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Article abstract—*Objective:* To test the hypothesis that MRI-based measurements of hippocampal volume are related to the risk of future conversion to Alzheimer's disease (AD) in older patients with a mild cognitive impairment (MCI). *Background:* Patients who develop AD pass through a transitional state, which can be characterized as MCI. In some patients, however, MCI is a more benign condition, which may not progress to AD or may do so slowly. *Patients:* Eighty consecutive patients who met criteria for the diagnosis of MCI were recruited from the Mayo Clinic Alzheimer's Disease Center/Alzheimer's Disease Patient Registry. *Methods:* At entry into the study, each patient received an MRI examination of the head, from which the volumes of both hippocampi were measured. Patients were followed longitudinally with approximately annual clinical/cognitive assessments. The primary endpoint was the crossover of individual MCI patients to the clinical diagnosis of AD during longitudinal clinical follow-up. *Results:* During the period of longitudinal observation, which averaged 32.6 months, 27 of the 80 MCI patients became demented. Hippocampal atrophy at baseline was associated with crossover from MCI to AD (relative risk [RR], 0.69, $p = 0.015$). When hippocampal volume was entered into bivariate models—using age, postmenopausal estrogen replacement, standard neuropsychological tests, apolipoprotein E (APOE) genotype, history of ischemic heart disease, and hypertension—the RRs were not substantially different from that found univariately, and the associations between hippocampal volume and crossover remained significant. *Conclusion:* In older patients with MCI, hippocampal atrophy determined by premorbid MRI-based volume measurements is predictive of subsequent conversion to AD.

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For patients who develop AD, the transition from a normal cognitive state to clinically recognizable AD occurs gradually over years.[1] It is presumed that the pathologic substrate of the cognitive decline that characterizes AD follows a similar slowly progressive course, with gradual accumulation of degenerative pathology of AD ongoing for years, perhaps even decades, before manifestation of unequivocal clinical symptoms. Memory impairment is usually the initial manifestation of dementia in AD. That the transition from normal cognition to AD is gradual, however, presents clinicians with a common and difficult diagnostic problem: Does evidence of a mild memory impairment in an older individual represent the earliest manifestation of AD or more benign forgetfulness that may not progress to dementia? Clinical criteria for the classification of patients with a mild cognitive impairment (MCI) have been established.[2-4] The rate at which MCI patients convert to AD is substantially greater than that of the general older population,[2,5-8] and MCI patients are the subject of several more recent treatment trials.

Structural and functional imaging findings are diagnostic markers of AD.[9] Most imaging studies, however, have been cross-sectional in nature and have been designed to demonstrate differences between older controls and patients who were already demented. Prior studies addressing prediction of future dementia have been done with relatively few patients with familial AD,[10] with the oldest old,[11] or using subjective image assessment.[12] We addressed this issue by conducting imaging studies and then longitudinally following-up individuals who were at increased risk of AD because of the diagnosis of MCI. The imaging measurement evaluated was MRI-based volume measurements of the hippocampi. We chose this measurement because 1) medial temporal lobe limbic structures, particularly the hippocampus, play a central role in memory function and are the site of the earliest neurofibrillary pathology in AD[13,14]; 2) memory impairment is the hallmark of early AD[15]; and 3) MRI detects subtle medial temporal lobe damage in AD.[11,16-19] In this study, we tested the hypothesis that premorbid MRI-based hippocampal volume measurements in patients with MCI were related to the risk of subsequent conversion to AD. We also determined whether the predictive power of hippocampal volume measurements was independent of

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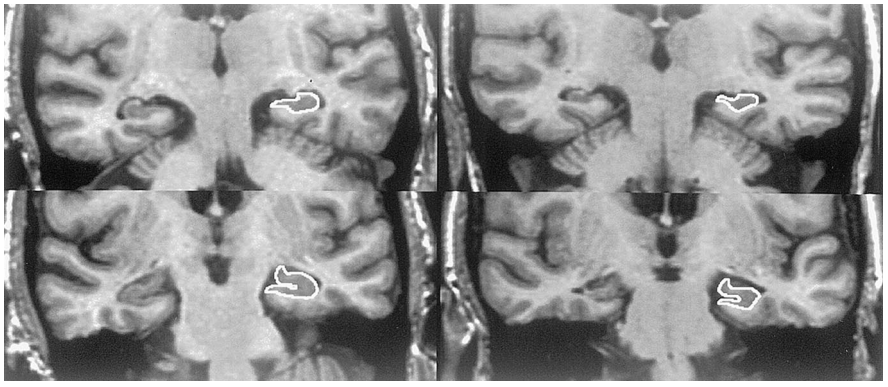

Figure 1. Neuroanatomic boundaries. The column of images on the left are cropped oblique coronal MR images through the temporal lobes of a 75-year-old woman. The upper image is through the body of the hippocampus and lower image is through the head of the hippocampus. This mild cognitive impairment (MCI) patient remained stable over 49 months of clinical follow-up. At baseline her hippocampal W score was 0.21. On the right are matched imaging sections of a 70-year-old woman, who was initially categorized as having MCI, but became demented after 43.5 months of follow-up. Her hippocampal W score was −2.48 at entry into the study. The hippocampi of the patient who became demented (right) are visibly atrophic relative to the stable patient (left) despite the fact that the crossover patient was 5 years younger. The anatomic outlines of the left hippocampus are indicated.

other potential predictor variables—age, apolipoprotein E (APOE)genotype, estrogen replacement, performance on selected measures of cognitive performance, hypertension, and ischemic heart disease.

