

Neuropathology of older persons without cognitive impairment from two community-based studies

D.A. Bennett, MD; J.A. Schneider, MD; Z. Arvanitakis, MD; J.F. Kelly, MD; N.T. Aggarwal, MD; R.C. Shah, MD; and R.S. Wilson, PhD

Abstract—Objective: To examine the relation of National Institute on Aging–Reagan (NIA–Reagan) neuropathologic criteria of Alzheimer disease (AD) to level of cognitive function in persons without dementia or mild cognitive impairment (MCI). **Methods:** More than 2,000 persons without dementia participating in the Religious Orders Study or the Memory and Aging Project agreed to annual detailed clinical evaluation and brain donation. The studies had 19 neuropsychological performance tests in common that assessed five cognitive domains, including episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability. A total of 134 persons without cognitive impairment died and underwent brain autopsy and postmortem assessment for AD pathology using NIA–Reagan neuropathologic criteria for AD, cerebral infarctions, and Lewy bodies. Linear regression was used to examine the relation of AD pathology to level of cognitive function proximate to death. **Results:** Two (1.5%) persons met NIA–Reagan criteria for high likelihood AD, and 48 (35.8%) met criteria for intermediate likelihood; 29 (21.6%) had cerebral infarctions, and 18 (13.4%) had Lewy bodies. The mean Mini-Mental State Examination score proximate to death was 28.2 for those meeting high or intermediate likelihood AD by NIA–Reagan criteria and 28.4 for those not meeting criteria. In linear regression models adjusted for age, sex, and education, persons meeting criteria for intermediate or high likelihood AD scored about a quarter standard unit lower on tests of episodic memory ($p = 0.01$). There were no significant differences in any other cognitive domain. **Conclusions:** Alzheimer disease pathology can be found in the brains of older persons without dementia or mild cognitive impairment and is related to subtle changes in episodic memory.

NEUROLOGY 2006;66:1837–1844

It has long been known that older persons without dementia accumulate neuropathologic changes of Alzheimer disease (AD).¹ This observation has been replicated by numerous groups over the past 20 years.^{2–13} However, the extent to which the presence of AD pathology in persons without cognitive impairment is associated with level of cognition has not been extensively investigated. We are aware of only three studies that have examined the relation of AD pathology to cognition in persons without dementia.^{6,14,15} However, two of these studies did not exclude persons with mild cognitive impairment (MCI).^{6,14} Since there is increasing evidence that persons with MCI often have AD pathology,^{13,16,17} it would be of interest to examine the relation of AD pathology to cognition in persons without dementia or MCI.

We are conducting two large, community-based, longitudinal clinical-pathologic studies of aging and

AD: The Religious Orders Study¹³ and the Rush Memory and Aging Project.¹⁸ Both studies enroll persons without dementia who must agree to annual detailed clinical evaluation and organ donation at the time of death. The studies have identical diagnostic procedures and 19 cognitive performance tests in common. To date, 134 persons without cognitive impairment close to the time of death have died and had a complete postmortem examination. This provided us with an opportunity to examine the relation of AD pathology to level of function in different cognitive abilities in a large number of persons.

Methods. Religious Orders Study. Participants were older Catholic nuns, priests, and brothers without known dementia who agreed to annual clinical evaluations and signed an informed consent and an Anatomic Gift Act donating their brains to Rush investigators at the time of death.¹³ The study was approved by the Institutional Review Board of Rush University Medical Center. Subjects come from about 40 groups in 12 states across the

Editorial, see page 1801

From Rush Alzheimer's Disease Center (D.A.B., J.A.S., Z.A., J.F.K., N.T.A., R.C.S., R.S.W.) and Departments of Neurological Sciences (D.A.B., J.A.S., Z.A., N.T.A., R.S.W.), Pathology (Neuropathology) (J.A.S.), Internal Medicine (J.F.K.), Family Practice (R.C.S.), and Behavioral Sciences (R.S.W.), Rush University Medical Center, Chicago, IL.

Supported by National Institute on Aging grants P30AG10161, R01AG15819, R01AG17917, K08AG00849, and K23AG23675.

Disclosure: The authors report no conflicts of interest.

Received May 19, 2005. Accepted in final form February 23, 2006.

Address correspondence and reprint requests to Dr. David A. Bennett, Rush Alzheimer's Disease Center, 600 South Paulina, Suite 1028, Chicago, IL 60612; e-mail: dbennett@rush.edu

country. The study has a rolling admission and 1,056 persons completed a uniform structured baseline clinical evaluation between January 1994 and November 2005. Follow-up evaluations, identical in all essential details, were performed annually by examiners blinded to previously collected data. Participation in the annual follow-up evaluations exceeds 95% of survivors. The autopsy rate exceeds 90% with 314 autopsies of 333 deaths, including 106 autopsies of persons without cognitive impairment of 113 deaths. The neuropathologic evaluation was completed on the first 98 of these persons at the time of these analyses.

Rush Memory and Aging Project. Participants were older community-dwelling persons without known dementia who agreed to annual clinical evaluations and signed an informed consent and an Anatomic Gift Act donating their brains, spinal cords, and selected nerves and muscles to Rush investigators at the time of death.¹⁸ The study was approved by the Institutional Review Board of Rush University Medical Center. Subjects come from about 40 retirement communities and senior subsidized housing facilities across northeastern Illinois. The study has a rolling admission and 1,071 persons completed a uniform structured baseline clinical evaluation between October 1997 and November 2005. Follow-up evaluations, identical in all essential details, were performed annually by examiners blinded to previously collected data. Participation in the annual follow-up evaluations exceeds 90% of survivors. The autopsy rate exceeds 75% with 118 autopsies of 152 deaths, including 39 autopsies of persons without cognitive impairment of 50 deaths. The neuropathologic evaluation was completed on the first 36 of these persons at the time of these analyses.

