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# A four year prospective study of age-related cognitive change in adults with Down's syndrome

C. OLIVER,[1] L. CRAYTON, A. HOLLAND, S. HALL AND J. BRADBURY

*From the School of Psychology, University of Birmingham; Department of Psychology, Institute of Psychiatry, London; and Department of Psychiatry, University of Cambridge*

## ABSTRACT

**Background.** While neuropathological studies indicate a high risk for Alzheimer's disease in adults with Down's syndrome, neuropsychological studies suggest a lower prevalence of dementia. In this study, cognitive deterioration in adults with Down's syndrome was examined prospectively over 4 years to establish rates and profiles of cognitive deterioration.

**Methods.** Fifty-seven people with Down's syndrome aged 30 years or older were assessed using a battery of neuropsychological tests on five occasions across 50 months. Assessments of domains of cognitive function known to change with the onset of Alzheimer related dementia were employed. These included tests of learning, memory, orientation, agnosia, apraxia and aphasia. The individual growth trajectory methodology was used to analyse change over time.

**Results.** Severe cognitive deterioration, such as acquired, apraxia and agnosia, was evident in 28·3% of those aged over 30 and a higher prevalence of these impairments was associated with older age. The rate of cognitive deterioration also increased with age and degree of pre-existing cognitive impairment. Additionally, deterioration in memory, learning and orientation preceded the acquisition of aphasia, agnosia and apraxia.

**Conclusions.** The prevalence of cognitive impairments consistent with the presence of Alzheimer's disease is lower than that suggested by neuropathological studies. The pattern of the acquisition of cognitive impairments in adults with Down's syndrome is similar to that seen in individuals with Alzheimer's disease who do not have Down's syndrome.

## INTRODUCTION

Age-related changes in adults with Down's syndrome (DS) have received considerable attention, primarily because of the observation that people with DS develop the neuropathological changes of Alzheimer's disease (AD) in early life and with increasing age (Ball & Nuttall, 1980; Liss *et al*. 1980; Yates *et al*. 1980; Wisniewski *et al*. 1985; Mann, 1993). Neuropathological studies have shown that by the age of 30 years, amorphous amyloid deposition will have been present in the brain for some years and plaques and tangles, predominantly in the amygdala, hippocampus and association areas of the frontal, temporal and parietal cortex characteristic of AD, are invariably present (Mann & Esiri, 1989).

These neuropathological observations acquire greater significance when considered alongside observed indices of premature ageing (Ponzsonyi *et al*. 1964; Rarick & Seefeldt, 1974; Martin, 1978; Carr & Hollins, 1995), a reduced life expectancy for people who have DS (see Carr, 1994) and the evidence for a role of a gene on chromosome 21 in Alzheimer's disease (Whalley, 1993). Recent research has examined the associations between different alleles for apolipoprotein (Royston *et al*. 1996; Farrer *et al*. 1997), the amyloid precursor protein (Rumble *et al*. 1989), located on chromosome 21, and

[1] Address for correspondence: Professor Chris Oliver, School of Psychology, University of Birmingham, Edgbaston, Birmingham B15 2TT.

Alzheimer's disease in DS (see Holland & Oliver, 1995). There is also tangential evidence for the development of Alzheimer's disease in people with DS from studies employing positron emission, computer assisted tomography (Schapiro *et al*. 1992), electroencephalogram and P300 evoked potential latency recordings (Blackwood *et al*. 1988; Muir *et al*. 1988; Soininen *et al*. 1993).

In combination, the neuropathological, imaging and psychophysiological studies, suggest a very high risk for people with DS for developing AD with age and thus corresponding cognitive and behavioural deterioration should be evident. However, the investigation of age-related cognitive changes in adults with Down's syndrome is problematical because of variability in the degree of pre-existing cognitive impairments and the floor effects in assessments that arise due to the presence of substantial pre-existing cognitive impairments (Oliver, 1999). These problems often preclude the application of unmodified diagnostic criteria for dementia which, while varying in their detail (see DSM-IV, 1994; ICD-10, 1992; NINCDS-ADRDA, 1984), all require evidence of functional decline in memory, decline in at least one other area of cognitive function (e.g. aphasia, apraxia, agnosia, executive function) and/or deterioration in personality in the absence of clouding of consciousness. For people with DS, if there is evidence of memory or other cognitive impairments it is not clear if this is due to pre-existing or acquired neurological dysfunction (Oliver, 1999).

Cognitive and behavioural impairments indicative of dementia in adults with DS have been described in cross-sectional, longitudinal and case studies (see Oliver & Holland, 1986; Crayton & Oliver, 1993). Case studies relating neuropathological evidence to cognitive and behavioural decline, have relied on informant's retrospective accounts that might be inaccurate. Although cross-sectional studies might be compromised by cohort effects, there is some consensus in the findings that cognitive and behavioural performance in adults with DS in older age groups is poorer in comparison to younger age groups (Owens *et al*. 1971; Dalton *et al*. 1974; Dalton & Crapper, 1977; Wisniewski *et al*. 1978; Thase *et al*. 1982, 1984; Zigman *et al*. 1987; Haxby, 1989; Crayton *et al*. 1998). While the domains of cognitive and behavioural impairment assessed are not always specific to the dementia that accompanies AD (e.g. Zigman *et al*. 1987), studies have demonstrated specific deficits in orientation (Wisniewski *et al*. 1978; Thase *et al*. 1982, 1984), object identification (Owens *et al*. 1971; Wisniewski *et al*. 1978; Thase *et al*. 1982) and memory (Dalton *et al*. 1974; Dalton & Crapper, 1977; Wisniewski *et al*. 1978; Crayton *et al*. 1998).