Patients and methods. *Recruitment and evaluation of subjects.* Eighty consecutive MCI patients were recruited from the Mayo Clinic AD Center and AD Patient Registry (ADC/ADPR), which are prospective, longitudinal studies of aging and dementia.[20] Informed consent was obtained for participation in the studies, which were approved by the Mayo Institutional Review Board. Study participants were assigned to diagnostic group categories during (ADC/ADPR) consensus committee meetings consisting of a geriatrician, neurologists, neuropsychologists, psychometrists, and nurses who had seen the patient. Relevant diagnostic categories were those of MCI and AD. Criteria for the diagnosis of MCI were the following[2,3]: 1) memory complaint documented by the patient or collateral source; 2) normal general cognitive function, as determined by measurements of general intellectual function and screening instruments; 3) normal activities of daily living, as documented by history and record of independent living[21]; 4) dementia ruled out by Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised (DSM-III-R) criteria,[22] and met no National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD[1]; 5) objective memory impairment, defined by performance at 1.5 standard deviations below age and education-matched controls on indices of memory function[23]; 6) age 60 through 89 years; and 7) Clinical Dementia Rating score of 0.5.[24]

Ascertainment of endpoint. The primary endpoint or dependent variable in this study was the crossover of individual MCI patients to the AD category during longitudinal follow-up. Patients were enrolled throughout the study period. All study patients underwent clinical/neuropsychological reevaluations at approximately 12-month intervals. Twenty-six patients had a single serial follow-up assessment, 13 had two follow-up assessments, and 41 had three or more follow-up assessments. MCI patients who remained unchanged cognitively were characterized as stable, and the mean follow-up time for these patients was 33.5 ± 17.9 months. Patients who became demented, all of whom received the diagnosis of probable AD at that time, were designated as crossover patients; the mean follow-up time (from enrollment to crossover) for these patients was 30.8 ± 17.3 months. The diagnosis of dementia was made according to DSM-III-R criteria.[22] The diagnosis of probable AD was made according to NINCDS-ADRDA criteria.[1]

An MRI examination of the brain was performed within 4 months of the initial clinical assessment in all patients. These MRI studies were used in the diagnostic process only to exclude treatable causes of cognitive impairment. The hippocampal volume data were unknown to the consensus committee throughout the study.

MRI methods. All imaging studies were conducted at 1.5 T (Signa, General Electric Medical Systems, Milwaukee, WI), using a standardized imaging protocol.[25] Measurements of intracranial volume were derived from a T1-weighted sagittal sequence with 5-mm contiguous sections. Volume measurements of the hippocampi were derived from a T1-weighted three-dimensional (3D) volumetric spoiled gradient recalled echo sequence, with 124 contiguous partitions, 1.6-mm slice thickness, a 22-cm × 16.5-cm field of view, 192 views, and 45° flip angle.

All image processing steps in every patient were performed by the same research associate who was blinded to all clinical information (age, sex, clinical course) to insure that the volumetric data were unbiased. Validation studies have shown the intra-rater test-retest coefficient of variation of hippocampal volumetric measurements to be 1.9% with this method.[26] The 3D image data set of each patient was realigned into an orientation perpendicular to the principal axis of the left hippocampal formation. The imaging data were then interpolated in-plane to the equivalent of a 512 × 512 matrix and magnified 2×. The voxel size of the fully processed image data was 0.316 mm^3. The borders of the hippocampi were manually traced on the work station screen for each image slice sequentially from posterior to anterior. Typically, 40 to 50 imaging slices were measured for each hippocampus. In-plane hippocampal anatomic boundaries were defined to include the CA1 to CA4 sectors of the hippocampus proper, the dentate gyrus, and the subiculum (figure 1).[25] The posterior boundary of the hippocampus was determined by the oblique coronal ana-

tomic section on which the crura of the fornices were defined in full profile.

Intracranial volume was determined by tracing the margin of the inner table of the skull on contiguous images from the sagittal sequence.

Apolipoprotein E genotyping. DNA was extracted from peripheral leukocytes and amplified by PCR.[27] PCR products were digested with HhaI, and the fragments were separated by electrophoresis on an 8% polyacrylamide nondenaturing gel. The gel was then treated with ethidium bromide for 30 minutes, and DNA fragments were viewed by ultraviolet illumination.

Assessment of clinical variables. The presence or absence of hypertension and ischemic cardiac disease was assessed by review of medical records. Patients were recorded as being positive for hypertension if hypertension or its treatment was identified at any point in time in the medical record. Patients were considered to have ischemic heart disease if any of the following were identified: angina pectorus, myocardial infarction, coronary bypass surgery, or coronary angioplasty. The time of menopause and the presence or absence of estrogen replacement therapy were also extracted from the medical records.

Statistical methods. The hippocampal volume measurements of each patient were normalized for interpatient variation in head size by dividing hippocampal volume by the total intracranial volume of that particular patient. We previously determined age- and sex-specific normal percentiles for normalized hippocampal volume in a group of 126 cognitively normal older controls using the MRI volumetric method described.[25] Age- and sex-specific normal percentiles for each of the 80 MCI patients were determined using this normal-value database. Each percentile was then converted to a W score. The W score is the value from a standard normal distribution corresponding to the observed percentile. For example, for a standard normal distribution, the 50, 5, and 2.5 percentiles are given by 0, -1.645, and -1.96, respectively. Thus, a patient with a hippocampal volume (adjusted for age and sex) at the fifth percentile in the normal value database would receive a W score of -1.645. Similarly, a patient at the 50th percentile would receive a W score of 0. When this method of assigning W scores is applied to the normal older control patient database, the resulting W scores precisely follow a standard normal distribution. W scores in other study populations, including our MCI cohort, can then be compared directly to this standard distribution, providing a framework for comparing hippocampal volume measurements among individual patients, appropriately corrected for age, sex, and head size.

