Relation of cognitive activity to risk of developing Alzheimer disease

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R.S. Wilson, PhD
P.A. Scherr, PhD, ScD
J.A. Schneider, MD
Y. Tang, PhD
D.A. Bennett, MD

Address correspondence and reprint requests to Dr. Robert S. Wilson, Rush Alzheimer's Disease Center, Rush University Medical Center, 600 South Paulina, Suite 1038, Chicago, IL 60612
rwilson@rush.edu

ABSTRACT

Background: Frequent cognitive activity in old age has been associated with reduced risk of Alzheimer disease (AD), but the basis of the association is uncertain.

Methods: More than 700 old people underwent annual clinical evaluations for up to 5 years. At baseline, they rated current and past frequency of cognitive activity with the current activity measure administered annually thereafter. Those who died underwent a uniform postmortem examination of the brain. Amyloid burden, density of tangles, and presence of Lewy bodies were assessed in eight brain regions and the number of chronic cerebral infarctions was noted.

Results: During follow-up, 90 people developed AD. More frequent participation in cognitive activity was associated with reduced incidence of AD (HR = 0.58; 95% CI: 0.44, 0.77); a cognitively inactive person (score = 2.2, 10th percentile) was 2.6 times more likely to develop AD than a cognitively active person (score = 4.0, 90th percentile). The association remained after controlling for past cognitive activity, lifespan socioeconomic status, current social and physical activity, and low baseline cognitive function. Frequent cognitive activity was also associated with reduced incidence of mild cognitive impairment and less rapid decline in cognitive function. Among 102 persons who died and had a brain autopsy, neither global nor regionally specific measures of neuropathology were related to level of cognitive activity before the study, at study onset, or during the course of the study.

Conclusion: Level of cognitively stimulating activity in old age is related to risk of developing dementia. *Neurology*® 2007;69:1911–1920

GLOSSARY

AD = Alzheimer disease; **MCI** = mild cognitive impairment.

Alzheimer disease (AD) is among the most feared consequences of old age. The enormous public health problems posed by the disease are expected to increase during the coming decades as the proportion of old people in the Unites States increases, underscoring the urgent need for strategies to prevent the disease or delay its onset. During the past decade, several large prospective studies have observed that older people who frequently engage in mentally stimulating activities are less apt to develop AD or experience cognitive decline.[1-11] Although this research suggests that being cognitively active in old age may reduce risk of AD, it is also possible that diminished cognitive activity is an early manifestation of the disease itself or that late life cognitive activity is a proxy for cognitive activity and socioeconomic advantage earlier in life.

In the present study, we examine the relation of cognitive activity to the development of AD using data from the Rush Memory and Aging Project, a clinical-pathologic study of risk factors for common chronic conditions of old age.[12] Past cognitive activity was

Supplemental data at www.neurology.org

retrospectively assessed at baseline. Assessment of current cognitive activity plus cognitive function testing and clinical classification of mild cognitive impairment (MCI), dementia, and AD took place at baseline and annually thereafter. Those who died had a uniform neuropathologic examination to quantify amyloid plaques, neurofibrillary tangles, Lewy bodies, and cerebral infarction. In analyses, we tested the hypothesis that more frequent late life cognitive activity is associated with reduced incidence of AD. We subsequently tested whether other factors could account for the association and conducted analyses using incident MCI and change in cognitive function as outcomes. We also examined change in cognitive activity during the study period and the relation of cognitive activity to the neuropathologic lesions most commonly associated with dementia.

METHODS Participants. All participants are from the Rush Memory and Aging Project, a longitudinal clinical-pathologic study of risk factors for common chronic conditions of old age that began in 1997 and is ongoing. Eligibility requires agreement to annual clinical evaluations and brain donation at death. The study was approved by the Institutional Review Board of Rush University Medical Center.

Persons were recruited from continuous care retirement communities and subsidized housing facilities in the Chicago area. After a presentation about the study, persons expressing interest in participation met with project personnel who explained the study in further detail and obtained informed consent.

Participants underwent a uniform clinical evaluation at baseline which was repeated annually thereafter with examiners blinded to all previously collected data. The evaluation included a structured medical history, complete neurologic examination, and detailed testing of cognitive function. On the basis of this evaluation, an experienced clinician classified persons with respect to dementia and AD following the guidelines of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association.[13] These criteria require a history of cognitive decline and impairment in at least two cognitive domains, one of which must be memory to meet AD criteria, as detailed elsewhere.[14,15] MCI was classified using criteria previously established in this[16] and other[17] cohorts which required evidence of impairment in at least one cognitive domain in the absence of dementia.

