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Visual memory predicts Alzheimer's disease more than a decade before diagnosis

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Abstract—*Background:* Recent studies have suggested that AD may reflect a chronic process that begins many years before the clinical expression of dementia. The current study examines premorbid Benton Visual Retention Test (BVRT) and Wechsler Adult Intelligence Scale–vocabulary (WAIS-voc) test scores in order to determine whether long-term deficits in these tests can predict the development of AD decades later in the Baltimore Longitudinal Study of Aging (BLSA). *Method:* Participants are volunteers from the BLSA, a multidisciplinary study of normal aging conducted by the National Institute on Aging. A total of 1,425 BLSA participants who were older than 60 years were included in the analyses. Cox proportional hazards models were used to estimate the relative risk of developing AD associated with BVRT and WAIS-voc scores at different time periods up to 20 years before the diagnosis of AD. *Results:* The relative risks for 6 or more BVRT errors vs less than 6 errors at 1 to 3, 3 to 5, 5 to 10, and 10 to 15 years before the diagnosis of AD were 5.69, 2.11, 1.76, and 1.83 ($p < 0.05$). The relative risk for 15 or more years before diagnosis was not significant ($p > 0.10$). WAIS-voc scores were not significantly associated with the risk of AD in any time period. *Conclusions:* A greater number of errors on the BVRT is associated with an increased risk of AD up to 15 years later. Poor visual memory performance may represent an early expression of AD years before diagnosis. This result suggests the need to continue to revise views on the natural history of AD and the possibility of an increased window of opportunity for preventive treatment before definitive diagnosis.

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Several studies have recently suggested that poor cognitive performance can precede clinical dementia, particularly AD, by several years before the diagnosis can be made. Most of these investigations examined premorbid cognitive performance only a few years before diagnosis and the results suggest that poor performance, particularly on tests of verbal memory, may represent a preclinical phase of the disease.[1-5] Two unique studies, however, have suggested that cognitive abilities in early life may also predict the development of dementia in late life. One of these studies was conducted in twins discordant for AD. In this study, poorer scores on subtests of IQ tests predicted which twin was most likely to develop AD.[6-8] Another, more recent, study investigated the relationship between the development of AD in elderly nuns and the linguistic characteristics of autobiographies they had written between ages 18 and 21 years.[9] Nuns with lower scores on idea density were at higher risk of developing AD many years later.

Some years ago, Katzman and Kawas[10] suggested that overt AD might be the endpoint of a chronic process that began decades earlier. This led us to the following question: how many years before the diagnosis of dementia can poorer cognitive performance be detected? We hypothesized that tests of visual memory might provide some indication of early cognitive abnormalities. We examined this issue in participants of the Baltimore Longitudinal Study of Aging (BLSA), a longitudinal study of normal aging that has been conducted for more than 40 years by the National Institute on Aging.

Subjects and methods. *Study population.* Subjects in this study are from the BLSA, a longitudinal study conducted by the National Institute on Aging that was initiated in 1958 to examine normal aging.[11] Originally limited to men, women began entering the study in 1978; more than 2,600 subjects have been recruited since its inception. The cohort comprises well-educated volunteers who return to the study every 2 years for 2.5 days of multidisciplinary tests. Subjects met inclusion criteria for this study if they had completed the Benton Visual Retention Test (BVRT) or Wechsler Adult Intelligence Scale–vocabulary (WAIS-voc) at least once, had at least one additional follow-up evaluation for determination

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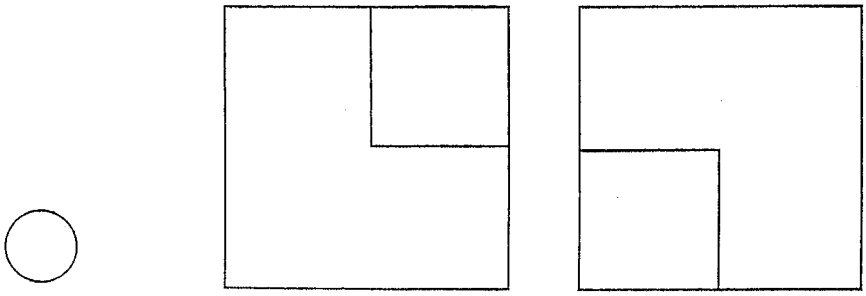

Figure. Example of Benton Visual Retention Test stimuli. Reprinted from: Benton Visual Retention Test, Fifth Edition. *Copyright © 1992 by The Psychological Corporation, a Harcourt Assessment Company. Reproduced with permission. All rights reserved.*

of outcome, and were more than 60 years of age at last follow-up (n = 1,425). The current report included follow-up until September 30, 1999.

