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The assessment of memory impairment in adults with Down syndrome: The effect of increasing task load on test sensitivity.

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Abstract

The effect of increasing the number of stimuli to be recalled was investigated to evaluate whether sensitivity for memory impairment was enhanced in adults with Down syndrome when using higher task load. Three levels of load were compared across three groups of adults: cognitive deterioration (CD), no cognitive deterioration over age 40 (NCD-40+) and no cognitive deterioration under 40 (NCD -U40). The CD group showed impaired performance in comparison to the NCD-40+ group at all levels of task load with performance declining over four years. The NCD-40+ group showed no impairment in performance compared to NCD -U40 group except when task load was high. The implications for the identification of dementia and age related cognitive change are discussed.

Introduction

Evidence for the age related increase in prevalence of Alzheimer's disease in Down Syndrome is derived from studies of neuropathology, psychophysiology, imaging and neuropsychology (Oliver & Holland, 1986). Speculation on the cause of Alzheimer's disease in Down syndrome has focussed on genes associated with Alzheimer's disease located on chromosome 21 (Beyreuther, Dyrks, Hilbich *et al.*, 1992; Farrer, Crayton, Davies *et al.*, 1997) and premature aging in adults with Down syndrome (Royston, Mann, Pickering-Brown *et al.*, 1996).

Accurate and sensitive early diagnosis of dementia in adults with Down syndrome is heavily dependent on assessment of cognitive performance. Cross-sectional studies have shown that older adults who have Down syndrome show poorer performance on assessments of explicit memory, tests of orientation, word finding and apraxia (Dalton, Crapper and Schlotterer, 1974; Wisniewski, Howe, Gwyn-Williams *et al.*, 1978; Zigman, Schupf, Lubin *et al.*, 1987). Longitudinal studies have demonstrated that decline in new learning and explicit memory precede other deficits and are therefore earlier signs of dementia (Burt, Loveland, Chen *et al.*, 1995; Devenny, Silverman, Hill *et al.*, 1996; Oliver, Crayton, Holland *et al.*, 1998, Devenny, Hill, Patxot, et al., 1992; Krinsky-McHale, Devenny & Silverman, 2002). From examining explicit memory performance using a match to sample paradigm Dalton, Crapper and Schlotterer (1974) showed that delay is an important variable for performance. In combination these studies indicate that tests of explicit memory that can vary demand might be the most sensitive to the earliest signs of dementia.

Oliver, Crayton, Holland *et al.* (1998) showed that poor performance by adults with Down syndrome on the delayed response and conditioned associative learning test, part of the

Cambridge Neuropsychological Automated Test Battery, (Sahakhian, Morris, Evenden *et al.*, 1988) was associated with decline in areas indicative of dementia. There are a number of strengths to this test. It differentiates participants with Alzheimer's disease from those with Parkinson's and age matched controls (Sahakian, Morris Evenden *et al.,* 1988) and is sensitive to the earliest changes of Alzheimer's disease (Fowler, Saling, Conway *et al.,*1995; 1997). Poor test performance is evident in participants with questionable dementia (Morris, McKeel, Storandt *et al*., 1991, Strohle, Richert, Maier *et al*., 1995) and predictive of dementia status two years later (Fowler, Saling, Conway *et al.,* 2002). The test comprises increasing task load with new learning and so can evaluate the earliest signs of dementia and the impact of task load on working memory. In the general population age-related deficits in working memory are evident when task load increases (Dobbs and Rule, 1989). This association between aging, task load and working memory might be accounted for by age related cognitive slowing, declining processing resource or increases in disinhibition for task irrelevant information (Craik, Anderson, Kerr *et al*., 1995). Any deficit in task load related working memory has relevance to cognitive change associated with normal aging and thus purported accelerated aging in Down syndrome.

The results of the Oliver *et al.* prospective study of adults with Down syndrome showed that performance on the delayed response and conditioned associative learning task in participants deemed to have developed significant cognitive impairments (aphasia, apraxia, agnosia) over a four year period was significantly poorer at the beginning of the study than for those who did not develop significant cognitive impairments, thus suggesting that decline in performance on this task might precede or accompany the development of more significant cognitive impairments consistent with dementia. However, performance on the delayed response and conditioned associative learning task was evaluated by a summary score that

aggregated data across levels of task load and data were not analysed for each level of task load, in this case an increasing number of stimuli. Similarly younger and older participants who did not evidence significant cognitive decline were not compared on their performance at different levels of task load. Performance on this task by older adults who have Down syndrome who do not evidence significant signs of cognitive decline might be compromised when task load is high but not when task load is low. This might be observed either because the early pathology of Alzheimer's disease is developing or because there is acceleration of normal age related cognitive change.

