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Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI

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Abstract

Objective—To examine the neural basis of cognitive complaints in healthy older adults in the absence of memory impairment and to determine whether there are medial temporal lobe (MTL) gray matter (GM) changes as reported in Alzheimer disease (AD) and amnestic mild cognitive impairment (MCI).

Methods—Participants were 40 euthymic individuals with cognitive complaints (CCs) who had normal neuropsychological test performance. The authors compared their structural brain MRI scans to those of 40 patients with amnestic MCI and 40 healthy controls (HCs) using voxel-based morphometry and hippocampal volume analysis.

Results—The CC and MCI groups showed similar patterns of decreased GM relative to the HC group on whole brain analysis, with differences evident in the MTL, frontotemporal, and other neocortical regions. The degree of GM loss was associated with extent of both memory complaints and performance deficits. Manually segmented hippocampal volumes, adjusted for age and intracranial volume, were significantly reduced only in the MCI group, with the CC group showing an intermediate level.

Conclusions—Cognitive complaints in older adults may indicate underlying neurodegenerative changes even when unaccompanied by deficits on formal testing. The cognitive complaint group may represent a pre–mild cognitive impairment stage and may provide an earlier therapeutic opportunity than mild cognitive impairment. MRI analysis approaches incorporating signal intensity may have greater sensitivity in early preclinical stages than volumetric methods.

Memory complaints, a cardinal feature of mild cognitive impairment (MCI)[1] that confers a high risk of Alzheimer disease (AD),[2,3] are reported in 25 to 50% of the older adult population.[4] Longitudinal research on older adults with cognitive complaints (CCs) has yielded inconsistent findings,[5–12] although a range of associated factors including apolipoprotein E (APOE) genotype, depression, somatic concerns, female sex, and older age have been identified.[4,13–19]

Normal aging, MCI, and AD have been associated with loss of gray matter (GM).[20,21] Many studies have used manual tracing of regions of interest (ROIs) to assess medial temporal lobe (MTL) structures in AD and MCI.[22–25] Voxel-based morphometry (VBM) assesses tissue compartments on a voxel-by-voxel basis and has the advantages of automation, reliability, and unbiased comprehensive sampling across the brain.[26] Regional decline in

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GM volume has been reported in healthy adults, as a function of age,[27–29] with more pronounced reduction in patients with MCI[30,31] or AD.[22,30,32–36] Regions reported most frequently include MTL structures, cingulate, and diffuse cortical association regions.[22,30,32–36] Prior studies had not quantitatively examined the severity of CCs in preclinical AD and directly assessed the relationship to GM.

We used ROI and VBM analyses to examine the structural underpinnings of memory complaints in older adults with normal memory test performance compared to individuals with MCI and healthy controls (HCs). We hypothesized that individuals with CCs would show decreased GM density in MTL and other cortical regions, as well as an intermediate level of hippocampal volume reduction between MCI and controls. We also hypothesized that subjective and objective measures of memory would be related to GM density.

Methods

Participants were 120 older adults consecutively enrolled into the Dartmouth Memory and Aging Study. The sample included 40 individuals with significant CCs despite normal cognitive test performance (CC group), 40 patients with MCI (MCI group), and 40 HCs (HC group) with no significant CCs or deficits. Two additional participants, one with MCI and one HC, were excluded from the present analyses due to suboptimal image quality. Participants were recruited through use of flyers, public lectures, newspaper advertisements, and referrals from our medical center's General Internal Medicine, Community Health, and Geropsychiatry Clinics. The sample was predominantly white, with one Asian and one Hispanic participant, consistent with the demographic composition of the surrounding northern New England region. Participants provided written informed consent according to procedures approved by the Institutional Committee for the Protection of Human Subjects.

Screening for eligibility included standardized phone interview with a memory screen,[37,38] in-person interview, and review of medical records. Inclusion criteria were at least 60 years of age, right-handed, fluent in English, and at least 12 years of formal education or a GED. Participants were required to have an informant who knew them well and could answer questions about their cognition and general health. The relationships of the informants to the participants were spouse or significant other (70%), adult child (14%), and friend or other family member (16%); this distribution did not differ between groups. Exclusion criteria included any medical, psychiatric, or neurologic condition (other than MCI) that could significantly affect brain structure or cognition, history of head trauma with loss of consciousness lasting more than 5 minutes, history of substance dependence, and factors contraindicating MRI. Nonamnestic forms of MCI[39,40] were excluded. One MCI patient was taking a cholinesterase inhibitor, and no participant was taking any other psychoactive medication.

Methods of assessment

Participants underwent a detailed neuropsychological evaluation, including measures of memory, attention, executive function, language, spatial ability, general intellectual ability, and psychomotor speed as well as standard dementia screens. Tests included Mini-Mental State Examination,[41] Mattis Dementia Rating Scale-2,[42] California Verbal Learning Test (CVLT-I or CVLT-II),[43,44] Boston Naming Test,[45] Trail Making Test (original or DKEFS),[46,47] Wechsler Adult Intelligence Scale III (Digit Symbol, Digit Span, Block Design, Vocabulary, and Information subtests),[48] Wechsler Memory Scale (WMS-III: Logical Memory [LM] and Visual Reproduction subtests),[49] and Wisconsin Card Sorting Test (short form).[50,51] Estimates of baseline intellectual functioning included the American National Adult Reading Test[52] and the Barona Index.[53]

Multiple inventories were employed including the Memory Self-Rating Questionnaire,[54] self and informant versions of the Neurobehavioral Function and Activities of Daily Living Rating Scale,[55,56] self and informant versions of the Informant Questionnaire on Cognitive Decline in the Elderly,[57] the four cognitive items from the Geriatric Depression Scale (GDS),[58] 10 cognitive items from a telephone-based screening for MCI,[37] and 23 items from the Memory Assessment Questionnaire,[59] adapted in part from the Functional Activities Questionnaire.[60] A Cognitive Complaint Index was calculated as the percentage of all items endorsed.

