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Paired associate performance in the early detection of DAT

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Abstract

Subjects underwent longitudinal neuropsychological assessment in order to retrospectively determine which measures of cognitive function best predicted later development of dementia of the Alzheimer type (DAT). Three groups of subjects were studied: normal controls, patients with early DAT, and questionable dementia subjects (QD). All subjects were assessed using a battery of standard neuropsychological measures and two subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB), paired associate learning and delayed matching to sample. A structured interview was also used to elicit a profile of the subject's daily functioning. Subjects were assessed every 6 months for 2 years. At the 6 month assessment, almost half of the QD group exhibited significant deterioration in scores on the computerized paired associate learning subtest, while maintaining their scores on standard measures. At the conclusion of the study, all of this QD subgroup fulfilled the NINCDS–ADRDA criteria for probable DAT pertaining to significant cognitive and functional deterioration. Performance on the CANTAB paired associate learning subtest identified the onset of progressive memory deterioration in a subgroup of QD subjects. In almost all cases this was well before significant deterioration was noted on standard neuropsychological measures. Paired associate learning performance may therefore be a valuable tool for the early, preclinical detection and assessment of DAT. (*JINS*, 2002, *8*, 58–71.)

Keywords: Alzheimer's disease, Questionable dementia, Neuropsychology, CANTAB, Hippocampus

INTRODUCTION

Probable Alzheimer's disease (dementia of the Alzheimer type or DAT) is diagnosed clinically according to the NINCDS–ADRDA criteria (McKhann et al., 1984). These demonstrate near 100% accuracy in typical patients when compared to pathological diagnosis (Morris et al., 1988), and even in a multi-site setting with mixed dementia patients have a high sensitivity and specificity of diagnosis (Blacker et al., 1994; Klatka et al., 1997). However by the time the diagnosis can be made according to these criteria there is substantial neuropathology present, with extensive degeneration and loss of neurons (Levine et al., 1993; Scholtz, 1987; Terry et al., 1981). This is most severe in the temporoparietal area, with prominent involvement of limbic regions including the hippocampus, amygdala and entorhinal cortex (Killiany et al., 2000; Rossor, 1987).

The cholinesterase inhibitors represent the first therapeutic agents for the symptomatic treatment of DAT (Conway, 1998; Knopman & Morris, 1997; Small, 1998) and may also contribute to a slowing in the progression of the disease (Knopman, 1996). In addition, a range of therapeutic options to reverse, slow or halt progression of DAT are under current clinical investigation (Brodaty & Sachdev, 1997; Knopman & Morris, 1997). However, to exploit these therapeutic advances, the disease needs to be diagnosed at earlier stages than is currently possible. Patients with clinically questionable dementia (QD) are of particular interest in this regard. Such subjects have symptomatic memory problems but daily functioning is either not affected or only slightly impaired. Previous studies have shown that approx-

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imately 24 to 75% of individuals in this group fulfill criteria for DAT at later assessment (Flicker et al., 1991; Masur et al., 1994; Morris et al., 1991; Rubin et al., 1989; Tierney et al., 1996b; Tuokko et al., 1991). These subjects may also exhibit significant hippocampal and entorhinal atrophy on MRI (DeLeon et al., 1992; Killiany et al., 2000). At initial assessment, QD subjects perform significantly worse than control subjects on tests of memory, particularly those involving delayed recall and associate learning tasks (Morris et al., 1991; Strohle et al., 1995; Tierney et al., 1996a, 1996b). However, there is significant overlap in cognitive performance on these tasks between QD and control subjects, such that the two groups cannot be sufficiently distinguished using the neuropsychological tests alone (Morris et al., 1991; Storandt & Hill, 1989; Strohle et al., 1995).

Although metabolic changes are believed to be the earliest manifestations of DAT (Reiman et al., 1996; Soininen & Scheltens, 1998) it is generally accepted that the disease first becomes apparent clinically in the form of deterioration in recent memory (Petersen et al., 1994). Accordingly, tests of this construct have been shown to be most efficacious in the detection of early, even preclinical, DAT (Howieson et al., 1997; Small et al., 1997; Small et al., 1995). Such deterioration may even pre-date structural changes evident on neuroimaging (Fox et al., 1998). Recent research by our group has indicated that two subtests of the Visual Memory Battery of the Cambridge Neuropsychological Test Automated Battery (CANTAB; Morris et al., 1987) are particularly sensitive to changes in early DAT. Performance of the delayed matching to sample and paired associate learning subtests are impaired in DAT (Morris et al., 1987; Sahakian et al., 1988; 1990) and in a longitudinal study we found that scores on these subtests classified 88% of early DAT patients at initial assessment (Fowler et al., 1995), and 100% at 12-month reassessment (Fowler et al., 1997). The performance of QD subjects on computerized and standard neuropsychological measures was similar to normal controls when first assessed. However, it was of great interest to note that at 6-, and then 12-month reassessments, almost half of the QD group deteriorated on the CANTAB paired associate learning and delayed matching to sample subtests. In contrast, over the same interval their scores on standard tests (WAIS–R FSIQ, WMS–R GMI, MMSE, and Controlled Oral Word Association Test) were maintained (Fowler et al., 1997). The deterioration was such that there was no overlap in scores on the CANTAB paired associate learning test between the deteriorating and stable subjects in the QD group. This indicated that the tests were defining a subgroup of QD subjects with deteriorating memory with high sensitivity.

We now present the results of the standard neuropsychological assessment of the QD group and their performance on the CANTAB measures at 18 and 24 months after the initial assessment. At the conclusion of the study, subjects were independently reassessed according to selected NINCDS–ADRDA criteria. Activities of daily living were also measured by structured interview.

METHODS

Research Participants

The study comprised three groups: 19 controls, 21 questionable dementia subjects and 16 subjects with early DAT. Recruitment and diagnostic criteria have been described in previous reports (Fowler et al., 1995; 1997). Briefly, subjects with a history of neurological illness other than DAT or any other past or concurrent physical or psychiatric disorder that might impair performance on testing were excluded. All subjects underwent a full medical examination prior to entering the study. The DAT group was recruited through referrals to the Department of Neuropsychology at the Austin and Repatriation Medical Centre, Melbourne, Australia. In accordance with the NINCDS–ADRDA criteria these patients exhibited cognitive deficits on neuropsychological testing consistent with an early dementing process, and were considered to be within the first few years of the illness. The average length of deterioration noted by caregivers was found to be approximately 1 to 2 years prior to the initial assessment, and all DAT patients were still living at home attended by carers. None of the subjects were employed, but all remained capable of everyday chores and activities such as shopping, gardening, housework and hobbies. All DAT subjects were continent and were able to manage personal hygiene independently or with minimal assistance. There was no evidence of movement disorders in any of the DAT patients.