In addition to hippocampal volume, other predictor variables for crossover to AD that were evaluated included age, APOE genotype, Mini-Mental State Examination (MMSE),[28] Dementia Rating Scale (DRS),[29] Wechsler Memory Scale–Revised–Logical Memory II Subtest–Paragraph Retention score (WMS-R-LMRII),[30] Auditory Verbal Learning Test–Percent Delayed Retention score (AVLT),[31] the total free-recall and delayed-recall indices from the Free and Cued Selective Reminding Test (FCSRT),[32] and the Controlled Oral Work Association Test total final score (COWAT). Estrogen replacement, hypertension, and ischemic heart disease were also modeled as potential predictor variables.[33] In the APOE $\epsilon 4$ risk analysis, patients were stratified into those with genotypes known to increase the risk of AD (3/4, 4/4) and those who were $\epsilon 4$ noncarriers (2/3, 3/3).[34] Six patients who were $\epsilon 2/4$ were excluded from the APOE risk analysis because the association between AD and $\epsilon 2/4$ is unclear.

Although a direct comparison of the W scores of patients who did and those who did not crossover seems natural, the length of follow-up varied among patients. Direct comparisons between patients who crossed over versus those who did not were therefore analytically inappropriate. To accommodate variable follow-up periods, life-table methods were used to evaluate patient characteristics relating to crossover rather than discriminate function analyses or logistic regression. Each predictor variable was evaluated univariately. Because of sample size limitations, extensive multivariate modeling was not feasible. The possibility of confounding between hippocampal W score and other variables was assessed by fitting bivariate models evaluating hippocampal W score with each of the other predictor variables individually. APOE status, estrogen replacement, hypertension, and ischemic heart disease were entered as dichotomous variables in all analyses. All tests were two-sided. Estimates of relative risk (RR) were obtained using usual, semiparametric Cox regression testing methods. A nonparametric version of Cox regression testing was used for hypothesis testing for quantitative variables. For these same reasons, confidence intervals are not reported for estimates of risk.

Tests of hypotheses for quantitative risk factors using Cox regression testing are sensitive to departures from normality; in this case, more accurate probability statements are obtained using logit rank tests.[35] Because some of the data were skewed, with the degree of skew varying among successive risk sets, the logit rank test was used both univariately and bivariately in hypothesis testing.[35] The logit rank tests were implemented computationally by treating the logit rank scores for each of the quantitative variables in each risk set as time-dependent covariates in a Cox regression model.

Kaplan-Meier survival curves showing the probability of crossover for patients stratified by hippocampal W scores into three groups ($W \geq 0$, $0 > W > -2.5$, $W \leq -2.5$) were used for display purposes only, to illustrate the association between hippocampal volume and crossover to AD. The W score $W \geq 0$ was selected a priori. This is a natural cut point, indicating values in patients that are equal or greater than the mean value among controls. The cutoff point $W \leq -2.5$ was selected post-hoc to optimally display the gradient of the RR of crossover associated with hippocampal atrophy. A W score of -2.5 corresponds to approximately the 1 percentile (more precisely, the 0.6 percentile) among controls. These W score cut points were used for display purposes only (figure 2, table 1). All statistical analyses (tables 2 and 3) were performed using hippocampal W score as a continuous variable.

Results. Of the 80 patients who were classified as having MCI at entry into the study, 3 died during the follow-up period, 2 of these after they had converted to AD. The mean hippocampal W score of these 80 MCI patients was -1.24 ± 1.24, corresponding to the 11 percentile of volumes among controls after correction for age, sex, and head size. Of the entire group of 80 MCI patients, 13 had hippocampal W scores ≥ 0 at entry into the study, indicat-

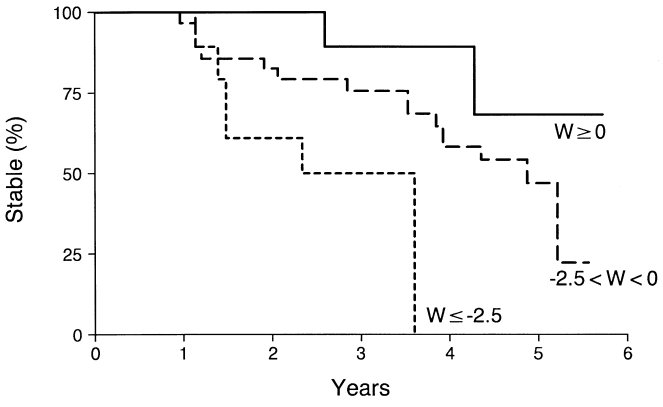

Figure 2. Hippocampal W score and crossover. Kaplan-Meier curves of patients whose hippocampal W score at baseline was ≥0 (n = 13), 0 > W > −2.5 (n = 54), and ≤−2.5 (n = 13).

ing hippocampal volumes that were at or above the mean value expected for age- and sex-matched controls. Thirteen had hippocampal W scores ≤ −2.5. Fifty-four had W scores between 0 and −2.5. Patients in the three W-score groups were similar on most demographic, clinical, and cognitive testing variables (see table 1). During the period of observation, 27 of the 80 MCI patients converted to AD. Of the 13 MCI patients with hippocampal W scores ≥ 0 at baseline, 2 converted to AD; 19 of 54 with W scores between 0 and −2.5 crossed over; and 6 of 13 with W scores ≤ −2.5 crossed over (see figure 2).