A board-certified geropsychiatrist (R.B.S.) ruled out depression, dementia, and other Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) Axis I psychiatric disorders based on a semistructured evaluation that included the Hamilton Rating Scale for Depression (HAM-D)[61] and GDS.[58] A neurologic examination and the original and revised Hachinski Ischemia Scale[62,63] were also completed.

Structural brain MRI scans, described below, were reviewed by a board-certified neuroradiologist (A.C.M.), blinded to clinical status, to rule out incidental pathology. White matter changes were rated on a scale adapted from the Age-Related White Matter Changes Scale.[64,65] In an effort to enhance sensitivity to subthreshold microvascular or other white matter changes, we added intermediate scores for subtle but detectable white matter changes that were judged within (0.5) or beyond (0.75) those typical for age. The resulting scale included the following designations: 0 = no lesion (including symmetric, well-defined caps or bands); 0.5 = white matter changes noted but age appropriate or less than expected for age; 0.75 = white matter changes noted are more than expected for age; 1 = focal lesions; 2 = beginning confluence of lesions; 3 = diffuse involvement of the entire region/with or without involvement of U fibers.

Group classification and characterization

Group classifications (HC, CC, MCI) were based on results of the neuropsychological assessment, self and informant report indices, and the geropsychiatric and neurologic evaluation. A multidisciplinary clinical consensus panel reviewed each case according to the criteria outlined in table 1. The decision to characterize a participant as having significant CCs was determined by a consensus evaluation of self and informant responses; those considered to have significant CCs typically endorsed 20% or more of the items on the Cognitive Complaint Index.

The Cognitive Complaint Index and its component scores are presented in table 2. Based on the study classification criteria, the Cognitive Complaint Index was by definition elevated in both the MCI and CC groups relative to the HC group ($p < 0.001$; figure 1). The CC and MCI groups did not differ and endorsed approximately three times as many complaints as the HC group. Assessment of memory performance was based on age, education, and gender-adjusted scores. The adjustment was made using the mean, SD, and β coefficients obtained from an expanded healthy demographically balanced control group. The MCI participants performed 1.5 SDs below the adjusted mean of HCs on at least one verbal memory test score (CVLT Total 1–5, Short Delay, Long Delay, WMS-III LM I or LM-II; table 2). On average, the MCI group was below the −1.5-SD level on 3.58 (1.39) of the five scores. By contrast, the CC group was below the −1.5-SD level on 0.85 (1.05) of the five scores, similar to the HC group, which had 0.35 (0.74) scores below the cutoff. A composite verbal memory Z score was calculated as the mean of the Z scores of the above five measures and results are shown in table 2 and figure 1. The MCI group differed from the CC and HC groups on both composite memory Z score and the number of tests below cutoff. The CC and HC groups did not differ from each other after adjustment for multiple comparisons.

On depression measures, there were no significant elevations or between-group differences on the HAM-D. Although the CC and MCI groups scored an average of 2 points higher than the HC group on the adjusted GDS (four cognitive items deleted), all three group means were well within normal limits (table 2). No participant showed depression on the comprehensive geropsychiatric evaluation.

With the exception of a sex difference, there were no significant group differences in demographics (table 2). There was a group difference in APOE genotype, with the CC group showing a preponderance of E4-negative individuals (table 2). Sex and APOE genotype were used in secondary analyses to clarify their potential relationship with GM density.

Imaging

Scan acquisition—Scans were obtained on a GE Signa 1.5-T Horizon LX magnet with echo speed gradients using a standard head RF coil. A T1-weighted three-dimensional spoiled gradient echo (SPGR) coronal volume was acquired. Parameters were TR = 25, TE = 3 or min, flip angle = 40 degrees, 1 NEX, and slice thickness = 1.5 mm (no skip), yielding 124 contiguous slices with a 24-cm field of view and a 256 × 256 matrix with 0.9375 mm in-plane resolution. We also acquired a fast spin echo T2-weighted scan as a screen for focal lesions or other incidental findings (TR = 3000, TE = 96, 3 mm contiguous axial slices).

Preprocessing and VBM—Scans were reconstructed from slice data using scripts written in Matlab (Mathworks, Inc.). Data were then resampled to isotropic 1-mm^3 voxels, aligned visually to the AC-PC plane using BRAINS software,[66,67] and reformatted to the axial plane. VBM was performed using locally developed automation scripts to implement the optimized methods described by Good et al.[33] and Ashburner and Friston[68] Briefly, the T1-weighted AC-PC–aligned SPGR volumes were resampled to 1.5-mm^3 voxels and segmented to extract GM maps. A custom age-appropriate brain template was used for automated removal of extracerebral tissue including the skull and meninges. GM maps were then spatially normalized to the GM prior probability template using a 12-parameter model including nonlinear basis functions as implemented in the Statistical Parametric Mapping package (Wellcome Department of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm/). The normalized scans were then smoothed using an isotropic spatial filter with full width half maximum of 12 mm to help account for individual differences in gyral anatomy. The smoothed normalized GM maps were used for subsequent analyses.

