ORIGINAL CONTRIBUTION

A Prospective Study of Cognitive Function and Onset of Dementia in Cognitively Healthy Elders

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Objective: To examine the earliest cognitive changes associated with the onset of dementia as well as changes associated with normal aging.

Design: Longitudinal evaluation of participants with annual clinical and psychometric examinations for up to 15½ years.

Setting and Participants: Elderly volunteers (n=82) enrolled with a Clinical Dementia Rating of 0 (cognitively intact) in longitudinal studies.

Interventions: None.

Main Outcome Measures: Clinical Dementia Rating and results of a 1½-hour psychometric battery.

Results: As estimated with survival analysis, 40% of participants had a Clinical Dementia Rating greater than 0 (cognitive decline) within 12 years of enrollment; 59% of these were judged to have dementia of the Alzheimer type or incipient dementia. Participants with poorer performance on psychometric testing at enrollment were at higher risk for cognitive decline subsequently. The rate of change in psychometric performance before clinically detectable cognitive change occurred was not significantly different between those who eventually developed dementia and those who remained stable, except for performance on the Logical Memory subtest of the Wechsler Memory Scale. When subtle cognitive decline was clinically detected, however, an abrupt deterioration in performance on independently administered psychometric tests was observed.

Conclusions: Cognitively healthy elderly people maintain stable cognitive performance when measured longitudinally by both careful clinical evaluation and repeated psychometric testing. This stability is maintained unless and until they develop a dementing illness, at which time a sharp decline in performance is observed.

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DETECTING Alzheimer disease in its early stages challenges researchers and clinicians alike. To warrant a diagnosis of dementia of the Alzheimer type (DAT), cognitive impairment must interfere with previous levels of functioning in usual activities.[1,2] This determination, which often is difficult when dementia is very mild, generally relies on reports of subtle cognitive and functional decline from either the individual or a knowledgeable collateral source. Performance on a standardized battery of tests of cognitive function may not be helpful in very mild stages of DAT because cognitive abilities vary among healthy individuals, and decline may not always be reflected by scores in impaired ranges. An alternative strategy to the 1-time administration of such a battery is longitudinal assessment.[3]

We examined the longitudinal course of cognitive performance in a group of cognitively healthy individuals who were enrolled for comparison with a group who had DAT at entry in the context of a study of aging and DAT. These persons received annual clinical evaluations and independent neuropsychological assessments for up to 15½ years; these clinical evaluations have been sensitive in detecting the earliest clinical manifestations of DAT.[4] This approach permitted the ascertainment of the proportion of cognitively healthy participants who experienced cognitive decline and the number of these who developed symptoms consistent with DAT. In addition, by examining the longitudinal patterns of psychometric performance in relation to the clinical detection of dementia, we could determine whether clinically detectable dementia appears when "normal" age-associated cognitive decline[5,6] crosses a critical thresh-

SUBJECTS AND METHODS

SAMPLE

Details concerning recruitment and enrollment of participants as well as assessment methods have been published previously.[13,14] Briefly, 82 elders (31 men and 51 women) were enrolled as healthy volunteer controls in 2 longitudinal studies of DAT and were examined annually unless prevented by death, refusal, or distant relocation. Fifty-seven persons were enrolled between 1979 and 1981; 25 were enrolled between 1984 and 1986. People with potentially confounding psychiatric, neurologic, or medical conditions were excluded. At entry, all individuals were living independently in the community. Ages ranged from 64 to 83 years (mean, 71.6±4.8 years). Mean (±SD) education was 13.3±3.2 years. Data from these individuals have been included in numerous earlier reports from our longitudinal studies comparing DAT with normal aging. This is the first report, however, of the long-term follow-up of these healthy individuals.