At the time of these analyses, 931 participants had finished the baseline evaluation (including the cognitive activity questionnaire) and been found not to have dementia. Of these, 29 persons died before the first annual follow-up evaluation and 73 had been in the study less than 1 year. Of the remaining 829 persons, 775 (93.5%) had follow-up data. Per-

sons in this subgroup completed from two to six annual evaluations per individual (mean = 3.5, SD = 1.2), during which time they missed only 2% of evaluations for reasons other than death (a total of 70 missing visits involving 62 participants). They had a mean age of 80.4 years (SD = 7.4), a mean of 14.5 years of education (SD = 3.0), and a mean Mini-Mental State Examination score at baseline of 28.0 (SD = 2.1); 75% were women and 91% were white and non-Hispanic. As would be expected in this age group, people had a range of clinically diagnosed (e.g., stroke, 9.7%; PD, 1.0%; major depression, 3.2%) and self reported (e.g., head trauma with loss of consciousness, 6.1%; hypertension, 53.6%; hypothyroidism, 19.7%; broken hip, 5.9%; incontinence [at least several/week], 21.7%) medical conditions. During the study period, 84 people died, with mortality rates of 0.007 for age <75 (2 deaths/283.2 person-years), 0.025 for ages 75 to 84 (25/1005.4), and 0.075 for age >84 (57/763.6).

Assessment of cognitive activity participation. Past and current frequency of participation in cognitively stimulating activities was assessed with a structured questionnaire at baseline.[18] There were 30 items on past activity including 11 about childhood (3 items for age 6 and 8 items for age 12), 10 items about young adulthood (age 18), and 9 items about middle age (age 40). There were 9 items about current activity which were readministered annually. We focused on common activities in which seeking or processing information played a central role and which had minimal physical demands or social requirements to enhance the applicability of the scale to people of diverse ethnic and socioeconomic backgrounds. Items included activities like reading a newspaper, playing games like chess or checkers, visiting a library, or attending a play. Frequency of participation was rated from 1 (once a year or less) to 5 (every day or about every day). Composite measures of current (9 items) and past (30 items) cognitive activity were formed by averaging the item scores in each period. In previous research, these measures have been shown to have adequate short term temporal stability and internal consistency, and higher scores have been associated with higher levels of educational attainment and cognitive function.[18,19]

Assessment of cognitive function. At each annual evaluation, a battery of 20 cognitive tests was administered in an approximately 1-hour session. One test, the Mini-Mental State Examination, was used for descriptive purposes but not in analyses. The remaining 19 tests included seven measures of episodic memory: Word List Memory, Word List Recall, and Word List Recognition and immediate and delayed recall of the East Boston Story and Logical Memory. Semantic memory was accessed with a 15-item form of the Boston Naming Test, Verbal Fluency, and a 15-item word recognition test. Working memory was evaluated with Digit Span Forward and Digit Span Backward and a modified version of Digit Ordering. Perceptual speed was assessed with Number Comparison, the oral version of the Symbol Digit Modalities Test, and two measures from a modified version of the Stroop Neuropsychological Screening Test: the number of color names correctly read minus the number of errors and the number of colors correctly named minus the number of errors. Visuospatial ability was assessed with a 15-item form of the Judgment of Line Orientation Test and a 16-item form of Standard Progressive Matrices.

To minimize floor and ceiling artifacts and other forms of measurement error, composites of two or more cognitive

tests were used in analyses. A composite measure of global cognition was constructed from all 19 tests. In addition, based in part on a factor analysis of the tests at baseline,[18,19] composite measures of episodic memory (7 tests), semantic memory (3 tests), working memory (3 tests), perceptual speed (4 tests), and visuospatial ability (2 tests) were formed. For each composite measure, raw scores on individual tests were converted to z scores using the baseline mean and SD for the entire cohort. The z scores on the component tests were then averaged to yield the composite score. Further information on the individual tests and the derivation of these composite scores is contained in previous publications.[18,19]

Assessment of covariates. Six items about activities involving social interaction (e.g., visiting a relative or friend) were used to assess participation in social activity at baseline. Persons rated frequency of participation in each activity from 1 (once a year or less) to 5 (every day or almost every day). The mean item score was used in analyses, as previously described.[15,20]