It can be hypothesised, therefore, that there might be an interaction between age, the number of stimuli to be recalled and the presence of acquired cognitive impairments indicative of dementia other than memory loss. Specifically, it can be predicted that those who have acquired cognitive impairments will perform poorly at all stimulus levels in comparison to an age matched group who do not evidence acquired cognitive impairments other than memory loss. Additionally, because of the emerging pathology of Alzheimer's disease or the accelerated development of cognitive impairments of normal aging, older participants will perform poorly in comparison to younger participants when task load is high but not low. In this study these hypotheses were tested by analysing the performance of the cohort described by Oliver *et al.* on the delayed response and conditioned associative learning test at varying levels of task load.

Method

Participants

Participants were drawn from a sample of 57 individuals with Down Syndrome included in a previous study (Oliver, Holland, Crayton *et al.*, 1998). All individuals had participated in

serial neuropsychological assessments designed to measure cognitive deterioration in adults with Down syndrome over a 50 month period. Of these, 52 (91.2%) participants had completed all six assessments (at 0, 6, 13, 20, 25 and 50 months), and these were included in the present study. The mean age of the sample was 41.82 years (SD = 7.37) and 31 (59.6%) were female. None of the participants showed challenging behaviour, none had significant sensory impairments that were uncorrected by aids and all were able to understand simple commands. The mean age equivalent scores (in months) attained on the British Picture Vocabulary Scale (BPVS; Dunn, Dunn & Whetton, 1982) and the Vineland Adaptive Behavior Scales (VABS; Sparrow, *et al.*, 1984) were 63.13 (SD = 29.77) and 69.90 (SD = 25.32) respectively. Of the 52 participants for whom full datasets were available, 12 (23.01%) showed cognitive deterioration according to the criteria described in Oliver, Holland, Crayton *et al.* (1998). These criteria specified that for cognitive deterioration to be evident, serial neuropsychological assessments should demonstrate acquired aphasia, apraxia and agnosia. This was established by applying the individual growth-trajectory perspective (Willet, 1988) to the raw scores of the picture naming, picture identification and actions on request tests (see Oliver, Holland, Crayton *et al.*,1998) over the four year period. This method fits individual regression lines over time and thus the Beta coefficients indicate the direction and degree of slope. A negative Beta coefficient on all three tests was taken to indicate cognitive deterioration. A secondary analysis revealed that when these deficits were present, acquired impairments in learning and memory were also evident, thus supporting the method of allocation to groups. Of the 12 participants in the cognitive deterioration (CD) group, five were deemed to be experiencing "severe" cognitive deterioration and seven, "moderate" cognitive deterioration in the Oliver *et al.* study, based on the results of serial neuropsychological tests. In the Oliver *et al.* study, those in the Moderate Cognitive Deterioration group showed evidence of deficits in learning and memory and mild signs of

the development of agnosia, aphasia and apraxia which had developed in the last four years. Those in the Severe Cognitive Deterioration group, showed substantial impairments in learning and memory and significant apraxia, aphasia and agnosia which had developed in the last four years.

The remaining 40 participants, who were deemed to be free of cognitive impairments, were assigned to one of two 'No Cognitive Deterioration' groups: individuals aged 40 years and over (NCD-40+, n = 21) and those individuals aged under 40 years (NCD-U40, n = 19). The mean age of the individuals in the CD, NCD-40+ and NCD-U40 groups was 47.80 years (SD = 6.98, range = 32.75 to 56.00), 45.11 years (SD = 3.52, range = 40.08 to 53.92) and 34.40 (SD = 3.95, range = 28.33 to 39.92) respectively. There was a significant difference between the ages of the CD and NCD-U40 groups ($t(16)$ unequal variances = 6.06, $p < 0.001$) but not between the CD and the NCD-40+ groups ($t(14)$ unequal variances = 1.25, NS). Therefore, the CD and NCD-40+ groups were comparable in age. Group comparisons using a one-way ANOVA just failed to reach significance between the three groups prior to the onset of decline in the CD group on the Vineland Adaptive Behavior Scales, ($F(2,49) = 3.05$, $p = 0.06$) and on the British Picture Vocabulary Scale, ($F(2,49) = 2.67$, $p = 0.08$). Post hoc comparisons using Tukey's HSD revealed the CD group scored significantly lower than the no cognitive deterioration groups on the VABS and the BPVS.

