Rate of memory decline in AD is related to education and occupation

Cognitive reserve?

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Article abstract—*Objective:* To determine whether the rate of decline in performance on a memory test is more rapid in AD patients with higher versus lower educational and occupational attainment. *Background:* Epidemiologic and imaging studies have suggested that, given comparable clinical severity of dementia, AD pathology is more advanced in patients with higher educational and occupational attainment. Because educational and occupational attainment should not influence the progression of AD pathology, and because severe AD pathology will eventually produce a mortality-causing condition, people with higher attainment might experience clinical AD for a shorter time and have a more rapid clinical progression. *Methods:* A total of 177 AD patients were tested yearly for up to four study visits with the Selective Reminding Test (a memory test). Analysis of prospective change in the total recall score was performed by applying generalized estimating equations to regression analyses with repeated measures. *Results:* At the initial visit, scores were comparable in the high- and low-education and the high- and low-occupation groups. Overall, memory scores declined by approximately 1 point yearly ($p < 0.01$). There was a more rapid decline in memory scores in patients with higher educational ($p < 0.057$) and higher occupational attainment ($p < 0.02$). The authors then stratified patients based on their initial memory scores. The more rapid decline in memory scores associated with higher educational and occupational attainment was noted only in the group with low initial scores ($p < 0.05$ for both). The full group and stratified group analyses were also repeated controlling for other potentially relevant variables including age, gender, race, ethnicity, and the presence of extrapyramidal signs, stroke, or at least one apolipoprotein E-ϵ4 allele. The results remained unchanged. *Conclusions:* Memory declined more rapidly in AD patients with higher educational and occupational attainment. This adds support to the idea that the discontinuity between the degree of AD pathology and the observed clinical severity of AD is mediated through some form of reserve. **Key words:** Memory decline—AD—Cognitive reserve—*APOE*.

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Several lines of evidence suggest that aspects of life experience such as educational or occupational attainment provide a "cognitive reserve" against the clinical manifestation of the neuropathologic changes of AD. Higher educational and occupational attainment has been associated with a reduced risk of incident dementia.[1-3] Furthermore, imaging studies have suggested that given comparable clinical severity of dementia, AD pathology is more advanced in patients with higher educational and occupational attainment.[4-6] These findings suggest that the degree of reserve might influence the level of pathologic severity at which clinical manifestations of AD emerge. However, the progression of the AD pathology itself probably does not differ as a function of cognitive reserve. Because severe AD pathology will eventually produce a mortality-causing condition, it is therefore possible that people with higher educa-

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tional and occupational attainment will actually experience clinical AD for a shorter period of time. Along these lines, we have demonstrated that, in AD patients matched for clinical severity, those with higher educational and occupational attainment actually died sooner.[7] If the period of time in which patients with higher socioeconomic status experience clinical AD is foreshortened, it is possible that the progression of the clinical manifestations of dementia in these patients will be more rapid. We tested this possibility in a prospectively followed cohort of patients with AD. We predicted that the rate of decline in performance on a memory test would be more rapid in AD patients with higher than with lower educational and occupational attainment.

Methods. *Subjects.* All subjects met National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD.[8] The patients were followed as part of the Washington Heights–Inwood Columbia Aging Project. Two ascertainment methods were used to enlist the patients. The majority of the patients were identified from a prospectively followed 50% sample of residents in a defined region of Washington Heights–Inwood. All patients with prevalent and incident dementia were included in the sample. We had also established previously a case report network designed to collect reports of possible cases of dementia within the study area. A subset of the prevalent cases of AD and all patients with incident AD identified through this registry were also included in our current sample of AD patients.

All patients were followed annually. Analyses were limited to patients with at least one follow-up visit. Patients were required to meet diagnostic criteria for AD at every study visit. A total of 177 patients met these criteria and were included in the analyses.

Procedures. Outcome measure. We chose the total recall score on the Selective Reminding Test (SRT)[9] as the outcome measure because this continuous measure is sensitive to the progression of AD and was collected at each study visit. As part of the SRT, subjects are given six trials to learn a list of 12 unrelated words. The list is first read to the subject, who attempts to recall it. After each recall attempt, subjects are reminded only of those words that had not been recalled successfully. The total recall score consists of the sum of all words recalled over the six trials.