Physical activity at baseline was measured with questions adapted[21] from the 1985 Health Interview Survey.[22] There were five activities (e.g., walking for exercise). For each activity, persons indicated if they had engaged in it during the preceding 2 weeks and if so, they were asked the number of occasions and duration of each. These data were summed over the five activities to indicate hours of physical activity per week, as reported elsewhere.[14,15]

Three indicators of early life household socioeconomic status, mother's education, father's education, and father's occupation coded according to perceived prestige,[23] were converted to z scores and averaged to yield a composite index, as described in an earlier publication.[24] In addition, community level (census tract, ward, or county) indicators of socioeconomic conditions in early life were obtained by linking birth address to data from the 1920 census. Three indicators, proportion of children aged 6 to 13 years who were in school, literacy rate in those aged 6 years or older, and mean Duncan socioeconomic index[25] of the head of the household, were converted to z scores and averaged to yield a composite measure, as described elsewhere.[24,26]

At the baseline evaluation, we assessed current income and income at age 40. Persons were asked to select one of 10 levels of total family income using the "show-card" method.[27]

Previously established composite measures of vascular burden were derived from the baseline medical history and clinical evaluation.[28] Vascular risk factors was the number of three factors present (i.e., diabetes, hypertension, smoking) and vascular conditions was the number of four conditions present (i.e., heart attack, stroke, congestive heart failure, and claudication).

Neuropathologic examination. The brain was removed in a standard fashion,[29] cut coronally into 1-cm-thick slabs, immersion fixed in 4% paraformaldehyde for 48 to 72 hours, and then placed in graded glycerol/dimethylsulfoxide in phosphate buffered saline for storage. Fixed tissue from eight regions was dissected into 0.5-cm-thick blocks that were embedded in paraffin: the entorhinal cortex proper, CA1/subiculum, dorsolateral prefrontal cortex, superior frontal cortex, inferior temporal cortex, angular/supramarginal gyrus cortex, anterior cingulate cortex, and calcarine cortex. Two blocks were obtained from adjacent 1 cm slabs from the neocortex and cut into 20 μm sections. For the hippocampal formation, sections were cut from consecutive 1-cm slabs throughout its length (up to six blocks per case).

As previously described,[14,15,29] amyloid-beta was labeled with MO0872 (Dako, Carpentaria, CA, 1:100), which identifies both the 1-40 and 1-42 length amyloid-beta fragments, using diaminobenzidine as the reporter with 2.5% nickel sulfate to enhance immunoreaction product contrast. All sections were run with identical incubation times on an automated immunohistochemical stainer (Biogenex, San Ramon, CA). Control sections processed without primary antibodies were included in all runs and showed no specific staining. To capture images of amyloid-beta stained sections for quantitative analysis of plaque deposition, we used a systematic random sampling scheme with a custom algorithm.[30] After camera and illumination calibration, 24-bit color images obtained at each sampling site were converted to eight-bit grayscale images. The percent area occupied by amyloid-beta immunoreactive pixels was calculated using the public domain Object-Image 1.62p15 (developed by Norbert Vischer, http://simon.bio.uva.nl/object-image.html). The analysis algorithm segmented each image into labeled and background compartments using one of two histogram-dependent automatic thresholding procedures, iterative self-organizing data analysis and triangulation.[30] The percent areas for each section were then averaged for each region of interest, and the regional indices were averaged to yield a composite measure of amyloid burden.

Paired helical filament tau was labeled with an antibody specific for phosphorylated tau, AT8 (Innnogenex, San Ramon, CA, 1:800 in 4% horse serum). All experimental and control (no primary antibody) sections were run using identical incubation times on the automated immunohistochemical stainer. We quantified tangle density per mm² with a stereologic mapping station which included a Leica DMRBE microscope and a computer (Millennia Mme, Micron Electronic, Inc.) equipped with StereoInvestigator software version 5.00 (MicroBrightField, Inc., Colchester, VT). After a region of interest was delimited at low power, a grid of predetermined size was randomly placed over the entire region, magnification was raised to 400×, and the program was engaged to direct the motorized stage on the microscope to stop at each intersection point of the grid for sampling. The operator focused through the section depth as the fields were visualized on the video monitor within the superimposed counting frame and counted all objects within the 150 × 150 μm counting frame that did not touch the exclusion lines of the box. Approximately 50% of the area of a delimited region of interest was quantified. The regional measures of tangle density were averaged to form a composite measure of tangle density, and Braak stage [32] was rated from 0 to 6 based on the distribution and severity of tangles, as previously reported.[29]