Measures

In addition to the BPVS and the VABS, all participants completed a test battery consisting of five neuropsychological tests ("orientation", "picture naming", "picture identification", "acting on request" and a "card sorting task") and four experimental computerized tests of visual memory (pattern recognition, spatial recognition, matching-to-sample and delayed response

and conditioned associative learning). These latter tests had been previously employed by Sahakian *et al.* (1988). The data from the delayed response and conditioned associative learning test will be reported here.

The participants were tested using an Acorn BBC microcomputer fitted with a touch sensitive screen. The computer controlled the generation of all visual stimuli, provided feedback to the participant and recorded the participants response to the stimuli. Prior to each test, the experimenter asked the participant to sit in front of the computer screen and to respond to a series of prompts. All of the tests were preceded by practice trials to assess whether the participant understood the procedures.

Participants were initially shown six filled white squares arranged around the edges of the screen. Each square was then successively "opened" for three seconds (i.e. it became unfilled) in a randomised order, with one of the squares revealing an abstract pattern. With the six filled squares remaining on the screen, the hidden pattern then appeared in the middle of the screen. Each trial required the participant to indicate which of the squares the pattern had previously occupied by touching one of the squares on the screen. If the participant correctly identified the location of the stimulus, the message "all correct" appeared on the screen and the participant proceeded to the next phase of the test. If the participant was incorrect, the squares were successively reopened in a random order, each for two seconds, as a "reminder" to the participant of the location of the pattern whereupon no further feedback was given to the participant until the correct location was chosen by the participant. The trial was then repeated either until the participant correctly identified the location of the stimulus or if the participant had responded incorrectly for ten trials, whereupon the test was terminated.

Following completion of two phases in which one stimulus was revealed in the squares, the number of stimuli required to be correctly located by the participant on each trial was increased to two stimuli (for two phases) and three (for two phases). In the two stimuli phases for instance, two of the six squares would reveal patterns when briefly opened. One of these

patterns would then be presented in the centre of the screen (the order of presentation of the two patterns was random with respect to the order in which they were revealed in the squares), the participant being required to correctly identify which of the squares it had previously occupied. The second pattern was then presented, the participant again being required to correctly identify which of the squares it had previously occupied. If the participant was incorrect on one or both of the stimuli, the squares were again reopened as a reminder and so on.

The dependent variable was the number of trials taken per phase by each participant to correctly identify the stimuli, where the maximum score of ten was assigned to those phases which were not attempted by a participant because the test had been terminated at an earlier stage (see Sahakian *et al.*, 1988).

Results

Figure 1 shows the mean number of trials taken to complete the test at a given stimulus level broken down by group and plotted by time of assessment.

+++ Insert Figure 1 here +++

A 3 x 3 x 6 (group x stimulus x time) Analysis of Variance (ANOVA) with repeated measures on the last two factors revealed a significant three-way interaction, $F(20,490) = 1.61$, $p < .05$). In order to clarify the nature of this interaction, two sets of analyses were conducted and the results are shown in Table 1. In the first set of analyses, performance was compared for the CD and NCD-40+ groups only. A separate 2 x 6 (group x time) ANOVA was performed for each level of stimulus.

+++ Insert Table 1 here +++

Results for this analysis revealed a significant group × time interaction when one stimulus was required to be identified and a significant main effect of group when two and three stimuli were required to be identified. These results indicated that performance significantly deteriorated across time of assessment for those in the CD group when one stimulus was required to be identified in comparison to those in the NCD-40+ group. In addition, performance remained at lower levels for those in the CD group, in comparison to those in the NCD-40+ group, when two and three stimuli were required to be identified.

In the second set of analyses, performance was compared for the NCD-U40 and NCD-40+ groups only. A separate 2 x 6 (group x time) ANOVA was performed for each level of stimulus. Results of the analyses (also shown in Table 1) revealed a significant main effect of group when three stimuli were required to be identified, but not when one or two stimuli were required to be identified. These results indicated that those in the NCD-40+ group performed at significantly lower levels on the task in comparison to the NCD-U40 group when three stimuli were required to be identified but not when either one or two stimuli were required. There was no evidence that performance on the task for those in the NCD-40+ had deteriorated across time.

Discussion

In this study it was possible to examine the effect of task load on learning and memory performance in adults with Down syndrome and the interaction with age and the presence of cognitive impairments indicative of dementia. Membership of the cognitive deterioration group was determined by decline in performance over four years on assessments that did not involve memory and which are normally indicative of Alzheimer like dementia. Consequently, this group comprised individuals who were showing signs of dementia but this was not defined by poor memory performance. The interpretation of the decline in performance on the delayed response and conditioned associative learning is therefore not confounded by the cognitive deterioration group having been defined by decline in memory.