CLINICAL EVALUATION

Research-trained physicians administered a semistructured interview to each participant and to a knowledgeable collateral source, together with a neurologic examination of the participant. The clinician then rated each participant in 6 areas of cognitive function: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. A Clinical Dementia Rating (CDR) was assigned according to published rules to indicate the presence or absence of dementia and, if present, its severity.[15,16] Interrater reliability for the CDR has been established.[17] A CDR of 0 indicates no dementia (cognitively intact); CDRs of 0.5, 1, 2, and 3 indicate questionable or very mild, mild, moderate, and severe dementia, respectively. All participants in this study received a CDR of 0 at time of entry. Subsequent evaluations were scheduled approximately annually and were conducted without reference to previous interviews. At time of death, the entire clinical assessment record was reviewed and an expiration summary, including a final CDR, was prepared as discussed elsewhere.[18]

On the basis of our research experience with the diagnosis of questionable DAT and beginning in 1990, the CDR 0.5 category was separated into 3 subcategories: very mild DAT[13,19,20] (very mild cognitive decline involving impairment in memory and 3 or more additional areas of cognitive function), incipient DAT (very mild cognitive decline suggestive of DAT but in fewer than 4 areas of function), and uncertain dementia (very mild cognitive change, but the clinician is not sure that it represents very mild or incipient DAT).[21] The "uncertain" dementia group is a focus of ongoing research at our center; it probably represents a heterogeneous group of people, some of whom may have the beginning symptoms of DAT.

All procedures and methods for obtaining informed consent from participants and collateral sources were approved by the Human Studies Committee of Washington University, St Louis, Mo.

PSYCHOMETRIC BATTERY

A 1½-hour battery of psychometric tests was administered by trained psychometricians, usually within a few weeks of each clinical assessment. None of these psychometric tests was used in the clinical assessment or CDR assignment, and neither the clinicians nor the psychometricians were aware of the others' results. As described elsewhere,[14] the battery included measures of both episodic and semantic memory, visuospatial ability, language, executive function, and attention (**Table 1**).

A principal-components analysis of the psychometric test scores at entry for the entire sample produced a single factor (according to the screen test) accounting for 34% of the variance. All psychometric measures had loadings of 0.37 or greater (maximum, 0.73 for Wechsler Adult Intelligence Scale [WAIS] Block Design) except Crossing-off (0.29), indicating a general factor of cognitive ability in these older adults who exhibited no dementia. Factor scores for each individual at each time of testing were computed by means of the weights from this principal-components analysis. These factor scores were standardized, with the use of the mean and SD at time of entry.

old or whether the diagnosis of dementia correlates with an abrupt change from previous performance.[7] Finally, we asked whether there were differences in cognitive performance at the time of entry into the study between those who did and did not develop dementia. Differences existing years before clinically detectable cognitive change would support accumulating evidence that suggests an increased risk for dementia in those with poorer initial levels of ability.[8-12]

RESULTS

CLINICAL OUTCOME AND NEUROPATHOLOGICAL FINDINGS

We used the product-limit estimator (Kaplan-Meier) to estimate the proportion of individuals developing dementia over time. The end point was the first clinical assignment of a CDR greater than 0. Death (n=18), unavailability for follow-up (n=2), and June 1, 1995, were used as censoring points for those remaining with a CDR of 0 throughout the study. As shown in **Figure 1**, an estimated 40% developed a CDR greater than 0 within 12 years after initial examination. Most (>80%) of these people were not assigned a CDR greater than 0 until after the first 5 years of follow-up, consistent with the presumption that the observed decline did not represent erroneous classification at entry.

Twenty-seven individuals (9 men and 18 women) were assigned a CDR greater than 0 during the course of the study. Participants whose rating declined were older at entry (73.6±4.9 years) than those whose rating did not (70.7±4.6 years). There was no difference in years of education between the 2 groups (13.4±3.4 vs 13.2±3.2).

People were grouped on the basis of the rating that indicated the most severe cognitive deterioration. Of the