Only hippocampal volume, DRS, FCSRT free recall, and age were statistically significant predictor variables in univariate analyses of the risk of crossover (see table 2). The interpretation of hippocampal W-score result is that for each one-unit increase in the hippocampal W score (i.e., less atrophy), the RR for crossover declined by 31%. The risk of crossover declined with advancing decade of age. Carriers of the APOE ϵ4 allele were 49% more likely to cross over than noncarriers. Patients with better scores on the cognitive tests were less likely to cross over. The one exception was that of the COWAT, with a RR of 1.01 and a nonsignificant p value. The association between estrogen replacement and crossover was not significant ($p = 0.864$). Patients with a history of hypertension were more likely to cross over than those without, and patients with a history of cardiac ischemic disease were less likely to cross over than those without such a history, although neither of these associations were significant.

Separate bivariate analyses were performed with hippocampal volume, together with each of the other predictor variables (see table 3). Hippocampal volume was significant in all models. The RR ratios of hippocampal volume in all bivariate models were similar to those observed univariately, suggesting the independence of hippocampal volume as a risk factor for crossover relative to each of the other predictor variables evaluated.

Discussion. Based on life-table analysis, we estimate that 9% of MCI patients with hippocampal W scores ≥ 0 at baseline will convert to AD within 3 years, compared with 26% of those with hippocampal W scores between 0 and −2.5 and 50% of those with W scores ≤ −2.5. There is considerable controversy whether all MCI patients will eventually progress to AD or whether MCI represents a relatively stable condition in some. Our results indicate only that the rate of conversion is greater in MCI patients with smaller hippocampi and do not address the lifetime risk of conversion.

Old age is an established risk factor for AD, and in a cross-sectional prevalence study, older age would be expected to be associated with a greater prevalence of AD.[36] This is not the case in a study such as ours because the rate at which individuals with MCI progress to AD does not necessarily accelerate with age. The 80 MCI patients in this cohort shared a similar cognitive and demographic profile at study entry (see table 1). It is possible that because AD is a clinically heterogeneous disorder, patients with incipient AD who were younger may have had a more rapidly progressing form than those who were older.[37]

This work focused on the prediction of crossover using hippocampal volume measurements. The intent was not to conduct an exhaustive assessment of possible neuropsychological testing instruments as predictors of crossover but to test the hypothesis that the predictive power of imaging studies is independent of other potential predictor variables, such as standardized neuropsychological tests.[2,38] The MMSE and DRS are measures of general cognitive function,

Table 1 *Characterization of patients with mild cognitive impairment*

Hippocampal W score	n	Age, y,* mean ± SD	Male sex, n (%)	MMSE,† mean ± SD	DRS,‡ mean ± SD	Education, y, mean ± SD	APOE ϵ4,§ n (%)	Follow-up, mo, mean ± SD¶	Crossover to AD, n (%)
≥0	13	79.6 ± 6.1	6 (46.2)	26.2 ± 2.3	127.3 ± 6.9	11.7 ± 3.1	4 (30.8)	42.4 ± 15.4	2 (15)
Between 0 and −2.5	54	78.3 ± 6.4	23 (42.6)	26.7 ± 2.3	127.6 ± 9.4	13.3 ± 3.5	19 (35.2)	32.5 ± 18.4	19 (35)
≤−2.5	13	73.7 ± 8.2	4 (30.8)	25.3 ± 3.4	126.5 ± 8.6	13.7 ± 3.1	6 (46.2)	23.3 ± 10.7	6 (46)
Total	80	77.7 ± 6.8	33 (41.25)	26.4 ± 2.5	127.4 ± 8.8	13.1 ± 3.4	9 (36.25)	32.6 ± 17.6	27 (34)

* Age at time of MRI study, i.e., at time patient entered into the study.
† Mini-Mental State Examination (MMSE) score when patient entered the study. Maximum score is 30.
‡ Dementia Rating Scale (DRS) score when patient entered the study. Maximum score is 144.
§ Number of patients in each group who were carriers of APOE genotypes known to confer an increased risk of AD: ϵ3/4 and 4/4. Patients (n = 6) with ϵ2/4 were not included.
¶ Follow-up is from time of entry into study to conversion to AD in those patients who crossed over.

Table 2 *Risk of crossover: Univariate analyses*

Variable	Relative risk	*p* Value
Hippocampal W score	0.69	0.015
Age (decades)	0.62	0.042
APOE ϵ4	1.49	0.349
Mini-Mental State Examination	0.82	0.089
Dementia Rating Scale	0.97	0.026
WMS-R	0.96	0.638
AVLT	0.99	0.251
FCSRT Free Recall	0.97	0.015
FCSRT Delayed Recall	0.99	0.089
COWAT	1.01	0.316
Hypertension	1.63	0.272
Ischemic heart disease	0.55	0.272
Estrogen replacement	1.09	0.864

WMS-R = Wechsler Memory Scale–Revised–Logical Memory II Subtest–Delayed Paragraph Recall; AVLT = Auditory Verbal Learning Test–Percent Delayed Retention; FCSRT = Free and Cued Selective Reminding Test; COWAT = Controlled Oral Word Association Test.