Lewy bodies were identified with antibodies to alpha synuclein (clone LB509 monoclonal, Zymed, San Francisco, CA; 1:2000), a specific immunohistochemical stain for Lewy bodies. Immunohistochemistry for alpha synuclein was done with 6 μm sections of paraformaldehyde fixed tissue, and after pretreatment with 90% formic acid, with control slides included in each run, as reported elsewhere.[29] All sections were evaluated by light microscopy for intraneuronal Lewy bodies. Because Lewy bodies were relatively uncommon, they were treated as present or absent in analyses.

We examined the 1-cm slabs from each hemisphere for evidence of cerebral infarctions, as previously described.[33]

	Past cognitive activity	Current social activity	Current physical activity	Age	Education	Current income	Age 40 income	Community SES	Household SES	Global cognition
Current cognitive activity	0.54	0.44	0.12	−0.11	0.30	0.25	0.15	0.08	0.20	0.45
Past cognitive activity	—	0.35	0.08	−0.01	0.44	0.19	0.12	0.07	0.27	0.34
Current social activity		—	0.14	−0.16	0.16	0.11	0.07	−0.04	0.05	0.30
Current physical activity			—	−0.07	0.06	0.08	0.00	−0.04	−0.01	0.00
Age				—	−0.04	0.00	−0.26	0.11	−0.08	−0.31
Education					—	0.35	0.15	0.15	0.40	0.36
Current income						—	0.38	0.14	0.28	0.27
Age 40 income							—	0.11	0.22	0.15
Early community SES								—	0.19	0.10
Early household SES									—	0.30

*Pearson correlations.
$p < 0.01$ for correlation coefficients with an absolute value of 0.10 or greater.
SES = socioeconomic status.

We identified the age, volume, and location of all cerebral infarctions visible to the naked eye. In analyses, old cortical and subcortical infarctions affecting gray or white matter were included whereas microscopic stroke, acute and subacute infarction, and brainstem and cerebellar infarctions were excluded, and those without infarction were contrasted with one infarction and multiple infarction subgroups.

Data analysis. We first examined the crude associations of cognitive activity measures with covariates, follow-up participation, and AD. All subsequent analyses controlled for the effects of age, sex, and education. The association of cognitive activity with incident AD was examined in a series of Cox proportional hazards models.[34] We first examined current and past activity in separate models and then put them together in a core model. We repeated the core model with terms for social and physical activity; with indicators of socioeconomic status across the life span, first separately and then together; with composite measures of vascular burden; and excluding persons with low cognitive function at baseline. We also examined the relation of cognitive activity to incident MCI in a proportional hazards model that was repeated excluding persons with low baseline cognitive function.

We used linear mixed-effects models (i.e., models with fixed and random effects[35]) to analyze change in cognitive function and to examine how cognitive activity was related to change. Cognitive activity and other covariates were modeled as fixed effects, and random effects were incorporated for individual baseline level of cognitive performance and individual rate of change in performance. This approach allowed us to examine the relation of cognitive activity to both baseline cognitive function and rate of change in function while simultaneously accounting for individual differences in baseline cognitive ability and how rapidly it changed, as described in more detail elsewhere.[36,37] Each model had terms for time (in years since baseline) and time squared to capture nonlinear change in cognitive function; for cognitive activity to control for the relation of cognitive activity to cognitive function at baseline; and for the interaction of activity with time to test the association of activity with linear change in cognitive function. Terms for current activity and current

activity by time were included in the first model that was repeated excluding those with low baseline cognitive function; the second model substituted past for current activity; and the third model included both current and past activity and their interactions with time. We then repeated the third model with measures of specific cognitive domains in place of the global cognitive measure.

We also analyzed change in cognitive activity with mixed-effects models. The initial model had terms for time and for age, sex, education, and their interactions with time. In a subsequent analysis, we added terms for mild cognitive impairment and its interaction with time.

In the clinical-pathologic analyses we regressed each measure of cognitive activity on each measure of neuropathology in separate models adjusted for age at death, sex, and education.