Table 1. Psychometric Performance Before Clinical Detection of Dementia*

	Effect of Age	Intercepts			F	Slopes			F
		Stable	DAT/IDAT	Uncertain		Stable	DAT/IDAT	Uncertain	
Wechsler Memory Scale[22]									
Mental control	−0.05†	7.61	6.91	6.49	3.36†	0.00	0.05	0.01	0.77
Logical memory	−0.06†	9.86	10.69	8.46	2.80	−0.01	−0.16	−0.07	8.80‡
Digit span									
Forward	−0.08§	7.08	6.53	6.07	6.11§	−0.01	0.06	0.09	2.70
Backward	−0.08§	5.30	5.05	4.17	4.05†	−0.02	−0.03	0.06	2.54
Associate learning	−0.07§	13.38	13.44	11.25	2.24	0.06	0.02	0.06	0.33
Benton Visual Retention[23]									
Recall (No. correct)	−0.13‡	5.98	5.23	5.73	1.92	0.00	0.01	−0.06	0.58
Copy (No. correct)	−0.01	9.43	9.21	9.61	0.57	0.04	0.04	−0.06	2.72
Wechsler Adult Intelligence Scale[24]									
Information	−0.04	21.03	19.60	19.39	1.01	0.00	0.00	0.00	0.21
Block Design	−0.11‡	30.95	27.49	27.80	2.37	−0.03	0.01	−0.03	0.65
Digit Symbol	−0.10‡	48.19	41.49	44.05	3.22†	−0.07	−0.10	−0.05	0.54
Trailmaking A, s[25]	0.09§	40.00	44.80	50.13	4.21†	0.07	0.23	0.06	2.60
Crossing-off[26]	−0.05	171.70	165.80	171.40	0.21	−0.06	−0.14	−0.06	1.08
Boston Naming Test[27]	−0.06§	54.85	50.51	53.41	4.90§	0.01	−0.01	0.02	0.35
Word Fluency (S+P)[28]	−0.05	31.97	29.10	24.08	2.66	0.02	0.00	0.00	0.29
Factor score	−0.11‡	0.32	−0.24	−0.49	5.35§	−0.01	−0.05	−0.01	1.16

**DAT indicates dementia of the Alzheimer type; IDAT, incipient DAT; S+P, letters "*s*" and "*p*". For all tests except Trailmaking A, a higher score indicated better performance. The values in the column labeled "Effect of Age" are standardized regression coefficients of age with the intercept. A negative value indicates poorer performance with increasing age; the reverse is true for Trailmaking A. The intercept values for the 3 groups are least squares means estimating average performance at time of entry, adjusted for age (in original units). The average standardized slopes indicate rate of change per year. Estimates were based on 1 to 15 times of assessment (mean, 9.3) for the stable group, 3 to 14 times of assessment for the DAT/IDAT group (mean, 9.6), and 3 to 15 times of assessment for the uncertain group (mean, 9.2). The* df *for the numerator of the F ratios comparing the 3 groups was 2; they varied from 454 to 467 for the denominator because of missing data.*

†P≤*.05.*

‡P≤*.001.*

§P≤*.01.*

27 people who deteriorated clinically, 16 were classified as having DAT (n=10) or incipient DAT (n=6) and 11 as having uncertain dementia. Eleven of these 27 died, and 6 of these had brain autopsies. Five of the 6 were in the DAT/incipient DAT group, and Alzheimer disease was confirmed in 4 on the basis of conventional histological criteria.[18,29] The remaining subject had developed clinical symptoms of Parkinson disease after entry into the study; at autopsy, pathological Parkinson disease was present, but pathological changes were insufficient to meet criteria for Alzheimer disease. The 1 participant in the uncertain dementia group whose brain was examined histologically had Alzheimer disease.

Fifty-five individuals (22 men and 33 women) remained cognitively stable, and 9 of the 18 who died had brain autopsies. Six of these 9 showed no evidence of Alzheimer disease; the other 3, however, did. Two of these 3 sustained major head trauma as the result of pedestrian/motor vehicle accidents that resulted in death within 2 days for 1 person and within 138 days for the other.[18] Neuropathological data for all but 3 of the 15 people who had autopsies have been published previously.[4,18,30,31]

PSYCHOMETRIC PERFORMANCE BEFORE CLINICALLY DETECTABLE COGNITIVE CHANGES

Psychometric performance before clinically apparent cognitive changes was examined for 3 groups: stable, DAT/incipient DAT, and uncertain dementia. The stable group

