Brain structure and cognition in a community sample of elderly Latinos

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Abstract—Background: Previous studies have found that hippocampal atrophy and white matter hyperintensities (WMH) on MRI are linked to cognitive impairment and dementia. The authors measured these variables in a population-based cohort of older Mexican Americans with a wide spectrum of cognitive ability, ranging from normal cognition to dementia. Objective: To investigate whether these structural brain changes were seen in individuals prior to the development of dementia and how these changes were related to the presence of dementia. Methods: A sample of 122 subjects was selected from the Sacramento Area Latino Study on Aging, and subjects were categorized into four groups of increasing levels of cognitive impairment: normal, memory impaired (MI), cognitively impaired but not demented (CIND), and demented. Hippocampal volume was quantified using a region of interest approach. WMH was rated on a semiquantitative scale as the percent of total volume of white matter. Results: Hippocampal volume was significantly reduced in CIND and demented individuals, and WMH were significantly increased in demented subjects. MI subjects did not have any significant changes in hippocampal volume or WMH. The risk for developing dementia was significantly and comparably increased in subjects with either hippocampal atrophy or high WMH. However, the risk for dementia increased dramatically in subjects with both hippocampal atrophy and a high degree of WMH. Conclusion: Reductions in hippocampal volume may be present before dementia but not until cognitive impairment is relatively severe. Because there is a synergistic effect between high WMH and hippocampal atrophy, interactions between vascular and degenerative processes may be important determinants of dementia.

It is now believed that intellectual decline begins with a prodromal phase that is characterized by cognitive impairment sufficiently severe to meet criteria for dementia. There have been many different characterizations of such conditions, including mild cognitive impairment and age-associated memory impairment. Because reduced hippocampal volume assessed by MRI is a sensitive marker for AD, it has been proposed as a method to assess the risk for progression to dementia in individuals who do not yet meet criteria for AD. Imaging of brain structure in such groups of subjects has suggested that hip-
pocampal atrophy may be associated with cognitive impairment and may predict decline to dementia.\textsuperscript{7,8} However, these studies are often selective in their inclusion criteria and are based on research clinic samples that invariably exclude a large portion of the general population and therefore fail to capture the full breadth of individuals falling between normal cognition and dementia. We measured cognitive function and brain structure in a population-based sample of individuals who encompass the entire spectrum of cognitive impairment and comorbid conditions.

In addition to evaluating hippocampal volume, we also evaluated the extent of white matter hyperintensities (WMH), which are commonly seen on MRI scans of elderly individuals across the entire spectrum of cognitive ability. WMH are associated with age,\textsuperscript{9-11} cognitive impairment,\textsuperscript{10,12,13} and cardiovascular risk factors\textsuperscript{14,15} and have been suggested as a marker for ischemic vascular dementia.\textsuperscript{16} However, the association between WMH and cognitive impairment or dementia is variable.\textsuperscript{17,18} Differences in study populations and associated pathologic processes may account for some of these discrepancies. Because of the high prevalence of WMH in population studies and because of their variable association with cognitive dysfunction, we examined the contributions of WMH in conjunction with hippocampal volume to better define the substrate of cognitive impairment in aging. This report is based on an MRI component of a cohort study of cognitive impairment in a population-based sample of Mexican American individuals older than 60 years of age who are participants in the Sacramento Area Latino Study on Aging (SALSA).

**Methods. Subject sampling.** The SALSA project recruited 1,789 Hispanic individuals older than 60 years of age in 1998 to 1999. Sampling was based on identification of predefined census tracts with a high density of Hispanic residents, and individuals residing in those locations were contacted by the study investigators or called in to participate. The study population was restricted to six counties in the California Central Valley. The target population was selected by identifying all 1990 census tracts and updating them from other sources, characterizing them by the percent of eligible residents (aged older than 60 years and Hispanic) and selecting all tracts in which the percent of eligible individuals was at least 10%. The sampling fraction obtained for Sacramento County was 32% for men and 46% for women. The overall response rate among those individuals contacted was 85%. The University of California at Davis Institutional Review Board approved the study, and all subjects gave informed consent to participate in the study.