Procedures. Cognitive procedures. Extensive multidisciplinary investigations were conducted on BLSA participants during their biennial visit,[11] but only two standardized psychometric tests were consistently and regularly administered throughout the study: the BVRT,[12] a measure of nonverbal memory, and the WAIS vocabulary test.[13] These standardized psychometric tests were introduced in 1960 and were administered every 6 years until 1991 when the BVRT administration was increased to every 2 years and the WAIS-voc was discontinued. The BVRT is a test of memory for designs and visuo-constructional skills. The test consists of 10 stimulus cards. See the figure for an example of the stimuli. In the standard procedure used in this study, each card is displayed for 10 seconds and removed from sight. The task is to reproduce the design on the card, and no time limit is imposed. The score is the total number of errors on all 10 designs. In addition, the types of errors can be characterized as errors of addition, distortion, misplacement, omission, perseveration, rotation, and size.

Determination of dementia. Since 1986, participants of the BLSA also receive a neurologic examination and a battery of neuropsychological tests. Some participants who were unable to come to the center for evaluation received home visits. These procedures allowed the identification of all subjects who developed dementia and AD since the inception of the study. Medical records, laboratory tests, and informant questionnaires were obtained for subjects who presented with cognitive problems. The diagnostic status of each subject was assigned during a multidisciplinary conference on the basis of all available information. A clinical diagnosis of dementia and AD was assigned using Diagnostic and Statistical Manual of Mental Disorders, third edition, revised[14] and National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association[15] criteria. BVRT and WAIS-voc scores were not used in the determination of the clinical diagnosis. These procedures have been described in detail in a previous publication.[16]

Statistical analysis. Simple descriptive statistical analyses of the time trends of the BVRT and WAIS-voc were performed and summary statistics of the scores at different ages including means, medians, and ranges were calculated. Cox proportional hazards regression[17] with time-dependent covariates was used to estimate the relative risk (RR) of diagnosis of AD associated with BVRT errors and WAIS-voc scores. Chronological age was used as the time scale with delayed entry to account for different ages at enrollment into the BLSA. The model compares each patient with AD to all subjects in the study who were alive and free of AD at the age when the AD case was diagnosed. Subjects were censored at the age of their last visit, age at death, age when diagnosed with another dementia, or age when lost to follow-up.

Cognitive scores were examined as continuous variables and as categorical variables. For categorization of BVRT errors, scores were divided into two approximately equal-sized categories based on the median of the BVRT error distribution: zero to five errors (reference category) and six or more errors. Similarly, the two categories for the WAIS-voc scores were >65 points (reference category) and ≤ 65 points. The relative risks of AD were estimated for different time periods up to 20 years before the age at diagnosis of AD (1 to 3, 3 to 5, 5 to 10, 10 to 15, and 15 to 20 years). Separate analyses were performed for each of the intervals before diagnosis. If subjects contributed more than one score for a particular interval, their scores were averaged and the average was then categorized into the appropriate error category. The number of incident AD cases contributing to each interval ranged from 24 to 80. The analyses were adjusted for education and sex by including them as binary covariates (sex: 0 if male and 1 if female; education: 0 if <16 years of education and 1 if ≥ 16 years of education). Cognitive scores were also analyzed as linear and quadratic terms in a separate set of regression analyses.

A more in-depth analysis was performed to determine the contribution of different BVRT error types on the risk of AD. Continuous variables for the seven error types (addition, distortion, misplacement, omission, perseveration, rotation, and size) were included in a Cox regression analysis along with covariates for sex and education. The relative risks for the Cox models were estimated by SAS PROC PHREG version 8.01 (Cary, NC).

Results. A total of 1,425 participants (1,004 men and 421 women) from the BLSA were included in this study (see table 1 for demographic characteristics). The mean age at last follow-up was 78.1 years (range 61 to 102). The mean length of time between study entry and last follow-up was 17.0 years. More than 72% of subjects had at least a college education. There were a total of 144 incident cases of AD during the follow-up period. Table 1 also shows demographic characteristics of the patients with AD.

