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Cognitive and Behavioural Development of Israeli Males with Fragile X and Down Syndrome

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We dedicate this manuscript to the memory of our colleague Dr Naomi Amir, a pioneer and leader in paediatric neurology in Israel, who passed away during the latter stages of the project. Her contributions to paediatric neurology in Israel and to the children and families she cared for are a legacy to us all.

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Hebrew translations of the Kaufman Assessment Battery for Children (K-ABC) and the Vineland Adaptive Behaviour Scales (VABS) were administered to 17 Israeli males with fragile X and 17 with Down syndrome matched for chronological and mental ages. When differences in the initial baselines were considered, the pattern of findings was generally consistent with previous reports. On the K-ABC, the males with fragile X scored higher on some subtests of the Simultaneous Domain but not on any of those of the Sequential Domain. On the VABS, superior scores of the males with fragile X on the Daily Living Skills and Communication domains is consistent with prior evidence of their relative strength on the former and the specific weakness of persons with Down syndrome on the latter. These differences between the males with fragile X and Down syndrome with regard to functioning on various domains and subdomains highlight the need to carefully examine the profiles of aetiologically homogeneous groups of persons.

The study of unique profiles of development among specific aetiological groups of persons with mental retardation is essential for all aspects of research and intervention in the field of mental retardation (Burack, 1990; Cicchetti & Beeghly, 1990; Dykens, 1998). Although there is considerable variation across individuals and developmental levels within the various subgroups, the differentiation among aetiologies is essential for delineating group-specific developmental patterns (Burack, Hodapp, & Zigler, 1988, 1990; Hodapp, Burack, & Zigler, 1998; Loveland & Tunali-Kotoski, 1998). This strategy allows researchers both to assess the extent to which certain features are either unique to persons with a specific aetiology or are generally characteristic of persons with mental retardation (Wagner, Ganiban, & Cicchetti, 1990), and to examine the relation between psychological or behavioural functioning and specific anatomical or physiological features (Pennington & Bennetto, 1998). Empirical work about the development of persons with fragile X is indicative of the advances that are possible with this framework of studying specific aetiologies. Fragile X is the most common inherited cause of mental retardation and is caused by the excessive repetition of three nucleotide sequences (C-G-G) (Dykens, 1998; Pennington & Bennetto, 1998). Males are more often affected and typically show mild to moderate mental retardation, whereas two-thirds of females, who carry and transmit the fragile X gene, show mild cognitive difficulties (Dykens, 1998). The identification of this syndrome led to the recognition of unique patterns of neurological, cognitive, and social functioning among affected persons (Dykens, Hodapp, & Leckman, 1994).

Unique patterns of cognitive strengths and weaknesses among males with fragile X were first assessed with the Kaufman Assessment Battery for Children (K-ABC; Kaufman & Kaufman, 1983a,b). The K-ABC, a test of...
intelligence commonly used with persons with various types of developmental and learning disabilities, is considered a gauge of specific neurological and psychological processes (Dykens et al., 1994; Kaufman & Kaufman, 1983a,b). In particular, the emphasis is on a differentiation between subtests thought to reflect sequential processing and those thought to be indicative of simultaneous processing. Males with fragile X typically display a general deficit in sequential as compared to simultaneous processing (Dykens, Hodapp, & Leckman, 1987; Dykens, Hodapp, Ort, & Leckman, 1993; Hodapp, Dykens, Ort, Zelinsky, & Leckman, 1991; Hodapp et al., 1992), whereas children with Down syndrome show relatively uniform levels of functioning for sequential and simultaneous processing (Hodapp et al., 1992; Pueschel, Gallagher, Zartler, & Pezzullo, 1987). As compared to CA- and MA-matched groups of males with Down syndrome, and nonspecific mental retardation, males with fragile X scored lowest on the Sequential Domain and specifically on the Hand Movement subtest, whereas those with Down syndrome scored highest on this subtest (Hodapp et al., 1992).

Similarly, males with fragile X display group-specific patterns in adaptive functioning as measured by the Vineland Adaptive Behavior Scales (VABS; Sparrow, Balla, & Cicchetti, 1984), commonly used as a measure of adaptive functioning in the study of persons with intellectual handicaps (e.g. Loveland & Kelley, 1988). The VABS consists of 11 subdomains that make up 4 general domains, including communication, daily living, socialisation, and motor skills. On this test, males with fragile X both living in institutions (Dykens, Hodapp, & Leckman, 1989a) and in the community (Dykens, Leckman, Paul, & Watson, 1988) score higher on the Daily Living Skills as compared to the Communication and Socialisation domains. Conversely, children with Down syndrome tend to show a relative deficit in the Communication domain, and similar levels of functioning in the Socialisation and Daily Living Skills domains (for a review, see Loveland & Tunali-Kotoski, 1998).