Diagnostic evaluation. All subjects had the same standardized evaluation at each study visit. Evaluations were conducted in either English or Spanish, based on the subjects' primary language and their opinion of which language would yield a better performance. A physician elicited the medical/neurologic history and conducted a standardized physical and neurologic examination. Formal assessments of activities of daily living were also administered. All ancillary information, including medical charts and CT scans or MR images if available, was included in the evaluation.

The neuropsychological battery took approximately 1 hour to complete and contained tests of memory (short- and long-term verbal[9] and nonverbal[10]), orientation,[11] abstract reasoning (verbal[12] and nonverbal[13]), language (naming,[14] verbal fluency,[15] comprehension,[16] and repetition[16]), and construction (copying[17] and matching[10]). Test scores were evaluated using a fixed paradigm.[18] Criterion scores were applied to each test score, and subjects performing below these scores on two of the three aspects of memory testing as well as two other areas (orientation, language, abstract reasoning, or construction) were considered to have a sufficient cognitive deficit to meet the criteria for dementia.

Information from these evaluations was presented at a diagnostic conference of physicians and neuropsychologists, and a consensus diagnosis was made. The diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised, criteria,[19] and required evidence of cognitive deficit based on the neuropsychological scores, as well as evidence of impairment in social or occupational function based on the formal functional assessments, elicited history, or both. When dementia was diagnosed, all available data were evaluated to determine the type of dementia present. For the diagnosis of probable or possible AD, we used the criteria of the NINCDS-ADRDA.[8]

Data analysis. Analysis of prospective change in the memory score was performed by applying generalized estimating equations (GEE) to regression analyses with repeated measures.[20] This statistical method takes into account the multiple visits per subject and the fact that the characteristics of the same individual over time are likely to be correlated. The repeated measures for each subject are treated as a cluster. The initial GEE models consisted of group and time main effects, and a group $\times$ time interaction effect. For example, in the case of education, the regression model provided estimates of the association of the memory score with educational group (high and low), follow-up time, and the interaction of group and time. A significant group effect indicates a difference in scores between the two educational groups at the initial visit. A significant time effect indicates a marked change in test scores over time. A significant interaction of group and time indicates differential rates of change in the test score as a function of group.

The primary analysis focused on the differential rate of change in memory scores over time as a function of educational and occupational attainment. Education was stratified at ≤ 8 years and >8 years. Occupational attainment was dichotomized as follows: At the initial visit, the subject's primary occupation (i.e., occupation of longest duration) was recorded and classified based on the following United States census categories: student, housewife, unskilled/semiskilled, skilled trade or craft, clerical/office worker, manager business/government, and professional/technical. A housewife who had been employed for a substantial period of her adult life (i.e., more than 10 years) was classified according to that occupation. We did not include 11 patients who were classified as housewives only in the occupational analyses, because this classification could not be fit directly into accepted social class hierarchies. The remaining classifications were grouped into low (unskilled/semiskilled, skilled trade or craft, and clerical/office worker) and high (manager business/government and professional/technical) occupational levels.

The rate of change in memory scores over time might be in part a function of the initial score, because higher initial scores are less subject to a "floor effect," where observing

Table 1 *Demographics and clinical features of patients at the initial visit (n = 177)*

Variable	Data
Age, y; mean (SD)	81.5 (7.5)
Sex, % female	81.4
Race, % black	48.0
Ethnicity, % Hispanic	50.8
Clinical dementia rating, %	
Mild (1)	77.4
Moderate (2)	18.6
Severe (3)	4.0
History or evidence of stroke, %	19.8
Extrapyramidal signs (n = 161)*, %	23
At least one APOE-ε4 allele (n = 121)†, %	28.2
SRT total recall score, mean (SD)	16.7 (6.7)

* The remaining 16 patients had drug-induced extrapyramidal signs and were not included in analyses that used this variable.
† *APOE* genotypes were not available for the remaining patients. Analyses that used this variable were limited to the 121 patients.

SRT = Selective Reminding Test.

further progression is difficult. We evaluated this possibility by stratifying patients into two groups based on their initial total recall scores, using the median initial score as the stratification point. We then repeated our analyses of the effects of educational and occupational attainment on progression of memory scores in separate groups of patients with high and low initial scores.