After recruitment and enrollment, a multistage screening approach was employed to evaluate participants for cognitive impairment and dementia (figure 1). The first stage consisted of screening using two cognitive instruments, the Modified Mini-Mental State Examination (3MSE)\textsuperscript{19,20} and a test of verbal episodic memory taken from the Spanish and English Neuropsychological Assessment Scales (SENAS).\textsuperscript{21} The SENAS battery is a multidimensional test battery for the assessment of cognitive functioning in elderly individuals that has psychometrically matched Spanish and English versions. The verbal delayed recall test consisted of five learning trials of a 15-word list. Subjects were tested on immediate recall and delayed recall after reading a distracter word list. At screening, subjects scoring at or above the 20th percentile on both instruments were categorized as normal, while those scoring below the 20th percentile on either instrument were selected for further examination. All percentile cutoffs were determined using age, education, sex, and language adjustments.

The second phase of evaluation included administration of the remaining five scales comprising the SENAS: tests of verbal and nonverbal semantic memory, verbal conceptual thinking, verbal attention span, and pattern recognition. In addition, at this visit the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)\textsuperscript{22} was administered. The IQCODE assesses functional ability in comparison with function at an earlier time point. In addition to those individuals scoring below the 20th percentile of memory on screening instruments, a random sample of 20% of all subjects underwent this more extensive examination.

Participants who scored below the 10th percentile on one or more of the SENAS and below the 20th percentile on the IQCODE were referred for a clinical (history and physical) examination by a neurologist. Following the neurologic examination, laboratory testing was performed as clinically indicated in cases diagnosed as demented.

**Subject sampling and categorization.** The sampling scheme described was used to assign patients to categories for purposes of dementia ascertainment in the SALSA sample. Dementia prevalence will be the subject of a separate report. The imaging study reported here represents a substudy of the SALSA project that sampled 122 individuals to obtain normal individuals and those with a broad spectrum of cognitive impairment. Subjects were selected randomly from the SALSA cohort with exclusionary criteria limited to only those subjects with a contraindication to MRI examination or a history of severe long-standing mental illness. Subjects were sorted into four groups based on the following criteria.

**Normal.** These individuals were derived from the 20% random sample who underwent the full neuropsychological battery. They scored above the 20th percentile on both screening tests and did not meet criteria for referral for clinical examination.

**Memory impaired (MI).** Individuals in this category underwent the full neuropsychological battery and had scores below the 20th percentile on the verbal delayed recall test but did not meet criteria for referral for clinical examination. Thus, these individuals all had impaired memory, sometimes with other mild cognitive impairments as well, but did not have functional impairment.

**Cognitively impaired but not demented (CIND).** These subjects all underwent neurologic examination and therefore had performed poorly on one or more neuropsychological scales and the IQCODE. After examination, these cases went to case adjudication and did not meet criteria for dementia. Operational criteria for dementia required clinically significant impairment in two or more cognitive
domains and clinically significant impairment of independent functioning.

Demented. These subjects were deemed demented after clinical neurologic examination and met operational criteria for dementia at case adjudication. Imaging data were not used in adjudicating the presence of dementia.

**MRI data acquisition.** All MR images were collected on a GE 1.5-T Signa Horizon LX NV/i System (Signa, General Electric, Milwaukee, WI). Three sequences were obtained: a sagittal fast spin-echo T2-weighted pulse sequence (repetition time [TR], 3,000 ms; echo time [TE], 94 ms; field of view [FOV], 24 cm; slice thickness, 5 mm; slice gap, 1 mm; matrix, 256 × 224), an axial oblique spin-echo T2-weighted sequence (TR, 2,420 ms; TE, 20 and 90 ms; 44 slices; FOV, 24 × 24 cm; slice thickness, 3 mm; slice gap, 0 mm; matrix, 256 × 192), and a T1-weighted, coronal three-dimensional spoiled gradient recalled echo, inversion recovery–prepped sequence (TE, 1.9 ms; flip angle, 20°; FOV, 24 cm; matrix, 256 × 256; 124 contiguous slices; slice thickness, 1.6 mm).