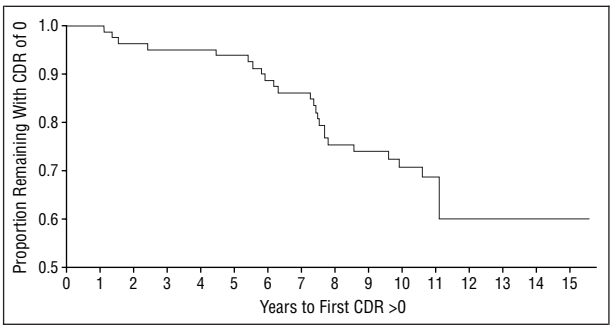

Figure 1. *Results of Kaplan-Meier analysis of 82 participants enrolled as cognitively healthy (Clinical Dementia Rating [CDR], 0) controls, with the end point being the first evaluation in which CDR was greater than 0. Death, unavailability for follow-up, and June 1, 1995, were used as censoring points.*

remained with a CDR of 0 throughout the longitudinal follow-up period. The DAT/incipient DAT group deteriorated to a CDR greater than 0 and met clinical criteria for a diagnosis of DAT or incipient DAT. The uncertain dementia group deteriorated from a CDR of 0 to one of 0.5, but the clinicians were uncertain of the reason for the cognitive changes and therefore unwilling to give a clinical diagnosis of DAT or incipient DAT.

Longitudinal data for each psychometric test as well as the composite factor score were compared for the 3 groups by means of a mixed general linear model.[32] Only data from assessments before the first time an individual received a CDR greater than 0 were included in

these analyses. A regression line was estimated for each person and was identified by its intercept (the estimated score at first time of testing) and slope. In the mixed analysis of variance model reported herein, mean intercepts and mean slopes were estimated for each of the 3 groups, with the intercepts and slopes within a group randomly distributed around these group mean values. Comparison of the mean intercepts of the 3 groups indicates whether those who became demented had lower initial performance levels. Comparison of the mean slopes of the 3 groups indicates whether there are differences among the rates of longitudinal decline before clinical detection of dementia. Because psychometric performance is often correlated with age, age was included in the model and allowed to correlate with the intercept. Therefore, the comparisons of the intercepts are age adjusted in a manner similar to an analysis of covariance and corrected for the greater age at enrollment of those who declined beyond a CDR of 0 than of those who did not. An examination of the individual data plots, the estimated random effects, and the observed residuals confirmed the reasonableness of the selected model across the various measures. There was a mean of 9 assessments per individual, and the number of assessments was similar for each of the 3 groups (see first footnote to Table 1).

As expected, greater age was related to poorer initial performance for most measures (first column, Table 1). More important, the 3 groups differed significantly in initial performance (indicated by the intercepts) for the composite factor score as well as 6 of the individual measures, even after adjusting for age (Table 1). In contrast, the standardized slopes of the 3 groups (the rate of decline in psychometric performance) were significantly different for only 1 measure: Wechsler Memory Scale (WMS) Logical Memory. For this test, those who remained stable had an essentially flat course over time (mean slope, –0.01), whereas those who later became demented had a downward pattern (mean slope, –0.16) before the clinical detection of dementia. The slope for the uncertain dementia group fell between the other 2 (mean slope, –0.07). The slopes of the majority of the other measures, including the factor score, were remarkably flat, differing little from 0. Tasks measuring executive function and speeded psychomotor performance (Trailmaking A, WAIS Digit Symbol, Crossing-off) demonstrated poorer performance over time for all 3 groups. This is not surprising given the extensive literature on slowing with age.[33] Although the declines on these 3 measures appear to be steepest in the demented group, the differences were not statistically significant ($P>.05$).

PSYCHOMETRIC PERFORMANCE AND ITS RELATIONSHIP TO CLINICALLY DETECTED COGNITIVE CHANGE

To examine the relationship between psychometric performance and clinically detected cognitive change, the standardized factor scores were plotted as a function of age for each individual over the entire length of the study. Each plot was classified independently by 2 of us (E.H.R., M.S.) as declining or not declining over time on the basis of visual examination; interrater reliability was high ($\kappa=0.94$). The evaluators were unaware of the CDRs associated with each time of testing.