Table 3 *Risk of crossover: Bivariate analyses*

Variables	Relative risk	*p* Value
Hippocampal W score	0.71	0.032
Age (decades)	0.64	0.081
Hippocampal W score	0.70	0.018
APOE ϵ4	1.39	0.460
Hippocampal W score	0.72	0.011
Mini-Mental State Examination	0.84	0.068
Hippocampal W score	0.70	0.024
Dementia Rating Scale	0.97	0.043
Hippocampal W score	0.72	0.017
WMS-R	0.97	0.840
Hippocampal W score	0.70	0.023
AVLT	0.99	0.430
Hippocampal W score	0.74	0.026
FCSRT Free Recall	0.97	0.026
Hippocampal W score	0.72	0.029
FCSRT Delayed Recall	0.99	0.170
Hippocampal W score	0.68	0.026
COWAT	1.00	0.980
Hippocampal W score	0.63	0.011
Hypertension	1.88	0.220
Hippocampal W score	0.68	0.023
Ischemic heart disease	0.73	0.560
Hippocampal W score	0.68	0.067
Estrogen replacement	0.91	0.670

WMS-R = Wechsler Memory Scale–Revised–Logical Memory II Subtest–Delayed paragraph recall; AVLT = Auditory Verbal Learning Test–Percent Delayed Retention; FCSRT = Free and Cued Selective Reminding Test; COWAT = Controlled Oral Word Association Test.

whereas the AVLT, WMS-R-LMII, and FCSRT indices are tests of memory.[28,32] The COWAT is a test of verbal fluency, measuring attention and language skills.[39] In bivariate analyses paired with hippocampal W score, the associations with risk of crossover were statistically significant for the DRS and FCSRT free recall.

Other studies have found an association between postmenopausal estrogen replacement and decreased risk of developing AD.[40,41] No significant association between crossover and estrogen replacement was observed in the women of this MCI group, however. The nonsignificant p value ($p = 0.067$) observed for hippocampal W score as a predictor of crossover when paired with estrogen bivariately (see table 3) may simply be the result of reduced statistical power when men were excluded from the analysis.

Polymorphisms of the APOE gene are a significant risk factor for developing late-onset AD.[34] The ϵ4 allele confers both an increased risk of developing AD and also lowers the mean age at onset in a dose-dependent fashion, whereas the ϵ2 allele is protective. A trend was present in our data indicating that the ϵ3/4 or 4/4 genotypes conferred a 49% increased RR (see table 2) of crossover relative to an MCI patient with the ϵ2/3 or 3/3 genotypes. APOE genotype does not influence the rate of clinical progression in patients with established AD.[42] We suspect, however, that if the follow-up period were extended to increase the number of crossover events, APOE ϵ4 would emerge as a significant risk factor for crossover. In an earlier study analyzing the risk of crossover as a function of several known risk factors (including age, family history, a variety of cognitive testing instruments, and APOE genotype), APOE ϵ4 emerged as the most powerful predictor variable[2]; however, imaging variables were not considered in that study.

Unlike genetic markers, which are present at birth, imaging studies can only identify progression of the disease itself. This is true for both structural imaging measures and functional measures such as PET, because imaging studies become abnormal only when the disease process itself has produced deviation from normal cerebral function or anatomy.[43,44] Ideally, the imaging findings should represent markers of incipient disease. Our data suggest that MRI-based volume measurements of the hippocampi fulfill this criteria.

Our results generally agree with those of several studies. Fox et al.[10] studied 7 patients in their 40s and 50s who were members of a family with an amyloid precursor protein 717 Val-Gla pedigree. Hippocampal volume declined more rapidly in those who

declined cognitively than in those who remained stable. de Leon et al.[12] used visual assessment of the size of the perihippocampal CSF spaces on CT and found individuals with atrophy were more likely to progress to dementia. As part of a study of the oldest-old, Kaye et al.[11] found that the temporal lobes but not hippocampi were smaller in those who declined cognitively than in those who remained stable. The unique aspect of our study was the combined use of all the following features: 1) a rigorous quantitative MRI-based measurement; 2) a fairly large longitudinal cohort (n = 80); 3) MCI patients, who are at risk for typical sporadic AD; and 4) patients whose age was fairly typical for onset of AD rather than at the extremes of the age spectrum.

There are several limitations to this study that cannot be fully addressed at this time. The criterion used to determine the endpoint was the clinical diagnosis of AD. At our center, the clinical diagnosis of probable AD is 81% accurate compared with the pathologic diagnosis of definite AD. Thus, absolute determination of the endpoint in this study can only be ascertained in the future at autopsy. Despite the small sample size, a significant relation between premorbid hippocampal volume and crossover to AD was demonstrated, which illustrates both the strength of the association and the clinical potential of the technique. Moreover, this association was not altered when evaluated in the context of a series of bivariate analyses, which included many known risk factors for AD. Additional studies with larger sample sizes are needed, however, to more accurately delineate the rate at which risk of crossover increases with increasing hippocampal atrophy and the possibility that the relation may be nonlinear and the role of interactions with other predictor variables.

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Neuropsychological correlates of apathy and depression in patients with dementia

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Article abstract—*Objective:* To investigate the association between apathy and depression, and specific cognitive deficits in AD. *Background:* Apathy and depression are frequent behavioral disorders in patients with AD. However, the neuropsychological correlates of these disorders have rarely been examined. *Methods:* A comprehensive neuropsychological and psychiatric evaluation was carried out in 72 patients with AD with apathy and depression, 29 patients with AD with apathy only, 31 patients with AD with depression only, and 52 patients with AD with neither apathy nor depression (control group). *Results:* Patients with apathy had significantly lower scores on tests of verbal memory, naming, set shifting, and verbal fluency compared with patients without apathy. The association of depression and apathy produced significantly more severe deficits compared with apathy only on a test of abstract thinking. Finally, depression in the absence of apathy was not associated with more severe cognitive impairments compared with the AD control group. *Conclusions:* Apathy, but not depression, is associated with significantly more severe frontal lobe related cognitive deficits in AD.