The average scores attained at different ages for all subjects are shown in table 2. Subjects who eventually developed AD are also included here, but only scores before time of diagnosis were included. Overall, the mean number of scores each subject contributed to the study was 3.3 and ranged from 1 to 10. The mean number of errors on the BVRT increased with age from 3.11 for subjects under age 50 to 9.73 for subjects over age 90. These changes do not necessarily generalize to normal aging because they include subjects who eventually developed AD in a highly

Table 1 *Demographic characteristics of all subjects and patients with AD*

Characteristics	Whole cohort	Patients with AD
No.	1,425*	144
No. (%) of men	1004 (70.5)	92 (63.9)
No. (%) with college education or higher	1031 (72.4)	109 (75.7)
Mean years of follow-up (range)	17.0 (0.5–40.7)	15.1 (1.9–37.4)
Mean age at last follow-up, y (range)	78.1 (61.1–102.3)	84.3 (61.8–97.7)

* Wechsler Adult Intelligence Scale–vocabulary analyses included 1,393 subjects owing to missing data.

Table 2 *Summary statistics for cognitive test scores by age category**

	BVRT†		WAIS-voc†	
Age at assessment, y	N‡	Mean (SD)	N‡	Mean (SD)
<50	298	3.11 (2.28)	300	64.08 (10.18)
50–59	546	3.72 (2.60)	546	64.97 (9.54)
60–69	815	4.67 (3.05)	681	65.00 (10.04)
70–79	760	6.78 (4.01)	608	65.61 (8.80)
80–89	380	9.09 (4.50)	267	63.26 (10.83)
90+	40	9.73 (5.72)	19	58.00 (15.39)

* Scores were averaged if subjects contributed more than one data point for a particular age category. For subjects who eventually developed AD, their scores before AD diagnosis are included.
† Higher scores in the BVRT and lower scores in the WAIS-voc indicate poorer scores.
‡ The sum of N is greater than the total number of subjects in the study because subjects can contribute scores to multiple age categories.

BVRT = Benton Visual Retention Test; WAIS-voc = Wechsler Adult Intelligence Scale–vocabulary.

educated cohort. On the WAIS-voc, mean scores did not change significantly with age.

Table 3 shows the mean scores of patients with AD for each of the decades before their age at diagnosis. BVRT scores of cases with AD were worse than scores for the whole cohort even decades before diagnosis. For example, subjects diagnosed with AD during their 60s had, on average, a score of 5.50 before their 50s, 6.00 during their 50s, and an average score of 10.67 during their 60s; the whole cohort had average scores of 3.11, 3.72, and 4.67 for the same age categories. The average score for people diagnosed in their 70s or 80s was also higher than that of the entire cohort for each prior age decade. In sharp contrast, the performance of cases with AD on the WAIS-voc did not appear worse than the performance of the whole cohort.

Table 4 shows the results of the Cox proportional hazards regression analyses estimating the risk of AD associated with BVRT errors and WAIS-voc scores. A high number of BVRT errors was associated with an increased risk of developing AD at specified periods before diagnosis. Thus, subjects with six or more BVRT errors were almost twice as likely to develop AD 10 to 15 years later when compared to subjects with zero to five errors. When BVRT errors were analyzed as a continuous linear term in the regression analysis, similar results were obtained. BVRT errors were significantly associated with an increased risk of AD at 1 to 3 years before diagnosis (RR 1.26, 95% CI 1.18 to 1.34), 3 to 5 years before diagnosis (RR 1.10, 95% CI 1.03 to 1.18), and 5 to 10 years before the diagnosis of AD (RR 1.10, 95% CI 1.03 to 1.17). There was a weak association between BVRT errors and risk of AD at 10 to 15 years before diagnosis (RR 1.08, 95% CI 0.997 to 1.17). BVRT errors were not significantly associated with the risk of AD at 15 to 20 years before diagnosis (RR 1.06, 95% CI 0.95 to 1.17). There was no interaction of sex and the neuropsychological scores although women had a somewhat increased risk of AD in our study. Models that included a quadratic term for BVRT errors in addition to the linear term were fitted, but the quadratic term was not significant for any of the intervals before diagnosis.

The Cox proportional hazards regression analysis of WAIS-voc scores showed nonsignificant and inconsistent associations with the risk of AD in all time periods, although there were some trends toward protection with higher vocabulary scores (see table 4). Again, there was no interaction of sex, WAIS-voc scores, and risk of AD. A quadratic term was not significant for any of the intervals before diagnosis in models that included a quadratic term for WAIS-voc scores in addition to the linear term.