Clinical evaluation procedures. All subjects underwent a uniform, structured, clinical evaluation that included a self-report medical history obtained by a trained research technician and nurse, a neurologic examination by a trained nurse, and cognitive function testing by a trained neuropsychological test technician as previously reported.^{18,19} Years of formal education, lifetime and current occupation, and history of change in memory and other cognitive abilities relative to 10 years earlier were documented. History of stroke, Parkinson disease (PD), depression, head trauma, and other conditions with the potential to cause cognitive impairment were obtained by structured questionnaire. All medications used in the prior 2 weeks were directly inspected and recorded. A complete neurologic examination was performed by trained nurses who documented evidence of stroke and parkinsonian signs.

Diagnostic classification. Diagnostic classification of dementia and AD proceeded in a three-step process combining mechanical decision rules and clinical judgment as previously described.^{18,19} First, because performance on neuropsychological tests is strongly associated with level of education, we developed cutoff scores for rating impairment on 11 commonly used tests and adjusted them for four educational strata. The adjustments were based on review of the literature and extensive pilot testing. Second, a neuropsychologist, blinded to subject age, sex, and race, reviewed the results of the computer-generated impairment ratings, the other cognitive tests, and selected clinical data including education, occupation, sensory and motor deficits, and effort, and rendered a clinical judgment regarding the presence of cognitive impairment, dementia, and AD. Third, a clinician with expertise in the evaluation of older persons with cognitive impairment reviewed all available data, including the raw neuropsychological test results and the neuropsychologist's impression, briefly interviewed and examined the participant, and rendered a clinical judgment regarding meaningful cognitive decline, evidence of stroke, PD, depression, and other common conditions and whether they were contributing to dementia. Selected summary information from the evaluation performed by the nurses and research assistants, the neuropsychologist's opinion of cognitive impairment, and the clinician's selected clinical judgments were entered into a laptop computer and an actuarial decision tree generated seven clinical diagnoses. Dementia required meaningful decline in cognitive function with impairment in multiple areas of cognition, and AD required dementia and progressive loss of episodic memory based on the criteria of the joint working group of the National Institute of Neurologic and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA).²⁰ MCI referred to those persons rated as impaired on cognitive testing by the neuropsychologist but not demented by

the examining clinician as previously described.^{18,19} Stroke was defined as a focal neurologic deficit lasting 24 hours based on a structured clinical history, supported by a neurologic examination, and subtyped according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST).²¹ A diagnosis of cognitive impairment related to stroke was made according to the National Institute of Neurologic Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia, and was based on a temporal relation of stroke to impaired cognition by history, and the pattern of focal findings on neurologic examination, except that brain scans were not routinely available.²² Parkinsonism required two or more cardinal parkinsonian signs, and PD required parkinsonism and either bradykinesia or resting tremor as recommended by the Core Assessment Program for Intracerebral Transplantation (CAPIT).²³ A diagnosis of PD was further supported by a history of response to levodopa or the examining physician's opinion that the individual would likely respond to dopaminergic agents. Finally, major depression was based on Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R criteria supported by a subset of items from the Diagnostic Interview Schedule.²⁴ Other more rare conditions that cause dementia among older persons in the community (e.g., Lewy body disease, frontotemporal dementia, symptomatic hydrocephalus) were made by clinical judgment. Difficult cases were subjected to case conferencing with a neuropsychologist and neurologist.

At the time of death, all available clinical data were reviewed by a neurologist and a summary diagnostic opinion was rendered regarding the most likely clinical diagnosis at the time of death. Difficult cases were subjected to case conferencing with a second neurologist and a neuropsychologist. Persons without cognitive impairment, i.e., those without dementia or MCI, are the subject of the present analyses.

Cognitive performance tests. The two studies had 19 cognitive performance tests in common (including some tests for which only subsets of items were in common). The tests were selected to assess a broad range of cognitive abilities commonly impaired in older persons without dementia. One test, the Mini-Mental State Examination (MMSE),²⁵ was used to describe the cohort but not used in the composite scores, and one test, Complex Ideational Material, was used for diagnostic classification purposes only. The remaining 17 tests were used to assess five domains of cognitive function¹⁷⁻³¹ as previously described.^{18,19,32,33} Briefly, episodic memory was evaluated with seven tests including immediate and delayed recall of story A from Logical Memory and of the East Boston Story, and Word List Memory, Recall, and Recognition from the Consortium to Establish a Registry for AD (CERAD). Semantic memory was assessed with three tests including a 15-item version of the Boston Naming Test, Verbal Fluency, and a 10-item reading test. Working memory was also assessed with three tests, including Digit Span Forward and Backward and Digit Ordering. There were two tests of perceptual speed, including Symbol Digit Modalities Test, and Number Comparison. Finally, there were two tests of visuospatial ability, including a 15-item version of Judgment of Line Orientation and a 9-item version of Standard Progressive Matrices.

The tests from each area of cognition were converted to z scores, using the mean and SD from the baseline evaluation of all participants, and averaged to yield summary measures of each area of cognitive function as previously described.^{18,19,32,33} Summary measures have the advantage of minimizing floor and ceiling effects, and other sources of random variability. A valid summary score required that at least half of the component scores be present.