Hippocampal volume and ROI analysis—Methods for manual segmentation of the hippocampus have been described elsewhere,[69,70] and our protocol[71] is summarized briefly here. Images were reformatted into isotropic 1-mm voxels and resampled into the plane perpendicular to the long axis of the hippocampus using BRAINS.[66,67] Manual traces were performed in the coronal plane with reference to markings placed in the orthogonal views to guide boundary determination. The anterior boundary, visualized in the sagittal plane, included the point where the alveus, a thin band of white matter, was observed between the hippocampus and amygdala. Additional anterior boundary landmarks in the axial plane included the uncal notch indicating the beginning of the coronal nucleus of the amygdala. The posterior boundary was defined in the sagittal plane where the tail of the hippocampus was surrounded by white matter on three sides.[72] The lateral border of the hippocampus was the CSF of the temporal horn of the lateral ventricle. On the inferior bank, the subicular complex was included. The boundary with the entorhinal cortex was defined by outlining the subiculum in the sagittal plane superiorly, adjacent to the lateral ventricle, as well as inferiorly, adjacent to the uncinate fasciculus.[69,73] The medial edge was bounded by the

CSF in the uncal and ambient cisterns, and the dorsomedial boundary included the choroidal fissure.

Hippocampal volume and ROI template procedure—Left and right hippocampal volumes were calculated for each participant by summing the coronal slice areas and then adjusted for age and total intracranial volume using a regression model. Inter- and intrarater reproducibility assessed by intraclass correlation coefficients were >0.94 for both the left and right hippocampi. Templates for the left and right hippocampi were constructed by averaging the ROIs derived from the HC group on a voxel-by-voxel basis in Montreal Neurological Institute atlas space. Individual ROIs were smoothed using an isotropic 3-mm FWHM filter prior to averaging. These ROI templates were then used to extract hippocampal GM signal intensity values from VBM for all participants.

Statistical analyses

The GM maps derived from VBM were analyzed on a voxel-by-voxel basis using general linear model and random effects methods. Analysis of variance (ANOVA) was used to assess group differences in GM density using a two-stage approach. First, we examined the hypothesized MTL region of interest. Second, we performed an unbiased whole brain analysis of GM using a more stringent spatial threshold. For the hypothesized MTL region, we employed a small volume search area with a family-wise error threshold of 0.05 and a minimum cluster size (k) of seven contiguous voxels (24 mm^3). For the whole brain analysis, we used a threshold of 0.001 at the voxel level and k of 75 contiguous voxels (253 mm^3). Major clusters identified on the whole brain analyses by the omnibus F test were further analyzed using the following ROI approach. Spherical ROIs were centered at the cluster local maxima. Because brain structures of varying sizes were included in the analyses, we used a diameter of 6 mm for the ROI to standardize GM sampling. For each ROI, the first eigen-variate of signal intensity was subjected to further analysis using the Tukey honestly significant difference test to assess pairwise group differences. A series of covariance analyses was used to assess the relationships between GM reduction and memory in the combined sample (n = 120). For episodic memory performance and memory complaints, we analyzed the composite verbal memory Z score and the Cognitive Complaint Index. Hippocampal volume data were analyzed by ANOVA with planned comparisons after adjustment for age and total intracranial volume (ICV) with regression-based estimates of these covariates derived from the HC group.

Results

Group differences on VBM

Group differences in GM density were found in bilateral MTL and distributed cortical regions (table 3). As expected, the MCI group showed reduced GM density relative to the HC group in distributed brain regions, including bilateral medial temporal, frontotemporal, and other neocortical areas (figure 2, table 3). The CC group showed a similar, although slightly more circumscribed, pattern of reduced GM density relative to the HC group (figure 2, table 3). There were no regions in which the MCI or CC group showed higher GM density than the HC group.

Relationship between GM and memory

The composite verbal memory Z score was lower in those with reduced GM density, predominantly in bilateral medial temporal and distributed cortical regions (figure 3 and table E-1 on the *Neurology* Web site at www.neurology.org). No regions showed increased GM density with a reduction in verbal memory. A higher Cognitive Complaint Index indicated a reduction in GM density, predominantly in bilateral medial temporal and other cortical and subcortical regions (table E-1; figure 4). No regions showed an increase in GM density as complaints increased, nor did GM density diminish with fewer complaints.

Additional analyses

We examined several relevant covariates including sex, APOE genotype, and total ICV. Although each covariate slightly attenuated the regional effect sizes, all areas showing group differences in GM density in the original analysis remained significant. Using the white matter ratings scale described above, three HCs, three patients with MCI, and no CC group members had subtle white matter hyperintensities greater than expected for age. No participant had diffuse hyperintensities. We repeated the analysis of group differences after excluding these participants with subtle white matter changes of presumed microvascular etiology and one additional MCI patient with enlargement of the Sylvian fissure; regions showing group differences in the original analysis remained significant again with a slight reduction of effect size.

