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Memory decline in healthy older people

Implications for identifying mild cognitive impairment

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Article abstract—*Background:* Criteria for mild cognitive impairment require objective evidence of a memory deficit but do not require objective evidence of memory decline. Application of these criteria may therefore result in the misclassification of older patients with memory decline as normal because their neuropsychological test performance at a single point in time may be within normal limits. This study aimed to identify and characterize older people with memory decline. *Method:* Word list delayed recall (WLDR) test performance was assessed on five occasions during a 2-year period in a cohort of healthy older individuals. Older people with declining (n = 35) and nondeclining (n = 66) WLDR scores were identified. Both subgroups were then compared on apoE genotype, Clinical Dementia Rating, and neuropsychological test performance at the fifth assessment. *Results:* Thirty-four percent of the group with declining memory recorded a Clinical Dementia Rating of 0.5, compared with 5% of the nondeclining memory group. No between-group differences were observed in cognitive domains other than memory, self-reported cognitive failures, or the proportion of each group carrying the apoE epsilon 4 allele. *Conclusions:* A large proportion of healthy older individuals show memory decline, which may represent the early stages of a potentially more severe cognitive impairment. Further investigation is necessary to determine the relationship between apoE genotype, self-reported cognitive impairment, and memory decline in older people.

NEUROLOGY 2001;56:1533–1538

Neuropathologic evidence supports the assertion that there is a long prodromal period in the AD process.[1] The first domain of cognition to show deterioration during this prodrome is episodic memory.[2,3] Retrospective studies of patients with probable AD have shown that subtle episodic memory impairments can be detected as many as 20 years before diagnosis.[3-5] This promising finding suggests that the careful assessment of memory in older people may provide the earliest indication of AD. However, prospective studies indicate that approximately only 50% of older people with mild episodic memory impairments progress to develop clinically recognizable AD.[6,7] The low specificity of memory impairments for predicting the subsequent development of AD is also manifest in the conflicting results of studies that have challenged groups of memory-impaired older people with measures of other putative risk factors for AD, including hippocampal atrophy[8-10] and the apoE epsilon 4 (apoE-4) allele.[11,12]

Currently, individuals at risk for developing AD on the basis of impaired memory are identified by comparison of their memory test performance with a cut-score estimated from some normative group.[2,13] However, a number of factors may interfere with the accurate identification of at-risk individuals when such identification is made on the basis of a single cognitive or clinical assessment. For example, mem-

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Supported by project grant 96/0353 from the National Health and Medical Research Council of Australia.

Received July 11, 2000. Accepted in final form February 8, 2001.

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Table 1 *Demographic and cognitive data for the entire healthy older cohort (n = 254) and for subjects enrolled in the current study (n = 101) at entry*

Characteristics	Entire cohort	Current subjects
No.	254	101
Age, y	63.1 (9.0)	62.2 (7.9)
Education, y	12.8 (3.9)	13.2 (3.9)
Gender, F/M	174/80	73/28
NART estimated IQ	121.5 (4.6)	123.1 (4.8)
MMSE	28.5 (1.4)	28.8 (1.2)
Categorical verbal fluency	20.6 (5.4)	21.4 (5.5)
Confrontational naming	14.4 (0.8)	14.5 (0.8)
Constructional praxis	9.6 (1.3)	9.7 (1.1)
Word list learning	21.8 (3.9)	22.9 (3.5)
Word list delayed recall	7.2 (1.9)	8.0 (1.4)
State anxiety	31.7 (9.0)	30.9 (8.1)
Trait anxiety	34.9 (9.2)	34.4 (8.1)
Depression	8.5 (6.6)	7.3 (5.2)

All data are presented as group mean (± standard deviation).

NART = National Adult Reading Test; MMSE = Mini-Mental State Examination.

ory impairments in older people can be static and unrelated to any neurodegenerative disease process.[14] Second, levels of depressive or anxiety symptoms may be increased in older individuals, albeit insufficient to meet criteria for a psychiatric diagnosis, and are often exacerbated by the assessment process. These symptoms may interfere with performance on memory tasks,[15,16] making the individual appear impaired when they are not. Third, there is a large amount of variability in memory test performance in the healthy older population.[17] Memory test performance that has declined significantly from a previous level but is still within normal limits may therefore be misclassified as normal. In such cases, it is insufficient to assess memory on a single occasion, as declining test performance can only be identified objectively by longitudinal assessment.