Models were graphically and analytically validated. Programming was done in SAS.[38]

RESULTS Cognitive activity measures. At baseline, the measure of current cognitive activity had a mean of 3.2 (SD = 0.7; range: 1.0 to 4.7) and the measure of past cognitive activity had a mean of 3.1 (SD = 0.6; range: 1.4 to 4.6), with higher scores denoting more frequent activity. In general, higher levels of both current and past cognitive activity were associated with being more socially and physically active and having higher socioeconomic status and cognitive function (table 1). Neither current nor past cognitive activity was associated with missing some or all follow-up data (all $p > 0.200$).

Cognitive activity and incidence of AD. During up to 5 years of observation, 90 persons developed AD. The rates of incidence were 0.018 for age <75 (5 cases/280.4 person-years), 0.024 for ages 75 to 84 (23/974.2), and 0.091 for age >84 (62/678.0). Five people who developed other forms of

Table 2 Characteristics of persons who did or did not develop Alzheimer disease*

Characteristic	Incident AD (n = 90)	Unaffected persons (n = 685)	p Value[†]
Age, y	84.4 (6.0)	79.8 (7.0)	<0.001
Education, y	14.7 (3.2)	14.4 (3.0)	0.467
Men, %	35.6	23.2	0.011
White non-Hispanic,%	91.1	90.4	0.821
MMSE score	26.2 (2.7)	28.2 (1.8)	<0.001
Global cognitive function score	−0.46 (0.52)	0.20 (0.49)	<0.001
Current cognitive activity	2.9 (0.7)	3.2 (0.7)	<0.001
Past cognitive activity	2.9 (0.6)	3.1 (0.6)	0.042
Social activity	2.3 (0.6)	2.7 (0.6)	<0.001
Physical activity	3.5 (4.0)	3.1 (3.7)	0.234
Early household SES	−0.01 (0.74)	−0.01 (0.75)	0.987
Early community SES	0.01 (0.80)	0.09 (0.67)	0.416
Age 40 income	4.5 (2.1)	5.2 (2.4)	0.013
Baseline income	6.0 (2.8)	6.6 (2.5)	0.081
Vascular risk factors	1.2 (0.8)	1.2 (0.8)	0.678
Vascular conditions	0.4 (0.7)	0.3 (0.6)	0.143

*All data are presented as mean (SD) unless otherwise indicated.
[†]Based on t tests except for men and white non-Hispanic (chi-square association tests), MMSE score and physical activity (Wilcoxon two-sample tests), and vascular risk factors and conditions (Cochran-Armitage trend tests).
MMSE = Mini-Mental State Examination; SES = socioeconomic status.

dementia were excluded from analyses of incident AD. At the time of the baseline evaluation, those who subsequently developed AD were older and more apt to be men than subsequently unaffected persons, their cognitive functioning was lower, and they participated less in cognitive and social activities (table 2).

To determine the relation of cognitive activity to risk of AD, we constructed a proportional hazards model with a term for current cognitive activity. This and all subsequent models also included terms to control for age, sex, and education. In this analysis, more frequent activity was associated with reduced incidence of AD (RR = 0.58; 95% CI: 0.44, 0.77). Thus, as shown in the figure, which is based on this analysis, a cognitively inactive person (dotted line, score = 2.2, 10th percentile) was 2.6 times more likely to develop AD than a cognitively active person (solid line, score = 4.0, 90th percentile).

Frequency of past cognitive activity was also associated with risk of AD (RR = 0.56; 95% CI: 0.36, 0.88). To see if past cognitive activity could account for the relation of current cognitive activity to risk of AD, we analyzed current and past activity in the same model. In this core analysis, the effect of past activity was eliminated (RR = 0.80; 95% CI: 0.49, 1.30) and the effect of current activity was not substantially changed (RR = 0.47; 95% CI: 0.34, 0.66).

Because social and physical activity were related to cognitive activity and have been associated with AD risk,[4,7,15] we repeated the previous