The QD subjects had complaints of progressive memory loss but were found to perform in the normal range on neuropsychological testing, and thus did not fulfill NINCDS–ADRDA criteria for DAT. All QD subjects lived at home with no assistance. They were either in their usual employment situation, or were retired on the basis of age only. These subjects were recruited either from referrals to the Neuropsychology Department at the Austin and Repatriation Medical Centre, or through advertisements in the local press requesting volunteers with a history of mild gradual memory loss to take part in medical research. Controls were recruited by advertising within the Austin and Repatriation Medical Centre, and by approaching carers of subjects in the DAT group. The study was approved by the Ethics Committees of the University of Melbourne, Australia and the Austin and Repatriation Medical Centre, and informed consent was obtained from all participants and/or carers.

Materials and Procedures

The initial assessment involved two separate sessions of 2 to 3 hr each within 14 days of each other, and usually on consecutive days. Subjects were retested at 6, 12, 18, and 24 months after initial assessment using the same protocol (Fowler et al., 1995, 1997). All subjects completed the study with the exception of 1 DAT patient who died of pneumonia between the 18 and 24 month reassessments.

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Standard psychometric measures

These included the full Wechsler Adult Intelligence Scale–Revised (WAIS–R), the Wechsler Memory Scale–Revised (WMS–R), the Mini Mental State Examination (MMSE), the Controlled Oral Word Association Test (COWAT) using the letters *F*, *A*, and *S* (Benton and Hamsher, 1976), the Rey Auditory Verbal Learning Test (RAVLT), the Rey Complex Figure Test (RCFT), the Austin Maze (Walsh, 1978) and Categorical Fluency (Monsch et al., 1992). At the initial and 24 month assessments a structured interview (SI) was conducted (usually by telephone) with the spouse, child or carer of each subject (see Appendix). This asked about recent changes in the subject's memory and cognition, activities of daily living, mood, personality and behavior, and was designed to elicit a relatively objective profile of the subject's daily functioning and difficulties (if any). In all except three cases the family member or carer interviewed was the same at zero and 24 months.

CANTAB tests

The paired associate learning and delayed matching to sample subtests from the CANTAB Visual Memory Battery were also administered.

Paired Associate Learning. In this subtest subjects are required to remember patterns associated with different locations on the screen. Six white boxes appear evenly spaced around the screen, and are opened one by one in a random order for 3 s each. To begin with only one box contains a pattern. After all six boxes have opened and closed the pattern appears in the middle of the screen, and the subject is required to touch the box in which the pattern was located earlier. If correct the task proceeds to the next set of patterns. If an error is made however, the trial is repeated (to a maximum of 10 trials) until the correct choice is made. After two correct sets with a single pattern the number of patterns is increased to two for two sets, three for two sets, then to six, and finally eight for one set each. Whenever the subject makes a mistake the whole of that set is repeated and all boxes are again opened. No feedback for correct responses is given.

Outcome measures for this subtest include maximum set size achieved, trials to criterion, and errors to criterion. We used total errors to criterion (PAL), which has been previously shown to correlate highly with all other measures (Fowler et al., 1995). Errors to criterion denotes how many errors were made before the completion of the test, so that a larger score indicates greater difficulty with the task. An adjusted score is used for subjects not completing the test: Subjects who do not reach a set (say the eight item trial if they failed at six items) are allocated the error score of the worst subject attempting that set. This is added to their total error score to give an adjusted total, which will then represent the same level attempted for each subject (Sahakian et al., 1988).

Delayed Matching to Sample. In this subtest subjects must match patterns in either a delayed or simultaneous condition. One area of the screen depicts a pattern subdivided into quadrants, which differ in terms of color and configuration. This pattern is contained in a red box and represents the *sample*. Beneath this are four white boxes representing the *choice* stimuli, each containing a different pattern, one of which is identical to the sample. Another two boxes contain patterns which differ from the sample only in terms of color or relative position of the quadrants. The final box contains a pattern that has minimal overlap with the sample. To discourage subjects encoding the sample pattern on the basis of one quadrant only, all four choice patterns have one quadrant in common with the sample. In the simultaneous condition the sample and all of the choice stimuli are present on the screen simultaneously, and the subject must select the choice pattern that matches the sample exactly. In condition two (referred to as zero delay) the sample is presented singly for 3 s and its removal is immediately followed by the four choice stimuli. In the final two conditions there are delays of 4 and 12 s. Subjects must touch the choice stimulus that exactly matches the sample. If the response is incorrect the subject may choose again until the correct answer is reached or all choice stimuli have been selected. There are three practice trials, and then 20 test trials over which delay condition is counterbalanced.

Outcome measures are the total number correct responses overall and in the various conditions. In this study all four conditions were administered. We found that the most discriminative was the number correct out of six on the longest, or 12 s, delay condition, the results of which are presented here.

Classification of control and QD subjects at 24 months

We were interested in determining whether individual subgroup membership could be "diagnosed" by examining performance on the standardized neuropsychological procedures. Scores of each control and QD subject on the standard measures at each of the five 6-monthly assessments were printed onto a separate card for each subject and all identifying information removed. Two experienced clinical neuropsychologists were then asked to group the individuals into deteriorating and non-deteriorating categories on the basis of worsening in memory and one other cognitive domain. These guidelines were issued to reflect the NINCDS–ADRDA criteria (McKhann et al. 1984), where the dementia syndrome is confirmed by progressive worsening of memory and at least one other area of cognitive function.

Statistical analysis

Definition of the QD-deteriorating and QD-stable groups was made *post hoc* on the basis of a paired associate learning error score greater than 30 and a deterioration of greater

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than 10 in the error score between zero and 6 months or 6 and 12 months. In the QD group, each of the neuropsychological measures was analyzed using a repeated measures analysis of variance with time of analysis as the repeated factor and *deteriorating* and *stable* as the grouping factor. For the SI questions, Mann–Whitney *U* test were performed on each of the questions to determine if there was a difference between the QD-deteriorating and QD-stable groups at initial assessment and 24 months. The ability of the SI questions to independently identify QD subgroups was assessed by entering scores on all questions at 24 months into a one dimensional cluster analysis, using the Ward method with a-squared Euclidean distance metric, and average linkage between groups.

RESULTS

CANTAB Paired Associate Learning Performance

Demographic data for the three subject groups at entry is presented in Table 1. As previously reported, performance on the CANTAB paired associate learning subtest clearly differentiated between the control and early DAT groups from the initial assessment, and there was a convincing split into a stable and a deteriorating group on performance of this test in the QD subjects at 6 and 12 months. We were particularly interested, therefore, to focus on the abilities of the QD subjects on follow up at 18 and 24 months. Mean scores of the QD-deteriorating and QD-stable subgroups on the paired associate learning subtest are presented in Figure 1. Performance of the control group and early DAT group are also shown.