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Apathy and depression are among the most prevalent behavioral disorders in patients with AD.[1,2] In a recent study that included 101 consecutive patients with AD, we found that 46% had clinically significant apathy.[2] Our study also demonstrated several significant correlates of apathy in AD, such as more severe impairments in activities of daily living, more severe extrapyramidal signs, and a significantly higher frequency of both major depression and dysthymia compared with nonapathetic patients with AD. Although we also demonstrated a significant association between apathy and memory deficits, the study was limited because it included only a small sample of patients with AD with apathy only.

Thus, for the current study we examined a separate consecutive series of 185 patients with probable AD who were assessed with a comprehensive neuropsychological battery that included tests of verbal and visual memory, abstract reasoning, auditory attention, set shifting, verbal fluency, visuospatial reasoning, verbal comprehension, naming, constructional praxis, and manual dexterity. To examine the influence of apathy and depression on cognitive functions, our study had a 2×2 design, and included patients with AD with depression but no apathy, apathy but no depression, both apathy and depression, and neither apathy nor depression.

Patients and methods. *Patients.* A consecutive series of 233 patients who attended the dementia clinic of our institute complaining of memory problems were screened for participation in the study. After neurologic and neuropsychological evaluation, 35 patients met the State of California AD Diagnostic and Treatment Centers criteria for vascular dementia,[3] and 13 additional people had a normal assessment. Both groups were excluded from further evaluations. Thus, the final sample of our study included 133 patients who met National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD,[4] and 51 patients with memory deficits on the neuropsychological evaluation but no deficits in other cognitive domains (this group had a Clinical Dementia Rating [CDR]

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of 0.5,[5] which is classified as questionable dementia). We decided to include patients with a CDR of 0.5 because most of these patients were reported to progress into stages of definite dementia.[6] Moreover, the inclusion of patients with mild cognitive impairment may protect against a floor effect (i.e., lack of between-group differences due to a poor performance across all cognitive tasks).

Psychiatric examination. After informed consent, a psychiatrist blinded to the neuropsychological findings carried out a structured psychiatric evaluation using the following instruments.

Structured clinical interview for Diagnostic and Statistical Manual of Mental Disorders–IV (DSM-IV). The structured clinical interview for DSM-IV is a semistructured diagnostic interview assessing signs and symptoms necessary for the major Axis I DSM-IV diagnoses.[7] The interviews were carried out with the patients and at least one first-degree relative who knew them well. Based on the structured clinical interview for DSM-IV responses, DSM-IV diagnoses of major depression or dysthymia were made.

Hamilton Depression Scale. The Hamilton Depression Scale (HAM-D) is a 17-item interviewer-rated scale for rating the severity of symptoms of depression.[8] TheHAM-D was administered to the caregiver.

Overt Aggression Scale. The Overt Aggression Scale (OAS) measures specific aspects of aggressive behavior based on observable criteria.[9] Aggressive behaviors are divided into four categories: verbal aggression, physical aggression against objects, physical aggression against self, and physical aggression against other people.

Dementia Psychosis Scale. This is an 18-item scale that quantifies the severity and types of delusions in demented patients at the time of the psychiatric evaluation. This scale was rated by a psychiatrist with the patient and at least one close relative or caretaker. We have demonstrated the validity and reliability of this scale in AD.[10]

Apathy Scale. This scale includes 14 items that are scored by the patient's relative or caretaker.[11,12] Each question has four possible answers, scored from 0 to 3. Thus, the Apathy Scale scores range from 0 to 42 points, and higher scores indicate more severe apathy. We have demonstrated the reliability and validity of the Apathy Scale in AD.[11]

All instruments included in the psychiatric assessment (except for the Apathy Scale, which was developed by one of the authors [S.E.S.]) were translated from English into Spanish and back-translated by a certified translator with the help of a bilingual neuropsychiatrist (S.E.S.).

Neuropsychological examination. Each patient was assessed by a neuropsychologist blinded to psychiatric findings using the following test battery.

Mini-Mental State Examination. The 11-item Mini-Mental State Examination (MMSE) has been found to be reliable and valid in assessing general cognitive functions and serves as a cognitive screening instrument in patients with dementia.[13]

Buschke Selective Reminding Test. This test measures verbal learning and memory during a multiple-trial list-learning task.[14] The patient listens to a list of words, and recalls as many words as possible. Each subsequent learning trial involves the presentation only of those words that were not recalled on the immediately preceding trial. The outcome measure was the total number of words recalled.

Benton Visual Retention Test. This test assesses visual perception and nonverbal memory. Patients are exposed to geometric designs for 10 seconds and are immediately presented with a card containing the correct design among three foils. The patient is asked to select the previously presented design. There are 10 trials, and the number of correct responses is the outcome measure.[15]

Similarities. This subtest of the Wechsler Adult Intelligence Scale provides a measure of abstract reasoning.[16] Patients were instructed to state the similarity between two words. Responses were scored according to the standardized criteria as indicated in the manual.

Digit Span. This subtest of the Wechsler Memory Scale examines auditory attention, and includes two parts. Both consist of seven pairs of number sequences that the examiner presents at the rate of one per second. In the first part (Digits Forward), the patient is asked simply to repeat a string of numbers (from two to eight numbers in length) exactly as it is given. In the second part (Digits Backwards), the patient is asked to recite the string of numbers (from two to eight numbers in length) in reversed order.[17]

Wisconsin Card Sorting Test. This test measures the ability to develop and apply new concepts and subsequently shift sets, which requires the subjects to suppress a previously correct learned response and learn a new one.[18] Assessment of the overall proficiency of the test was judged by the number of categories achieved (maximum of six).