**Hippocampal volume.** The sampled hippocampus included the hippocampus proper (CA1–CA3), dentate gyrus, and subicular complex. A region of interest approach using previously described software was used to delineate the boundaries of the hippocampus. First, the T1-weighted coronal data set was resliced to be aligned perpendicular to the long axis of the left hippocampal formation. The borders of the hippocampus were manually traced on contiguous 1.6-mm coronal slices in the anterior to posterior direction. Although the borders were traced on the coronal slices, the corresponding sagittal and axial views were relied on to verify hippocampal boundaries. Hippocampal volume was determined using an in-house program to create a volume out of the areas traced on contiguous slices. A single rater, blinded to age, sex, and group membership, traced all regions. Intrarater reliability was determined for both the right hippocampus and the left hippocampus. Intraclass correlation coefficients were 0.98 for the right hippocampus and 0.96 for the left hippocampus. Intrarater reliability was assessed a second time, ∼8 months later to

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**Figure 1.** Classification scheme for subjects in the Sacramento Area Latino Study on Aging. 3MSE = Modified Mini-Mental State Examination; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; * = five subscales from the Spanish and English Neuropsychological Assessment Scales battery including verbal and nonverbal semantic memory, conceptual thinking, attention span, and pattern recognition.
ensure that there was no drift in measurements; intraclass correlation coefficients were 0.94 and 0.95 between the first and second ratings for the right hippocampus and the left hippocampus, respectively.

The boundaries of the hippocampus in each subject were identified using anatomic landmarks. The rostral pole of the hippocampus was identified in coronal and sagittal images. Typically, the temporal horn of the lateral ventricle surrounded the lateral and dorsolateral portions of the hippocampus at this level. The hippocampus could also be differentiated from the overlying amygdala by the white matter of the alveus that surrounded the hippocampus.

At rostral levels, the dorsal border of the hippocampus was formed either by the amygdala (medially) or by the lateral ventricle (laterally). The ventricle forms the lateral border, and the ventral border is the white matter deep to the hippocampus and subiculum. At these rostral levels, the portion of the uncus that connects the caudal amygdala with the hippocampus was included within our measurements. Caudal to the amygdala, the boundaries of the hippocampus are made by the ventricle (dorsally), the laterally adjacent white matter, and the white matter subjacent to the subiculum that separates it from the entorhinal cortex (rostrally) and then from the parahippocampal cortex (caudally). The fimbria was not included in the measurements. The posterior boundary of the hippocampus was traced to the section in which the fornix has a dorsomedial trajectory toward the corpus callosum and is distinct from the hippocampal formation. To divide the hippocampus into rostral (anterior) and caudal (posterior) portions, the boundary was set at the rostral limit of the lateral geniculate nucleus.

Intracranial volume (ICV) was determined by manually outlining the margin of the inner table of the skull on contiguous 10-mm axial slices in a superior to inferior direction. The superior boundary was the top of the skull, and the inferior boundary was the most superior level at which the cerebral peduncles were visualized. The orbits were excluded from ICV. Two raters with high interrater reliability (intraclass correlation coefficients, 0.97) traced ICV.

White matter signal hyperintensity. WMH were rated using a semiquantitative scale designed to measure the degree of WMH in MR images. Ratings were made on contiguous 2.5-mm axial proton density images. The scale is an analog scale, using a 100-mm straight line on which the origin is labeled “none” and the terminus is labeled “very severe.” The rater examined each slice of the brain and drew a vertical line on the scale corresponding to the assessment of the total volume of WMH as a percent of total white matter. The percent of WMH was then characterized by measuring the distance from the vertical line to the origin of the scale. The scale was supplemented with a series of eight reference images that were quantified for the percent of WMH. These reference images had been separately segmented into gray matter, white matter, CSF, and WMH using a semiautomated segmentation program. Thus, the actual percent of WMH was known for these images, and they could be used as a reference for the rating scale.

All ratings were performed by a single rater with high intrarater reliability (ICC, 0.97). In addition, the rater tested the validity of the scale by using the semiquantitative rating scale on a different series of 20 brains that had been segmented. The volumes of WMH determined quantitatively by the segmentation program and the rater were highly correlated ($r = 0.94$).

Statistical analysis. Analysis of variance followed by Fisher’s protected least significant difference (PLSD) post hoc analyses were used to determine group differences on demographic variables such as age and education. Pearson correlation coefficients were used to determine group differences on language and sex.