More recently, prospective longitudinal studies have appeared (Dalton & Crapper, 1977; Hewitt *et al*. 1985; Wisniewski *et al*. 1985; Fenner *et al*. 1987; Lai & Williams, 1989; Burt *et al*. 1995; Devenny *et al*. 1996; Dalton & Fedor, 1998). These studies have further clarified the impairments associated with ageing in DS and the sequence in which the impairments are acquired. In summary, the results indicate that the profile and acquisition of cognitive and behavioural impairments in adults with DS is similar to that seen in the general population. Lai & Williams (1989) and Dalton & Fedor (1998) both document the sequence of decline to be similar to that seen in AD in the general population. However, exceptions to this conclusion are the studies of Devenny *et al*. (1996), which reported that over 95% of their sample of 91 adults with DS (including 27 aged 50 or over) 'maintained their initial performance levels' (p. 219) and Burt *et al*. (1995) who reported that in their sample of 34 adults (age range 22 to 56, no further data available) 'age related changes in functioning were not occurring' (p. 261).

Taken together, cross sectional and longitudinal studies reveal wide variations in prevalence estimates for the clinical diagnosis of dementia. Lai & Williams (1989), for example, reported that 51% of their cohort had evidence of functional decline with a mean age of onset of dementia of 54·2 years. Prevalence rates of dementia increased with age in the 53 people living in an institutional setting, from 8% in the 35–49 age group to 75% in those over 60 years. In a review of prevalence estimates, Aylward *et al*. (1995) document prevalence rates of dementia in DS to vary from a few percent for adults between 30–39 years of age, 10% to 25% in those aged between 40–49 years, 20% to 50% in those 50–59 years of age and between 30% and 75% in those above 60 years of age. This overview of prevalence is in contrast to the

findings of Burt *et al.* (1995) and Devenny *et al.* (1996).

The reasons for this variability are unclear and a number of factors may be influential. The sensitivity, reliability and validity of assessments employed to detect the earliest signs may vary, as may the statistical and 'diagnostic' criteria invoked for decline or dementia to be deemed evident. There is also substantial variability in participant selection and sample size, factors discussed by Burt *et al.* (1995) and Devenny *et al.* (1996). This is particularly relevant, as the detection of earliest signs of dementia is increasingly the focus of longitudinal designs and this may necessitate excluding those who have already experienced decline or those with greater pre-morbid cognitive impairments.

Despite this variability in prevalence estimates, the most striking feature of the findings from these studies is that the presence of identified cognitive impairments falls far below that which would be predicted from the neuropathological data (see Liss *et al.* 1980; Ropper & Williams, 1980; Wisniewski *et al.* 1985). This discrepancy adds to the importance of studies of the profile and acquisition of cognitive and behavioural impairments, as it is necessary to use assessments of sufficient sensitivity to ensure that impairments are indeed absent.

In this study, a cohort of adults with DS was followed prospectively over 50 months to observe the neuropsychological and functional changes that occur with age. The aim of the study was to examine the age-related changes in cognitive and functional ability over time and to establish whether the pattern of change observed was what might be expected given the higher risk of AD in adults with DS. Similar to the studies of Devenny *et al.* (1996) and Burt *et al.* (1995), inclusion criteria for participants were employed to rule out those with severe pre-existing cognitive impairments or a discernible dementia. Some of the assessments employed to identify acquired cognitive impairments were those used by Sahakian *et al.* (1988) to demonstrate differences between the dementia associated with Alzheimer's disease and that of Parkinson's disease in the general population. Thus, some of the assessments used in this study have previously been validated on participants who did not have DS or a pre-existing cognitive impairment.

## METHOD

### Participants

Adults with DS aged 30 years or over were identified in four London boroughs. Initial screening of pre-existing cognitive impairments or advanced dementia was undertaken in order that those who might be unable to undertake the tests from the start of the study could be excluded. The inclusion criteria for the study were the presence of DS (if possible confirmed chromosomally), age 30 years or older at the time of inclusion, no evidence of a significant sensory impairment or of severe cognitive impairments and informed consent given by the participant and/or assent by proxy. The presence of impairments sufficiently severe to preclude participation was assessed by interview with carers and potential participants. Participants were excluded if they had speech limited to only a few words or were unable to understand simple instructions (e.g. 'sit down'). It was not established whether the impairments had always existed or were acquired (see, Crayton *et al.* 1998).

Of 128 people with DS identified, 70 (54·7%) fulfilled all criteria and made up the cohort. Of these 70 participants, thirteen (18·6%) individuals did not complete at least one test from the battery on at least three occasions over the study period. These participants were excluded from the sample, since there would be insufficient data available for longitudinal analysis (see data analysis below). In this paper we report the findings on the 57 participants who completed a sufficient number of the tests on all six occasions to allow longitudinal analysis.