The performance of the cognitive deterioration group at the level of one stimulus to be recalled declined over the four year period, a pattern that was not evident for the age comparable group, and this finding is consistent with a developing dementia (Fowler *et al*., 1995). However, this pattern was less evident at the levels of two and three stimuli as floor effects became evident. These floor effects were less evident for the age comparable group. This finding was not reported in the initial analysis by Oliver *et al.* (1998) as it was masked by the aggregate score employed in that study and others (e.g. Sahakhian *et al*., 1988). At the levels of two and three stimuli there was a main effect for group with the cognitive deterioration group performing significantly less well than the age comparable group. In combination these results demonstrate that poor performance and decline in performance on the delayed response and conditioned associative learning task appear consistent with the ongoing development of cognitive deficits associated with dementia in adults with Down syndrome. This finding is consistent with other reports of compromised performance on tests of explicit memory and learning in adults with Down syndrome (Devenny, Hill, Patxot, Silverman & Wisniewski, 1992; Krinsky-McHale, Devenny and Silverman, 2002).

The significance of this finding becomes evident when the performance of the groups aged under and over 40 who do not evidence signs of dementia is compared. Whilst there is no difference between the groups at the level of one and two stimuli, there is a significant difference between the groups at the level of three stimuli. This finding indicates that in adults with Down syndrome aged over 40 who do not evidence other signs of dementia, deficits in learning and memory become apparent when the task load is sufficiently high.

One interpretation of this result is that some individuals in the over 40 age group are experiencing the early signs of dementia, and thus the group mean is lowered, and the assessments of aphasia, apraxia and agnosia used to allocate participants to groups either were insufficiently sensitive to identify the very earliest signs of dementia. Alternatively these deficits had not yet developed. Either interpretation is consistent with the age related prevalence of Alzheimer's disease in people with Down syndrome, the evidence for memory

deficits preceding other impairments from longitudinal studies and, by implication, from cross-sectional designs, and the sequence of decline evident in the general population. These interpretations are also consistent with the sequential pattern of decline identified by Oliver *et al*. (1998) in single cases when delayed response and conditioned associative learning data using a more crude analysis were considered. Supportive evidence for the early development of dementia interpretation could have been derived from a group by time interaction at the three stimulus level. Just as performance in the cognitive deterioration group declined over time at the one stimulus level so it might have been expected that the over 40 group with no signs of cognitive deterioration should evidence decline at the three stimuli level. However, the results of this analysis showed a significant main effect but no interaction. Visual inspection of the right hand panel of figure 1 does show increased differentiation of the two groups at the fifth and sixth time points in comparison to other time points. This trend suggests that further time points might have yielded a significant interaction. Finally, given the evidence that adults with Down syndrome show signs of early ageing such as chromosomal aneuploidy and premature alopecia, skin and skeletal changes and menopause (see Whalley, 1993) it is possible that the difference in the two groups can be explained by an accelerated ageing effect as opposed to an acquired dementia. There is evidence that normal aging is associated with task load within working memory (Dobbs and Rule, 1989) and this association may be accounted for by the general resource model that suggests the development of age-related decline in cognitive resources (Salthouse, 1991). This might be exacerbated in Down syndrome by virtue of pre-existing impairment, in accordance with the reserved capacity hypothesis, or accelerated age associated decline.

There are a number of features of this study that should be noted. A screening process had eliminated potential participants with a more severe degree of intellectual disability hence the findings may not be generalizable to all persons with Down syndrome. It is also clear that floor effects rapidly emerged in the deteriorated group even at the lowest task load. In combination these factors may limit the utility of the test to tracking decline in more able persons. Finally, the sample size of the cognitively deteriorated group was comparatively

small and this may have limited the power in the examination of interactions. Further research should seek to replicate these results with attention to these limitations.