The overwhelming majority (48 of 54) of people in the clinically stable group had nondeclining psychometric factor scores on visual inspection. (One person in the stable group was tested only at entry and, therefore, could not be classified.) Of the 6 who showed a declining pattern, 5 had developed medical conditions (eg, stroke, depression, frailty, major personality change) time-linked to declining psychometric performance. None of these, however, had been considered to have a CDR other than 0 on clinical examination. The sixth case had a fluctuating pattern. Thirteen of the 16 individuals in the DAT/incipient DAT group had declining factor scores over time; only 3 of the 11 people in the uncertain dementia group demonstrated a declining pattern. Group was significantly associated with pattern, $\chi^2(2, N=81)=30.75$, $P<.001$.

Figure 2 shows the longitudinal factor scores plotted by age for the 16 people in the DAT/incipient DAT group; 13 of these plots demonstrated decline and 3 no decline. In almost all cases, the onset of deterioration in psychometric performance and clinical change as assessed by the CDR were concurrent.

To examine in more detail psychometric performance after the onset of dementia, analyses were performed in which the individual trajectories estimated in the model described earlier for points before dementia onset were extrapolated to all points at or after the time when the clinical examination resulted in a CDR greater than 0. These extrapolations represent the scores predicted if the rate of change before dementia onset remained stable after dementia onset. Residuals (observed minus predicted) were computed for each person at each of these assessments. These residuals were then subjected to a mixed-model analysis of variance, similar to the one described for Table 1, to estimate the mean intercepts and mean slopes for the DAT/incipient DAT and uncertain dementia groups after clinical detection of dementia. A mean slope of 0 represents no difference in the rate of change in scores before and after dementia onset.

The mean slopes for the residuals are shown in **Table 2**. Slopes differed significantly from 0 on the factor score and on 8 of the psychometric measures in the DAT/incipient DAT group, indicating greater decline than predicted on the basis of performance before the clinical detection of dementia. These 8 measures cover a broad range of cognitive function, including tests of verbal memory (WMS Associate Learning), nonverbal memory (Benton Visual Retention), semantic memory (WAIS Information), language (Boston Naming Test), visuospatial performance (WAIS Block Design), executive function (WAIS Digit Symbol, Trailmaking A), and attention (WMS Mental Control). Interestingly, the increased rate of decline in WMS Logical Memory observed in the DAT/incipient DAT group before dementia onset did not show a further increase after dementia was clinically diagnosed. None of the mean slopes of the residuals for the uncertain dementia group was significantly different from 0.