Trajectories of paired associate learning performance in each subject are shown in Figure 2. The split that was evident in the performance on the paired associate learning test in the QD group was maintained at the 18- and 24-month assessments. The QD-stable subgroup maintained their level of performance, and there was no difference between the QD-stable subgroup and the control group at any of the five assessments. The performance of the QD-deteriorating subgroup continued to worsen over the course of the study and by 24 months was not significantly different from that of the early DAT subjects, consistent with the floor effects on this subtest. The distinguishing characteristic of the QD-deteriorating subgroup was the consistent worsening in performance by each subject at almost every assessment, similar to that seen in the early DAT group. In comparison to the early DAT group, at the 12-month assessment the mean paired associate learning error scores in the QD-deteriorating subgroup was similar to that of the early DAT group at the initial assessment (Figure 1). However, the range of scores was much narrower (48–72 in the QD-deteriorating subgroup at 12 months *vs*. 18–102 in the early DAT group at zero months). Of particular interest, 1 subject in the control group also exhibited a pattern of deterioration on paired associate learning performance (Figure 2).

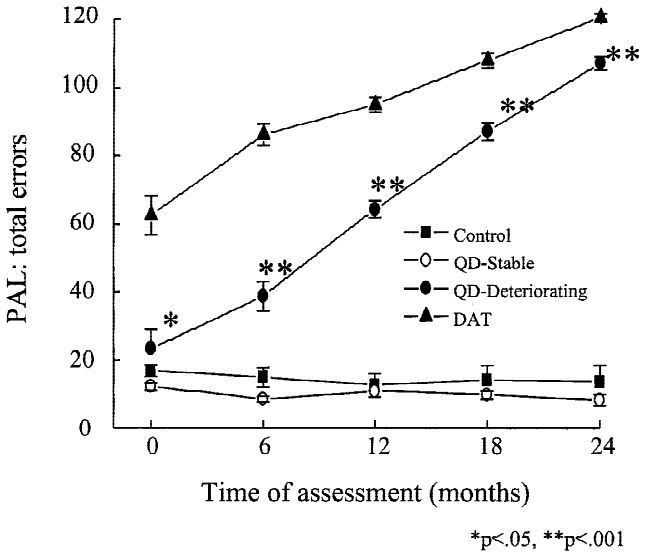

Fig. 1. Mean scores on CANTAB Paired Associate Learning subtest: Total errors.

CANTAB Delayed Matching to Sample Performance

Mean and individual performances of the two QD subgroups on the 12-s condition in the CANTAB delayed matching to sample test are shown in Figure 3. As with the paired

Table 1. Demographic data of the control, QD, and early DAT groups and the QD-deteriorating (QD-D) and QD-stable (QD-S) subgroups from the QD group

Variable	Control	QD	*QD-S*	*QD-D*	Early DAT
N	19	21	*12*	*9*	16
Age (years)*	59 (6)	58 (7)	*56 (6)*	*59 (7)*	65 (5)
Sex (M/F)*	5,14	8,13	*4,8*	*4,5*	8,8
Years education*	13 (3)	12 (3)	*12 (2)*	*11 (2)*	12 (3)
Premorbid IQ*	116 (11)	108 (9)	*109 (9)*	*106 (8)*	108 (8)
MMSE*	29.9 (0.3)	29.3 (0.7)	*29.6 (0.5)*	*29.0 (0.9)*	25.1 (2.0)

**M* (*SD*)

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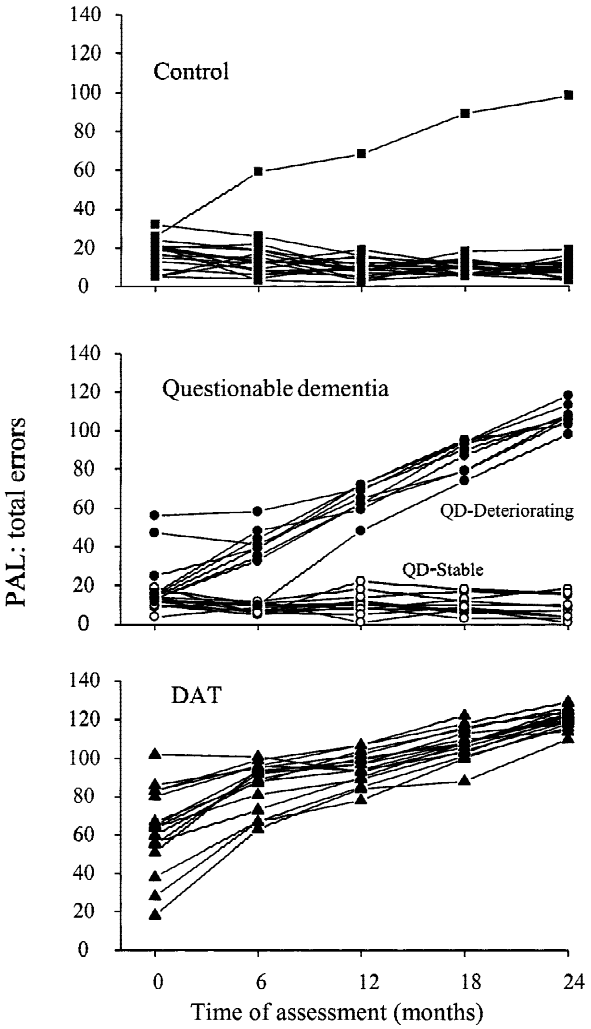

Fig. 2. Individual trajectories on CANTAB PAL.

associate learning test, the majority (7/9, or 78%) of QD-deteriorating subjects exhibited a decline in performance on this task at the 6-month reassessment, and by 12 months all had deteriorated. In contrast, performance of the QD-stable subgroup was maintained. There was not such a clear split in delayed matching to sample performance in the individual trajectories of subjects, however the range of possible scores on this test was restricted.

Discriminant Function Analysis

Subjects in the study were classified initially into groups on the basis of their performance on the standard neuropsychological measures. There was speculation about the ability of the computerized measures to classify patients. Stepwise discriminant function analyses were carried out at each of the five assessments with group membership as the criterion, and PAL and DMTS performance as the predictors. Since interest centered on the cognitive spectrum extending between normality and early DAT, the QD category was included as an essential region of this spectrum. From a longitudinal perspective, however, it does not represent a logical *outcome* variable. Therefore the probability of QD membership was set at zero for the purposes of discriminant function analysis. This effectively excludes the QD category from the criterion variable on the assumption that QD subjects will be diagnosed eventually as either dementing or non-dementing. Relevant mathematical and statistical properties of each discriminant function analysis are shown in Table 2.