### Measures

A test battery was administered to each participant on six occasions, at a mean of 0, 6, 13, 20, 25 and 50 months. The battery of neuropsychological tests chosen was designed to assess: memory, learning, orientation, aphasia, agnosia and apraxia. Details of the tests used are given in detail in Crayton *et al.* (1998). The tests are summarized in this paper. The British Picture Vocabulary Scale (BPVS) (Dunn *et al.* 1982) and the Vineland Adaptive Behavior Scales (VABS) (Sparrow *et al.* 1984) were also employed as measures of receptive language and adaptive behaviour respectively. Memory and learning

were assessed using the visual memory battery of the Cambridge Neuropsychological Automated Test Battery (CANTAB), using a touch sensitive screen (see Sahakian *et al.* 1988). This included pattern recognition, spatial recognition, simultaneous and delayed matching to sample, and delayed response and conditional associative learning tasks. For this study, only the data from delayed response and conditioned associative learning are presented, as this involves both learning and remembering and because other tests were prone to significant floor effects (see Crayton *et al.* 1998).

Orientation was assessed using the relevant section of the CAMCOG, part of the Cambridge Assessment for Mental Disorder in the Elderly (CAMDEX, Roth *et al.* 1986). The naming of 14 pictures of everyday objects and identification of pictures following a verbal instruction, were used to assess for aphasia and agnosia. In each part of the test a maximum score of 14 was possible. Apraxia was assessed by asking participants to carry out simple actions (e.g. 'clap your hands!'). If they were unable to carry out this action on request, they were given a second verbal prompt. A maximum score of 10 was possible, scored if actions were carried out on verbal request.

Three additional tests were added to the battery at a later stage and administered on three occasions (at 20, 25 and 50 months respectively). In the verbal memory test (adapted from the Memory for Sentences test, Terman & Merrill, 1960), on each trial, participants were asked to listen to a sentence and then to repeat the sentence aloud. On the first trial the sentence consisted of four words. On successive trials however, the length of the sentence was gradually increased. On the last trial, participants were asked to repeat a sentence containing 13 words. The dependent variable was the number of words correctly recalled. Two equivalent forms were administered. The maximum possible score was 98.

In the memory for objects test, participants were presented with 10 everyday objects and asked to name them. Any objects incorrectly named were then discarded. Of the remaining objects, two were randomly selected and participants were again asked to name them to ensure test integrity. One of the objects was then covered while the participant was watching, and participants were asked to recall what object had just been covered up. This trial was then repeated, but this time the object was covered while the participant's eyes were closed. Participants were then asked to report which object had been covered. The procedure was then repeated with a further two objects, followed by two trials with three objects, two with four, two with five, and two trials with six objects. In the 'memory for pictures' test, participants were presented with 10 pictures of everyday objects and asked to name them. The procedure was then identical to that followed for 'memory for objects' test. For both the memory for objects and the memory for pictures tests the maximum possible score was 10.

### Data analysis

As noted in the introduction, the analysis of longitudinal data is problematical when the baseline assessment is variable between participants, the time period between assessments is variable and a number of assessments have been employed. To overcome these problems, parts of the data analysis were conducted using the 'individual growth-trajectory perspective' (Willet, 1988). This analysis is similar to the hierarchical linear modelling described by Bryk & Raudenbush (1987, 1992) and adopted by Devenny *et al.* (1996). By adopting this model, individual performance on each test was assumed to either increase or decrease linearly over time and the error in this model may be estimated.

Data analysis was conducted in four stages. First, regression lines for each assessment, for each participant were derived. The regression equation yields an index of rate of change throughout the study (the slope parameter) in which a positive value indicates an increase in performance and a negative value indicates decline. A measurement error value (the standard error) is also produced, indicating the precision of the fit of each slope. The standard error of all participants' slope values for 95% of the eight tests was below one. This reflects the adequacy of the proposed simple linear model. Secondly, the index of rate of change for each participant on tests of aphasia, apraxia and agnosia for each individual was examined, to identify significant cognitive decline associated with the secondary stages of dementia and to

derive an overall index of cognitive deterioration. Thirdly, index of cognitive deterioration was employed as a dependent variable to examine the association with age and pre-existing cognitive impairment. Fourthly, the index of cognitive deterioration was examined in relation to performance and decline on learning, memory and orientation tests to determine the sequence of decline.

## RESULTS

Although one inclusion criteria was an age of 30 or over, when ages were checked with documentation, four participants were aged between 28 and 30. As age group was not an independent variable for all analyses, these participants were included in all analyses except for the prevalence by age-group cross tabulation.

Thirteen (18·6%) individuals who did not complete a sufficient number of tests to allow a longitudinal analysis, and were therefore excluded from the 70 who did meet inclusion criteria, were compared with the remaining 57 with respect to age, VABS age equivalent score and sex. There was no difference between the age of those included (mean = 42·34, S.D. = 7·26) and those excluded (mean = 44·85, S.D. = 7·86; $t(68)$ equal variances = 1·10, NS) or the sex ratio, where 59·6% of those included were female, compared with 40·4% of those excluded ($\chi^2(1) = 1{\cdot}93$, NS). However, those included had higher age equivalent scores on the VABS (mean age equivalent = 67·67, S.D. = 25·49) than those who were excluded (mean age equivalent = 47·15, S.D. = 18·66; $t(68)$ equal variances = 2·73, $P < 0{\cdot}01$).