Brain autopsy procedures. Brain autopsies were performed at Rush and 11 predetermined sites across the United States for nearly all cases. Following drainage of CSF, brains were removed and weighed. The brainstem and cerebellum were removed. The cerebral hemispheres were placed in a Plexiglas jig and cut coronally into 1 cm slabs. Slabs from one hemisphere were fixed for 3 to 21 days in 4% paraformaldehyde at which time they underwent complete macroscopic evaluation and dissection of diagnostic blocks, including midfrontal, superior or middle temporal, inferior parietal cortex, entorhinal cortex, hippocampus, anterior basal ganglia, anterior thalamus, and substantia nigra. These were embedded in paraffin, cut into 6 μ m sections, and mounted on glass slides. Brain autopsy procedures have been described previously.^{13,34}

Pathologic diagnoses of AD. Bielschowsky silver stain was used to visualize neuritic plaques, diffuse plaques, and neurofibrillary tangles in the frontal, temporal, parietal, entorhinal cortex, and the hippocampus. Neuropathologic diagnoses were made by a board-certified neuropathologist blinded to age and all clinical data. A neuropathologic diagnosis was made of no AD, possible AD, probable AD, or definite AD based on semiquantitative estimates of neuritic plaque density as recommended by CERAD.³⁵ The neuropathologic diagnosis of AD by CERAD was modified to be implemented without adjustment for age and clinical diagnosis, as previously reported.¹³ Thus, a CERAD neuropathologic diagnosis of AD required moderate (CERAD probable AD) or frequent neuritic plaques (CERAD definite AD) in one or more neocortical regions. Braak stages 0 through VI were based upon the distribution and severity of neurofibrillary tangle pathology.³⁶ All cases also received a neuropathologic diagnosis of no AD, low likelihood AD, intermediate likelihood AD, or high likelihood AD based on the Braak score for neurofibrillary pathology and the CERAD estimate of neuritic plaques as recommended by the National Institute on Aging (NIA)-Reagan criteria.³⁷ To obtain a pathologic diagnosis of AD by Reagan criteria required either an intermediate likelihood AD (i.e., at least Braak stage 3 or 4 and CERAD moderate plaques) or a high likelihood (i.e., at least Braak stage 5 or 6 and CERAD frequent plaques). Details of the pathologic diagnoses of AD have been described previously.^{13,34}

Pathologic diagnoses of cerebral infarcts and Lewy body disease. For each brain we identified the age, volume (in mm³), side, and location of all macroscopic cerebral infarctions as previously reported.^{13,34} Lewy bodies were identified with antibodies to alpha-synuclein as previously described¹³ and recorded as nigral predominant, limbic type, or neocortical type as recommended by the Report of the Consortium on DLB International Workshop.³⁸

Data analysis. We first present descriptive information separately for subjects from the Religious Orders Study and the Memory and Aging Project. Because the test scores were very similar we combined the two cohorts for further analyses. We then present descriptive information for persons who do and do not meet NIA-Reagan pathologic criteria for AD. Finally, linear regression was used to examine the relation of the presence of NIA-Reagan neuropathologic criteria to level of function for each cognitive system. All models controlled for age, sex, and education. Additional analyses were performed that controlled for cerebral infarctions and Lewy bodies. Analyses were performed in SAS,³⁹ and model validation was carried out using analytic and graphical techniques.

Results. A total of 134 persons did not have cognitive impairment proximate to death, including 98 persons from the Religious Orders Study and 36 persons from the Memory and Aging Project. Persons in the Memory and Aging Project were 3 years older at death, more likely to be female, and had about 5 fewer years of education (table 1). The MMSE scores were greater than 28 in both studies (see table 1). Similarly, the groups had comparable scores on the remaining 18 cognitive tests, with Religious Orders Study participants having marginally higher scores on some tests but slightly lower scores on others.

Pathologic diagnoses in the Religious Orders Study and Memory and Aging Project. The figure shows the distribution of persons meeting the modified CERAD neuropathologic criteria for AD, Braak stage, and NIA-Reagan neuropathologic criteria for AD separately for each study. About 45% of both groups met criteria for probable or definite AD (table 2). About a quarter of persons in both studies were Braak Stage IV. Five percent of persons in the Religious Orders Study were Braak Stage V and none were Braak Stage VI. None of the subjects in the Memory and Aging Project were Braak Stage V or VI. Only two subjects, both in the Religious Orders Study, met criteria for high likelihood AD. However, about a third of subjects in both studies met criteria for intermediate likelihood AD.

Cerebral infarctions were present in nearly a quarter of

Table 1 Selected demographic and clinical characteristics of subjects without cognitive impairment in the Religious Orders Study (ROS) and the Memory and Aging Project (MAP)

Characteristics	ROS	MAP
N	98	36
Age at death, y, mean (SD)	82.5 (6.5)	85.4 (5.6)
Male, n (%)	49 (50.0)	13 (36.1)
Non-Hispanic white, n (%)	96 (98.0)	34 (94.4)
Education, y, mean (SD)	18.6 (3.5)	13.6 (4.0)
Cognitive function tests, mean (SD)		
MMSE proximate to death	28.8 (1.4)	28.6 (1.5)
Episodic memory		
Word List Memory	18.1 (3.9)	17.7 (4.2)
Word List Recall	5.8 (1.9)	6.0 (1.8)
Word List recognition	9.8 (0.8)	9.9 (0.3)
East Boston Story Immediate	9.9 (1.6)	9.4 (1.8)
East Boston Story Delayed	9.4 (1.7)	9.1 (1.6)
Logical Memory Ia Immediate	13.8 (3.6)	12.4 (4.3)
Logical Memory IIa Delayed	12.4 (3.7)	10.8 (3.6)
Semantic memory		
Boston Naming Test	13.7 (1.1)	14.1 (1.2)
Verbal Fluency	31.0 (8.7)	31.9 (6.7)
Reading test	8.5 (1.8)	8.1 (2.0)
Complex Ideational Material	7.7 (0.5)	7.8 (0.5)
Working Memory		
Digit Span Forward	7.9 (1.7)	8.9 (2.1)
Digit Span Backward	6.1 (1.8)	7.1 (2.4)
Digit Ordering	7.4 (1.6)	7.2 (2.0)
Perceptual speed		
Symbol Digit Modalities Test	35.2 (8.3)	37.4 (10.0)
Number Comparison	22.7 (6.6)	22.8 (10.1)
Visuospatial Ability		
Judgment of Line Orientation	10.7 (2.8)	10.7 (2.8)
Standard Progressive Matrices	7.7 (1.5)	7.7 (1.5)

