Age at Scan	3.4	0.06	4.8	0.03	0.36	0.55	7.4	0.007
Gender	17.6	<0.0001	20.1	<0.0001	29.3	<0.0001	7.0	0.009
Education	4.2	0.04	2.5	0.11	0.84	0.36	0.11	0.74
APOE4	0.02	0.88	0.28	0.60	1.1	0.30	0.06	0.81
TIV	254.0	<0.0001	169.5	<0.0001	129.4	<0.0001	261.5	<0.0001

Table 3B. Grey matter volumes in selected neocortical regions from the ICBM atlas.

	Post. Cingulate		Inf. Parietal Left		Inf. Temporal		Fusiform	
	F ratio	p-value	F ratio	p-value	F ratio	p-value	F ratio	p-value
Group	0.08	0.92	0.22	0.80	0.46	0.63	0.63	0.53
Age at Scan	0.44	0.51	0.32	0.57	0.94	0.33	0.11	0.74
Gender	1.1	0.30	0.13	0.72	14.0	0.0002	15.5	0.0001
Education	0.08	0.78	0.35	0.56	0.04	0.84	1.3	0.26
APOE4	0.20	0.65	0.001	0.97	0.06	0.81	0.01	0.94
TIV	281.7	<0.0001	154.0	<0.0001	306.8	<0.0001	434.8	<0.0001