At each assessment, one discriminant function emerged. At the initial assessment this accounted for 79.4% of the variance. All NC subjects were correctly classified. Thirteen of the 16 DAT patients (81%) were correctly classified, with the remaining 3 cases assigned to the NC group. Of the QD subjects, 95% were assigned to the NC group; only 1 case was classified as DAT at this point. Over subsequent reassessments further QD subjects were classified as belonging to the DAT group: 3 at 6 months, 8 at 12 months, and 9 out of the 21 (or 43%) at both 18 and 24 months. By 24 months the discriminant function analysis accounted for 97.6% of the variance. All DAT subjects were correctly classified at this occasion (note that 1 DAT patient had died by this assessment, as mentioned above). All NC subjects except 1 were also classified correctly. This individual is clearly identified on the PAL trajectories (Figure 2).

In summary, at each assessment the majority of both NC (95–100%) and DAT (81–100%) subjects were correctly classified, suggesting that the predictive capability of the computerized measures is high. Nearly all QD subjects were assigned to the NC group at the initial and 6-month assessments. However, by the 12-month assessment over one-third of these subjects were assigned to the DAT group. This rose to 43% at the 18- and 24-month assessments (Table 3).

Classification of Control and QD Subjects at 24 Months

Scores of all control and QD subjects on the standard neuropsychological measures at the five assessments were reviewed by blinded, independent neuropsychologists who rated them on the basis of deterioration in memory and at least one other cognitive domain. Of the 40 subjects, 11 were placed in the deteriorating category. These 11 subjects included all 9 QD-deteriorating subjects defined in terms of paired associate learning performance. The remaining 2 subjects were the control subject noted to be deteriorating on paired associate learning, and a member of the QD-stable subgroup who exhibited no evidence of deterioration on the computerized tests or the structured interview.

Performance on Standard Neuropsychological Tests

We have previously shown that the QD subgroups did not differ with regard to age, gender, years of education, or

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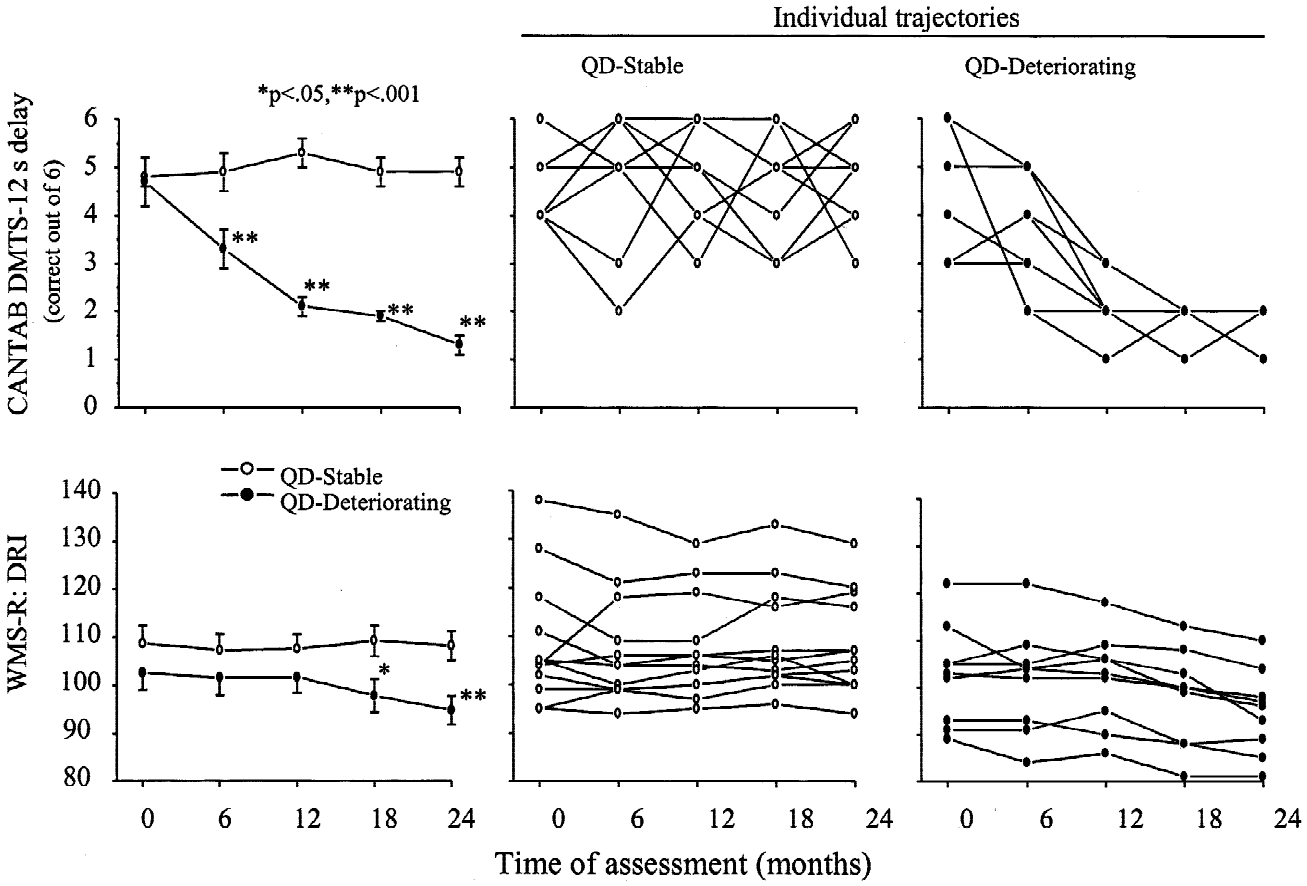

Fig. 3. Mean scores and individual trajectories of QD subgroups on CANTAB DMTS subtest and WMS–R Delayed Recall Index.

occupational level (Fowler et al., 1997; see also Table 1). There was also no significant difference in a demographically based estimate (Wilson et al., 1987) of premorbid IQ (Table 1).

The performance of the QD-deteriorating and QD-stable groups on the standard neuropsychological tests are shown in Figure 4 and Table 4. The QD-deteriorating subgroup had significantly lower scores at all assessments on WAIS–R Full Scale IQ (FSIQ), although as noted previously (Fowler et al., 1997), mean FSIQ values remained within the average range at all assessments. The performance of the QD-deteriorating subgroup was significantly poorer than the QD-stable subgroup from the 12-month mark on the MMSE, Austin Maze, and RCFT recall. It is important to emphasize that there was considerable overlap in individual performance even at the 24-month assessment. Subgroup differences on Category Fluency and the WMS–R General Memory Index (GMI) did not reach significance until the 18 month assessment, while the COWAT did not discriminate between the groups at any time (Table 4).