Hippocampal volume and GM density

Age- and ICV-adjusted hippocampal volumes are shown in figure 5 (top row). As expected, there were between group differences (left: $F(2,117) = 7.55$, $p = 0.0008$; right: $F(2,117) = 8.67$, $p = 0.0003$). The MCI group showed hippocampal volume reduction compared to both the HC (left and right both $p < 0.0005$) and CC (left and right both $p < 0.005$) groups. The HC and CC groups did not differ. Although all groups showed larger right than left volumes, there was no group by hemisphere interaction. Age-adjusted GM density for the left and right hippocampal template ROIs are shown in figure 5 (bottom row). There were between-group differences (left: $F(3,116) = 25.06$, $p < 0.0001$; right: $F(3,116) = 22.77$, $p < 0.0001$). Both the CC and MCI groups showed reduction of GM density vs HC (CC < HC, left $p = 0.024$ and right $p = 0.008$; MCI < HC, left and right $p < 0.001$). The CC and MCI groups did not differ. There was a trend toward higher GM values for the left than right hemisphere across groups ($p = 0.08$) but no group x hemisphere interaction.

Discussion

This study characterized the pattern of regional GM loss in older adults with marked CCs but normal test performance. The MCI and CC groups showed a similar pattern of reduced GM density in bilateral medial temporal, frontal, and other distributed brain regions. This pattern of findings indicates that structural brain changes similar to those seen in MCI are present even in cognitively intact, nondepressed older adults with significant memory complaints. The changes were slightly more extensive in the MCI group than the CC group compared to the HC group, suggesting that the CC group may represent a point on a continuum between normal aging and MCI. Significant CCs may signify a very early stage of the dementing process for some individuals and may constitute a pre-MCI stage in these cases.

Models suggesting a continuum from normal aging to AD, however, have been questioned based on neuropathologic evidence of changes characteristic of AD in some individuals with MCI.[74] Such data are not presently available for CC cohorts. Prior studies[75] have reported elevated incidence of conversion to dementia in individuals with CCs meeting criteria for Clinical Dementia Rating 0.5 (“questionable dementia”).[76] The results of our ongoing longitudinal study will ultimately help to clarify the relative rates of conversion to dementia from CCs and MCI. Follow-up with neuropsychological and neuroimaging methods will help determine the cognitive trajectory, progression of structural brain changes, and diagnostic outcomes within each group.

Across the entire combined sample of older adults, reduction of GM density in medial temporal and other regions was correlated with both subjective memory complaints and verbal learning performance. This indicates that the structural brain changes seen in the CC and MCI groups have functional significance in terms of memory ability. Together with prior research relating frontal metabolism to subjective memory ratings in older adults,[77] these findings highlight the importance of CCs in the clinical evaluation of older adults and suggest that those who present with significant CCs warrant evaluation and close monitoring over time. Although subtle cognitive anomalies may be present many years before dementia onset,[78–80] incorporating information on cognitive complaints[81] and structural changes may be important for prognosis. As new treatments and preventive strategies for MCI and AD are developed and refined, the earliest possible accurate detection of people at increased risk of dementia will take on critical importance.

The design of this study enabled us to rule out factors commonly associated with memory complaints in older adults, including depression, other DSM-IV Axis I disorders, psychoactive medication, and significant white matter pathology.[6,82–84] Therefore, our data indicate that GM atrophy and associated cognitive changes can occur independently of these factors. Other notable strengths of this study are the comprehensive nature of the assessment of CCs including both self and informant perception as well as the combination of VBM GM density and hippocampal volume ROI analyses in the same cohort.

A potential limitation in terms of the generalizability of our results is that most participants had high education and estimated baseline intellect. High baseline functioning or cognitive reserve may buffer the effects of brain pathology on cognition.[85,86] High baseline individuals may be more likely to express subjective complaints before objective measures can detect decline. Our study warrants replication in cohorts with lower levels of baseline functioning given the potential implications for early diagnosis. Our results can not be generalized to nonamnestic subtypes of MCI,[39] which may show a different profile on neuroimaging. Within amnestic MCI, we did not attempt to assess whether single and multiple domain subtypes can be distinguished using structural MRI.