We also evaluated several classes of variables to determine whether they were associated with differential rates of disease progression or whether they should be included as covariates in the educational and occupational attainment analyses. In all instances, the value of the variable at the patient's initial visit was used. Sociodemographic variables included age, gender, race (white/black), and ethnicity (Hispanic/non-Hispanic). Neurologic variables included the presence of stroke based on the neurologic evaluation, clinical history, and any available scan information; and the presence of extrapyramidal signs based on selected items from the Unified Parkinson's Disease Rating Scale. Apolipoprotein E (*APOE*) genotype information was included in our models as available, dichotomized to whether the patient has at least one ε4 allele.

Results. Demographic features of the cohort at the initial study visit are summarized in table 1. There was a maximum of five follow-up visits (mean, 1.7 visits) and patients were followed for an average of 2.4 years. Table 2 summarizes the mean total recall scores on the SRT, the number of study visits, and the mean follow-up time for patients with low and high educational or occupational attainment. In no patient did these values differ across the low and high groups.

As expected, in the overall cohort of patients, the total recall score declined significantly over time. The change in scores was approximately 1 point yearly ($\beta = -1.04$, $p < 0.0001$).

Table 3 summarizes the GEE analyses of educational and occupational attainment. For education, there was no significant group effect, indicating that memory scores in the two groups were comparable at the initial visit. There was a trend toward a significant educational interaction × time interaction ($p < 0.057$), suggesting that patients with higher educational attainment had more rapid decline in their memory scores. Figure 1 illustrates the progression of scores over time in each educational group based on the regression lines derived from the GEE model. Similarly, for occupation there was no significant group effect, but there was a significant occupation × time interaction ($p < 0.02$; see table 3). Patients with higher occupational attainment had more rapid decline in their memory scores. Figure 2 illustrates the progression of scores over time in each occupational group based on the regression lines derived from the GEE model.

We evaluated the possibility that the more rapid decline in scores in patients with higher educational and occupational attainment was related to an unequal distribution of higher memory scores at the initial visit. First, we used chi-square analyses to evaluate the distribution of patients with higher baseline scores as a function of educational

Table 2 *SRT total recall scores, number of study visits, and length of follow-up in years in the subjects as a whole, the high and low educational and occupational attainment groups, and the groups with high and low initial memory scores*

Variable	n	SRT score, mean (SD)	No. of visits, mean (SD)	Length of follow-up, y; mean (SD)
Total group	177	16.8 (6.9)	2.69 (0.90)	2.41 (1.37)
Education				
Low	49	17.2 (5.9)	2.63 (0.89)	2.29 (1.37)
High	128	16.5 (7.0)	2.72 (0.91)	2.72 (0.91)
Occupation				
Low	133	16.8 (7.0)	2.73 (0.92)	2.48 (1.39)
High	33	16.5 (6.1)	2.67 (0.89)	2.37 (1.37)
Initial memory score group				
Low	98	11.9 (4.5)	2.69 (0.85)	2.35 (1.38)
High	79	22.7 (3.2)	2.70 (0.97)	2.37 (1.37)

SRT = Selective Reminding Test.

Table 3 *Generalized estimating equations (GEE) analyses of the relationship between educational or occupational attainment and the rate of decline in memory test scores over time*

Variable	Covariates in the GEE models		
	Time	Variable	Time × variable
All subjects			
Education group	−1.65*	−0.97	0.82†
Occupation group	−0.87*	0.22	−0.95*
Low initial memory scores			
Education group	−1.61*	−1.85	1.79*
Occupation group	0.04*	1.71	−1.44*
High initial memory scores			
Education group	−1.55*	−0.19	−0.30
Occupation group	−1.74*	−0.39	−0.64

Each row represents a separate analysis. Analyses were calculated initially for the entire patient group, and then for patients with low or high memory test scores at the initial visit. Table values are the β-values for each covariate in the model.