The RAVLT is of particular interest as recent studies have shown that list learning tasks can predict dementia in memory-impaired nondemented subjects (Bondi et al., 1994; Tierney et al., 1996a, 1996b). In both the recognition trial and the sum of words recalled on Trials 1 to 5 from the RAVLT there was a marked difference in performance between the QD-deteriorating and QD-stable subgroups from the initial assessment (Figure 4). In contrast to the CANTAB paired associate learning test, however, there was no marked deterioration in the QD-deteriorating subgroup on either parameter over the course of the study, and there was considerable overlap in individual performance in the two groups.

Table 2. Discriminant function analyses at each assessment

Assessment	Eigenvalue	Wilks's Lambda	Chi-Squared
0 months	1.58	0.39	50.28
6 months	2.79	0.26	70.55
12 months	2.10	0.32	60.03
18 months	2.01	0.33	58.37
24 months	1.84	0.35	54.27

Note. All chi-squared values were associated with 2 degrees of freedom and were significant beyond the .005 level.

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Table 3. Classification on the basis of PAL and DMTS scores

Initial assessment			
		Predicted group membership	
Actual group	N	NC	DAT
NC	19	19	0
		100%	0%
QD	21	20	1
		95%	5%
DAT	16	3	13
		19%	81%
6-month assessment			
		Predicted group membership	
Actual group	N	NC	DAT
NC	19	18	1
		95%	5%
QD	21	18	3
		86%	14%
DAT	16	0	16
		0%	100%
12-month assessment			
		Predicted group membership	
Actual group	N	NC	DAT
NC	19	18	1
		95%	5%
QD	21	13	8
		62%	38%
DAT	16	0	16
		0%	100%
18-month assessment			
		Predicted group membership	
Actual group	N	NC	DAT
NC	19	18	1
		95%	5%
QD	21	12	9
		57%	43%
DAT	16	0	16
		0%	100%
24-month assessment			
		Predicted group membership	
Actual group	N	NC	DAT
NC	19	18	1
		95%	5%
QD	21	12	9
		57%	43%
DAT	15	0	15
		0%	100%

The performance of the QD-deteriorating and QD-stable subgroups on subtests from the standard neuropsychological tests that are most closely related to the CANTAB paired associate learning and delayed matching to sample tests are shown in Figures 3 and 5. On the delayed recall index from the WMS–R the subgroups differed from the 18-month mark onward, due to a decline in performance of the QD-deteriorating group (Figure 3). However, there was considerable overlap in the scores of both subgroups even at 24 months. The sensitivity of the verbal and visual paired associate learning tasks from the WMS–R to discriminate between the subgroups was different (Figure 5). On the verbal task a significant difference between the two groups emerged from 12 months onwards, but there was also some overlap in the individual performances between the groups. The visual paired associate learning task was less sensitive to differences between the two subgroups and only at 24 months was there a significant difference between QD-deteriorating and QD-stable.

Performance on the Structured Interview

Given that a number of QD subjects had exhibited deterioration in neuropsychological test performance over the 24 months of the study we were interested to see if functional performance or ability to carry out activities of daily living had also changed in these subjects, as deterioration in this realm is necessary for the diagnosis of DAT (McKhann et al., 1984). At the initial assessment only one item (Question 7), "Does he/she experience any difficulty with concentration during conversation/watching TV/reading books or newspapers?" significantly discriminated between the QD-deteriorating and QD-stable subgroups ($p = .035$). However, by 24 months 12 questions discriminated between the subgroups (Table 5).

A cluster analysis on the SI data from the QD group at 24 months identified two clear groups formed at a relatively early stage in the agglomeration sequence (Figure 6). One group consisted of 11 individuals, which included all 9 of the QD-deteriorating subgroup and two others. Retrospective analysis did not reveal any deterioration in computerized or standard neuropsychological test performance of these two individuals who did not belong to the QD-deteriorating subgroup. It is likely therefore that their inclusion in this cluster was due to rater unreliability. By contrast, cluster analysis carried out at the first assessment did not provide any well defined groupings (data not shown).

DISCUSSION

The striking finding from the present study was that performance on the CANTAB paired associate learning test identified the onset of *progressive* memory deterioration in a subgroup of QD subjects who over a 2-year period *all* fulfilled NINCDS–ADRDA criteria for probable DAT pertaining to progression of cognitive deficits, impaired functional ability, onset and conscious state. Over a 2-year period *all* QD-deteriorating subjects went on to exhibit significant cognitive and functional deterioration suggestive of early DAT. This finding is particularly notable as after the 6-month

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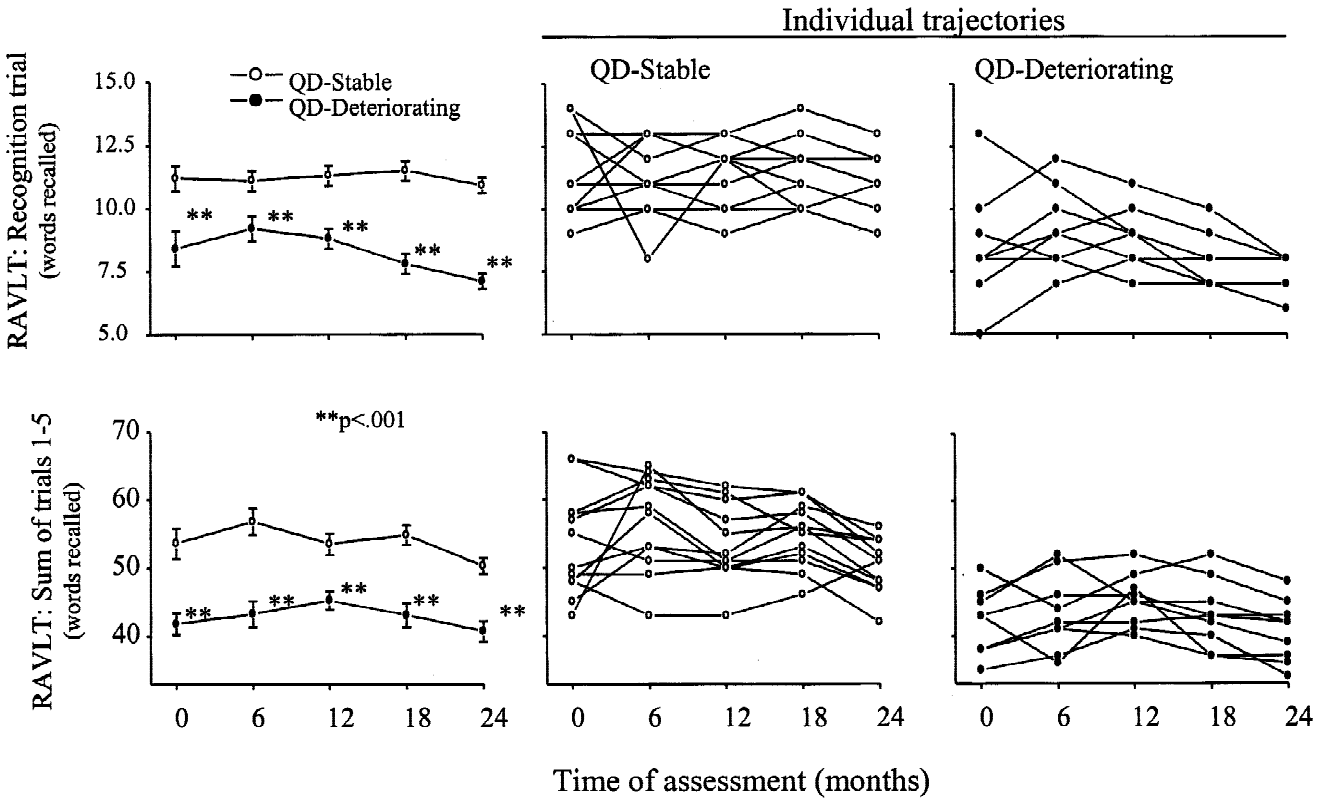