### The index of cognitive deterioration

For the first stage of the analysis, participants who had shown decline in areas of cognitive functioning associated with dementia and which occur after the acquisition of memory impairments were identified. In order to ascertain the degree of cognitive deterioration shown by an individual, the rate of decline on each of the

Table 1. *Characteristics and cognitive deterioration indices of members of the no cognitive deterioration, moderate cognitive deterioration, severe cognitive deterioration and cognitive deterioration groups*

| Group | Participant number | Sex | Age | Cognitive deterioration index | VABS age equivalent (months) |
|---|---|---|---|---|---|
| Moderate cognitive deterioration | 62 | F | 52·67 | −0·49 | 57 |
| | 29 | F | 56·00 | −0·50 | 102 |
| | 41 | F | 38·17 | −0·54 | 51 |
| | 74 | F | 51·17 | −0·56 | 51 |
| | 33 | M | 49·92 | −0·58 | 39 |
| | 24 | F | 47·33 | −0·67 | 89 |
| | 34 | F | 42·25 | −0·90 | 56 |
| | 12 | F | 32·75 | −0·97 | 51 |
| | Mean (S.D.) or % | *F* = 87·5% | 46·53 (8·16) | −0·65 (0·18) | 62 (21·65) |
| Severe cognitive deterioration | 58 | F | 46·17 | −4·52 | 45 |
| | 63 | F | 50·58 | −4·59 | 34 |
| | 75 | F | 50·00 | −5·04 | 56 |
| | 8 | M | 54·58 | −5·16 | 37 |
| | 48 | F | 47·25 | −5·47 | 37 |
| | 18* | F | 47·17 | −8·53 | 25 |
| | 10† | M | 51·83 | −13·58 | 50 |
| | Mean (S.D.) or % | *F* = 71·4% | 49·65 (3·00) | −6·70 (3·33) | 40·57 (20·47) |
| Cognitive deterioration | Mean (S.D.) or % | *F* = 80% | 47·99 (6·28) | −3·47 (3·81) | 52 (20·1) |
| No cognitive deterioration | Mean (S.D.) or % | *F* = 52·4% | 40·33 (6·54) | 0·23 (0·40) | 73·26 (25·06) |

* Died between 12 and 18 months.
† Died between 18 and 24 months.

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aphasia, agnosia and apraxia tests was examined. Those participants who showed decline on all three tests were deemed to show cognitive deterioration. Fifteen (26·3%) participants fulfilled this criterion. To derive an overall index of cognitive deterioration, the rate of decline values were summed. Examination of this cognitive deterioration index for the 15 participants showed eight (14% of the total sample) to fall between −0·49 and −1·00 and seven (12·3%) to fall between −4 and −14. As a bimodal distribution was apparent, two groups were formed and designated moderate cognitive deterioration and severe cognitive deterioration respectively. For some analyses these groups were combined to form a cognitive deterioration group. All other participants ($N = 42$, 73·7%) were allocated to a third group of no cognitive deterioration. Table 1 shows the participant characteristics and group membership for the 15 participants deemed to show cognitive deterioration and summary data for all groups.

To ensure the groups were partitioned by the criterion of the cognitive deterioration index, the mean cognitive deterioration indices for the three groups were compared. As the cell sizes are markedly different, the Kruskal–Wallis test was employed and the result showed a significant difference between the three groups ($\chi^2(2) = 33{\cdot}35$, $P < 0{\cdot}001$). Thus, it is clear that there is good differentiation between the groups.

### The association between cognitive deterioration, age, sex, pre-existing cognitive impairment, learning and memory

To examine the differences in the mean age of the groups as shown in Table 1, groups were compared using the Kruskal–Wallis test. The results of this analysis showed the age of those who showed cognitive deterioration to be significantly higher than those who did not ($\chi^2(2) = 14{\cdot}35$, $P < 0{\cdot}001$). Table 2 shows a breakdown of group membership by age group ($N = 53$, as four participants were under 30 and are excluded from the Table.) The data in this table reveal that 70% of those over 50 years showed cognitive deterioration, compared with 23% of those aged 40 to 49 years 11 months and 11·8% of those aged 30 to 39 years, 11 months. Analysis of the association between sex and cognitive deterioration, showed that although 80% of those showing cognitive deterioration were female, compared with 52·4% of the no cognitive deterioration group, this difference was not significant ($\chi^2(1) = 3{\cdot}50$, NS).

Table 2. *Number and percentage of participants in 10-year age bands showing cognitive deterioration*

| | Cognitive deterioration ($N = 53$) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | None | | Moderate | | Severe | | Total | |
| | *N* | (%) | *N* | (%) | *N* | (%) | *N* | (%) |
| 30 to 39 years 11 months | 15 | (88·2) | 2 | (11·8) | 0 | (0) | 17 | (100) |
| 40 to 49 years 11 months | 20 | (76·9) | 3 | (11·5) | 3 | (11·5) | 26 | (100) |
| 50 years and over | 3 | (30) | 3 | (30) | 4 | (40) | 10 | (100) |
| Total | 38 | (71·7) | 8 | (15·1) | 7 | (13·2) | 53 | (100) |

Further comparisons between the cognitive deterioration and no cognitive deterioration groups showed that at the first assessment the cognitive deterioration group had lower initial VABS mean mental age equivalent scores ($t(55)$ equal variances, 2·96, $P < 0{\cdot}01$), lower orientation scores ($t(31)$ unequal variances = 3·64, $P < 0{\cdot}001$) and lower delayed response scores ($t(55)$ equal variances = 3·4, $P = 0{\cdot}001$). In some respects therefore, those showing cognitive deterioration appeared to demonstrate more impairment at the first assessment.