Figure Hazard of developing Alzheimer disease
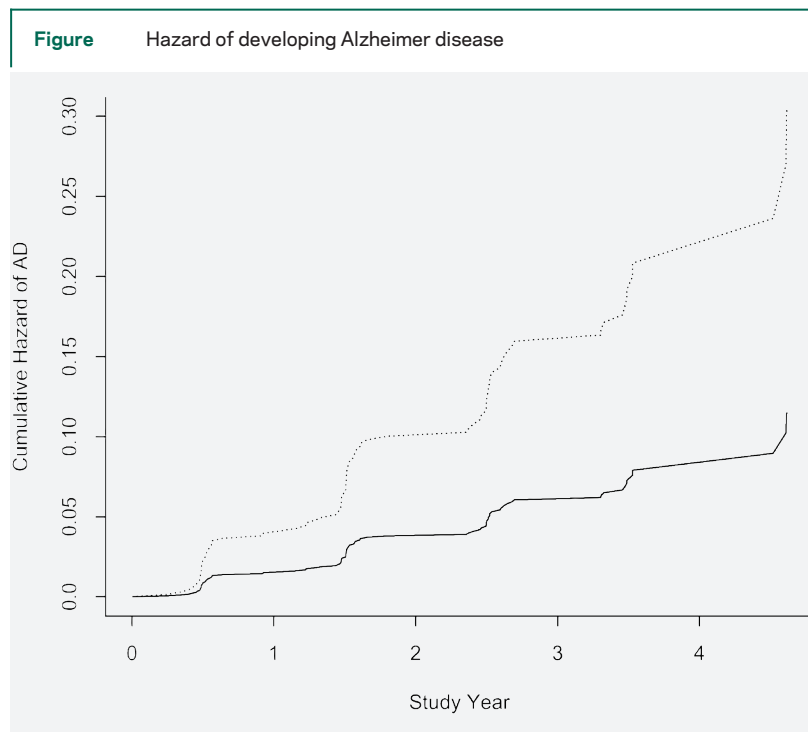
Cumulative hazard of developing Alzheimer disease in people with high (90th percentile, solid line) or low (10th percentile, dotted line) frequency of participation in cognitively stimulating activities at study onset.

Table 3 Relation of current and past cognitive activity to rate of global cognitive decline*

Model term	Model A Estimate	SE	p	Model B Estimate	SE	p	Model C Estimate	SE	p
Time	−0.019	0.010	0.053	−0.010	0.012	0.403	−0.013	0.012	0.284
Time squared	−0.014	0.003	<0.001	−0.015	0.003	<0.001	−0.015	0.003	<0.001
Current cognitive activity	0.256	0.024	<0.001				0.250	0.029	<0.001
Current activity × time	0.019	0.008	0.017				0.025	0.010	0.015
Past cognitive activity				0.183	0.034	<0.001	0.040	0.036	0.271
Past activity × time				0.027	0.011	0.017	0.013	0.013	0.305

*From separate mixed-effects models adjusted for age, sex, and education. Results show the effect of a one-unit change in activity score.

(core) analysis with terms for frequency of social and physical activity. The association of current cognitive activity with incidence of AD was essentially unchanged (RR = 0.58; 95% CI: 0.40, 0.83).

Cognitive activity is related to indicators of socioeconomic status which have been associated with risk of AD.[39,40] Therefore, we repeated the core analysis with four additional terms: composite indicators of household (e.g., father's occupational prestige) and community (e.g., proportion of children aged 6 to 13 in school) socioeconomic status in early life, income at age 40, and income at the time of the baseline evaluation. More frequent cognitive activity continued to show a robust association with risk of AD in this analysis (RR = 0.44; 95% CI: 0.28, 0.69) and in a subsequent analysis that also included terms for social and physical activity (RR = 0.53; CI: 0.32, 0.86). Results were also unchanged after controlling for composite measures of vascular risk factors and vascular conditions (RR = 0.58; 95% CI: 0.44, 0.77).

To see if the association of cognitive activity with risk of AD depended on a subgroup with low cognitive ability at baseline, we repeated the core analysis excluding those whose baseline global cognitive score was at or below the 10th percentile. Cognitive activity was related to incidence of AD in this model (RR = 0.63; 95% CI: 0.44, 0.91) and in a subsequent analysis using the 15th percentile as a cutpoint (RR = 0.61; 95% CI: 0.41, 0.92).

Cognitive activity and incidence of mild cognitive impairment. We next examined whether cognitive activity could predict the incidence of MCI among those initially free of cognitive impairment. Of 627 people without MCI or dementia at baseline, 199 (31.7%) developed MCI during follow-up. In a proportional hazards model adjusted for age, sex, and education, more frequent cognitive activity was associated with reduced incidence of MCI (RR = 0.71; 95% CI: 0.58, 0.87).