* $p < 0.05$.
† $p < 0.06$. All other values were not significant ($p > 0.10$).

and occupational attainment. In both cases there was no suggestion of an unequal distribution (for education, $\chi^2 = 0.03$, not significant; for occupation, $\chi^2 = 0.55$, not significant). We divided the patients into two groups based on their initial memory scores. Mean memory scores, as well as number of visits and years of follow-up in the two groups, are summarized in table 2. We then repeated the GEE analyses in these groups. For both education and occupation, the interaction effect was significant only in patients with low baseline scores and not in those with high baseline scores. We also repeated the full group and stratified group analyses, controlling for other potentially

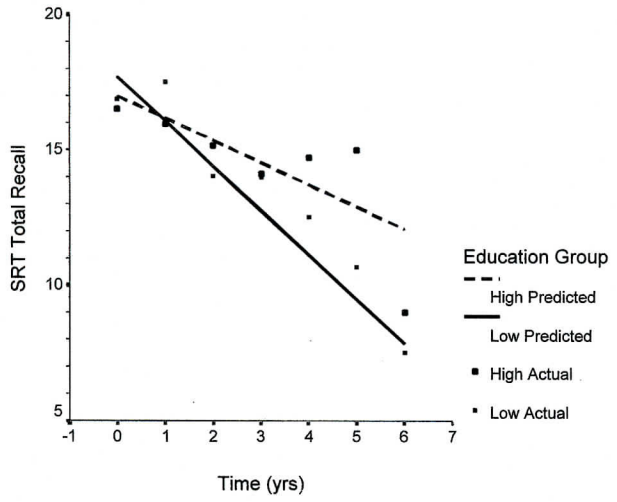

Figure 1. Decline in memory score over time in AD patients with high (>8 years) and low (≤8 years) educational attainment. Lines represent the general estimating equations regression models. Individual data points represent the actual data at each yearly interval. SRT = Selective Reminding Test.

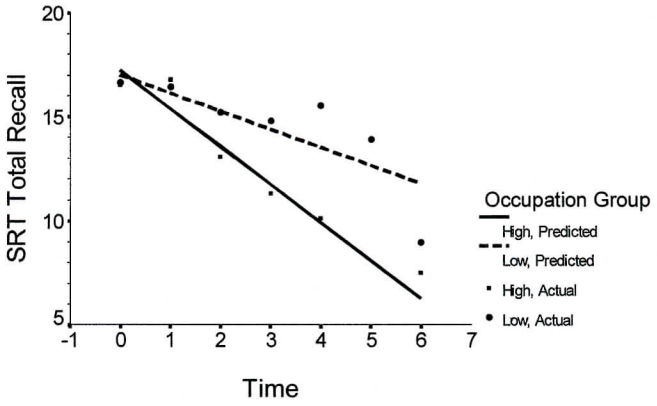

Figure 2. Decline in memory score over time in AD patients with high and low occupational attainment. Lines represent the general estimating equations regression models. Individual data points represent the actual data at each yearly interval. SRT = Selective Reminding Test.

relevant variables including age and Clinical Dementia Rating Scale score at the initial visit. The results remained unchanged.

GEE analyses were used to evaluate a series of variables that might modify the relation of educational and occupational attainment and memory decline. Potential confounders that were evaluated included gender, race, ethnicity, extrapyramidal signs, or the presence of stroke or at least one *APOE*-ϵ4 allele. In each case, the model included the covariates described earlier (e.g., education, time, and time × education interaction), as well as the potential confounder and appropriate interactions. The relationship described earlier remained unchanged. We also evaluated directly the relationship between rate of memory decline and each of these variables in simpler, separate GEE models that included each variable in turn, along with time and the interaction of that variable and time. The interaction with time was not significant for any of these variables (table 4).

Table 4 *Generalized estimating equations (GEE) analyses evaluating a series of variables that might modify the relation of educational and occupational attainment and memory decline*

Variable	Time	Variable	Time × variable
Age	−1.98	−0.13*	0.01
Gender	0.46*	1.11	0.51
Race	−1.26*	−1.38	0.50
Ethnicity	−0.82*	1.26	−0.39
Stroke	−0.91*	0.17	−0.45
Extrapyramidal signs	−3.09*	−0.12	−0.89
APOE	−1.27*	0.45	0.43
CDR Scale group	−1.01*	−3.26*	−0.12

In each case, the models included the variable of interest, time, and the time × variable interaction. Table values are the β-values for each covariate in the model.

* $p < 0.05$. All other values were not significant ($p > 0.10$).

CDR = Clinical Dementia Rating.