To further examine the relationship between BVRT and devel-

Table 3 *Mean cognitive test scores before diagnosis for patients with AD**

Age at assessment before diagnosis, y	Age at AD diagnosis, y				Whole cohort†
	60–69	70–79	80–89	90–102	
BVRT‡					
<50	5.50 (2)	3.75 (4)	4.00 (1)	NA (0)	3.11
50–59	6.00 (4)	6.00 (11)	4.44 (9)	2.00 (1)	3.72
60–69	10.67 (3)	6.39 (23)	5.03 (31)	7.00 (1)	4.67
70–79	—	11.67 (18)	7.53 (64)	5.80 (15)	6.78
80–89	—	—	11.25 (48)	9.83 (18)	9.09
90–102	—	—	—	12.17 (6)	9.73
WAIS-voc‡					
<50	58.00 (2)	59.75 (4)	66.00 (1)	NA (0)	64.08
50–59	64.50 (4)	61.55 (11)	67.67 (9)	62.00 (1)	64.94
60–69	64.00 (3)	62.43 (23)	64.45 (31)	64.33 (3)	65.00
70–79	—	60.13 (15)	65.15 (65)	64.53 (17)	65.61
80–89	—	—	61.74 (39)	62.58 (19)	63.26
90–102	—	—	—	62.25 (4)	58.00

Values are mean score (n). Scores are averaged if subjects contributed more than one data point for a particular age category.

* Only scores before age at diagnosis are included; scores at age of diagnosis are not included. Entries in the table corresponding to ages after diagnosis are indicated with a dash (—).
† Numbers were obtained from table 2 and includes scores before AD diagnosis for subjects who eventually developed AD.
‡ Higher scores in the BVRT and lower scores in the WAIS-voc indicate poorer scores.

BVRT = Benton Visual Retention Test; WAIS-voc = Wechsler Adult Intelligence Scale–vocabulary.

Table 4 *Association between cognitive test scores and development of AD for several intervals before diagnosis as estimated from Cox regression models*

Interval before diagnosis, y*	Relative risk	95% CI	*p* Value	Number of AD cases
BVRT†				
1–3	5.69	1.99–16.26	0.001	52
3–5	2.11	1.06–4.19	0.03	53
5–10	1.76	1.07–2.90	0.03	77
10–15	1.83	1.07–3.14	0.03	61
15–20	1.57	0.82–3.02	0.18	39
WAIS-voc‡				
1–3	2.31	0.90–5.93	0.08	24
3–5	1.43	0.72–2.83	0.31	38
5–10	0.84	0.52–1.35	0.47	80
10–15	1.34	0.79–2.28	0.28	61
15–20	1.86	0.98–3.53	0.06	42

Relative risks, 95% CI, and *p* values were computed using Cox proportional hazards regression with delayed entry, age as the time scale, age at diagnosis of AD as the event, and adjusted for sex and education. Scores were averaged if subjects contributed more than one data point for a particular interval before diagnosis.

* Separate analyses were performed for each interval before diagnosis. The intervals include the left but not the right endpoint (e.g., ≥1 year and <3 years).
† BVRT covariate defined as 1 if >5 BVRT errors, and 0 if ≤5 BVRT errors.
‡ WAIS-voc covariate defined as 1 if ≤65 WAIS-voc points, and 0 if >65 WAIS-voc points.

BVRT = Benton Visual Retention Test; WAIS-voc = Wechsler Adult Intelligence Scale–vocabulary.

opment of AD we examined the distribution of BVRT error types in all visits for all subjects included in the analyses. The averages (SD) over all subjects and visits for the different error types were as follows: 0.02 (SD 0.15) for addition errors, 2.64 (SD 2.30) for distortion errors, 0.55 (SD 0.91) for misplacement errors, 0.42 (SD 1.10) for omission errors, 0.75 (SD 0.98) for perseveration errors, 1.02 (SD 1.01) for rotation errors, and 0.17 (SD 0.50) for size errors.

No single error type was significantly and consistently associated with the risk of AD in the intervals before diagnosis. For example, in interval 10 to 15 years, size errors were most related to the development of AD (RR 1.53, 95% CI 1.04 to 2.2); in interval 3 to 5 years, errors of omission were most predictive (RR 1.19, 95% CI 1.04 to 1.37); in interval 5 to 10 years, errors of distortion were most predictive (RR 1.12, 95% CI 1.00 to 1.26). In keeping with the presumed preclinical phase of the disease, several error types (distortion, omission, perseveration, and size) were associated with the risk of AD 1 to 3 years later. Because of the small number of subjects with addition errors, we excluded the covariate for addition errors from the regression models.