Results were not substantially changed in analyses excluding those whose baseline global cognitive score was at or below the 10th percentile (of those without cognitive impairment at baseline; RR = 0.77; 95% CI: 0.61, 0.98) or the 15th percentile (RR = 0.76; 95% CI: 0.59, 0.99).

Cognitive activity and cognitive decline. Another means of assessing the impact of pre-existing cognitive impairment on findings is to measure the relation of cognitive activity to cognitive decline, the primary clinical manifestation of AD, while controlling for baseline level of cognitive ability. We did this in a series of mixed-effects models. To capitalize on all available cognitive data, we used the global measure of cognitive function in most analyses. At baseline, it ranged from −1.82 to 1.45 (mean = 0.12, SD = 0.54), with higher scores indicating better cognitive function. In the initial analysis (table 3, model A), there was a gradually increasing rate of cognitive decline in the group as a whole, as shown by the terms for time and time squared. More frequent cognitive activity at baseline was associated with a higher level of cognitive function at baseline and, with this effect controlled, a less rapid rate of global cognitive decline, as shown by the interaction of current cognitive activity with time. Results were similar in analyses excluding those whose baseline global cognitive score was at or below the 10th percentile (estimate for interaction of cognitive activity by time = 0.017, SE = 0.008, p = 0.031) or 15th percentile (estimate = 0.020, SE = 0.008, p = 0.019). In a subsequent analysis (table 3, model B), more frequent cognitive activity prior to old age was also associated with higher baseline cognition and reduced cognitive decline. With both current and past activity in the same analysis (table 3, model C), the association of current cognitive activity with cognitive decline was not substantially changed; by contrast, past cog-

nitive activity was no longer related to cognitive decline.

To determine whether the association of cognitive activity with cognitive decline varied across cognitive domains, we repeated the previous analysis (model C) with specific measures of cognition instead of the global cognitive score. In these analyses, more frequent cognitive activity at baseline was associated with reduced rates of decline in episodic memory (estimate for current cognitive activity $\times$ time = 0.043, SE = 0.014, p = 0.003), semantic memory (estimate = 0.032, SE = 0.012, p = 0.009), and perceptual speed (estimate = 0.034, SE = 0.016, p = 0.038) but not working memory or visuospatial ability. These effects are graphically summarized in figure E-1 on the *Neurology*® Web site at www.neurology.org.

Change in cognitive activity. Given evidence linking cognitive activity at baseline to subsequent development of MCI and AD, we next examined change in cognitive activity during the study period (mean of 3.5 assessments per individual, SD = 1.2, range: 2 to 6). If cognitive inactivity is a consequence of AD, activity level should decline at some point during the development of the disease. To look for evidence of such an effect in this cohort, we first constructed a mixed-effects model with terms for time and the effects of age, sex, and education. It showed a mean decrease of 0.06 unit per year on the cognitive activity scale (SE = 0.01, p < 0.001). We then repeated the analysis with terms for MCI, previously shown to predict incident AD in this cohort,[16] and its interaction with time. MCI at baseline was associated with less cognitive activity at baseline (estimate = −0.19, SE = 0.05, p < 0.001), but it was not related to change in cognitive activity (estimate = −0.01, SE = 0.02, p = 0.544).

Cognitive activity and age-related neuropathology. The most direct evidence that infrequent cognitive activity is a consequence of AD would be an association between cognitive activity and the pathology underlying the disease. At the time of these analyses, 140 eligible participants had died, with brain autopsies in 110 (78.6%) and completed postmortem examinations in 102. This latter group had a mean age at death of 87.7 (SD = 5.4), a mean of 14.0 years of education (SD = 3.3), and a mean Mini-Mental State Examination score of 23.5 (SD = 8.1) from their last evaluation before death. In a series of linear regression analyses, composite measures of amyloid, tangles, Lewy bodies, and infarction were not associated with level of cognitive activity at study onset (ta-

Table 4	Relation of neuropathology to frequency of participation in cognitively stimulating activities at study onset*		
Model term	Estimate	SE	p
Amyloid burden	0.002	0.028	0.943
Tangle density	−0.016	0.014	0.229
Braak stage	0.003	0.066	0.964
Lewy bodies	−0.130	0.222	0.561
One infarction	−0.304	0.229	0.188
Multiple infarction	−0.037	0.206	0.859

*From separate linear regression models adjusted for age at death, sex, and education.

ble 4). Results were comparable when analyses were repeated with different measures of cognitive activity (i.e., past level, mean level during study period) and with separate limbic (i.e., entorhinal cortex and hippocampus) and neocortical measures of amyloid, tangles, and Lewy bodies.