The association between cognitive deterioration and age, pre-existing degree of cognitive impairment and earlier neuropsychological signs of dementia, i.e. learning and memory was then examined. The cognitive deterioration index might be considered to represent the development of impairments which accompany dementia following the earlier signs of memory loss and disorientation. If this is the case then the cognitive deterioration index should be associated with memory impairments but not necessarily decline in memory over time. This is because those with a high cognitive deterioration index, will have already experienced memory decline which has now reached a low plateau. To examine this hypothesis, two analyses were conducted. First, a total cognitive impairment score was derived for each participant by summing the raw scores for the tests of aphasia, apraxia and agnosia at the fifth assessment. This score was then correlated with age, the VABS age

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Table 3. *Upper panel: Pearson correlation coefficients of the scores attained by participants at the fifth assessment. Lower panel: Pearson correlation coefficients of the rate of decline on tests shown by participants throughout the course of the study* (*a high negative value for the Cognitive Deterioration Index indicates a faster rate of decline*)

| | VABS age equivalent | Total cognitive impairment score | Orientation | Delayed response | Verbal memory | Memory for pictures | Memory for objects |
|---|---|---|---|---|---|---|---|
| Age | −0·23 | −0·18 | −0·29* | −0·52*** | −0·09 | −0·47*** | −0·28* |
| VABS age equivalent | | 0·53*** | 0·72*** | 0·63*** | 0·58*** | 0·60*** | 0·59*** |
| Total cognitive impairment score | | | 0·51*** | 0·55*** | 0·53*** | 0·71*** | 0·65*** |
| Orientation | | | | 0·70*** | 0·69*** | 0·56*** | 0·50*** |
| Delayed response | | | | | 0·55*** | 0·71*** | 0·62*** |
| Verbal memory | | | | | | 0·54*** | 0·52*** |
| Memory for pictures | | | | | | | 0·83*** |

| | Cognitive deterioration index | Orientation | Delayed response | Verbal memory | Memory for pictures | Memory for objects |
|---|---|---|---|---|---|---|
| Age | −0·36** | −0·29* | −0·14 | −0·50*** | −0·21 | −0·28* |
| VABS | 0·32* | 0·06 | 0·07 | −0·02 | 0·03 | −0·08 |
| Cognitive deterioration index | | 0·23 | 0·25 | 0·21 | 0·03 | 0·08 |
| Orientation | | | 0·10 | 0·42** | 0·25 | 0·21 |
| Delayed response | | | | 0·16 | 0·45** | 0·26 |
| Verbal memory | | | | | 0·28* | 0·52*** |
| Memory for pictures | | | | | | 0·57*** |

* $P < 0·05$; ** $P < 0·01$; *** $P < 0·001$.

equivalent score and memory, learning and orientation scores attained at the fifth assessment. Secondly, the cognitive deterioration index was correlated with age, the VABS age equivalent score attained at the first assessment and the rate of decline for the memory, learning and orientation scores. The results of these correlations are shown in Table 3.

From examining the upper panel of Table 3 it is clear that, at the fifth assessment, the total cognitive impairment score is significantly correlated with all memory scores and with orientation. Thus, the cognitive impairments associated with the later stages of dementia are associated with impairments of learning, memory and orientation. Also, all memory scores are correlated with each other, demonstrating internal consistency. It is also notable, that age does not correlate with the total cognitive impairment score. The lower panel of Table 3, showed that the cognitive deterioration index, or the acquisition of aphasia, agnosia and apraxia, does not correlate with a decline in memory. These two areas of decline are therefore independent of each other. However, the cognitive deterioration index does correlate with both age and VABS age equivalent score. This shows that the rate of decline is faster in those who are older and those who have a greater degree of pre-existing cognitive impairment.

To examine further the association between memory impairment, orientation and agnosia, aphasia and apraxia, the profiles of these test scores for the 15 participants showing cognitive deterioration across the 50 months were plotted. Figs. 1 *a*, *b* show the plots for those participants with moderate cognitive deterioration and severe cognitive deterioration respectively, with a summary plot for the no cognitive deterioration group for comparison. Visual inspection of these plots suggests that any decline in memory in those showing cognitive deterioration preceded the decline in the scores for aphasia, agnosia and apraxia. Participants 18, 10, 58, 63 and 74 all have very low learning and memory scores prior to aphasia, agnosia and apraxia scores declining. In contrast, participants 75, 8, 48, 12, 29 and 33 all appear to show decline in memory preceding that seen in aphasia, agnosia and apraxia. Orientation scores show similar variability but decline for the majority of participants appears to precede or coincide with decline in aphasia, agnosia and apraxia.