VBM may be sensitive to the earliest stages of dementia, before the onset of cognitive changes measurable on comprehensive neuropsychological evaluation. It has advantages and limitations as compared to an ROI-based approach involving manual tracing of specific brain structures.[33,87,88] VBM is largely automated and is therefore highly reproducible and much less labor-intensive than manual tracing. In addition, VBM may be ideal for application in the earliest stages of disease, when brain structural changes are so subtle that they cannot readily be detected visually. Our observation that the CC group showed significantly reduced hippocampal GM density but not volume reduction suggests that voxel-based approaches incorporating signal intensity may have greater sensitivity in early preclinical stages than volumetric methods. This finding warrants replication in view of the implications for early detection of those at elevated risk of dementia. VBM will likely be useful to aid in early detection, selection of participants in clinical trials, and treatment monitoring. However, VBM analyses are computationally demanding, and some processing steps, such as the use of age-specific templates, have yet to be fully standardized. These methodologic issues are discussed in detail by Ashburner et al.[89] Overall, VBM- and ROI-based approaches are likely to provide complementary information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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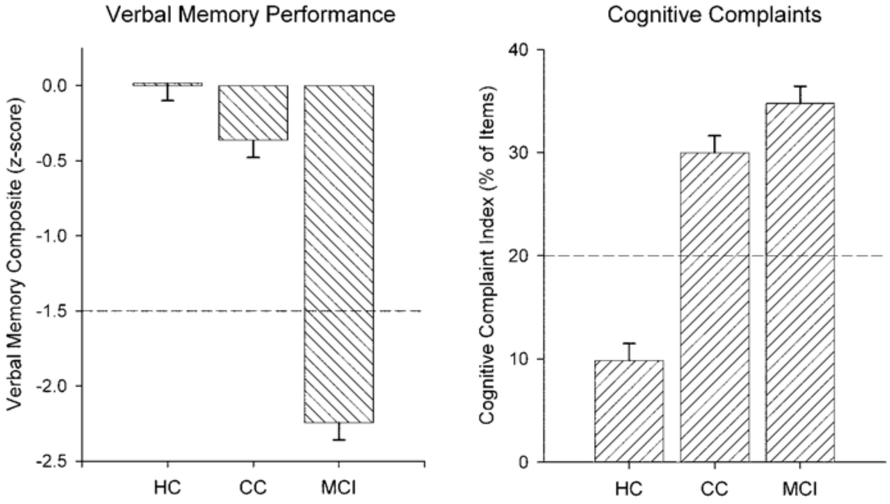

Figure 1.

Characterization of the healthy control (HC, n = 40), cognitive complaint (CC, n = 40), and mild cognitive impairment (MCI, n = 40) groups on verbal memory performance composite domain score and the Cognitive Complaint Index indicating the percentage of possible complaints. By definition, the HC group had normal memory performance and a low level of complaints, whereas the MCI group had significant complaints and deficits. The CC group had normal performance but was nearly as elevated in complaints as the MCI group.

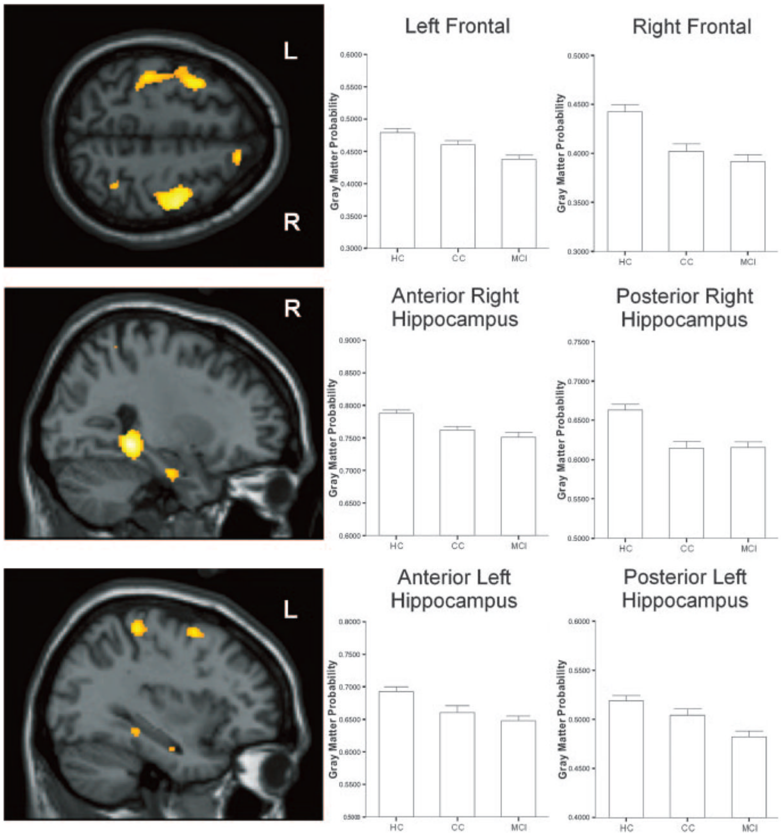

Figure 2.

Regions showing significant GM atrophy in the MCI and the CC groups compared to HC group. Displayed at the left of each panel are images showing selected regions with group differences in the overall analysis, including bilateral frontal (top), right hippocampus (middle), and left hippocampus (bottom, $p < 0.001$). Also displayed are graphs of group differences in signal intensity from spherical regions of interest in each of the corresponding brain areas. See text for full description of results of statistical analyses.