Analysis of covariance and Fisher’s PLSD post hoc analyses were used to compare hippocampal volumes across groups. Age and ICV were included as covariates. Because WMH were not normally distributed, WMH was categorized into three groups based on 25th percentile and 75th percentile cutoffs (low: ≤25th percentile, <4.0; medium: 25th to 75th percentile, 4.0 to 19.25; high: ≥75th percentile, >19.25), and chi-squared analysis was performed to test for independence between WMH and group membership. Post hoc cell contributions were used to determine what each cell contributed to the chi-squared statistic.

Pearson correlation coefficients were used to determine correlations between hippocampal volume and age and WMH and age. For the correlation analyses, hippocampal volumes were normalized to ICV (hippocampal volume/ICV × 100) to control for head size.

Logistic regression was performed to determine the relative contributions of WMH and hippocampal volume to cognitive status. For the analysis of dementia status, the normal, MI, and CIND groups were grouped together to form a nondemented group, and this group was compared with the demented group. The model included demented or nondemented as the dependent variable and age, education, average normalized hippocampal volume, and WMH as independent variables. For the purposes of logistic regression, the amount of WMH was categorized into a dichotomous variable because WMH are not normally distributed. To facilitate the comparison of the relative contributions of WMH and hippocampal volume to dementia status, hippocampal volume was also categorized into a dichotomous variable. The average normalized hippocampal volume was categorized into two groups, atrophied and normal. Subjects who fell below the 25th percentile of the entire sample were categorized as having hippocampal atrophy, while subjects who fell above the 25th percentile were categorized as having normal hippocampal volume. Similarly, the amount of WMH was categorized into two groups, low and high. Subjects who fell below the 75th percentile of the entire sample were categorized as having hippocampal atrophy, while subjects who fell above the 75th percentile were categorized as having normal hippocampal volume. Although these cutoffs are somewhat arbitrary, they were chosen to minimize and equalize the number of subjects with hippocampal atrophy or high WMH in the nondemented group. Of the 94 nondemented individuals with both hippocampal volume and WMH data, 12.7% were classified as having high WMH, and 11.7% were classified as having hippocampal atrophy.

Logistic regression was also used to determine the association between hippocampal atrophy or high WMH and dementia. The percentile cutoffs described above for atrophied vs normal hippocampus and high vs low WMH were also used in this analysis.
Pearson correlation coefficients were used to determine correlations between WMH and blood pressure in nondemented (normal, MI, and CIND) subjects. Separate analyses were used to test for independence between stroke history and level of WMH (high vs low as defined for the logistic regression model) and stroke history and dementia status (nondemented vs demented).

**Results.** Table 1 shows subject characteristics. Subjects in the demented group were older than subjects in the normal and MI groups (ANOVA: $p < 0.05$; Fisher PLSD test: $p < 0.05$). Subjects in the CIND group were older than subjects in the MI group (ANOVA: $p < 0.0001$; Fisher PLSD test: $p < 0.05$). No. of males/no. of females 12/13 23/35 3/11 14/11 No. using English/no. using Spanish† 14/11 37/21 4/10 8/17 Values are mean (SD) unless otherwise indicated.

* CIND subjects were older than MI subjects, and demented subjects were older than normal and MI subjects (ANOVA: $p < 0.05$; Fisher PLSD test: $p < 0.05$).
† MI subjects had more education than CIND and demented subjects (ANOVA: $p < 0.0001$; Fisher PLSD test: $p < 0.01$).
‡ Normal and MI subjects did not differ, CIND subjects differed from all groups, and demented subjects differed from all groups (ANOVA: $p < 0.0001$; Fisher PLSD test: $p < 0.05$).
§ All groups differed (ANOVA: $p < 0.0001$; Fisher PLSD test: $p < 0.05$).
¶ More demented subjects used Spanish; more MI subjects used English ($\chi^2$ test: $p < 0.05$).
MI = memory impaired; CIND = cognitively impaired but not demented; 3MSE = Modified Mini-Mental State Examination; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; ANOVA = analysis of variance; PLSD = protected least significant difference.