To test this hypothesized sequential decline,

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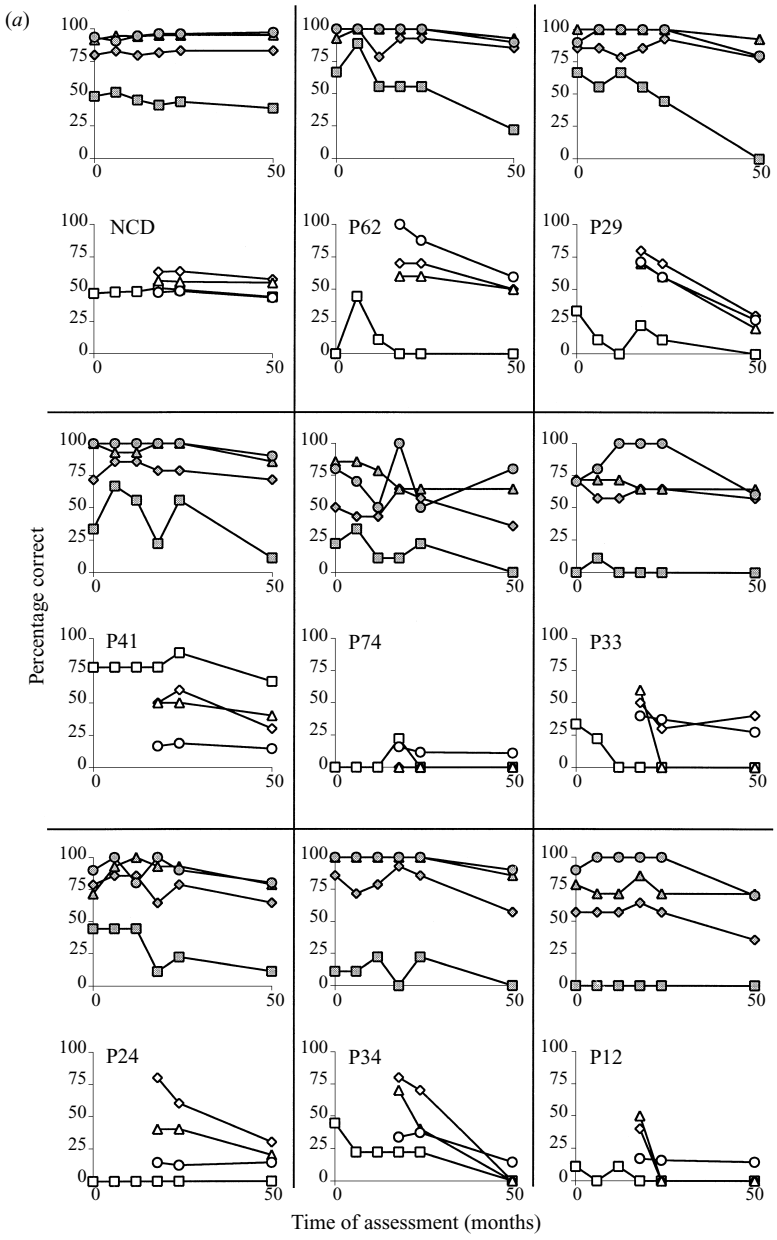


FIG. 1. For legend see facing page.

the mean scores on the memory and orientation tests, attained at the fifth assessment, were compared across the three groups. This analysis should show that memory and orientation scores are lower in the severe cognitive deterioration group than both the moderate cognitive deterioration and no cognitive deterioration groups. Conversely, the rate of decline on these tests, should be lower in the no cognitive deterioration and severe cognitive deterioration groups than the moderate cognitive deterioration group. This is because there is less decline in the severe cognitive deterioration group, as decline has already occurred and reached a low

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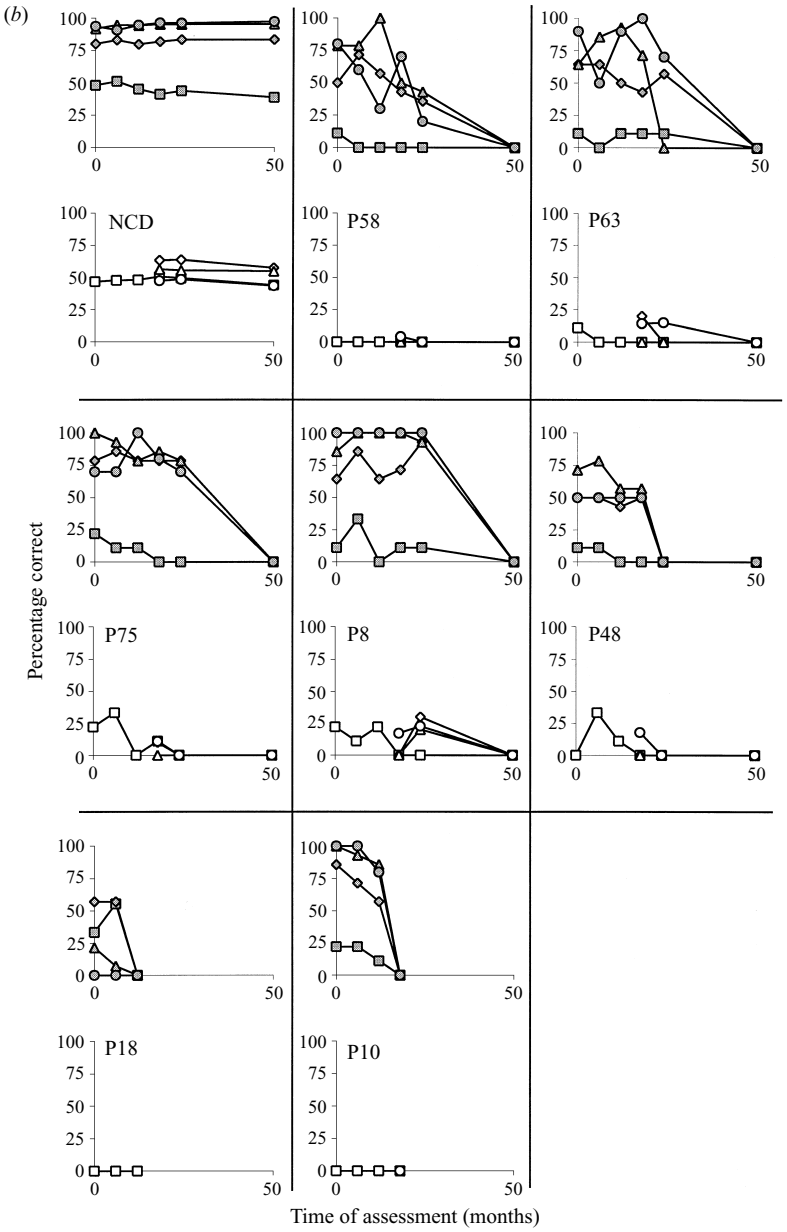