Controlled Oral Word Association Test. This test examines access to semantic information under a time constraint.[19] Patients were instructed to name as many words beginning with the letter "F" as they could in 1 minute. People's names and proper nouns were not permitted. The letters "A" and "S" were then presented successively, with 1 minute allowed for each letter. The score was the combined number of appropriate words produced in 3 minutes.

Raven's Progressive Matrices. This test measures visuospatial reasoning. Patients are presented with a spatial pattern problem with one part removed and four pictured inserts of potential matches, of which only one contains the correct pattern.[20] The patient has to select the correct piece to match the original spatial patterns. The patterns become increasingly complex over trials. The performance score is the number correctly identified.

Token Test. This test measures verbal comprehension of receptive language and response to commands in series of increasing complexity.[21]

Boston Naming Test. This test measures the ability to retrieve the name of line drawings of common objects of varying familiarity. The ability to access semantic information is assessed, and the number of correctly named objects is the outcome measure.[22]

Block Design. This test, part of the Wechsler Adult Intelligence Scale, examines the presence of constructional, executive, and perceptual abilities. Patients are presented with red and white blocks and are asked to construct replicas of printed designs. Accuracy of production is the outcome measure.[17] Time to completion was not considered in the final score.

Purdue Pegboard Test. This test assesses manipula-

Table 1 *Demographic and psychiatric findings*

	Control group	Depression group	Apathy group	Depression–apathy group
No. of patients	52	31	29	72
Age, mean y	70.0 (6.8)	70.8 (10.2)	72.0 (7.8)	71.1 (6.6)
Gender, % female	61	61	59	68
Education, mean y	11.6 (6.8)	10.2 (5.2)	12.3 (5.7)	10.7 (4.9)
Mini-Mental State Examination, mean scores	23.1 (4.2)	23.5 (4.1)	22.5 (4.6)	21.6 (5.7)
Hamilton Depression Scale, mean*	4.2 (3.9)	11.3 (5.4)	5.1 (5.4)	14.6 (7.9)
Apathy Scale, mean†	6.0 (3.8)	7.3 (3.6)	21.9 (6.5)	23.9 (7.0)
Overt Aggression Scale	0.4 (0.7)	0.8 (1.2)	0.9 (2.2)	0.5 (1.2)
Dementia Psychosis Scale	0.9 (2.1)	1.8 (2.6)	1.3 (1.8)	1.3 (2.7)
Probable AD (%)	62	67	73	78
Clinical Dementia Rating = 0.5 (%)	38	33	27	22

SDs are in parentheses.

* $F(3,181) = 34.1$; $p < 0.0001$.
† $F(3,181) = 135.6$; $p < 0.0001$.

tive dexterity. The apparatus consists of a board containing two parallel rows of 25 holes each and 50 metal pegs. Patients are asked to take the pegs with the dominant (e.g., right) hand and place them as quickly as possible in the right column of holes during a 30-second period. The same procedure is repeated with the nondominant hand, and the score is the number of pins inserted in the time period for each hand.[23]

Statistical analysis. Statistical analysis was carried out using means and SDs, analysis of variance (ANOVA), and post-hoc *t*-tests. Frequency distributions were calculated using chi-square tests and a Yates' correction for expected cell sizes of less than 5. All *p* values are two-tailed.

Results. *Demographic and psychiatric findings.* Our sample was divided into groups with apathy or depression based on the following diagnostic scheme: patients meeting the DSM-IV criteria of either major depression or dysthymia were included in the depressed group, whereas patients scoring more than 2 SD of the mean apathy scale score for an age-comparable normal control group (cutoff score = 14 points, as reported in a previous publication[2]) were considered apathetic. Four groups were thus construed: 1) apathy without depression (apathy-only group; n = 29); 2) depression without apathy (depression-only group; n = 31; 25 with dysthymia and 6 with major depression); 3) both depression and apathy (n = 72; 47 with dysthymia and 25 with major depression); and 4) neither apathy nor depression (control group; n = 52). No significant between-group differences were found for age, sex, years of education, MMSE scores, and scores of agitation and delusions (table 1).

Neuropsychological findings. A multivariate analysis of covariance for the neuropsychological variables showed a significant overall effect (Wilks' lambda = 0.65, $p < 0.05$). On individual comparisons, patients with apathy only had significantly lower scores than patients without apathy (with or without depression) on the following tests: Buschke-Total Recall ($F[3,169] = 3.34$, $p < 0.05$; apathy only versus depression only $p < 0.01$, apathy only versus control group $p < 0.05$) and the Boston Naming Test ($F[3,166] = 3.54$; $p < 0.01$; apathy only versus depression only $p < 0.05$; apathy only versus control group $p < 0.05$); and significantly lower scores than patients with depression only on the Buschke-Delayed Recall ($F[3,169] = 3.68$; $p < 0.01$). Patients with apathy (with or without depression) had significantly lower scores than patients without apathy (with or without depression) on the Wisconsin Card Sorting Test ($F[3,161] = 3.29$; $p < 0.05$) and verbal fluency ($F[3,168] = 4.51$; $p < 0.005$), and significantly lower scores than the control group on the Purdue Pegboard Test ($F[3,165] = 5.22$; $p < 0.001$). Finally, patients with apathy and depression had significantly lower scores than the other three groups on the Raven's Progressive Matrices ($F[3,165] = 3.77$, $p < 0.01$). No significant differences on any neuropsychological test were found between patients with depression only and the control group (table 2).