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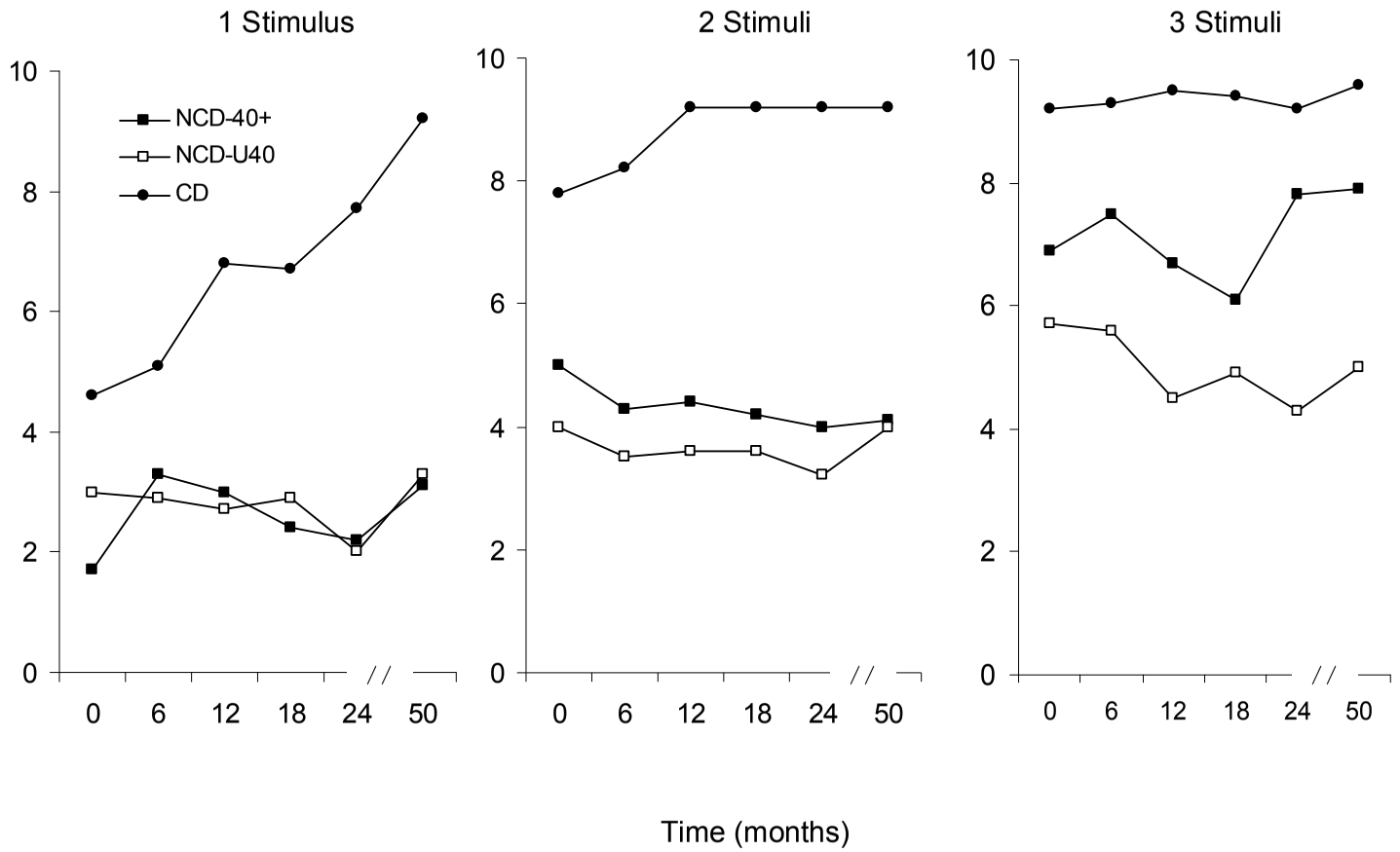
Table 1. Analysis of variance table for the data shown in Figure 1.

	Effect	DF	F values		
			1 Stimulus	2 Stimuli	3 Stimuli
CD vs. NCD-40+					
	Group	1,31	17.58***	19.02***	6.37*
	Time	5,155	5.23***	0.22	0.60
	Group x Time	5,155	3.41**	1.37	0.55
NCD-U40 vs. NCD-40+					
	Group	1,37	0.12	0.26	4.08*
	Time	5,185	2.03	0.70	0.50
	Group x Time	5,185	1.39	0.31	0.56

*** $p < 0.0001$
** $p < 0.001$
* $p < 0.05$

Legend for figure 1.

Mean number of trials to success for the ‘cognitive deterioration’ (CD), ‘No Cognitive Deterioration under 40’ (NCD-U40) and ‘No Cognitive Deterioration 40 and over’ (NCD-40+) groups broken down by time of assessment and number of stimuli to be recalled.


1 Stimulus
2 Stimuli
3 Stimuli
NCD-40+
NCD-U40
CD
0
2
4
6
8
10
0
6
12
18
24
50
Time (months)