Fig. 4. Mean scores and individual trajectories of QD subgroups on RAVLT Sum of Trials 1–5 and Recognition Trial.

Table 4. Mean scores (± SEM) on standard neuropsychological tests for QD-deteriorating and QD-stable subgroups over five assessments over 2 years

Test	Subgroup	0 months	6 months	12 months	18 months	24 months
FSIQ	QD-Stable	116 ± 2	118 ± 2	117 ± 2	117 ± 2	117 ± 2
	QD-Deteriorating	108 ± 3	109 ± 3**	108 ± 2**	108 ± 2**	107 ± 2**
GMI–WMS	QD-Stable	110 ± 3	107 ± 2	108 ± 3	108 ± 3	107 ± 3
	QD-Deteriorating	103 ± 4	101 ± 3	102 ± 3	99 ± 3*	96 ± 3*
DRI–WMS	QD-Stable	109 ± 4	107 ± 4	107 ± 3	108 ± 3	109 ± 3
	QD-Deteriorating	103 ± 4	102 ± 4	102 ± 4	102 ± 3*	98 ± 3**
MMSE	QD-Stable	29.6 ± 0.1	29.8 ± 0.1	29.8 ± 0.1	29.8 ± 0.1	29.9 ± 0.1
	QD-Deteriorating	29.0 ± 0.3	29.6 ± 0.2	29.1 ± 0.2**	29.0 ± 0.2**	28.7 ± 0.2**
Austin Maze	QD-Stable	64 ± 4	64 ± 4	62 ± 4	63 ± 4	63 ± 3
	QD-Deteriorating	75 ± 3	73 ± 3	74 ± 3	79 ± 3**	82 ± 3**
COWAT	QD-Stable	46 ± 3	48 ± 3	54 ± 3	53 ± 3	55 ± 3
	QD-Deteriorating	49 ± 4	55 ± 55	55 ± 4	53 ± 4	52 ± 4
Cat. Fluency	QD-Stable	61 ± 3	64 ± 3	62 ± 2	64 ± 1	63 ± 2
	QD-Deteriorating	54 ± 3	59 ± 0.8	60 ± 1	57 ± 2*	53 ± 2**
RCFT recall	QD-Stable	22 ± 1	25 ± 1	26 ± 1	28 ± 1	27 ± 1
	QD-Deteriorating	19 ± 1	19 ± 2	21 ± 2**	18 ± 2**	19 ± 1**
Block Design (WAIS-R)	QD-Stable	13.5 ± 0.9	13.8 ± 0.6	13.7 ± 0.7	13.5 ± 0.6	13.5 ± 0.5
	QD-Deteriorating	12.0 ± 0.4	11.4 ± 0.7*	12.0 ± 0.4	11.8 ± 0.4*	11.8 ± 0.5*

*$p < 0.5$, **$p < 0.01$ from univariate F test of group differences at each assessment from repeated measures ANOVA.
Note. FSIQ: full scale IQ from the Weschler Adult Intelligence Scale–Revised (WAIS–R); GMI–WMS: general memory index from the Weschler Memory Scale–Revised; DRI–WMS: delayed recall index from the Weschler Memory Scale–Revised; MMSE: Mini Mental State Examination; COWAT: Controlled Oral Word Association Test; RCFT recall: Rey Complex Figure Test free recall after 15 min.

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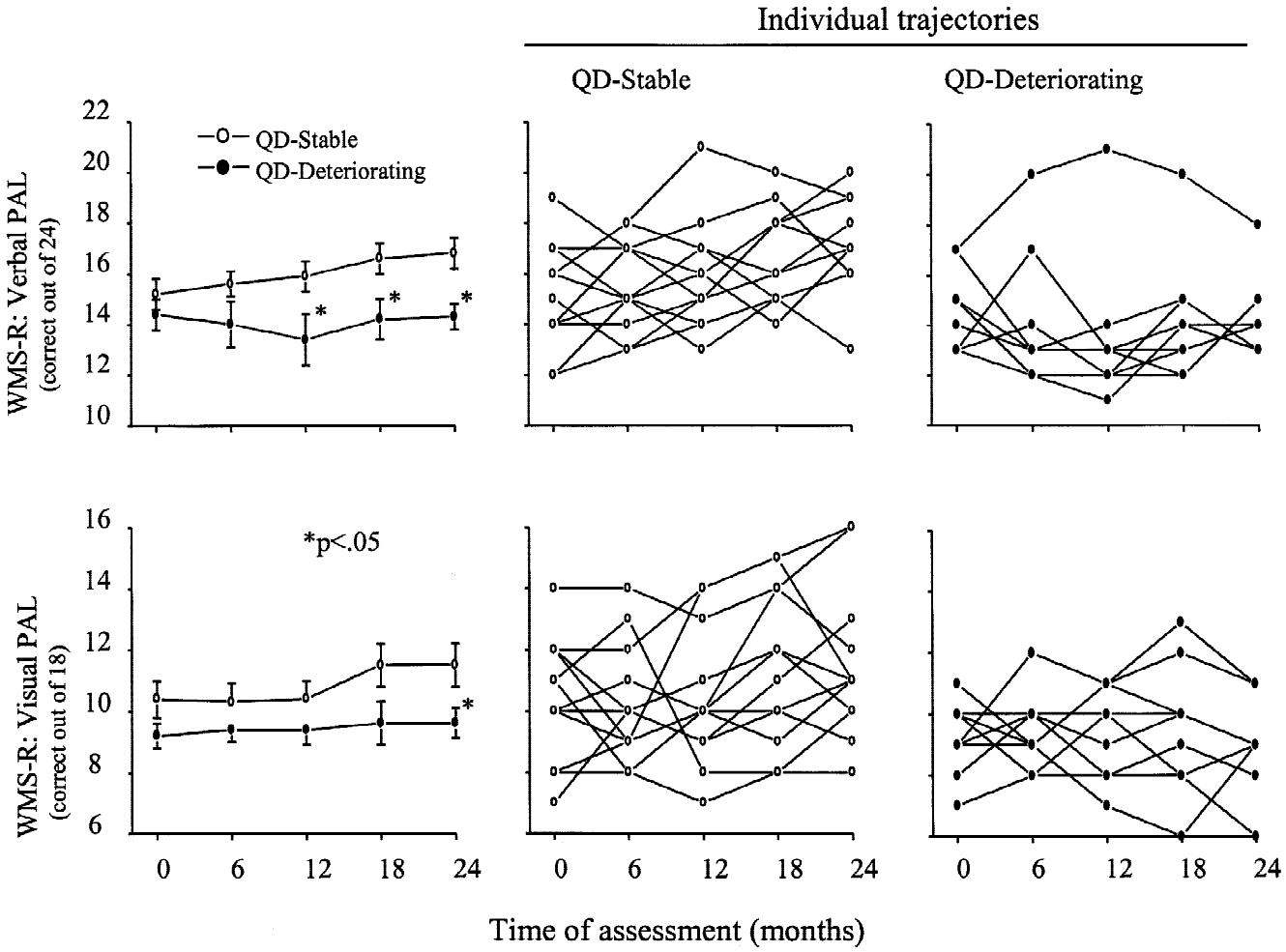