Religious Orders Study and nearly 15% of Memory and Aging Project participants (see table 2). Finally, Lewy bodies were present in just over 15% of Religious Orders Study and just over 10% of Memory and Aging Project participants (see table 2). These data are provided for descriptive purposes. There were too few persons with infarcts and Lewy bodies for meaningful correlations with cognition.

Relation of NIA-Reagan pathologic diagnosis to level of cognitive function. Because the clinical and pathologic findings in the two studies were similar, we combined data from both studies for analyses in order to increase study power. Fifty persons met NIA-Reagan neuropathologic criteria for high (n = 2) or intermediate (n = 48) likelihood AD, whereas 84 persons did not. Persons meeting neuropathologic criteria for AD were more than 4 years older (table 3). The MMSE scores of persons with and without a pathologic diagnosis of AD were nearly identical and

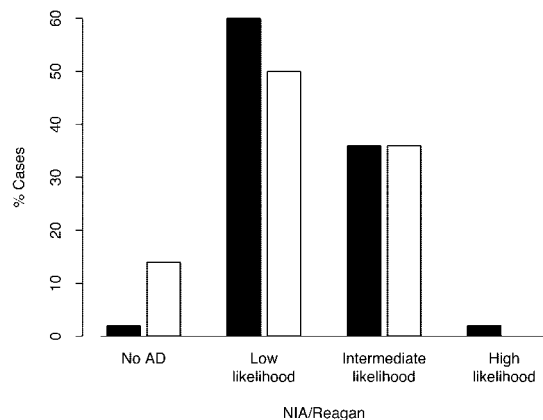
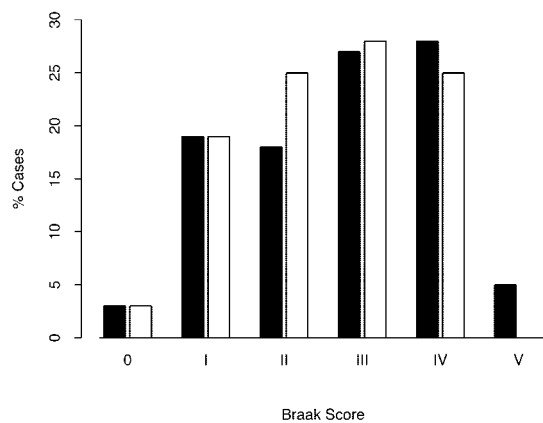
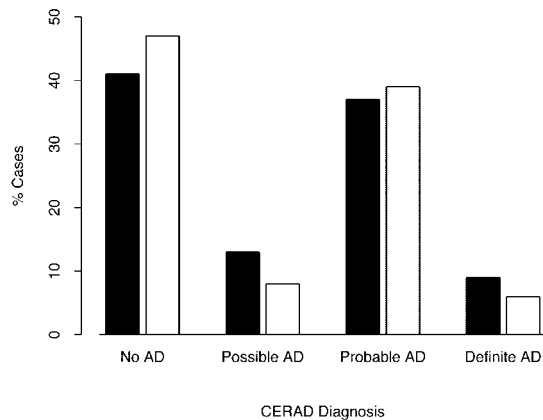


Figure. Barplots of Alzheimer disease pathology in persons without cognitive impairment; cases indicate percent of persons in each pathologic group in the Religious Orders Study (black) and Memory and Aging Project (white).

greater than 28 for both groups. Persons meeting NIA-Reagan criteria performed lower on 15 of the cognitive tests, the same on one, and higher on two (see table 3). The magnitude of these differences was quite small with a raw score differential of more than a point for only six tests, and more than two points for only two tests.

We next used linear regression to examine the association of the neuropathologic diagnosis of AD by NIA-Reagan criteria to performance on five different cognitive abilities, in analyses that controlled for age, sex, and education. Persons meeting NIA-Reagan criteria for intermediate or

Table 2 Selected pathologic characteristics of subjects without cognitive impairment in the Religious Orders Study (ROS) and the Memory and Aging Project (MAP)

Pathologic characteristics	ROS	MAP
CERAD AD		
Not present	40 (40.8)	17 (47.2)
Possible	13 (13.3)	3 (8.3)
Probable	36 (36.7)	14 (38.9)
Definite	9 (9.2)	2 (5.6)
Braak Score		
0	3 (3.1)	1 (2.8)
I	19 (19.4)	7 (19.4)
II	18 (18.4)	9 (25.0)
III	26 (26.5)	10 (27.8)
IV	27 (27.6)	9 (25.0)
V	5 (5.1)	0
VI	0	0
NIA-Reagan AD		
Not present	2 (2.0)	5 (13.9)
Low likelihood	59 (60.2)	18 (50.0)
Intermediate likelihood	35 (35.7)	13 (36.1)
High likelihood	2 (2.0)	0
Infarcts		
Not present	75 (76.5)	30 (83.3)
Present	23 (23.5)	6 (14.7)
Lewy bodies		
Not present	84 (83.6)	32 (88.9)
Nigral	7 (7.1)	1 (2.8)
Limbic	5 (5.1)	2 (5.6)
Neocortical	2 (2.0)	1 (2.8)

Values are n (%).