Differences between persons with fragile X and Down syndrome are also evidenced in developmental trajectories. Although both groups show IQ decline over time (for reviews, see Burack et al., 1988; Dykens et al., 1994), they vary with regard to age and pattern of this drop. The decline among children with Down syndrome is evidenced from infancy and continues through childhood and adolescence. The drop in IQ among children with fragile X begins considerably later. Hagerman (1989) cites 8 years as the beginning of the decline, whereas Hodapp et al. (1990) argue that it does not occur until 10–15 years and is related to the onset of puberty (Dykens et al., 1994).

The primary purpose of this study was to replicate findings of differences in psychological profiles between male children and adolescents with
fragile X and Down syndrome in a culture and language different than typically used in these types of studies. We administered Hebrew translations of the K-ABC and the VABS to Israeli male children and adolescents with fragile X and Down syndrome. In our study, age-equivalent scores were provided for the Sequential and Simultaneous subtests of the K-ABC and the Communication, Daily Living, and Socialisation domains of the VABS.

In order to maximise the extent to which group differences could be specifically attributed to aetiological distinctions, the groups were matched a priori on CA and nonverbal MA, as measured with the Leiter International Performance Scale. The groups were subdivided at age 13 in order to allow for the assessment of group differences in childhood and adolescence (Dykens et al., 1994).

**METHOD**

**Subjects**

Seventeen males with fragile X between the ages of 5.67 and 17.17 years were recruited to participate in this study. Individuals were diagnosed with fragile X on the basis of cytogenetic testing. Subsequent to the selection of the fragile X syndrome subjects, 17 males with Down syndrome between the ages of 5.50 and 18.33 years were recruited and matched by CA and approximate nonverbal mental age (MA) to the males with fragile X. All participants had a nonverbal MA of more than two and a half years as assessed with the Leiter International Performance Scale of Intelligence, and attended special education schools. None of the participants had a history of autism, gross motor impairments, epileptic seizures, EEG disturbances, or use of anti-epileptic medication, nor did they receive stimulant medication.

The groups were further subdivided according to age. The younger males with fragile X \((n = 10)\) had a mean CA of 8.45 years (SD = 2.58) and MA of 3.73 years (SD = 0.80), and the older males \((n = 7)\) a mean CA of 14.93 years (SD = 1.69) and MA of 4.96 years (SD = 0.70). The younger males with Down syndrome \((n = 9)\) had a mean CA of 8.93 years (SD = 2.61) and MA of 3.58 years (SD = 0.41), and the older males \((n = 8)\) a mean CA of 15.28 years (SD = 1.53) and MA of 4.42 years (SD = 0.87).

**Tests**

*Leiter International Performance Scale of Intelligence* (Leiter, 1948). This scale is a nonverbal means of assessing general intelligence, based upon conceptual thinking, for ages 2 years to adulthood. The test
necessitates matching blocks into notched spaces beneath a strip that is placed on a wooden frame. There are up to eight spaces to be filled according to the criteria in the strip. These criteria range from simple perceptual matching (colours, shapes, and combinations thereof) to abstract associations (genus), and from simple number concepts to analogous patterns.

Kaufman Assessment Battery for Children (Kaufman & Kaufman, 1983a,b). The K-ABC, an intelligence test designed for 2- to 12-year-old children, was translated into Hebrew for use with Israeli children. Due to potential cultural or language bias, some items were replaced on three subtests (Face Recognition, Photo Series, and Word Order). The version of the test we used is now standardised in Israel.

The K-ABC incorporates two domains of neuropsychologically based styles of information processing, sequential and simultaneous. The Simultaneous Processing domain is a measure of the ability to solve problems that involve the global integration of many stimuli at once, and is comprised of seven subtests: Magic Window, Face Recognition, Gestalt Closure, Triangles, Matrix Analogies, Spatial Memory, and Photo Series. The Sequential Processing domain is an assessment of the ability to process discrete stimuli presented in sequential or serial order, and is comprised of three subtests: Hand Movements, Number Recall, and Word Order. The Spatial Memory and Photo Series data were not included in the analyses as virtually none of the participants were able to attain basal performance.