Fig. 5. Mean scores and individual trajectories of QD subgroups on WMS–R Verbal and Visual PAL subtests.

Table 5. Mann–Whitney *U* analyses of Structured Interview (*p* values)

Question No.	Topic	Time 1	Time 6
1	Severity of memory loss	.139	.000**
2a	What does subject forget?	.405	.014*
2b	How often?	.251	.106
3a	Worsened over past year?	.464	.001**
3b	Severity of deterioration	.149	.000**
4	Have others noticed?	.261	.026*
5	Frequency of ADL difficulties	.372	.012*
6	Which ADLs are independent?	.998	.025*
7	Changes in concentration?	.350*	.009**
8	Episodes of disorientation?	.094	.025*
9a	Ever lost in familiar places?	.864	.319
9b	In unfamiliar places?	.921	.898
9c	Able to read map?	.576	.221
10	Changes in speech?	.159	.036*
11	Changes to handwriting?	.623	.414
12	Changes in personality?	.076	.024*
13	Nature of personality changes	.098	.033*

*$p < .05$, **$p < .001$.

assessment there was no overlap in the performance of the deteriorating QD subgroup with either the age-matched normal controls (except for the subject who later developed DAT) or the rest of the QD group. In fact, paired associate learning and delayed matching to sample performance had predicted QD subgroup membership in some cases as early as 6 months after initial assessment (Fowler et al., 1997). In contrast, there was substantial overlap in performance between the stable and deteriorating subjects in the QD group on the standard neuropsychological tests that tap similar cognitive abilities, the verbal and visual paired associate learning from the WMS–R. This demonstrates that the computerized paired associate learning task is a very sensitive determinant of memory deficits in the earliest stages of DAT. To add further validity to the findings, 1 subject in the normal control group also showed signs of deterioration on paired associate learning, and in addition fulfilled DAT criteria as outlined above. The evidence of progression of memory loss using the paired associate learning test was also notable. In the deteriorating subgroup of QD subjects, there was a progressive decline in paired associate learning performance at each 6 month interval in almost all subjects,

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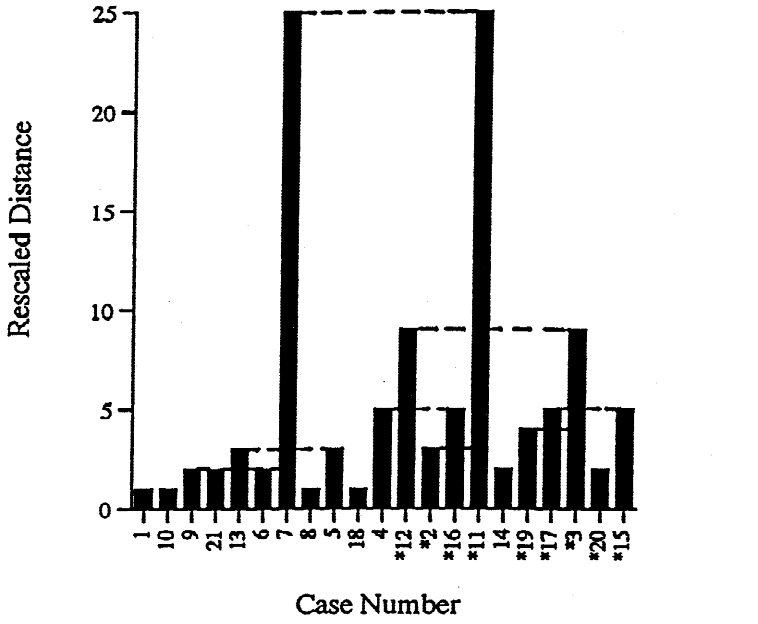

Fig. 6. QD group cluster analysis dendogram at 24 months.

such that over the course of the study they went from near ceiling performance to floor performance. Progression was also clearly obvious in the early DAT group. Performance on equivalent standard neuropsychological test did not decline appreciably over the course of the study. It is this rapid deterioration in paired associate learning performance that accords the test its high sensitivity in determining early DAT.

One aspect of the study that requires discussion is the definition of questionable dementia. Berg (1985) classified subjects with a clinical dementia rating (CDR) of 0.5 as QD on the basis of clinical assessment involving an examination and a structured interview with both the subject and a collateral source who knows the subject well. The subjects are rated as having mild-consistent forgetfulness with only doubtful impairment of other cognitive areas. These criteria have been shown to be reliable in follow-up studies (Rubin et al., 1989) and by pathological verification (Morris et al., 1991). Deficits on objective memory tests were not part of the criteria defined by Berg (1985), however, they have been included in recent studies (Morris et al., 1991; Strohle et al., 1995; Tierney et al., 1996a, 1996b). Also in recent studies, interference with daily functioning has been an inclusion criteria (Strohle et al., 1995; Tierney et al., 1996a, 1996b), although this was not a criterion set out by Berg (1985). In our study, QD subjects at entry performed within the normal range on standard neuropsychological measures and were not impaired in activities of daily living.

A number of studies have shown that between 25 and 75% of QD subjects go on to fulfill criteria for probable DAT at a later assessment (see Introduction). Although delayed recall and associate learning tasks can be useful in defining these groups there is significant overlap in cognitive performance, particularly between QD and control subjects (Morris et al., 1991; Storandt and Hill, 1989; Strohle et al., 1995). Tierney et al. (1996b) reported that performance on the RAVLT delayed recall task and an attention task were able to predict progression to DAT within 2 years in a group of QD subjects with an accuracy of 89% and sensitivity and specificity of 76 and 94% respectively. In support of these findings, in our study RAVLT test performance was significantly lower in the QD-deteriorating subjects compared to stable subjects at entry, although overlap between the groups was evident. Further deterioration in performance on RAVLT was seen in most QD-deteriorating subjects. It should be noted that the subjects in the Tierney et al. (1996b) study also had demonstrated impairment in performing activities of daily living at study entry and were therefore at a later stage of the disease progress than those in our study.