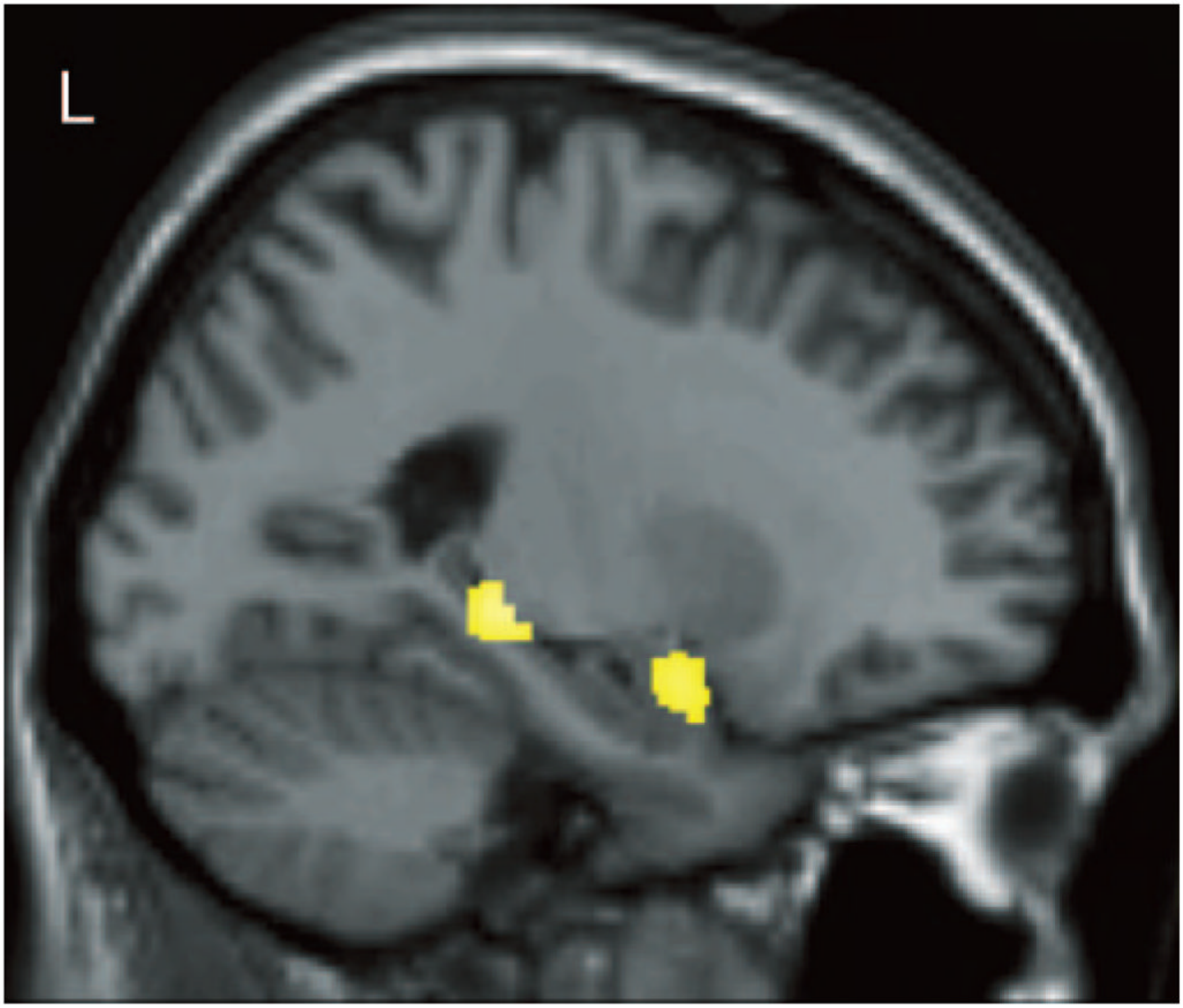

Figure 3.

Verbal learning performance was positively related to gray matter density in left medial temporal regions across the entire sample (N = 120, p < 0.001). See text for a detailed description of the statistical analyses and results.

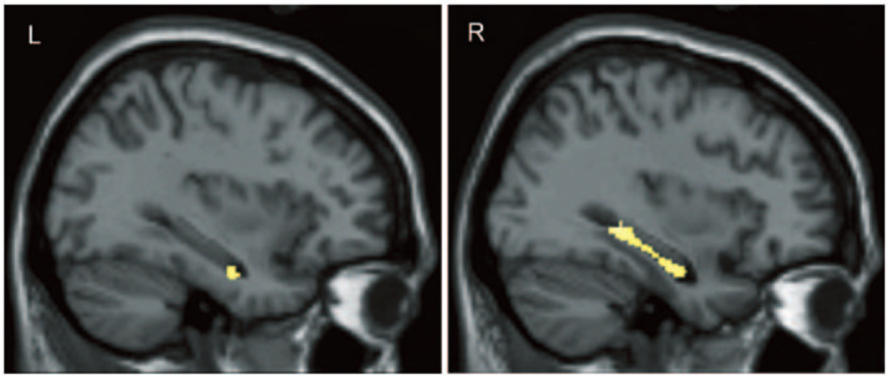

Figure 4.

Higher levels of cognitive complaints were associated with decreased gray matter density in the left and right hippocampi across the entire sample (N = 120, p < 0.001). See text for a detailed description of the statistical analyses and results.