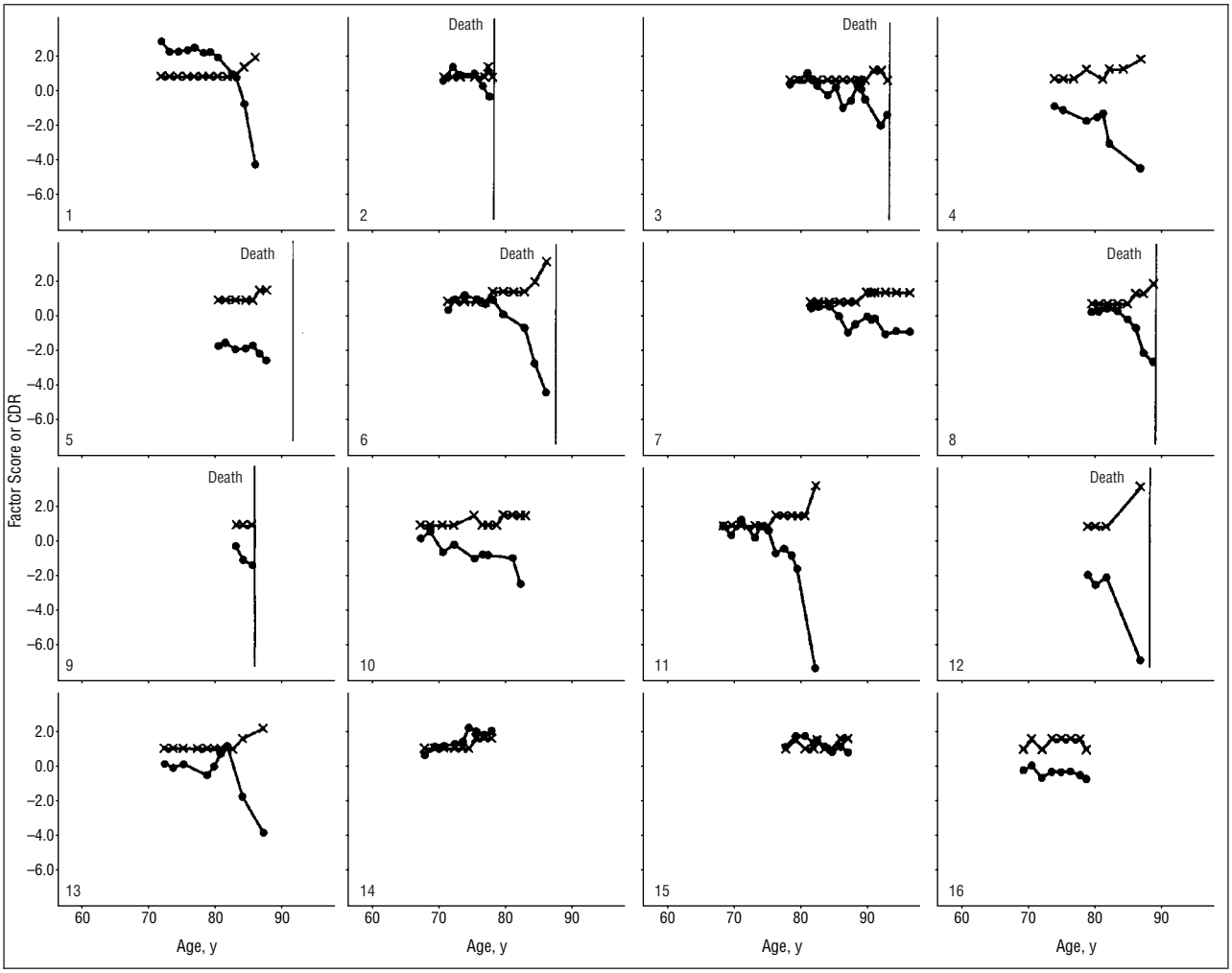

Figure 2. *Factor scores (dots) and Clinical Dementia Rating (CDR) (x's) by age for the 16 people in the dementia of the Alzheimer type/incipient dementia group. Subject 9 was judged to have incipient dementia on the basis of the expiration summary; information concerning this subject has been published as a case report.*[30]

COMMENT

Longitudinal examination of the clinical and psychometric performance of a group of older adults selected for their good cognitive and physical health showed that many had stable cognitive performance for up to 15½ years. The lack of longitudinal decline in psychometric performance is at variance with the cross-sectional age differences in cognitive function in older adults reported both in this report and in the literature.[34] Our data demonstrate that, on average, the older an individual is the first time the psychometric battery of tests is administered, the lower the score. The longitudinal stability of psychometric performance in the participants who remained with a CDR of 0, however, suggests that cognitively healthy older adults are capable of sufficient learning and acclimation from repeated testing to maintain their performance despite aging. Our finding of longitudinal cognitive stability in healthy older people has been observed previously.[35]

An estimated 40% of the participants in our study were given a CDR greater than 0 over 12 years; the majority of these (59%) had symptoms consistent with DAT or incipient DAT. The incidence of dementia in this sample of older adults was consistent with rates from epidemiologic studies.[36] Our rate is in the higher end of the reported range, which is compatible with the fact that we included individuals with subtle impairment who may not have been considered impaired in epidemiologic studies. Our data reinforce the importance of thorough evaluation of research participants with regard to cognitive status. Less thorough evaluation may result in an underestimation of the incidence of DAT as well as contamination of control samples by inclusion of participants with very mild DAT, as previously suggested.[3,18]

Most of the participants who developed the clinical symptoms of dementia demonstrated a sharp downward turn in global psychometric performance, in many cases after years of stability. The change in psychometric performance was detectable not only by statistical procedures comparing expected with actual scores, but also by visual examination of the curves plotting the annual global scores of each participant. Decline in global performance occurred simultaneously with the subtle clinical changes that led to the assignment of a CDR greater than 0 for the first time to previously cognitively healthy

Table 2. Average Standardized Slopes of Residual Longitudinal Psychometric Performance in DAT/IDAT and Uncertain Groups After Clinical Detection of Dementia*