Discussion. This study examined neuropsychological correlates of apathy in AD, and there were several important findings. First, patients with AD with apathy had significantly lower scores on tests of verbal memory, naming, set shifting, and verbal fluency than patients with AD without apathy. Second, the copresentation of both depression and apathy did not result in cognitive deficits greater than those for apathy alone, except on a test of abstract thinking, where patients with both apathy and depression had significantly lower scores than patients with apathy only. Finally, depression in the absence of apathy was not associated with more severe cognitive impairments, when depressed patients with AD are compared with patients with AD with neither apathy nor depression.

Before offering further commentary, several limitations of our study should be pointed out. First, we did not divide our sample of depressed patients with AD into those with major and dysthymic depression, and whether a specific type of depression was associated with more severe cognitive impairments could

Table 2 *Neuropsychological findings*

	Control group	Depression group	Apathy group	Depression–apathy group
Buschke Total Recall*	56.3 (18.2)	59.1 (18.7)	46.5 (18.3)	50.1 (18.2)
Buschke Delayed Recall†	3.0 (2.7)	4.2 (3.1)	2.0 (2.2)	2.7 (2.8)
Boston Naming Test*	16.0 (3.5)	16.0 (4.0)	13.5 (5.0)	14.0 (4.6)
Wisconsin Card Sorting Test (categ.)‡	3.3 (2.2)	3.7 (2.0)	2.4 (1.9)	2.4 (2.4)
Verbal Fluency‡	35.0 (11.3)	35.4 (9.4)	29.4 (10.5)	29.0 (10.9)
Raven's Progressive Matrices§	52.0 (32.0)	47.9 (33.0)	51.3 (34.3)	33.2 (33.6)
Purdue Pegboard Test¶	21.2 (5.3)	20.3 (5.6)	18.0 (6.5)	17.0 (6.2)
Block Design	4.1 (2.3)	3.8 (2.5)	3.7 (2.4)	3.0 (2.4)
Similarities	13.0 (6.5)	12.0 (5.6)	11.2 (6.8)	10.5 (7.3)
Benton Visual Retention Test	5.9 (2.1)	6.2 (2.3)	5.6 (1.9)	5.6 (2.1)
Token Test	21.1 (3.7)	20.5 (5.0)	19.7 (6.2)	18.7 (6.9)
Digits Forward	5.3 (1.0)	5.0 (0.7)	5.0 (1.0)	5.2 (1.4)
Digits Backward	3.5 (1.0)	3.5 (1.1)	3.5 (1.0)	3.3 (1.2)

SDs are in parentheses.

* Apathy only < control and depression groups ($p < 0.05$).
† Apathy only < depression only ($p < 0.01$).
‡ Apathy groups < no apathy groups ($p < 0.05$).
§ Depression–apathy < other three groups ($p < 0.01$).
¶ Apathy groups < control group ($p < 0.001$).

not be examined. However, in a recent study we could not find significant differences in cognitive function between patients with AD with major depression, dysthymia, or no depression.[1] Second, our study included patients with questionable dementia (i.e., patients with memory deficits on cognitive testing who did not meet the full criteria for probable AD), and whether all these patients will eventually meet the full criteria for AD is unknown. However, several studies demonstrated that most patients with questionable dementia do progress to the phase of overt dementia. [6] Moreover, in our study the proportion of patients with questionable dementia was similar in all four groups, and the inclusion of patients with mild cognitive impairments may have protected from lack of significant between-group differences due to a "floor effect." Another limitation is that we do not have neuropathologic confirmation of our clinical diagnoses. Thus, whether our patients with apathy had dementia with Lewy bodies (which was found to be significantly associated with more severe frontal dysfunction than classic AD)[24] cannot be ruled out. Finally, we measured the severity of depression with the HAM-D, which may potentially include apathy-related items. However, mean HAM-D scores for AD apathy-only and AD control groups were similar, suggesting that HAM-D scores were not influenced by the severity of apathy.

In a study that examined the neuropsychological correlates of apathy in patients with PD, we found that apathy (with or without depression) was associated with significantly more severe deficits on tasks of verbal fluency and verbal memory.[25] Similar to our current findings, patients with both apathy and depression did not show more severe cognitive deficits than patients with apathy only.[25] We suggested that apathy in PD may be akin to the concept of bradyphrenia, which was defined by Rogers[26] as a slowing of cognitive processing associated with impairment of concentration. In a preliminary study of the cognitive correlates of apathy in a smaller sample of patients with AD, apathy was significantly associated with more severe memory deficits.[2] The current study assessed a larger sample of patients with AD, and not only replicated the association between apathy and memory deficits, but showed that patients with AD with apathy (with or without depression) also had significantly more severe deficits on tasks of naming, verbal fluency, and set shifting, thus demonstrating a profile of cognitive deficits similar to those we found previously in patients with PD with apathy. However, apathy in AD may also correlate with overall cognitive disability, and future studies should examine the specificity of the current findings.

Verbal fluency, set shifting, and abstract thinking have all been considered cognitive abilities related to frontal lobe functioning.[27] Apathy has been attributed to disruption of corticosubcortical circuits involving the basal ganglia and the frontal lobes.[2] Cummings[27] suggested that lesions to the dorsolateral frontal cortex, anterior cingulate, or globus pallidus may produce both apathy and deficits on frontal lobe–related tasks, such as verbal fluency and set shifting. Several recent findings validate this hypothesis: first, we demonstrated that patients with stroke with apathetic behavior had a significantly

higher frequency of lesions involving the globus pallidus compared with patients with stroke without apathy.[11] Second, in both AD and PD, apathy was significantly associated with relatively more severe deficits on frontal lobe–related tasks.[25] Third, we found that apathy in AD was significantly associated with more severe extrapyramidal signs compared with patients with AD without apathy, which further suggests disruption of basal ganglia structures in patients with AD with apathy.[28]

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