The findings demonstrate that CANTAB paired associate learning subtest scores may be an effective predictor of DAT onset in contrast to standard measures of cognitive function. The paired associate learning paradigm was originally developed to investigate memory in monkeys (Mishkin & Pribram, 1956) with the animal required to remember the spatial location of a hidden object. This task was subsequently adapted for use with humans (e.g. Smith & Milner, 1981), and a computerized analogue developed as part of CANTAB (Morris et al., 1987). The superior performance of this test in determining DAT onset may be explained by its reliance on mesial temporal structures, particularly the hippocampus, that are implicated in the neuropathogenesis of DAT. A number of researchers have suggested that the formation of conjunctions between unrelated

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stimuli or concepts is the central mnemonic role of the human hippocampal system and associated parahippocampal structures (Cohen et al., 1999; Eichenbaum et al., 1994; Miller et al., 1993; Saling et al., 1993; Squire, 1992), and it is worth noting that hippocampal volumes correlate with verbal paired associate learning in cases with DAT (Deweer et al., 1995). The hippocampal system also plays a central role in forming a cognitive schema of spatial layouts, and it has long been supposed that this is the most fundamental cross species role of the hippocampus and associated parahippocampal regions (Burgess et al., 1999; O'Keefe & Nadel, 1978; Terrazas & McNaughton, 2000). The CANTAB paired associate learning task involves the ability to associate a stimulus (*what*) with a spatial location (*where*). Mesial temporal structures play an important role in the encoding and recall of spatial location (Maguire et al., 1998; Smith & Milner, 1989), although recent functional neuroimaging work suggests that the capacity to learn *what goes where* is also underpinned by a more extensive system that includes medial parietal and occipitotemporal cortex (Maguire et al., 1998; Maguire, 1999). Of further relevance to the CANTAB paradigm in early detection of dementia, associative recall of visual stimuli produces specific hyperperfusion in entorhinal cortex (Klingberg et al., 1994), now thought to be one of the first areas affected in Alzheimer's disease (Killiany et al., 2000). The CANTAB paired associate paradigm taps aspects of memory function that represent fundamental functions of the hippocampal system (Burgess et al., 1999; Cohen & Eichenbaum, 1993). Because there is very early involvement of this system in Alzheimer's disease, the paradigm is sensitive to key early cognitive changes in this condition. We suggest that it is worthy of development in its own right as a clinical tool.

In terms of other standard neuropsychological measures, the deteriorating QD subgroup were retrospectively found to have significantly lower FSIQ scores at the initial assessment that the nondeteriorating subgroup. However, mean FSIQ values of the deteriorating subgroup remained within the accepted normal range over all assessments, limiting their sensitivity in individual cases with very early cognitive change. All other standard tests did not discriminate between the groups until the 12 or 18 month assessments.

Neuropsychological assessment using CANTAB may have a number of advantages. The CANTAB system itself is well tolerated by elderly subjects, who generally prefer it to standard pen and paper measures (Morris et al., 1987; Sahgal et al., 1991). Furthermore, these tests are easily and accurately administered and scored, and have been shown to possess acceptable to high levels of concurrent validity and test–retest reliability (Fowler et al., 1995).

The findings of this study are limited somewhat by the relatively small number of subjects in each group. Furthermore, while participants were screened for depression using the SI and a clinical examination at initial assessment the use of an objective rating scale (such as the Hamilton Depression Scale; Hamilton, 1967) may more accurately exclude this possibility. The replication of this study with these caveats in mind is therefore recommended. Nonetheless we believe that the CANTAB paired associate learning subtest is a valuable tool for the early detection of DAT, and may also be a useful marker to assess therapeutic efficacy in DAT over relatively short trials.

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Appendix

STRUCTURED INTERVIEW

Activities of Daily Living Questionnaire

Please answer the following questions about _____.

For each question, please circle either Y (Yes) or N (No) or the description you feel best fits.

1. How would you describe his/her memory difficulties? _____

Negligible	Mild	Mild-Moderate	Moderate	Severe
(1)	(2)	(3)	(4)	(5)

2.(a) What sort of things does he/she forget?

Names	Y	N
Appointments	Y	N
Where they've put things, e.g. keys, glasses	Y	N
Day to day events	Y	N
Current events	Y	N
	(1 each)	(0 each)

2.(b) How often? _____

Never	Occasionally	Often
(0)	(1)	(2)

3.(a) Have his/her memory difficulties worsened over the past 6–12 months?

Y	N
(1)	(2)

3.(b) If yes, has this deterioration been: _____

Negligible	Mild	Moderate	Severe
(0)	(1)	(2)	(3)

4. Have others (e.g. children/relatives/friends) noticed his/her memory difficulties?

Y	N
(1)	(2)

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5. Does he/she experience difficulties with daily activities e.g., leaving taps running, forgetting to turn off appliances, or difficulty following recipes or other procedures? If so, how often? _____

Never	Occasionally	Often
(0)	(1)	(2)

6. Which activities can he/she carry out independently ie. without guidance or supervision?

Shopping	Y	N
Gardening	Y	N
Housework	Y	N
Repairs around the house	Y	N
Hobbies	Y	N
Driving	Y	N
Errands	Y	N
	(0 each)	(1 each)

7. Does he/she experience any difficulty with concentration during:

Conversation	Y	N
Watching TV	Y	N
Reading books or newspapers	Y	N
	(1 each)	(0 each)

8. Does he/she ever appear disorientated, i.e., confused about the date and/or place? How often? _____ _____

Never	Occasionally	Often
(0)	(1)	(2)

9.(a) Does he/she ever become lost or confused in unfamiliar environments?

Y	N
(1)	(0)

9.(b) In familiar environments?

Y	N
(1)	(0)

9.(c) Are they able to use a map or street directory?

Y	N
(0)	(1)

10. Have you noticed any changes in his/her speech e.g., work finding difficulties, trouble expressing him/herself? How often? _____

Never	Occasionally	Often
(0)	(1)	(2)

11. Have you noted any changes in his/her handwriting?

Y	N
(1)	(0)

12. Have you noticed any changes in his/her personality?

Y	N
(1)	(0)

13. Does he/she appear to be unduly

—worried	Y	N
—depressed	Y	N
—anxious	Y	N
—suspicious of others	Y	N
—aggressive	Y	N
—irritable	Y	N
	(1)	(0)

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