CERAD = Consortium to Establish a Registry for Alzheimer's Disease; AD = Alzheimer disease.

high likelihood AD scored about a quarter standard unit lower on episodic memory ($p = 0.01$) (table 4, Model 1). They also scored between 10% and 15% standard unit lower on tests of semantic memory and working memory, but these differences were not significant. The results were unchanged in analyses that controlled for cerebral infarctions and Lewy bodies (table 4, Model 2).

Discussion. We documented AD pathologic diagnoses in a large number of persons without dementia or MCI and examined its relation to cognitive function. We found that high likelihood AD by NIA-Reagan criteria was extremely rare in persons without cognitive impairment. However, more than a third met criteria for intermediate likelihood AD. Further, we found that the presence of sufficient AD pathology to meet criteria for intermediate or high likelihood AD by NIA-Reagan criteria was associated with subtle deficits in cognitive function, especially on tests of episodic memory. These data suggest that

Table 3 Selected demographic and clinical characteristics of subjects with and without pathologic Alzheimer disease (AD) by NIA-Reagan

Characteristics	NIA-Reagan pathologic AD	
	No	Yes
N	84	50
Age at death, y, mean (SD)	81.7 (6.7)	86.0 (4.8)
Male, n (%)	40 (47.6)	22 (44.0)
Non-Hispanic white, n (%)	81 (96.4)	49 (98.0)
Education, y, mean (SD)	17.4 (4.3)	17.0 (4.2)
Cognitive function tests, mean (SD)		
MMSE proximate to death	28.4 (1.4)	28.2 (1.6)
Episodic memory		
Word List Memory	18.6 (4.0)	16.9 (3.7)
Word List Recall	6.3 (1.8)	5.2 (1.8)
Word List Recognition	9.9 (0.4)	9.7 (1.0)
East Boston Story Immediate	9.9 (1.7)	9.5 (1.6)
East Boston Story Delayed	9.5 (1.5)	9.0 (2.0)
Logical Memory Ia Immediate	13.8 (3.8)	12.7 (3.9)
Logical Memory IIa Delayed	12.6 (3.9)	10.9 (3.2)
Semantic memory		
Boston Naming Test	14.0 (1.1)	13.5 (1.2)
Verbal Fluency	32.4 (8.1)	29.3 (7.9)
Reading test	8.4 (2.0)	8.3 (1.7)
Complex Ideational Material	7.7 (0.5)	7.7 (0.5)
Working Memory		
Digit Span Forward	8.2 (1.9)	8.1 (1.8)
Digit Span Backward	6.7 (2.1)	5.9 (1.9)
Digit Ordering	7.4 (2.0)	7.3 (1.1)
Perceptual Speed		
Symbol Digit Modalities Test	37.5 (8.7)	32.8 (8.3)
Number Comparison	22.4 (8.1)	23.2 (7.0)
Visuospatial Ability		
Judgment of Line Orientation	9.7 (3.0)	10.3 (2.6)
Standard Progressive Matrices	7.5 (1.5)	7.4 (1.7)

even slight impairment of episodic memory in older persons may signify the presence of pathology rather than representing a normal consequence of aging.

It has long been known that older persons without obvious dementia can have the pathology of AD. In the seminal observations on the brains of older persons without dementia, Tomlinson and colleagues observed cases with moderate senile plaques and rare neurofibrillary tangles in the neocortex.¹ This observation has been replicated in numerous studies by investigators from AD research centers across the county over the past 20 years.²⁻¹³ Table 5 compares findings from the Religious Orders Study and Memory and Aging Project to the results of several other studies that also provided data on CERAD or NIA-Reagan neuropathologic criteria. We found that

Table 4 Linear regression models examining level of cognition as a function of NIA-Reagan pathologic diagnosis

	NIA-Reagan pathologic AD		p Value	
	No	Yes	Model 1	Model 2
Episodic memory	0.44 (0.45)	0.18 (0.46)	0.01	0.004
Semantic memory	0.11 (0.47)	-0.05 (0.50)	0.16	0.17
Working memory	0.18 (0.71)	0.00 (0.58)	0.12	0.12
Perceptual speed	-0.15 (0.92)	-0.27 (0.77)	0.62	0.86
Visuospatial ability	0.03 (0.62)	0.12 (0.59)	0.26	0.85

Model 1 controls for age, sex, and education. Model 2 controls for age, sex, education, cerebral infarctions, and Lewy bodies. Values are mean (SD).

AD = Alzheimer disease.

about a third of persons met NIA-Reagan criteria for intermediate or high likelihood AD. This was similar to one recent study,¹⁵ much lower than another,⁵ but somewhat higher than three other studies.^{6,8,12} The results were similar when comparing findings for CERAD neuropathologic criteria for AD.

Most of the prior studies of AD pathology in persons without dementia were conducted prior to the wide recognition of MCI.⁴⁰ Since there is increasing evidence that persons with MCI often have the pathology of AD,^{13,16,17} it is of interest to know how often persons without dementia or MCI meet neuropathologic criteria for AD. We are aware of only one study that provided data on persons without dementia or MCI.¹⁵ Ten of 41 (24.4%) persons with a Clinical Dementia Rating (CDR) score of 0, similar to no cognitive impairment, met NIA-Reagan criteria for high likelihood AD and 2 (4.9%) met criteria for intermediate likelihood AD,¹⁵ consistent with the results of this study.