Memory impairment associated with neurodegenerative processes may therefore be identified more reliably if objective evidence of memory decline was required before diagnosis. If such methods were implemented, differences between static and progressive memory impairments would be obvious, and memory decline in high functioning individuals would become evident even if performance remained in normal limits. Despite the intuitive appeal of this approach, none of the classification systems currently used to identify patients at-risk for AD require objective evidence of memory decline.[2] In this study, we sought to determine the proportion of a cohort of healthy older individuals who had memory decline for 2 years. We also sought to determine the relationship between memory decline and other putative risk factors for AD, including apoE genotype, self-rated cognitive function, and performance on neuropsychological measures. Clinical Dementia Ratings (CDR) were also calculated to determine the proportion of older people with memory decline who met a standard clinical criteria for mild cognitive impairment (MCI).

Methods. *Subjects.* A total of 101 neurologically healthy older people participated in the study. All participants were recruited from a large cohort of older individuals participating in an ongoing investigation of aging being conducted at an independent research institute located in Melbourne, Australia. The mean age, mean education, ratio of men to women, and range of cognitive test performance among subjects in the current study are all representative of those reported previously in this cohort.[18-20] Table 1 shows demographic and cognitive results for the larger cohort (n = 254) and for the group of subjects enrolled in the current study (n = 101) at entry. All subjects spoke English as their first language. Inclusion and exclusion criteria for this study have been described elsewhere.[18-20] Informed consent was obtained from all participants before inclusion in the study.

Materials and Procedure. Parallel forms of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery[22] were administered at 6-month intervals to each subject on five occasions during a 24-month period. The CERAD battery consists of a confrontational naming test, a test of categorical verbal fluency, word list learning and word list delayed recall (WLDR) tests, a measure of constructional praxis (line drawing), a word list recognition task, and the Mini-Mental State Examination. The National Adult Reading Test (NART[23]) was administered on the first assessment to estimate intellect.

The WLDR measure was used to rate subject's cognitive status (declining memory or nondeclining memory), as it has been shown to be a valid and reliable measure of mild episodic memory impairment in healthy older people and in patients in the early stages of dementia.[24,25] For each subject, five data points for the WLDR score were plotted as a function of time in months since the baseline assessment. A least-squares linear regression was then fitted to these points, and the intercept and slope of this line were calculated. Subjects were classified as having memory decline if the slope of that regression equation was less than 0 (i.e., negative slope).[26,27] Subjects with a slope of 0 or greater were classified as nondeclining. On the fifth assessment, all subjects completed the State-Trait Anxiety Inventory (STAI[28]) and the Center for Epidemiologic Studies Depression rating scale (CES-D[29]). Self perceived cognitive decline was measured using the Cognitive Failures Questionnaire (CFQ[30]). Neuropsychological measures at the fifth assessment included the remaining CERAD subtests and another test of episodic memory (paired associative learning) that has shown a validity for identifying older people who progress to develop AD in samples of individuals with equivocal evidence of cognitive impairment.[31-33] At one of the five assessments, blood samples were collected from each subject. DNA was extracted from these samples to determine apoE genotype according to standard techniques described by Hixson and Vernier.[34] Finally, at the fifth assessment, each subjects' neurobehav-

Table 2 *Demographic data for older people with declining memory and nondeclining memory at assessment 5*

Characteristics	Declining memory	Nondeclining memory	*p* Value
No.	35	66	
Age, y	64.3 (7.4)	61.1 (8.0)	NS
Education, y	12.6 (3.5)	13.6 (4.0)	NS
Gender, F/M	24/11	49/17	NS*
NART estimated IQ	119.9 (6.3)	121.4 (5.6)	NS
WLDR slope	−0.3 (0.2)	0.2 (0.2)	<0.001
WLDR intercept	8.4 (1.5)	8.0 (1.1)	NS

All data are presented as mean (± standard deviation).