Pearson correlation coefficients were used to determine correlations between WMH and blood pressure in nondemented (normal, MI, and CIND) subjects. Separate $\chi^2$ analyses were used to test for independence between stroke history and level of WMH (high vs low as defined for the logistic regression model) and stroke history and dementia status (nondemented vs demented).

**Figure 2.** Means and SE for left and right normalized hippocampal volumes (raw volume/intracranial volume $\times 100$) by group. MI = memory impaired; CIND = cognitively impaired but not demented. Subjects in the CIND and demented groups had significantly smaller right and left hippocampal volumes than did subjects in the normal and MI groups ($p < 0.03$).
than those in all other groups (Fisher’s PLSD test; \( p < 0.05 \)).

CIND subjects selected for the imaging study did not differ from the larger sample of total CIND subjects in terms of age, sex, language, education, delayed recall, or 3MSE score. Demented subjects in the imaging study did not differ from the larger sample of demented subjects in terms of any of these variables except for age, as the demented subjects in the imaging study were younger than subjects in the overall cohort (72 vs 80 years of age; data not shown).

Both right and left hippocampal volumes differed by group (analysis of covariance with age and ICV as covariates: right, \( p = 0.0062 \); left, \( p = 0.0071 \)) (figure 2). Subjects in the CIND and demented groups did not differ from one another, and each group had smaller hippocampal volumes than the normal and MI groups (Fisher’s PLSD test; right, \( p < 0.03 \); left, \( p < 0.01 \)).

Of the 122 subjects, 119 were assessed for the percent of WMH. Three subjects (2 normal subjects and 1 MI subject) were excluded because of poor quality of the proton density scan. The amount of WMH differed by group (\( \chi^2 \) test; \( p = 0.0002 \)). Within the demented group, there were more subjects with high WMH (\( \geq 75\% \) percentile) and fewer subjects with low WMH (\( \leq 25\% \) percentile) than would be expected if WMH and groups were independent (\( \chi^2 \) post hoc cell contribution; \( p < 0.01 \)). For descriptive purposes, means and SE of WMH for each group are shown in figure 3.

Both right and left hippocampal volumes were inversely correlated with age (right: \( r = -0.396, p < 0.0001 \); left: \( r = -0.414, p < 0.0001 \)). WMH also correlated with age (\( r = 0.225; p = 0.02 \)) (figure 4).

Both hippocampal volume and WMH were strongly associated with dementia (table 2). Subjects with a small hippocampal volume were at least six times more likely to be demented than were subjects with a hippocampal volume above the 25th percentile. Subjects with WMH above the 75th percentile were nearly seven times more likely to be demented than were those with WMH below the 75th percentile.

When compared with a normal hippocampal volume and low WMH, either hippocampal atrophy or high WMH increased the risk for dementia (\( p < 0.001 \) for both), again with comparable odds ratios for both conditions (see table 2). Both hippocampal atrophy and high WMH also increased the risk of dementia (\( p < 0.0001 \), with an odds ratio of more than three times that for either hippocampal atrophy or high WMH.

There was a positive correlation between WMH and systolic blood pressure in nondemented subjects (\( r = 0.284; p < 0.006 \)). Nondemented subjects with high WMH also had a higher prevalence of previous stroke than did nondemented subjects with low WMH (\( \chi^2 \) test; \( p < 0.0001 \)). Demented subjects had a higher incidence of previous stroke than did nondemented subjects (\( \chi^2 \) test; \( p < 0.02 \)).

**Discussion.** Although neither hippocampal volume nor WMH was different in mildly MI individuals than in normal individuals, hippocampal volume was lower in CIND and demented subjects, and WMH was much higher in subjects in the demented group. Furthermore, in comparison with reduced hippocampal volume or high WMH alone, a combination of both structural brain changes more than tri-

![Figure 3](image3.png)

**Figure 3.** Means and SE of white matter hyperintensity (WMH) volumes as the percent of total white matter by group. MI = memory impaired; CIND = cognitively impaired but not demented.