The extent to which AD pathology is related to cognitive function in persons without dementia or MCI has not been extensively investigated. We are aware of only three studies that examined the relation of AD pathology to cognition in persons without dementia.^{6,14,15} One study reported a trend for differences on tests of memory.⁶ However, the study could only analyze data on 12 persons. A second study reported slightly lower performance on immediate paragraph recall and delayed recall in persons meeting the NIA-Reagan criteria for AD compared to persons not meeting the criteria.¹⁴ Since neither of these studies excluded persons with MCI, it is possible that the presence of persons with MCI in the analyses affected the results. That study, restricted to persons with CDR = 0, also found subtle cognitive deficits in persons meeting NIA-Reagan criteria. Specifically, they performed worse on a brief mental status test, showed a smaller practice effect on memory tests over time, and failed to benefit from practice on language test.¹⁵

Currently, AD is defined as progressive dementia

Table 5 Prospective studies of persons without dementia meeting CERAD or NIA-Reagan neuropathologic criteria for AD

Study/reference	Autopsy		Age, y	MMSE (range)	CERAD, %	NIA-Reagan, %	Infarcts, %	LB
	N	Rate, %						
ROS	98	94	85	28 (24–30)	46	38	23	14
MAP	36	78	85	28 (24–30)	44	36	17	11
8	59	86	84	28 (24–30)	25	12	36	7
11	109	<50	85	—	33	—	>33	9
9	11	32	>80	—	45	—	—	—
12	39	20	85	28 (24–30)	18	10	46	13
15	41	—	85	—	34	29	39	7
6*	31	—	86	28 (24–30)	45	23	10	10
10	9	—	92	—	44	—	—	—
5†	31	86	85	—	65	65	—	—
7‡	18	—	84	—	22	—	—	—

* MMSE available for 12 Duke participants.

† 86% autopsy rate for Nun Study; NIA-Reagan includes some unclassified individuals; 71 (60%) autopsies excluded from analyses including persons with infarcts or Lewy bodies.

‡ Only a third prospectively evaluated; subjects excluded if infarcts, Lewy bodies, or other pathologies were present.

CERAD = probable or definite Alzheimer disease (AD) by Consortium to Establish a Registry for Alzheimer's Disease neuropathologic criteria or something roughly equivalent (e.g., counts or estimates of neuritic plaques); NIA-Reagan = intermediate or high likelihood AD; MMSE = Mini-Mental State Examination; LB = Lewy bodies; ROS = Religious Orders Study; MAP = Memory and Aging Project.

during life²⁰ and the presence of a significant density of neuritic plaques and neurofibrillary tangles at autopsy.³⁷ However, it is becoming increasingly clear that large numbers of persons with MCI or without clinically evident cognitive impairment meet neuropathologic criteria for AD. Several terms have been used to describe these persons, including pathologic aging,⁴¹ preclinical AD,^{6,14,15} and subclinical AD.^{42,43} It is now well established that MCI is associated with significant morbidity and mortality,^{19,40} and AD pathology in persons without clinically evident cognitive impairment now appears to be associated with subtle cognitive deficits. Our data suggest that AD pathology may be associated with subtle cognitive deficits even in persons without MCI.

The results also provide evidence in support of the idea that some type of neural reserve can allow a large number of older persons to tolerate a significant amount of AD pathology without manifesting obvious dementia. The concept of reserve is increasingly recognized as having an important role in the expression of dysfunction in a variety of human disease states, including AD.^{2,44} Until recently, the concept of neural reserve was conceptualized primarily as a threshold model of brain reserve capacity.^{2,45-47} Like other physiologic systems, the functional organization of the brain was thought to be redundant, and a considerable amount of tissue destruction needs to occur before the system is compromised and disease becomes clinically evident. However, brain and neocortical size are crude correlates of cognition, at best, and they explain little of the marked individual differences in the information processing capacity of humans.⁴⁸⁻⁵¹ This has led some to posit that

they also differ in their efficiency and ability to respond to environmental challenges (e.g., disease pathology), a term sometimes called cognitive reserve.⁴⁴ Neuroimaging data accumulated over the past few years are consistent with this view. When conducting a cognitive task, aging is associated with lower activation of the brain regions used by young subjects but increased activation in other regions, reflecting either compensation by alternate networks or a loss of specialization (dedifferentiation) of neural networks.^{52,53} A similar activation pattern is seen when persons with mild AD are compared to older persons without AD.^{54,55} Several clinical-pathologic studies also suggest that factors such as education may modify the relation of AD pathology to level of cognitive function.^{2,56,57}

Finally, these data raise some issues regarding the use of dementia and AD as an outcome for analytic epidemiologic studies. To the extent that some risk factors for AD will enhance amyloid deposition and tangle formation,⁵⁸ inclusion of large numbers of persons without dementia who have AD pathology in the reference group could limit power to detect risk factors of small to moderate effect sizes. The fact that AD pathology is related to level of cognition function in this and other studies^{14,16} and change in cognitive function¹⁵ in persons without dementia suggest that change in cognition, especially change in episodic memory, may be a good surrogate outcome for AD for use in some analytic epidemiologic studies, and possibly in clinical trials. This has the potential to markedly increase study power at a reduced cost.