* Chi-square test of significance used.

NART = National Adult Reading Test; WLDR = word list delayed recall test; NS = not significant at the 0.05 level.

ioral function was assessed by a neurologist or neuropsychologist using the CDR scale.[35] These clinicians were masked to information from all other testing sessions and to genetic data. When data met the assumptions of normality, independent samples *t*-tests were used to examine group differences. When they did not, Mann-Whitney *U* nonparametric tests were used. To reduce the rate of false positives associated with multiple comparisons, group differences were considered to be significant if the *p* value or χ^2 statistic of the significance test was less than 0.01.

Results. For the entire group, regression estimates of performance on the CERAD WLDR test during the study period yielded slopes that ranged from −1.10 to +0.90 and intercepts that ranged from 5.9 to 10.5. The mean ± SD slope of WLDR performance over five visits for the entire group was 0.03 ± 0.33, and the mean intercept was 8.13 ± 1.24. Thirty-five subjects (34.7%) recorded a slope of less than 0 (negative slope) and were therefore classified as having declining memory. The remaining subjects (n = 66; 65.3%) were placed in the nondeclining memory group. Table 2 shows demographic data for each of these groups. The mean ± SD slope of the declining memory group was −0.31 ± 0.25, and the mean slope of the nondeclining memory group was 0.22 ± 0.20. For the declining memory group, this indicates a decrease in performance of 7.75% per year on the WLDR test (i.e., 0.775 of 10 possible words). For the nondeclining memory group, this represents an improvement in performance of 5.45% per year on the WLDR test (0.545 of 10 possible words). Although the slopes of the two groups were by definition different ($t(99) = 57.32$, $p < 0.001$), there were no significant differences between the intercepts of the declining memory (mean = 8.40, SD = 1.51) and nondeclining (mean = 7.98, SD = 1.07; $t(99) = 1.522$, $p = 0.134$) memory groups. Analysis of mean performance of both groups at all assessments indicated significant differences on WLDR score at assessments 2, 3, 4, and 5 but not at assessment 1. The magnitude of the difference in WLDR scores between the two groups increased from the first to the last assessment, as indicated by the increasing effect size described in table 3.

Table 4 summarizes the genetic, clinical, and neuropsychological status for the declining and nondeclining memory groups at the fifth assessment. Significant between group differences were observed on the percentage of subjects rated as having a CDR of 0.5. The declining memory group displayed significantly worse performance on the pattern–location paired associative learning test relative to the nondeclining memory group. No other group differences were observed.

Discussion. During a period of 2 years, a large proportion of healthy older individuals showed progressively worsening episodic memory function as measured by performance on the WLDR test. It is unlikely that the memory decline observed in these individuals was caused by any systemic medical or psychiatric illness because of the strict exclusion criteria used. The average rate of WLDR test decline in these subjects was approximately 0.775 words per year (from a maximum score of 10), although no individual classified as having declining memory met the clinical criteria for probable AD at the final assessment. Despite this decline, group mean performance on the WLDR test always remained within the normal limits established for the test (i.e., >6[21]). The rate of decline was greater than that observed in patients with severe probable AD on the same memory test,[27] although floor effects associated with the performance of the AD patients would most likely have reduced estimates of decline in this previous study. No differences were observed here between the declining memory and nondeclining memory groups on WLDR score at baseline (table 3), suggest-

Table 3 *Mean (± SD) word list delayed recall (WLDR) test performance of the declining and nondeclining memory groups on five consecutive assessments*

WLDR assessment	Declining memory	Nondeclining memory	Difference score	*p* Value	Effect size
1	8.0 (1.8)	8.0 (1.1)	0.0	0.96	0.00
2	7.9 (1.9)	8.7 (1.3)	0.8	0.02	0.05
3	7.5 (1.4)	8.7 (1.4)	1.2	<0.001	0.15
4	7.2 (1.9)	8.8 (1.0)	1.6	<0.001	0.22
5	6.8 (2.0)	9.0 (1.1)	2.2	<0.001	0.36

Difference scores are the mean of the nondeclining memory group minus the mean of the declining memory group.

SD = standard deviation; WLDR = word list delayed recall test score.