Age equivalent scores were calculated for each participant on each subtest. An attempt was made to administer all subtests to each participant, even if the test was above or below their level of functioning or chronological age (see Hodapp et al., 1991). Scaled domain scores were not computed since many of the participants in this study received raw scores of zero on more than one subtest in a given domain (see Kaufman & Kaufman, 1983a). In addition, scaled domain scores were not used because the CA of many of the participants exceeds the ages included in standardisation (i.e. over 12 years and 5 months).

Vineland Adaptive Behavior Scales: Expanded Interview Form (VABS; Sparrow et al., 1984). The VABS is a questionnaire-based test that is used to assess social competence from birth to 19 years among persons with and without handicaps (Sattler, 1992). A Hebrew translation of the VABS with the three adaptive behaviour domains of Communication, Daily Living Skills, and Socialisation, but not the one of Motor Skills, was used. Each domain is comprised of three subdomains: receptive,
expressive, and written language for Communication; personal, domestic, and community for Daily Living Skills; and interpersonal, play and leisure time, and coping skills for Socialisation. The scales provide age-equivalent scores to assess levels of functional abilities in each domain. In a pilot study, no differences in age-equivalents were found between the Israeli and the norms provided by the test originators.

RESULTS

The age-equivalent means for younger and older males with fragile X and Down syndrome on the subtests of the K-ABC and on the domains of the VABS are presented in Table 1.

Due to deviations from the assumptions of normality and the equality of variances, the age-equivalent scores were log-transformed prior to the analyses. The scores of the Spatial Memory and Photo Series were eliminated from the analyses as they were virtually all at the floor level.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Age Equivalent Scores (in Months) on the K-ABC and the VABS Domains for Subject Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subdomain</td>
<td>Fragile X</td>
</tr>
<tr>
<td></td>
<td>Age-Equivalents (mths)</td>
</tr>
<tr>
<td></td>
<td>M (SD)</td>
</tr>
<tr>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(n = 7)</td>
</tr>
<tr>
<td>K-ABC</td>
<td></td>
</tr>
<tr>
<td>Magic Window</td>
<td>40.67 (15.45)</td>
</tr>
<tr>
<td>Face Recognition</td>
<td>44.70 (12.53)</td>
</tr>
<tr>
<td>Hand Movement</td>
<td>32.40 (5.25)</td>
</tr>
<tr>
<td>Gestalt Closure</td>
<td>54.00 (28.50)</td>
</tr>
<tr>
<td>Number Recall</td>
<td>33.00 (3.16)</td>
</tr>
<tr>
<td>Triangles</td>
<td>44.10 (2.85)</td>
</tr>
<tr>
<td>Word Order</td>
<td>37.80 (3.80)</td>
</tr>
<tr>
<td>Matrix Analogies</td>
<td>51.60 (6.45)</td>
</tr>
<tr>
<td>Spatial Memory</td>
<td>48.00 (0.00)</td>
</tr>
<tr>
<td>Photo Series</td>
<td>60.00 (0.00)</td>
</tr>
<tr>
<td>VABS</td>
<td></td>
</tr>
<tr>
<td>Communication</td>
<td>43.90 (15.02)</td>
</tr>
<tr>
<td>Daily Living Skills</td>
<td>49.70 (21.11)</td>
</tr>
<tr>
<td>Socialisation</td>
<td>43.20 (20.75)</td>
</tr>
</tbody>
</table>

\[ ^{a}\text{Subjects younger than 13.} \quad ^{b}\text{Subjects older than 13.} \quad ^{c}\text{Minimum score of 48 months.} \quad ^{d}\text{Minimum score of 60 months.} \]
The score for the Magic Window subtest was missing for one subject from each group. The missing value was replaced by the appropriate group mean so that the participants’ scores in other subtests could be considered in the multivariate analysis.

**Group and Age Analyses with K-ABC Subtests**

A two-way multivariate analysis of variance (MANOVA) revealed overall differences in subtest scores between the males with fragile X and Down syndrome (Wilks’ lambda = 0.464, \( P = .011 \)) and between the younger and older participants (Wilks’ lambda = 0.440, \( P = .007 \)). There was no significant interaction between Group and Age.

Univariate \( F \)-tests of group differences revealed no differences between the males with fragile X and Down syndrome on any of the subtests of the Sequential Domain. However, in the Simultaneous Domain, the males with fragile X received higher age equivalent scores on the Magic Windows \( [F(1,30) = 11.72, \ P < .01] \), Face Recognition \( [F(1,30) = 9.60, \ P < .01] \), and Matrix Analogies \( [F(1,30) = 6.92, \ P < .05] \) subtests.