There are features of the study that lend confi-

dence to our findings. All subjects came to autopsy following high rates of clinical follow-up and autopsy. Uniform structured procedures were followed by examiners blinded to previously collected data. All postmortem data were collected by personnel blinded to clinical data. The study also has potential limitations. First, cognitive decline was assessed by a brief interview with the participants and informed by neuropsychological performance testing and mechanical decision rules. Some might argue that a detailed interview with a knowledgeable informant would be more sensitive.⁴ While this is possible, the published data would argue otherwise. For example, one study using a very careful and detailed informant interview reported that more than a third of persons with CDR = 0 met neuropathologic criteria for AD.¹⁵ Further, they found subtle cognitive deficits on neuropsychological performance testing similar to what was found in the present study. The results of the two studies are remarkably similar given the differences in case finding methodology. Second, the study did not employ routine neuroimaging or blood laboratory values. However, dementia and MCI are diagnoses based on behavior. Neuroimaging and laboratory studies inform the differential diagnosis once cognitive impairment is established. Further, the number of persons with cerebral infarctions in our study was substantially lower than in most other studies (see table 4). Finally, because the study relied on deceased subjects, the age range under investigation was older than living subjects in the community.

Acknowledgment

The authors thank the more than 1,000 nuns, priests, and brothers from across the country participating in the Religious Orders Study, and the more than 1,100 older persons from across northeastern Illinois participating in the Rush Memory and Aging Project. The authors thank the staff of the Rush AD Center and Rush Institute for Healthy Aging.

References

- Tomlinson BE, Blessed G, Roth M. Observations on the brains of nondemented old people. *J Neurol Sci* 1968;7:331-356.
- Katzman R, Terry R, DeTeresa R, et al. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Ann Neurol* 1988;23:138-144.
- Crystal HA, Dickson DW, Sliwinski MJ, et al. Pathological markers associated with normal aging and dementia in the elderly. *Ann Neurol* 1993;34:566-573.
- Morris JC, Storandt M, McKeel DW Jr., et al. Cerebral amyloid deposition and diffuse plaques in "normal" aging: evidence for presymptomatic and very mild Alzheimer's disease. *Neurology* 1996;46:707-719.
- Geddes JW, Tekirian TL, Soutanian NS, Ashford JW, Davis DG, Markesbery WR. Comparison of neuropathologic criteria for the diagnosis of Alzheimer's disease. *Neurobiol Aging* 1997;18:S99-S105.
- Hulette CM, Welsh-Bohmer KA, Murray MG, Saunders AM, Mash DC, McIntyre LM. Neuropathological and neuropsychological changes in "normal" aging: evidence for preclinical Alzheimer disease in cognitively normal individuals. *J Neuropathol Exp Neurol* 1998;57:1168-1174.
- Haroutunian V, Purohit DP, Perl DP, et al. Neurofibrillary tangles in nondemented elderly subjects and mild Alzheimer disease. *Arch Neurol* 1999;56:713-718.
- Davis DG, Schmitt FA, Wekstein DR, Markesbery WR. Alzheimer neuropathologic alterations in aged cognitively normal subjects. *J Neuropathol Exp Neurol* 1999;58:376-388.
- Lim A, Tsuang D, Kukull W, et al. Clinico-neuropathological correlation of Alzheimer's disease in a community-based case series. *J Am Geriatr Soc* 1999;47:564-569.

- Green MS, Kaye JA, Ball MJ. The Oregon brain aging study: neuropathology accompanying healthy aging in the oldest old. *Neurology* 2000;54:105-113.
- Neuropathology Group. Medical Research Council Cognitive Function and Aging Study. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Lancet* 2001;357:169-175.
- Knopman DS, Parisi JE, Salviati A, et al. Neuropathology of cognitively normal elderly. *J Neuropathol Exp Neurol* 2003;62:1087-1095.
- Bennett DA, Schneider JA, Bienias JL, Evans DA, Wilson RS. Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. *Neurology* 2005;64:834-842.
- Schmitt FA, Davis DG, Wekstein DR, Smith CD, Ashford JW, Markesbery WR. "Preclinical" AD revisited: neuropathology of cognitively normal older adults. *Neurology* 2000;55:370-376.
- Galvin JE, Powlishta KK, Wilkins K, et al. Predictors of preclinical Alzheimer disease and dementia: a clinicopathologic study. *Arch Neurol* 2005;62:758-765.
- Riley KP, Snowden DA, Markesbery WR. Alzheimer's neurofibrillary pathology and the spectrum of cognitive function: findings from the Nun Study. *Ann Neurol* 2002;51:567-577.
- Guillozet AL, Weintraub S, Mash DC, Mesulam MM. Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment. *Arch Neurol* 2003;60:729-736.
- Bennett DA, Schneider JA, Buchman AS, Mendes de Leon CF, Bienias JL, Wilson RS. The Rush Memory and Aging Project: study design and baseline characteristics of the study cohort. *Neuroepidemiology* 2005;25:163-175.
- Bennett DA, Wilson RS, Schneider JA, et al. Natural history of mild cognitive impairment in older persons. *Neurology* 2002;59:198-205.
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan E. Clinical diagnosis of Alzheimer's disease. Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939-944.
- Adams HP Jr., Bendixen BH, Kappelle LJ, et al. Subtypes of acute ischemic stroke definitions for multi-center clinical trials. *Stroke* 1993;24:35-41.
- Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies—Report of the NINDS-AIREN International Workshop. *Neurology* 1993;43:250-260.
- Langston JW, Widner H, Goetz CGT, et al. Core Assessment Program for Intracerebral Transplantations (CAPIT). *Mov Disord* 1992;7:2-13.
- Robins LN, Helzer JE, Ratcliff KS, Seyfried W. Validity of the Diagnostic Interview Schedule, II: DSM-III diagnoses. *Psychol Med* 1982;12:855-870.
- Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the mental state of patients for the clinician. *J Psychiatr Res* 1975;12:189-198.
- Welsh KA, Butters NC, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD), part V: a normative study of the neuropsychological battery. *Neurology* 1994;44:609-614.
- Wechsler D. Wechsler Memory Scale-Revised manual. San Antonio, TX: Psychological Corp., 1987.
- Kaplan E, Goodglass H, Weintraub S. The Boston Naming Test. Philadelphia: Lea and Febiger, 1983.
- Smith A. Symbol Digit Modalities Test manual-revised. Los Angeles: Western Psychological Services, 1982.
- Benton AL, Sivan AB, Hamsher K, Varney NR, Spreen O. Contributions to neuropsychological assessment. 2nd ed. New York: Oxford University Press, 1992.
- Raven JC, Court JH, Raven J. Manual for Raven's progressive matrices and vocabulary scales. Oxford, UK: Oxford University Press, 1992.
- Wilson RS, Beckett LA, Barnes LL, et al. Individual differences in rates of change in cognitive abilities of older persons. *Psychol Aging* 2002;17:179-193.
- Wilson RS, Barnes LL, Kreuger KR, Hoganson G, Bienias JL, Bennett DA. Early and late life cognitive activity and cognitive systems in old age. *J Int Neuropsych Soc* 2005;11:400-407.
- Schneider JA, Wilson RS, Bienias JL, Evans DA, Bennett DA. Cerebral infarctions and the likelihood of dementia from Alzheimer's disease pathology. *Neurology* 2004;62:1148-1152.
- Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* 1991;41:479-486.
- Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol (Berl)* 1991;82:239-259.
- Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. *Neurobiol Aging*. 1997;18(4 Suppl):S1-2.
- McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996;47:1113-1124.