Table 4 *Clinical, genetic, and neuropsychological outcomes in older people with declining memory and nondeclining memory at time 5*

Outcomes	Declining memory		Nondeclining memory	*p* Value
CDR 0.5 (% of group)	34.3		6.3	<0.001*
APOE genotype (% of group)				
ε4+	30.4		34.9	NS*
ε3/3	43.5		53.5	NS*
ε2/3	26.1		11.6	NS*
State anxiety	31.5 (9.6)		29.4 (7.9)	NS
Trait anxiety	31.9 (9.0)		31.7 (7.1)	NS
Depression	8.0 (7.0)		6.2 (5.3)	NS
Subjective cognitive function				
Memory subscale	13.1 (13.7)		12.8 (4.5)	NS
Perception subscale	10.7 (3.8)		10.5 (3.0)	NS
Motor action subscale	11.6 (4.2)		11.5 (5.0)	NS
Total	35.3 (10.5)		34.8 (11.5)	NS
Neuropsychological function				
MMSE	28.5 (1.4)		29.1 (1.0)	NS
Category verbal fluency	23.4 (5.1)		25.8 (4.7)	NS
Confrontational naming	14.6 (1.1)		14.8 (0.5)	NS*
Constructional praxis	10.1 (0.9)		9.9 (1.1)	NS*
PAL number of errors	20.5 (17.2)	>	10.2 (7.4)	<0.001
PAL list memory	7.7 (2.9)	<	9.5 (2.4)	<0.01
PAL number of trials	8.0 (3.6)	>	5.5 (2.4)	<0.001

All data are presented as mean (± standard deviation) unless otherwise stated.

* Chi-square test of significance.

CDR = clinical dementia rating of 0.5 (questionable dementia); ε4+ = presence of at least one *APOE* epsilon 4 allele; ε3/3 = two *APOE* epsilon 3 alleles; ε2/3 = presence of one *APOE* epsilon 2 allele and one *APOE* epsilon 3 allele; MMSE = Mini-Mental State Examination; PAL = pattern-location paired associative learning; NS = not significantly different at the 0.05 level.

ing that initial level of memory test performance could not predict group membership. Finally, levels of anxiety and depressive symptoms were equivalent in the declining memory and nondeclining memory groups, as was the frequency of complaints of impaired cognitive function. These findings have important implications for the clinical diagnosis of disorders, such as MCI and AD, because they suggest that cognitive decline can be detected in nondemented and high-performing older people using standard neuropsychological tests before these individuals meet conventional clinical criteria for cognitive impairment (i.e., CDR 0.5). However, detection of this decline requires the serial administration of valid and reliable neuropsychological tests over an extended period.

The proportion of individuals classified as having memory decline was larger than expected on the basis of epidemiologic estimates of the prevalence of AD or MCI in individuals older than age 65.[36,37] Health-related conditions other than neuronal degeneration (e.g., cardiac illness[38]) may have adversely affected cognitive performance in some individuals, increasing the estimated rate of memory decline among the current group of subjects. However, the strict exclusion criteria applied makes this explanation unlikely. The high estimate of memory decline may also result from psychometric limitations associated with administering the WLDR test to the same group of people on multiple occasions (e.g., ceiling effects). Alternatively, previous studies examining the prevalence of MCI among community-based cohorts may have underestimated the true rate of cognitive impairment through their inability to classify high functioning individuals who show mild memory decline as impaired. Regardless of the reason for the difference between current and previous estimates, it is unlikely that the cognitive abilities of 35% of people in their 60s will decline to a level indicative of a dementia. However, only further longitudinal analysis of the current cohort will determine the validity of this prediction. The study from which the current data are drawn was not designed to produce epidemiologic estimates of the prevalence of memory impairment or decline in the older community. That is, some components of the study design (e.g., the a priori exclusion of individuals with a history of cardiac or respiratory illness) may mean that the current cohort is not representative of the older community. However, these same components ensure that we are

able to detect mild changes in the cognitive function via methods such as those described in this report.