Univariate \( F \)-tests of age differences revealed that the older as compared to the younger males received significantly higher age equivalent scores on the Hand Movement \( [F(1,30) = 4.61, \ P < .05] \), Number Recall \( [F(1,30) = 11.00, \ P < .01] \), Word Order \( [F(1,30) = 4.94, \ P < .05] \), Magic Windows \( [F(1,30) = 5.47, \ P < .05] \), Face Recognition \( [F(1,30) = 15.92, \ P < .001] \), Triangles \( [F(1,30) = 5.67, \ P < .05] \), and Matrix Analogies \( [F(1,30) = 6.86, \ P < .05] \) subtests.

Univariate group by age interaction analyses revealed an interaction effect for the Matrix Analogies subtest \( [F(1,30) = 4.17, \ P < .05] \), and a marginal interaction for the Number Recall subtest \( [F(1,30) = 3.57, \ P < .07] \). In both cases, the discrepancy between the older and younger participants was greater for the males with fragile X than for those with Down syndrome.

**Group and Age Analyses with the VABS Domains**

A two-way MANOVA revealed that males with fragile X scored higher overall on the subdomains of the VABS than the males with Down syndrome (Wilks’ lambda = .754, \( P = .05 \)), and that older males scored higher overall as compared to younger males (Wilks’ lambda = .626, \( P < .004 \)). There was no significant interaction between Group and Age.

Univariate \( F \)-tests of group differences revealed that males with fragile X scored higher on the Daily Living Skills subdomain of the VABS \( [F(1,30) = 7.16, \ P < .01] \), and marginally higher on the Communication domain \( [F(1,30) = 4.12, \ P < .06] \).
Univariate $F$-tests of age differences revealed that the older as compared to the younger males scored significantly higher age equivalent scores on all the domains of the VABS: Communication $[F(1,30) = 13.54, P < .001]$, Daily Living Skills $[F(1,30) = 15.47, P < .001]$, and Socialisation, $[F(1,30) = 9.37, P < .01]$.

**DISCUSSION**

Profiles of cognitive functioning and adaptive behaviour were compared between groups of Israeli males with fragile X and Down syndrome matched for CA and nonverbal MA. Careful *a-priori* selection of participants was intended to minimise the extent to which differences between the groups could be attributed to extraneous factors. The findings are evidence from a non-English speaking country of differences on cognitive functioning and adaptive behaviour between males with fragile X and Down syndrome. The males with fragile X showed superior performance on several subtests of simultaneous processing on the K-ABC, and received higher scores on the Daily Living Skills Domains of the VABS and marginally higher scores on the Communication domain.

**Group Differences on the K-ABC**

The performance of males with fragile X did not differ from those with Down syndrome on any of the three subtests of sequential processing on the K-ABC (Dykens et al., 1987; Kemper, Hagerman, & Altschul-Stark, 1988). This is inconsistent with Hodapp et al.’s (1992) findings that children with fragile X are particularly deficient in this type of processing and that children with Down syndrome were superior to those with fragile X on the Hand Movement subtest. This discrepancy may be due to differences between the studies in the matching of groups as Hodapp et al. (1992) matched on the K-ABC which was also the dependent measure, and we a priori matched subjects on an independent test.

On the simultaneous domain, the males with fragile X scored significantly higher on the Magic Windows, Face Recognition, and Matrix Analogies subtests. The Magic Windows subtest measures the ability to identify and name an object whose picture is rotated behind a narrow opening such that only part of the picture is visible at any given time (Kaufman & Kaufman, 1983b). Performance on this subtest is enhanced by abilities to concentrate and attend.

The Face Recognition subtest is used to assess the ability to attend to one or two face photographs that are exposed briefly, and to subsequently select the correct face(s) shown in a different pose from among several in a group photograph (Kaufman & Kaufman, 1983b). This subtest involves visuomotor processing and measures visual search, scanning strategies,
facial perception, and face recognition. As with the Magic Windows subtest, performance on this subtest is facilitated by efficient attention and concentration (Kaufman & Kaufman, 1983b).

The Matrix Analogies subtest requires the selection of a picture or design that best completes a $2 \times 2$ visual analogy. Enhanced performance on this subtest is contingent on good impulse control and flexible response styles (Kaufman & Kaufman, 1983b).