39. SAS Institute Inc. SAS Online Doc R 9.1.3. Cary, NC: SAS Institute Inc., 2004.
40. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001;56:1133-1142.
41. Dickson DW, Crystal HA, Mattiace LA, et al. Identification of normal and pathological aging in prospectively studied nondemented elderly humans. *Neurobiol Aging* 1992;13:179-189.
42. Geerlings MI, Schmand B, Braam AW, Jonker C, Bouter LM, van Tilburg W. Depressive symptoms and risk of Alzheimer's disease in more highly educated older people. *J Am Geriatr Soc* 2000;48:1092-1097.
43. Kudo T, Imaizumi K, Tanimukai H, et al. Are cerebrovascular factors involved in Alzheimer's disease? *Neurobiol Aging* 2000;21:215-224.
44. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc* 2002;8:448-460.
45. Cummings JL, Vinters HV, Cole GM, Khachaturian ZS. Alzheimer's disease: etiologies, pathophysiology, cognitive reserve, and treatment opportunities. *Neurology* 1998;51(Suppl 1):S2-S17.
46. Mortimer JA. Brain reserve and the clinical expression of Alzheimer's disease. *Geriatrics* 1997;52(suppl 2):550-553.
47. Friedland RP. Epidemiology, education, and the ecology of Alzheimer's disease. *Neurology* 1993;43:246-249.
48. Schoenemann PT, Budinger TF, Sarich VM, Wang WS. Brain size does not predict general cognitive ability within families. *Proc Natl Acad Sci USA* 2000;97:4932-4937.
49. Mortimer JA, Snowdon DA, Markesbery WR. Head circumference, education and risk of dementia: findings from the Nun Study. *J Clin Exp Neuropsychol* 2003;25:671-679.
50. Borenstein Graves A, Mortimer JA, Bowen JD, et al. Head circumference and incident Alzheimer's disease: modification by apolipoprotein E. *Neurology* 2001;57:1453-1460.
51. Schofield PW, Logrosino G, Andrews HF, Albert S, Stern Y. An association between head circumference and Alzheimer's disease in a population-based study of aging and dementia. *Neurology* 1997;49:30-37.
52. Buckner RL. Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. *Neuron* 2004;44:195-208.
53. Stern Y, Habeck C, Moeller J, Scarmeas N, Anderson KE, Hilton HJ. Brain networks associated with cognitive reserve in healthy young and old adults. *Cereb Cortex* 2005;15:394-402.
54. Grady CL, Furey ML, Pietrini P, Horwitz B, Rapoport SI. Altered brain functional connectivity and impaired short-term memory in Alzheimer's disease. *Brain* 2001;124:739-756.
55. Sperling RA, Bates JF, Chua EF, et al. fMRI studies of associative encoding in young and elderly controls and mild Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2003;74:44-50.
56. Mortimer JA, Borenstein AR, Gosche KM, Snowdon DA. Very early detection of Alzheimer neuropathology and the role of brain reserve in modifying its clinical expression. *J Geriatr Psychiatry Neurol* 2005;18:218-223.
57. Bennett DA, Schneider JA, Wilson RS, Bienias JL, Arnold SE. Education modifies the association of amyloid but not tangles with cognitive function. *Neurology* 2005;65:953-955.
58. Bennett DA, Schneider JA, Wilson RS, Bienias JL, Berry-Kravis E, Arnold SE. Amyloid mediates the association of apolipoprotein E ϵ 4 to level of cognitive function in older persons. *J Neurol Neurosurg Psychiatry* 2005;76:1194-1199.

**ACCESS www.neurology.org NOW
FOR FULL-TEXT ARTICLES**

Neurology online is now available to all subscribers. Our online version features extensive search capability by title key words, article key words, and author names. Subscribers can search full-text article *Neurology* archives to 1999 and can access link references with PubMed. The one-time activation requires only your subscriber number, which appears on your mailing label. If this label is not available to you, call 1-800-638-3030 (United States) or 1-301-714-2300 (outside United States) to obtain this number.