Objective evidence of memory impairment on a single assessment is sufficient to obtain a classification of CDR 0.5 (questionable dementia) or MCI.[14,39] Approximately half of all older individuals classified as having MCI are diagnosed with neurodegenerative illness within 2 to 4 years.[33,37] In the current study, only 34.3% of individuals with declining memory were rated as impaired, according to CDR criteria at assessment 5. Although clinical scales such as the CDR are often used to stage dementia severity and monitor disease progression in patients with AD,[26,27] our results suggest that the sensitivity of CDR criteria for detecting memory decline in healthy older people is poor, because two thirds of older individuals with memory decline were misclassified as having normal cognitive function when this instrument was applied in the current cohort (i.e., false-negative diagnoses). Importantly, the proportion of the nondeclining memory group rated as CDR 0.5 at assessment five was low (i.e., approximately 5%), indicating that older individuals whose memory test performance remains static or improves are unlikely to meet conventional clinical criteria for impairment. Memory decline does not appear to be associated with impairment in other cognitive functions, because there were no differences observed between the performance of the declining memory and nondeclining memory groups on the remaining CERAD tests or the Mini-Mental State Examination at the final assessment. However, the presence of memory impairment in the memory decline group was validated by the observed impairments on the associative learning test. This measure has been shown previously to be sensitive and specific to the mild[40] and preclinical[33] stages of AD. Taken together, these findings emphasize the potential power of longitudinal analyses of cognitive function for the detection of individuals at risk for AD indicated by memory decline.

The apoE epsilon 4 allele is a genetic risk factor for late-onset sporadic AD and is thought to play a role in the neurodegenerative processes that are the hallmark of the disease.[41] A consistent finding from previous research has been that apoE 4 is associated with impaired memory.[12,42,43] In the current study, there was no difference in the proportion of the declining memory and nondeclining memory groups carrying the apoE 4 allele, suggesting that there is no association between apoE 4 and memory decline in healthy older people. This finding is consistent with some previous studies that have shown that the apoE genotype does not influence rate of cognitive decline in normal aging,[11] mild memory impairment, or AD.[44] However, apoE status is also related to cardiovascular health, and the exclusion of patients with cardiac illness from the current study may have influenced our results.[45] Alternatively, the small sample size (35 subjects in the declining memory group) in the current study may not have provided the statistical power necessary to detect a subtle relationship between apoE status and memory function.

It has been proposed recently that self-reported cognitive impairment may be one of the earliest behavioral markers of AD.[46] However, the association between mild memory decline identified objectively and subjective complaints of memory loss is inconsistently reported.[47] In the current study, ratings of cognitive failures did not differ between older individuals with declining and nondeclining memory. This may have arisen because the memory decline observed was subtle and may not manifest as cognitive failures that occur in the individuals' daily environment. This hypothesis is supported by previous studies that have suggested that older individuals with mild to moderate dementia may have some insight into their own memory deficit.[16] However, a negative relationship between severity of cognitive impairment and level of insight seems counterintuitive, and therefore, further investigation of subjective cognitive function in nondemented older people with mild and severe memory impairments are necessary to address this important issue.

Our results suggest that episodic memory decline can be detected among healthy older people before an objective memory deficit is evident using standard clinical criteria. This finding has important implications for the design and implementation of classification systems aimed at identifying individuals at increased risk for AD on the basis of cognitive test performance, because it suggests that the inclusion criteria for such systems should require objective evidence of cognitive decline. The current results also suggest that cognitive decline should be determined through the use of neuropsychological measures of memory that not only are sensitive and specific to the type of impairments observed in preclinical and early stages of AD, but also have psychometric properties adequate to allow the modeling of longitudinal performance. We are currently using more sophisticated statistical methods (e.g., hierarchical linear modelling[48]) to validate the regression method of measuring decline described in this article. Such statistical modeling may provide further insight into the changes in memory functions that occur with aging and the early stages of neurodegenerative disease. However, estimates of decline based on the regression approach provide an index of performance that can be calculated simply for single subjects and are meaningful clinically because the units of measurement are preserved in the calculations. Finally, our results are consistent with recent research that has suggested that the apoE epsilon 4 allele and subjective complaints of cognitive failures are not associated with memory decline in healthy older people.

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