![Figure 4](image4.png)

**Figure 4.** (A) Regression plot of age and normalized left hippocampal volume (\( r = -0.414; p < 0.0001 \)). (B) Regression plot of age and volume of white matter hyperintensity (WMH) as the percent of total white matter volume (\( r = 0.247; p < 0.01 \)). The hippocampal volume decreased with age, while the degree of WMH increased with age.
Table 2 Hippocampal volume and WMH, separately and combined, as predictors for cognitive status (demented vs. nondemented) adjusted for age and education in the SALSA imaging substudy

<table>
<thead>
<tr>
<th>Finding</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampal volume (normal vs atrophied)</td>
<td>6.27</td>
<td>2.00–19.65</td>
</tr>
<tr>
<td>WMH (low vs high)</td>
<td>6.67</td>
<td>2.21–20.14</td>
</tr>
<tr>
<td>Combined effect of hippocampal volume and WMH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal hippocampus, low WMH*</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Atrophied hippocampus, low WMH</td>
<td>14.21</td>
<td>3.19–63.40</td>
</tr>
<tr>
<td>Normal hippocampus, high WMH</td>
<td>13.03</td>
<td>2.95–57.56</td>
</tr>
<tr>
<td>Atrophied hippocampus, high WMH</td>
<td>44.67</td>
<td>8.43–236.57</td>
</tr>
</tbody>
</table>

Data are results of logistic regression analysis. Cognitive status (demented or nondemented) was the dependent variable, and age, education, normalized average hippocampal volume, and WMH were independent variables. For the combined effect of hippocampal volume and WMH, the degree of brain insult was the independent variable.

* Normal hippocampus, low WMH was the reference group.

WMH = white matter hyperintensity; SALSA = Sacramento Area Latino Study on Aging.

...led the risk of developing dementia, suggesting a synergistic effect.

There are several limitations to this study. First, the results are derived from a sample of Mexican American individuals and thus may not pertain to all ethnic groups. High levels of non–insulin-dependent diabetes and related vascular disease in Mexican Americans could influence cognitive function and the prevalence of WMH. Second, although subjects were randomly selected from the overall SALSA cohort to participate in the imaging study, response rates may have introduced a sampling bias. Indeed, the demented individuals in the imaging study were younger than the demented individuals in the overall SALSA cohort. Third, the small size of the CIND group is another limitation of the study. However, the CIND group was similar to the larger group of CIND subjects found in the overall study in every major respect. Finally, although subjects in the MI groups did not have hippocampal atrophy and those in the MI and CIND groups did not have elevated WMH, there is heterogeneity in hippocampal volume and WMH within these groups so that some individuals have smaller hippocampi and greater WMH. Although these individuals may be at greater risk for progression to dementia, this hypothesis awaits confirmation in a longitudinal study. There is also considerable heterogeneity in cognitive ability within the MI group. It is possible that some MI individuals are actually just on the low end of normal cognitive ability and will not decline further, while others have clinically significant memory impairment. Again, longitudinal follow-up of these individuals will prove to be valuable.

Our findings are in concordance with those of numerous previous studies that found significant reductions in hippocampal volume in dementia. There have also been studies that reported reductions in hippocampal volume in individuals considered to be at risk for developing dementia with some degree of mild or minimal cognitive impairment. We examined a wide range of individuals in between normal cognition and dementia and found reductions in hippocampal volume in the more severely impaired CIND individuals, but we did not find reductions in more mildly MI subjects.

Because of the heterogeneity of cognitive impairment and the different criteria employed in previously reported studies, it is somewhat difficult to compare our MI and CIND groups with other cognitively impaired but nondemented samples for whom reduced hippocampal volumes have been reported. Research clinic samples of individuals with cognitive impairment but not dementia may be defined by a variety of rating instruments such as the global deterioration scale or the clinical dementia rating scale or by psychometric tests. Such individuals may have minor functional deficits in addition to cognitive deficits. Patients selected from two epidemiologic samples defined by a clinical dementia rating scale of 0.5 or as having “minimal dementia” were found to have hippocampal atrophy, but it is difficult to compare the severity of their cognitive impairment with those of the MI and CIND groups in this study. The individuals in the MI group may be similar to those defined as having mild cognitive impairment by Petersen et al., as their memory performance was on average >1.5 SD below that of the controls. However, the MI subjects in this cohort did not present to a clinic with complaints of memory loss.