Discussion. A high number of errors in the BVRT was associated with an increase in the risk of developing AD years later. Subjects who scored six or more errors on the BVRT had approximately twice the risk of developing AD than did subjects with zero to five errors up to 15 years before the diagnosis of AD. The higher relative risk of the 1- to 3-year interval may indicate that the data in this period likely include the onset of AD for some individuals. In contrast, scores on the WAIS-voc test were not associated with the risk of AD.

We are aware that this study has some limitations. The BLSA participants are volunteers who are highly educated and predominantly male and white. The relative homogeneity of this cohort may limit our ability to generalize these results to the general population. However, those same characteristics are advantageous because they minimize the possible confounding effects of ethnicity and education. The differences in midlife cognitive scores cannot be explained by differences in education because all subjects in this study had similar high educational backgrounds. In addition, adjusting for education in the regression models did not change the results. Finally, the dissociation of BVRT results and WAIS-voc results in the same subjects further supports the notion that education did not determine the results of the study.

Despite these limitations, some aspects of this study merit special attention. There are very few studies of the association of premorbid cognitive abilities and development of AD. Most of the available investigations have data of relatively short duration before diagnosis and involved verbal, rather than visual, memory. In the Bronx Aging study cohort, borderline mental status scores were a powerful predictor for the development of dementia within 2 to 3 years. Similar results were obtained in the Personnes Agés quid (PAQUID) study, a population-based sample of elderly individuals in France.[18] These investigators noted that 2 years before clinical diagnosis of dementia, test scores were significantly lower in subjects who developed dementia than in those who were still normal. Of note, the strongest predictor of dementia among the seven tests administered was the BVRT, although a different type of administration was used (recognition rather than reproduction).

Similar results were obtained in another population-based sample, the Kungsholmen (Stockholm) Project. Baseline differences in the Mini-Mental State Examination, particularly the verbal memory item, were reported in subjects who went on to develop dementia after 3 and 6 years of follow-up.[19] With a longer duration of follow-up (average 6 years), the Framingham study found that measures of verbal memory and immediate attention span were significantly related to AD diagnosis. Results did not change when the analysis was restricted to individuals (n = 18) for whom the screening examination preceded clinical onset by 7 years or more. Our study, in contrast, reports cognitive scores up to 20 years before the diagnosis of AD in a much larger group of subjects. Our results suggest that the disease process may already be occurring decades before clinical symptoms appear.

Our results are consistent with those from the Nun Study.[9] In that study, a comparison of paragraphs written by 93 nuns (average age 22 years) showed that those with poorer scores on idea density

were at a higher risk of developing AD many years later. This interesting study, however, has limited applicability to the population at large.

The dissociation between BVRT and WAIS-voc results in this study is consistent with studies showing a differential decline of nonverbal memory and verbal intelligence throughout life.[20-22] In general, most investigators have noted vocabulary scores to be relatively stable during life,[23] even in early dementia.[24] The BVRT, in contrast, has been shown to demonstrate accelerated changes over the 6-year interval before onset in subjects who develop AD[25] and has previously been reported to be the most sensitive of eight neuropsychological tests in the detection of mild to moderate dementia (sensitivity = 0.66).[26]

We previously examined BVRT and WAIS-voc scores in a sample of 11 BLSA subjects who had come to autopsy.[27] We found that subjects with cerebral amyloid deposition consistent with AD had poorer performance on the BVRT 20 years before autopsy when compared to subjects without AD pathology (BVRT mean scores: AD group = 6.4, non-AD group = 1.5, $p < 0.01$). WAIS-voc scores, however, were not significantly different for the two groups (WAIS-voc scores: AD group = 71.4, non-AD group = 72, $p > 0.5$). This small autopsy series strongly supports our current findings in clinically diagnosed subjects with AD.

The results from the current study suggest that AD may be a disease process that begins much earlier than was previously believed. AD may be best represented as a chronic disease that is initiated and promoted by many factors throughout life.[10] In the long run, it is likely that the most effective therapies for AD would be those that prevent the disorder or arrest its progress early in the disease course. If the BVRT indeed identifies individuals in the preclinical stages of the disease, there may be an opportunity for early identification of subjects who are at high risk of developing AD.

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