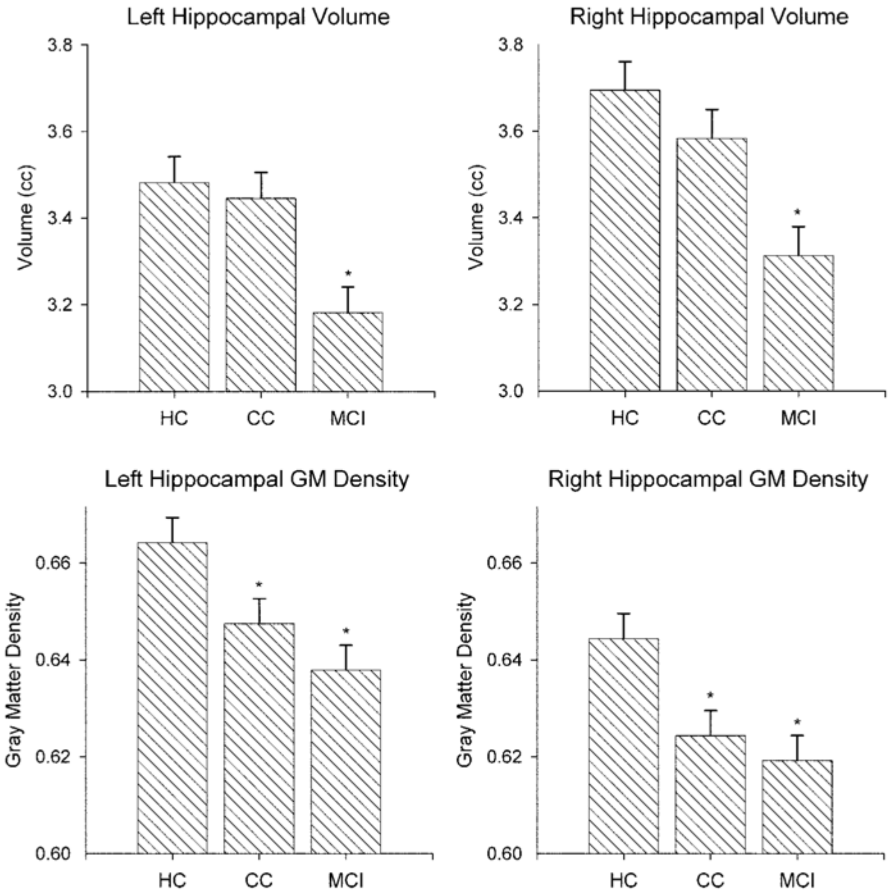

Figure 5.

Hippocampal volume and gray matter density by group. Age- and intracranial volume–adjusted means (± SE) for manually segmented left and right hippocampi are shown in the top row. Age-adjusted gray matter densities for the hippocampi are shown in the bottom row.

Table 1

Criteria used to classify study participants

	HC group	CC group	MCI group
1. Abnormal memory performance*			+
2. Significant memory complaints, corroborated by an informant†		+	+
3. Relatively preserved general cognitive functioning	+	+	+
4. Generally normal activities of daily living	+	+	+
5. No dementia	+	+	+
6. No depression or other major psychiatric disorder	+	+	+

[*] At least 1.5 SDs below the mean established for age- and education-matched controls on standardized tests of episodic memory.

[†] Endorsed at least 20% of possible cognitive complaints across all inventories or complaints deemed significant by clinical consensus.

HC = healthy control; CC = cognitive complaint; MCI = mild cognitive impairment.

Table 2

Participant characteristics

	HC group, n = 40	CC group, n = 40	MCI group, n = 40	*p* (post hoc differences)
Age, y	71.0 (5.1)	73.3 (6.0)	72.9 (7.1)	NS
Education, y	16.6 (2.7)	16.4 (2.8)	16.3 (3.3)	NS
Sex (M/F)	12/28	16/24	23/17	0.042
APOE E4 (−/+)[*]	24/16	31/9	20/18	0.063
ANART, est. of verbal IQ	122.8 (4.7)	120.7 (6.3)	120.7 (6.6)	NS
Barona FSIQ est.[†]	116.1 (5.6)	116.2 (5.4)	115.8 (6.1)	NS
MMSE (max. 30)	29.1 (1.0)	28.9 (1.2)	27.2 (2.2)	<0.001[**]
DRS total score (max. 144)	141.0 (2.1)	141.3 (2.4)	137.0 (4.6)	<0.001[**]
CVLT Total 1–5 (max. 80)[‡]	48.6 (6.8)	47.1 (8.6)	32.6 (6.0)	<0.001[**]
Short delay (max. 16)	11.2 (1.9)	10.4 (2.4)	5.4 (2.7)	<0.001[**]
Long delay (max. 16)	11.8 (2.0)	10.5 (2.8)	5.6 (2.7)	<0.001[**]
WMS-III LM immediate (max. 75)	48.0 (7.4)	45.6 (8.2)	33.6 (8.5)	<0.001[**]
LM delay (max. 50)	31.6 (6.1)	28.4 (6.8)	18.8 (7.9)	<0.001[**]
Verbal memory[§]				
Composite (*Z*)	0.01 (0.62)	−0.36 (0.79)	−2.24 (0.76)	<0.001[**]
Tests below cutoff	0.35 (0.74)	0.85 (1.05)	3.58 (1.39)	<0.001[**]
CC scales				
Overall CCI (%)[¶]	9.8 (6.4)	30.0 (9.5)	34.8 (13.9)	<0.001[§§]
Squire Memory (max. 18)	5.3 (3.5)	11.0 (3.8)	11.3 (4.4)	<0.001[§§]
ADL self (max. 54)	3.2 (3.0)	12.7 (6.7)	14.4 (9.6)	<0.001[§§]
ADL informant (max. 54)	1.7 (2.2)	8.0 (7.6)	13.2 (10.6)	<0.001[††]
IQCODE self (max. 16)	1.6 (2.3)	5.5 (3.0)	5.8 (3.5)	<0.001[§§]
IQCODE informant (max. 16)	2.2 (1.2)	3.9 (2.4)	5.3 (3.2)	<0.002[‡‡]
GDS cognitive items (max. 4)	0.4 (0.8)	2.0 (1.1)	2.1 (1.3)	<0.001[§§]
Memory interview (max. 10)	2.2 (1.7)	4.4 (1.9)	5.2 (2.5)	<0.001[§§]
MAQ (max. pace 23)	2.0 (1.6)	4.0 (2.0)	4.8 (1.9)	<0.001[§§]
GDS-NC (max. 26)	1.8 (2.5)	3.6 (3.1)	3.5 (3.2)	<0.01[§§]
HAM-D[61][#]	0.1 (0.3)	1.1 (1.8)	1.2 (2.0)	NS
Hachinski Ischemia score[62] (max. 18)	1.4 (0.5)	1.3 (0.5)	1.3 (0.5)	NS
Revised Ischemia score[63] (max. 52)[‖]	4.6 (0.9)	4.7 (1.1)	4.7 (1.3)	NS