The fact that MI individuals in this study did not seek medical attention for memory loss may be an important factor that differentiates such patients from others with mild cognitive impairment. The normal scoring on the IQCODE for this group suggests that there were no functionally significant consequences of poor memory test performance and that poor memory was generally not a complaint. These MI subjects were living independently, did not gain entry to the study through the health care delivery system, and did not spontaneously complain of memory loss. Previous studies suggest that complaints of memory loss increase the risk of cognitive decline in individuals with cognitive impairment. Thus, it is possible that complaints of memory loss and decrease in functional ability are significant factors in identifying patients with clinically significant impairment that could reflect underlying brain pathologic lesions. Such individuals may have a more...
severe form of memory loss than those without subjective complaints.

Another way in which our studies differ from previous examinations of this question is that the subjects in this study cover a wide range of cognitive impairment. Although MI subjects had relatively poor memory performance, CIND subjects had worse memory, decrements in 3MSE scores, and some functional problems. These individuals were undoubtedly more similar to patients with dementia than subjects in the MI group. Based on these results, we conclude that generally healthy individuals, even with memory impairment, who do not report to clinics with complaints of memory loss do not have significant structural brain changes. In contrast, individuals with more severe cognitive loss and some degree of functional disturbance do have these changes. This may reflect the fact that subjects in clinic samples of mild cognitive impairment actually reflect patients further along in the course of dementia than previously suspected and likely further along than subjects in our MI group. These findings have consequences for who is at risk for progressing to dementia. Based on these results, individuals with mild memory loss and no subjective complaints have no substantial anatomic brain changes and thus should be at relatively low risk for dementia, although those with more severe cognitive and functional loss have underlying brain changes that suggest they may be at risk for progression.

Finally, our sample is different from clinic populations with mild cognitive impairment in that they are from a single ethnic group and have relatively low educational levels and a high prevalence of cerebrovascular risk factors. Although low education could affect performance on memory tests, education-adjusted cutoffs were used in selecting subjects. In addition, the high prevalence of diabetes and cerebrovascular disease or the ethnic and cultural differences independent of education could be functioning independently from brain atrophy in affecting cognitive performance.

With regard to cerebrovascular disease, changes in white matter are potentially interesting. WMH are clearly associated with cognitive impairment in nondemented subjects and could theoretically account for mild degrees of cognitive impairment in this sample. However, WMH were not significantly greater in the MI and CIND groups than in other subjects, although they were more extensive in subjects with dementia. Although WMH may be associated with vascular dementia, they are also seen frequently in patients diagnosed with AD clinically. Thus, WMH could represent either a cerebrovascular cause of dementia or the presence of cerebrovascular disease that interacts with AD. The finding of a strong association between WMH and dementia is unusual and suggests that cerebrovascular disease may play an important role in the development of dementia, perhaps because of the prevalent risk factors for cerebrovascular disease in this population. For the nondemented subjects in this cohort, there was a significant positive correlation between WMH and systolic blood pressure. Nondemented subjects with high WMH also were more likely to have a history of stroke than were subjects with low WMH. Overall, demented subjects had significantly more WMH than did nondemented subjects and also were more likely to have a stroke history. This supports the notion that the contribution of WMH to dementia is due to increased vascular risk factors in this population.

The synergistic effects of hippocampal atrophy and WMH are striking, indicating that the presence of both findings is a greater risk for dementia than either factor alone. In this study sample, only 4% of individuals with normal hippocampal volume and low WMH were demented, while 67% with both hippocampal atrophy and high WMH were demented. Although the underlying pathologic condition is unknown, this synergy raises the possibility that two different pathologic processes, such as AD (represented by hippocampal atrophy) and cerebrovascular disease (represented by WMH), may be interacting to produce these results. Similar results have been suggested by analyses that showed that cortical gray matter volumes and WMH contribute independently to cognitive impairment in AD patients.

Results from this study provide some suggestions for the mechanisms underlying cognitive failure. Hippocampal atrophy may be a feature of cognitive impairment before dementia arises, but generally it is present in individuals who are further along the trajectory to dementia than those who have only mild and clinically insignificant memory loss. Abnormal white matter appears to act synergistically with this hippocampal atrophy in increasing the risk of dementia. Although either abnormality alone may be associated with both dementia and cognitive impairment, their coexistence in the same individual substantially increases the likelihood of dementia.

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References