DISCUSSION In this prospective observational study, old persons who reported being cognitively active were less likely to develop MCI and dementia and to experience cognitive decline than less cognitively active persons. The findings suggest that frequency of mentally stimulating activity during old age is related to incidence of dementia.

Several previous prospective studies have examined the relation of cognitively stimulating activity in older persons to age-related loss of cognition. With few exceptions,[41] this research, like the present study, has shown higher level of cognitive activity to be associated with reduced cognitive loss, in the form of incident mild cognitive impairment,[5,8] incident dementia or AD,[2,4,6,7,9,11] or cognitive decline.[1,3,10,11] Despite the consistency of the epidemiologic evidence linking cognitive activity with dementia, there has been little consensus about the basis of the association.

One hypothesis is that cognitive inactivity is really an early sign of AD that precedes overt dementia. The moderate correlation between baseline levels of cognitive activity and cognitive function is not germane because it would be expected whether cognitive activity was a cause or consequence of cognitive decline. Two other observations do bear upon the hypothesis. First, those who died had a uniform neuropathologic examination in which we quantified the four most common causes of dementia (i.e., amyloid plaques, neurofibrillary tangles, Lewy bodies, cerebral infarction) with particular emphasis on brain regions that support memory and cogni-

tion. Yet none of the cognitive activity measures was associated with composite measures of this pathology. By contrast, established early signs of AD such as olfactory dysfunction and parkinsonian gait not only predict dementia[42,43] but are also related to the pathologic lesions associated with dementia.[44,45] Second, cognitive activity predicted the development of MCI, an early sign of AD, but MCI did not predict subsequent decline in cognitive activity. These observations in conjunction with evidence linking cognitive activity to the development of dementia after very long periods,[2,6] including two decades in one study,[2] do not support the hypothesis that infrequent cognitive activity predicts AD because it is a prodromal sign of the disease.

Cognitive activity could be an indicator for some other variable related to AD. In particular, older people who are cognitively active may have always been more mentally active and socioeconomically advantaged, and it could be these earlier experiences or cumulative experiences that are critical rather than activity in old age. We did find that a retrospective measure of cognitive activity prior to old age predicted risk of AD. Nonetheless, controlling for past cognitive activity and for indicators of socioeconomic status across the life course did not affect the association of late life cognitive activity with AD risk. Also, after controlling for baseline level of cognitive function, which is probably highly correlated with lifelong level of cognitive function, late life cognitive activity still predicted subsequent rate of cognitive decline. These observations suggest that the association of cognitive activity with AD depends on activity in old age. That controlling for late life social and physical activity did not affect results implies that the cognitive nature of the activity is also critical to results.

Alternatively, the association of late life cognitive activity with maintenance of cognitive ability might reflect functional and structural changes that have occurred in neural systems underlying cognitive functioning in response to environmental stimulation.[46] That is, cognitive activity may enhance cognitive reserve.[47] Recent neuroimaging studies have shown experience-related differences in human brain structure. For example, posterior hippocampal volume is increased in persons with an occupation demanding navigational skills compared to controls[48]; gray matter density in Broca area is increased in orchestra musicians compared to nonmusicians[49]; and white matter volume in the left parietal lobe is correlated with the ability to learn novel speech sounds.[50] In addi-

tion, longitudinal studies have documented regional increases in brain volume in response to specific experiences like learning to juggle[51] or preparing for demanding tests of medical knowledge.[52] These data in conjunction with extensive research on animals support the idea that neural systems underlying memory and information processing are partially activity dependent. Being cognitively active, therefore, might contribute to cognitive reserve by helping to maintain efficiency in these underlying neural systems, by enhancing adaptation to age-related pathologic changes, or by a combination of these mechanisms.

This study has several strengths. Classification of MCI and AD was based on uniform evaluations and established criteria, and comparable results were obtained with cognitive decline as the outcome, making it unlikely that diagnostic bias affected findings. Results are based on previously established measures of cognitive activity, cognitive function, and AD pathology. High rates of participation in follow-up clinical evaluations and brain autopsy reduce the likelihood that selective attrition affected findings. A limitation is that these data are based on a selected group and a mean of less than 3 years of observation. In addition, the measure of past level of cognitive activity was based on retrospective report and may have been biased.

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