[*] APOE data missing for two participants in MCI group.

[†] Demographically based estimate of full-scale IQ.[53]

[‡] California Verbal Learning Test-I/II, Total Learning Trials 1 through 5 (maximum 80), short and long delay free recall (maximum 16 per trial).

[§] Composite is the mean age, education and sex adjusted *Z* score for the five verbal memory measures; tests below cutoff is the number of verbal memory tests out of five that fell ≥1.5 SDs below control group mean.

[¶] Cognitive Complaint Index (CCI), percentage of all complaint items endorsed in a positive (i.e., symptomatic) direction. See text for references for the component scales.

[#] Available for 43 participants (HCs, 15; CCs 16; MCI, 12).

[||] Available for 96 participants (HCs, 29, CCs, 34, MCI, 33).

For analyses of variance post hoc group contrasts:

[**] MCI vs HCs, CCs;

[††] MCI vs CC vs HC;

[‡‡] MCI vs HCs;

[§§] MCI, CC vs HC with direction indicated by the table values. For sex, $\chi 2$ differed for HCs vs MCI only. For APOE, MCI had a higher frequency of the E4 allele than CCs.

HC = healthy control; CC = cognitive complaint; MCI = mild cognitive impairment; NS = not significant; ANART = American National Adult Reading Test; FSIQ = full-scale IQ; MMSE = Mini-Mental State Examination; DRS = Dementia Rating Scale-2; CVLT = California Verbal Learning Test-I/II; WMS-III = Wechsler Memory Scale III; LM = logical memory; CCI = Cognitive Complaint Index; ADL = activities of daily living; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; GDS = Geriatric Depression Scale; MAQ = Memory Assessment Questionnaire; GDS-NC = Geriatric Depression Scale noncognitive items; HAM-D = Hamilton Rating Scale for Depression.

Table 3

Regions showing reduced gray matter density in MCI and CC groups relative to the HC group: brain region,[*] Montreal Neurological Institute atlas coordinates (mm), and individual group effects

Brain region	***x, y, z***	**HC > MCI**	**HC > CC**	**CC > MCI**
Hippocampal region of interest[†]				
Right subgyral, hippocampus	27, −39, −4	<0.001	<0.001	NS
Left parahippocampal gyrus, BA27	−26, −32, −6	<0.001	0.024	NS
Right parahippocampal gyrus, hippocampus	28, −12, −27	<0.001	0.015	NS
Left parahippocampal gyrus, BA28	−20, −18, −18	0.009	0.001	NS
Left parahippocampal gyrus, hippocampus	−32, −12, −22	0.001	0.022	NS
Whole brain[‡]				
Right precentral gyrus, BA4	48, −9, 52	<0.001	0.001	NS
Left middle frontal gyrus, BA6	−36, 4, 56	<0.001	NS	0.041
Right inferior frontal gyrus, BA47	14, 18, −21	<0.001	NS	0.015
Right middle temporal gyrus, BA21	51, −30, −2	<0.001	0.001	NS
Left insula, BA13	−38, −26, 15	<0.001	0.012	NS
Left medial frontal gyrus, BA11	−3, 52, −20	0.003	<0.001	NS
Right inferior temporal gyrus, BA20	48, 0, −45	<0.001	0.003	NS
Left angular gyrus, BA39	−44, −76, 27	<0.001	NS	NS
Left superior temporal gyrus, BA42	−63, −32, 18	0.002	<0.001	NS
Right cuneus, BA30	15, −70, 9	0.001	0.001	NS

[*] Spherical region of interest (diameter 6 mm) centered on representative voxel.

[†] The left and right hippocampal regions of interest templates were based on the mean of smoothed individual regions of interest from the 40 healthy controls. After thresholding, these regions of interest templates included portions of parahippocampal gyrus. Small volume search area with family-wise error threshold of 0.05 and minimum cluster extent (k) of seven.

[‡] $p_{\text{uncorr}} < 0.001$, k = 75.

HC = healthy control; MCI = mild cognitive impairment; CC = cognitive complaint; NS = not significant.