FIG. 1. Individual plots of performance on neuropsychological assessments across assessment points for all members of the moderate cognitive deterioration (*a*) and severe cognitive deterioration (*b*) groups and a plot of mean scores for the no cognitive deterioration group (NCD) for comparison. The upper graph in each panel shows the results of the orientation (▨), aphasia (◈), agnosia (▲) and apraxia (◍) assessments. The lower graph in each panel shows the results of the delayed response and conditioned associative learning task (□), object memory (◇), picture memory (△) and verbal memory (○). The number in the lower graph of each panel is the participant number (see Table 1).

stable plateau, and no decline in the no cognitive deterioration group as there is no acquired impairment. Fig. 2 shows the mean scores attained on each test at the fifth assessment and mean rate of decline for all memory tests and the orientation test broken down by group.

The upper panel of Fig. 2 shows that, as predicted, the memory and orientation scores

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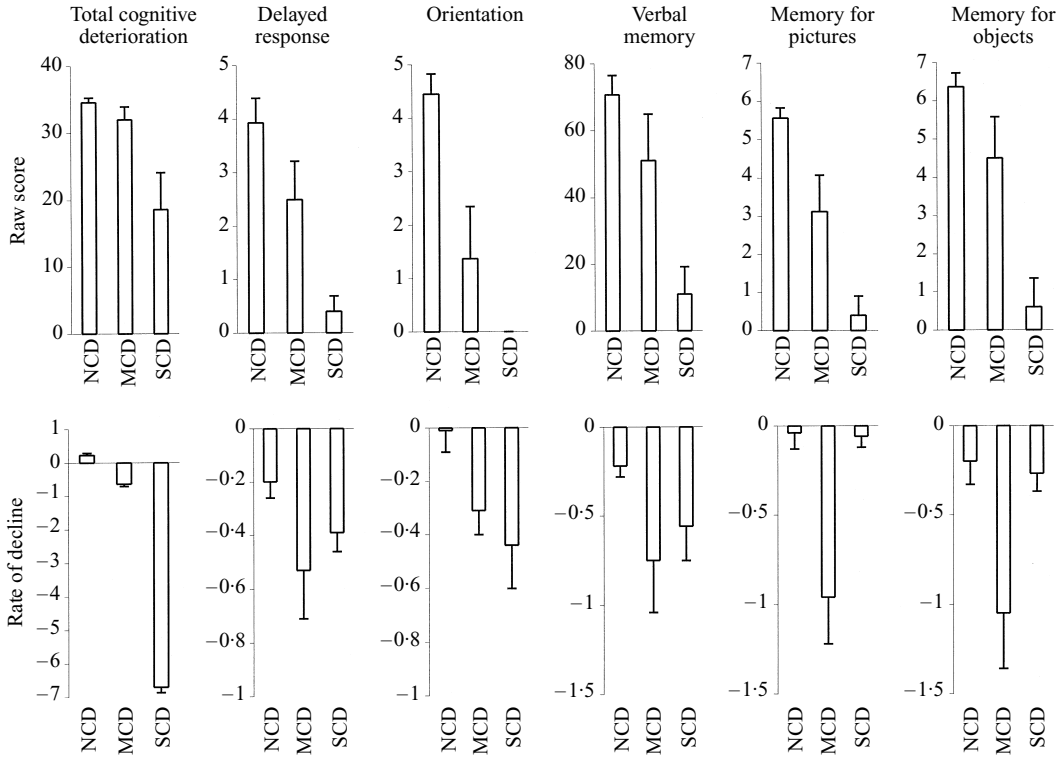


FIG. 2. Upper panel: mean test scores at the fifth assessment for no cognitive deterioration (NCD), moderate cognitive deterioration (MCD) and severe cognitive deterioration (SCD) groups on neuropsychological assessments involving a memory or learning component. Lower panel: mean rate of decline values on neuropsychological assessments involving a memory or learning component (high negative values indicate a faster rate of decline).

are lower for the moderate cognitive deterioration and severe cognitive deterioration groups than the no cognitive deterioration group. These differences were significant for orientation ($\chi^2(2) = 9{\cdot}64$, $P < 0{\cdot}01$), delayed response ($\chi^2(2) = 16{\cdot}04$, $P < 0{\cdot}001$), verbal memory ($\chi^2(2) = 12{\cdot}12$, $P < 0{\cdot}01$), memory for objects ($\chi^2(2) = 13{\cdot}42$, $P < 0{\cdot}01$) and memory for pictures ($\chi^2(2) = 16{\cdot}88$, $P < 0{\cdot}001$). The lower panel of Fig. 2 shows that, as predicted, for the four memory tests decline (as measured by the slope of the regression lines) was greater for the moderate cognitive deterioration group than the severe cognitive deterioration or no cognitive deterioration groups. This difference was significant for memory for objects ($\chi^2(2) = 6{\cdot}87$, $P < 0{\cdot}05$) and memory for pictures ($\chi^2(2) = 10{\cdot}32$, $P < 0{\cdot}01$) but not for verbal memory ($\chi^2(2) = 5{\cdot}57$, NS) or delayed response ($\chi^2(2) = 4{\cdot}70$, NS). Finally, the orientation decline scores were higher for the severe cognitive deterioration group than the moderate cognitive deterioration or no cognitive deterioration groups but the difference between groups was not significant ($\chi^2(2) = 4{\cdot}03$, NS).