Discussion. Our findings support the idea that clinical features of AD progress more rapidly in patients with higher educational and occupational attainment. Our results are comparable with those of Teri et al.,[21] who found that higher educational attainment was associated with a more rapid decline in Mini-Mental State Examination and dementia rating scale scores in patients with AD. Teri et al.[21] did not evaluate occupational attainment.

These findings add support to the concept that the discontinuity between the degree of AD pathology and the clinical severity of AD is mediated through some form of reserve. Some investigators have suggested the concept of "brain reserve."[22] This is a passive mechanism based on individual variation in brain size or synaptic density. Because AD reduces synaptic density, it might reduce initially the efficiency of particular cognitive processes by disrupting cortical–cortical connections between brain areas that mediate this process. Thus, individuals with more brain reserve might have more synapses to lose before AD is expressed clinically. In fact, some studies have suggested that larger brain size might be protective against dementia.[23-25] We favor the concept of cognitive reserve, which reflects active compensation for AD pathology. Differential reserve reflects individual differences in how the brain processes cognitive or functional tasks in the face of the disruption of AD pathology. Individuals with more educational or occupational attainment, or with higher premorbid IQ might use cognitive strategies that are less likely to be disrupted, or they might compensate more successfully for disease pathology by using brain structures or networks not used normally by individuals with intact brains.[26,27] The level of educational attainment in our study population was relatively low. This may limit the generalizability of the results to other populations, if differential reserve is more likely to be noted in patients with very low educational attainment.

The basic reserve-based explanation for our findings is illustrated in figure 3. Because patients with higher educational and occupational attainment have more cognitive reserve, more pathology is required before memory begins to be affected. However, AD pathology progresses independently from educational and occupational attainment, and when pathology becomes very severe there is no longer a substrate for cognitive reserve to come into play. Thus, the severity of AD pathology at the initiation of memory deficit varies as a function of reserve, but the level of pathology associated with severe clinical dysfunction does not vary as a function of reserve. The result is a shorter time between the initiation of memory loss and severe memory disability in patients with higher educational and occupational attainment. The current findings do not address directly cognitive, as opposed to brain, reserve, but might lend more support to the former. The observation that the most marked difference in the rate of memory decline between patients with high and low

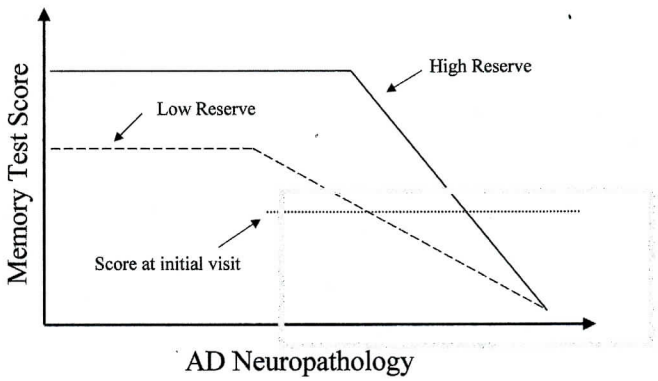

Figure 3. Theoretical model to explain the observation of more rapid progression in patients with higher educational or occupational attainment. The highlighted area of the figure coincides with the period of time reflected by the data in this paper.

educational and occupational attainment was seen in patients with lower initial memory scores is more consonant with the cognitive reserve concept. At any level of clinical severity, pathology would be more severe in the group with more reserve. However, the point at which cognitive reserve becomes less effective would be reflected by a rapid increase in the rate of clinical decline. The brain reserve hypothesis, on the other hand, does not provide a ready explanation for a change in the rate of clinical progression as pathology becomes more severe.

The nature of the reserve provided by educational and occupational attainment or intelligence is still unclear. We have suggested that reserve is the ability to maximize performance through differential recruitment of brain networks, which perhaps reflects the use of alternate cognitive strategies. By definition, the increased recruitment associated with reserve is a normal response to increased task demands, and is present in both healthy individuals and those with AD. Another alternative suggested by several investigators is that patients compensate for disease pathology by using brain structures or networks not utilized by healthy control subjects. In this case, patients with higher educational or occupational attainment might compensate more effectively. Preliminary imaging studies that we are conducting suggest that patients may use their reserve early in the disease process and compensate later, when pathology becomes more severe.[28]

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