Measure	DAT/IDAT	Uncertain
Wechsler Memory Scale		
Mental control	−0.28†	−0.16
Logical memory	−0.03	0.19
Digit span		
Forward	−0.12	0.03
Backward	0.03	0.16
Associate learning	−0.25‡	0.05
Benton Visual Retention		
Recall (No. correct)	−0.36§	0.31
Copy (No. correct)	−0.36	0.12
Wechsler Adult Intelligence Scale		
Information	−0.19†	−0.08
Block Design	−0.25‡	−0.05
Digit Symbol	−0.39§	−0.11
Trailmaking A, s	0.89†	0.17
Crossing-off	0.03	−0.01
Boston Naming Test	−0.45†	−0.18
Word Fluency (S+P)	−0.09	−0.02
Factor score	−0.60§	−0.08

**DAT indicates dementia of the Alzheimer type; IDAT, incipient DAT; S+P, letters "S" and "P". A negative residual raw score slope indicates greater decline per year than predicted based on an individual's longitudinal course before development of dementia, except for Trailmaking A, which was scored in the opposite direction. The statistical test (Student t) was of the null hypothesis that the mean slope for the group was 0.*

†P≤.01.

‡P≤.05.

§P≤.001.

individuals (CDR of 0). This implies that DAT interferes with a person's ability to maintain performance on repeated psychometric testing. This pattern is consistent with neuropathological and neuroradiological data that demonstrate qualitatively different patterns for normal aging and Alzheimer disease.[37-39]

The uncertain dementia group was heterogeneous with regard to the reasons the clinicians could not rate cognitive function as a CDR of 0. Some individuals' symptoms could be the result of very subtle DAT. Interpreting the observation that 3 of the 11 individuals in the uncertain dementia group demonstrated a pattern of declining global psychometric performance similar to the pattern seen in the majority of persons with DAT or incipient DAT would be speculative.

This pattern of an abrupt decline in global psychometric performance concurrent with clinically detectable cognitive change suggests a possible strategy to help detect dementia in its early stages, when intervention theoretically would be most useful.[3,12] This strategy would involve the longitudinal administration of a battery of psychometric tests. An abrupt decline in performance would alert the health care provider to the possible need for further clinical investigation.

Although global psychometric performance was stable on repeated testing before the development of clinically detectable cognitive changes, performance on 1 specific test, WMS Logical Memory, did deteriorate before the onset of detectable clinical changes and global psychometric deterioration. The WMS Logical Memory tests the ability to recall information contained in a brief prose passage. Although this single significant decline may merely represent capitalization on chance, one plausible interpretation of this finding is that functional or structural changes are occurring in brain regions subserving this form of memory before the more global and cataclysmic changes known to be present by the time of the earliest clinical manifestations of DAT. Further research is needed to determine the utility of WMS Logical Memory or similar tests in accurately predicting the development of DAT. Our sample is unusually healthy and well educated. Demonstrating the usefulness of changes in performance in WMS Logical Memory in a group of seniors more representative of the elderly population would also be important.

Our finding that those who developed dementia had initially lower performance levels has been reported by others.[8-12,40-43] The fact that few individuals in our study developed clinically detectable dementia within the first 5 years of follow-up speaks against initial misclassification of demented participants as having a CDR of 0 as a contributing factor to this observation. Comparatively poorer cognitive abilities throughout life may reflect a brain that is more susceptible to pathophysiological processes associated with dementia or is less able to compensate for Alzheimer disease–associated lesions (ie, the reserve hypothesis). This hypothesis does not imply that a person with poor intrinsic cognitive ability necessarily will develop dementia; many individuals in our sample with initially low scores maintained their levels of cognitive performance longitudinally.

In summary, people who eventually developed dementia performed less well on psychometric testing years before clinical symptoms were evident. At the time that subtle clinical changes were first noted, a sharp change in psychometric performance was also observed. Before global psychometric changes and before clinically detectable cognitive changes, the ability to recall information from a prose passage (WMS Logical memory) began to deteriorate. On the other hand, people who remained cognitively intact on the basis of clinical evaluation were able to maintain stable psychometric performance when measured longitudinally for periods up to 15 years. These data imply that abrupt decline from baseline cognitive performance on repeated evaluations may represent the onset of dementia rather than a benign aging process.

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