## DISCUSSION

In this study we examined cognitive deterioration in adults who have DS using a prospective longitudinal design. The focus of the study was to establish if the profile and sequence of early acquired cognitive impairments were consistent with that observed in the general population who do acquire a dementia resulting from Alzheimer's disease (e.g. Grady *et al.* 1988) when tests employed with the general population are used. For this reason, participants were screened in order to rule out those who had such substantial cognitive impairment by virtue of pre-existing neurological damage or an acquired dementia, such that they were unable to par-

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ticipate in the tests. This procedure is similar to that adopted by Devenny *et al*. (1996) and Burt *et al*. (1995) and consequently the estimates of the prevalence of cognitive deterioration might not be considered representative of the total population of those with DS.

In order to establish the sequence of acquired cognitive impairments, there were two phases of the study. In the first, a crude measure of change in terms of the acquisition of aphasia, apraxia and agnosia was employed because these acquired deficits are associated with dementia. The analysis of decline on these measures employed the use of slopes of linear regression lines which revealed a bimodal distribution. Consequently, it was clear that a number of participants (13·2% of those over 30), had experienced significant cognitive deterioration, while others (15·1% of those over 30) had experienced moderate cognitive deterioration. However, it should be noted that the majority of participants (71·7%) experienced no cognitive deterioration. These estimates of cognitive deterioration are high in comparison to the range described by Aylward *et al*. (1995) and those given by Lai & Williams (1989). This may be because the criteria employed in this study are not diagnostic for dementia but are operationalized in terms of cognitive impairment. It may also be influenced by enhanced test sensitivity. These estimates contrast with those of Burt *et al*. (1995) and Devenny *et al*. (1996), despite there being similarities in the deployment of a screening procedure to rule out those who may already show signs of dementia.

Cognitive deterioration was associated with two factors. The first is age and this confirms the findings of previous research (Hewitt *et al*. 1985; Fenner *et al*. 1987; Lai & Williams, 1989). However, it should be noted that 30% of participants over the age of 50 showed no cognitive deterioration throughout the course of the study. The absence of any cognitive deterioration in over 60% of adults with DS over the age of 40 confirms the findings of other longitudinal studies that there is a significant discrepancy between the estimates of dementia that might be derived from neuropathological and neuropsychological studies. In addition, the correlation between age and cognitive deterioration index shows that the rate of decline is positively associated with age. One interpretation of this finding is that a higher cognitive deterioration index is indicative of the later stages of dementia. The mean age of those showing cognitive deterioration was 48, lower than, but comparable to, the mean age of 54·2 reported by Lai & Williams (1989). Again, this may be due to this study using cognitive impairment as criteria as opposed to a broader diagnosis of dementia.

The second factor which appeared to associate to cognitive deterioration was the degree of pre-existing cognitive impairment. Similar to age, the degree of pre-existing cognitive impairment is associated with a faster rate of deterioration. The interpretation of this association is problematical. It is possible that lower scoring on these measures was identifying the very early stages of cognitive deterioration, or alternatively it may be that those individuals who have greater pre-existing cognitive impairment are more likely to experience deterioration.

To establish the sequence of decline, the cognitive deterioration index that was developed, was demonstrated to be significantly associated with impairments in orientation, memory and learning. However, it should be noted that poor performance on memory tests, for example, is correlated with poor performance on other measures indicative of global pre-existing cognitive impairment (Crayton *et al*. 1998). To analyse further the association between these two variables, the individual profiles of all participants who had experienced decline were examined. This analysis suggested a sequence in decline with deficits in memory and learning appearing to precede those of agnosia, aphasia, and apraxia. An analysis of this sequence demonstrated that memory, learning and orientation scores were lower in those who showed severe cognitive deterioration than those who showed moderate or no cognitive impairment deterioration. However the analysis of decline, as assessed by the slope of the regression lines, showed that deterioration was evident only in the moderate cognitive deterioration group as opposed to those showing no or severe cognitive deterioration. The most likely interpretation of this finding is that there is no learning and memory deterioration in those with no cognitive deterioration because a dementing process has not started and there is no decline in memory, learning and orientation in the severe

cognitive deterioration group because decline in these areas has occurred and individuals are now scoring at floor levels. However, in the moderate cognitive deterioration group decline in memory is evident and appears to be associated with the development of aphasia and apraxia. This sequence of the acquisition of early cognitive impairments is in accordance with that described by Lai & Williams (1989) and Dalton & Fedor (1998). In this study however, some of the assessments employed to establish this sequence had previously been validated in the general population (Sahakian *et al*. 1982).

In this study we examined the profile and sequence of the acquisition of cognitive impairments in adults with Down's syndrome. The results confirm those of previous studies (Owens *et al*. 1971; Dalton *et al*. 1974; Wisniewski *et al*. 1978; Thase *et al*. 1982; Lai & Williams, 1989) which show that cognitive deterioration is associated with age. However, the breakdown of age by cognitive deterioration presented in Table 2 shows that some individuals over 50 remain free of cognitive impairments. This finding suggests that estimates of the prevalence of dementia in adults with DS based purely on neuropathological studies tend to be inflated by the bias in their samples. However, it is entirely possible that participants in this study might have the neuropathological signs of Alzheimer's disease but these have yet to compromise intellectual functioning. Finally, we would conclude that it is possible to ascertain the early signs of cognitive deterioration in terms of learning and memory in adults with Down's syndrome when appropriate tests are employed.

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