These findings are consistent with previous evidence of a relative strength in general simultaneous processing among males with fragile X as compared to those with Down syndrome (Hodapp et al., 1992). However, the relative superiority on tasks that entail efficient attention, concentration, and impulse control is inconsistent with reports of attentional problems in males with fragile X (see Dykens et al., 1994; Wilens & Biederman, 1992). This apparent discrepancy may be attributable to the nature of the specific tasks. In all three tasks, correct responses on a preschool level can be achieved by rapidly perceiving visual gestalts with little further processing. Thus, males with fragile X syndrome may be better able to attend to simple visual perceptual tasks in which brief spurts of attention are required in a structured and motivating situation, but may be less successful sustaining attention in more mundane, typical settings. Furthermore, although superior to the performance of males with Down syndrome, the performance of the males with fragile X was still considerably below that which is typical for their developmental level as indicated by their nonverbal MAs.

Age Differences and Group by Age Interactions on the K-ABC

Across the two groups, the males older than 13 years scored higher than the younger ones on all three subtests of the Sequential Domain and on the Magic Windows, Face Recognition, Triangles, and Matrix Analogies subtests of the Simultaneous Domain of the K-ABC. Although the enhanced performance among the older participants may appear to be inconsistent with the apparent IQ declines in both groups, it highlights the notion that IQ decline is typically associated simply with slowed development and not with regressions in development.

For both the significant Group $\times$ Age interaction on Matrix Analogies (simultaneous domain) and the marginally significant one with Number Recall (sequential domain), the difference between the older and younger males with fragile X was greater than for the males with Down syndrome. These findings are minimal evidence of differences in age-related performance between the two groups (Dykens et al., 1994). As issues of
trajectory are essential for the timing and evaluation of interventions, more precise assessments of trajectories of development are needed. Data from longitudinal studies with larger subject groupings would be particularly informative.

Group and Age Differences on the VABS

The males with fragile X syndrome, as compared to those with Down syndrome, scored higher on the Daily Living Skills domain of the VABS and marginally higher on the Communication domain. No differences were found between the groups with regard to the Socialisation domain of the VABS. This is consistent with both the findings that males with fragile X syndrome score relatively high on the Daily Living Skills domain of the VABS and that the communication abilities of persons with Down syndrome are especially impaired (Dykens et al., 1988, 1989b). As expected, the older participants, across groups, scored higher on all the domains of the VABS.

Summary: Limitations, Inconsistencies, and Contributions

These findings highlight differences in functioning between males with fragile X and Down syndrome and thereby reflect the necessity of differentiating by aetiology among persons with mental retardation. Yet, even more precise analyses are now possible as groups of persons with fragile X and Down syndromes can be even further differentiated into subgroups. With recent advances in molecular testing, groups of persons with fragile X syndrome are further differentiated on the basis of molecular status. Those with more than 230 C-G-G repeats typically show full fragile X syndrome, whereas those with fewer repeats display less of the behavioural picture associated with the disorder (Dykens et al., 1994). Persons with Down syndrome are also differentiated with aetiological subtypes known as trisomy 21, mosaicism, and translocation (Gibson, 1978). However, we did not differentiate among the subgroups as molecular testing for the persons with fragile X was not available to us at the time of the testing. Accordingly, this study was intended to provide evidence of general group differences. In subsequent work, differentiating within the groups would provide an even more precise understanding of development.

The apparent discrepancies between the findings presented here and those from earlier studies are informative about the performance of persons with fragile X and Down syndrome on the Leiter scale, which was
used for matching the groups, and the K-ABC and VABS, which were used as the dependent measures. We did not find group differences on any of the Sequential subtests of the K-ABC despite other reports of relative superiority of males with Down syndrome. Similarly, we found no example of superior functioning of performance among the males with Down syndrome as compared to those with fragile X on the K-ABC or the VABS, whereas we found that the performance of the males with fragile X was superior on certain areas. These findings are convergent evidence that children and adolescents with Down syndrome score higher on the Leiter test in relation to the K-ABC and the VABS, whereas this is not the case with males with fragile X. Accordingly, findings that males with fragile X score higher than those with Down syndrome on certain subtests of the K-ABC and subdomains of the VABS needs to be considered within the context of potentially different baseline levels of functioning.

When differences in the initial baselines are considered, the pattern of findings is generally consistent with previous reports. On the K-ABC, the males with fragile X scored better than those with Down syndrome on subtests of the Simultaneous Domain but not on those of the Sequential Domain. On the VABS, the superior scores of the males with fragile X on the Daily Living Skills and Communication domains is consistent with prior evidence of their relative strength on the former and the specific weakness of persons with Down syndrome on the latter. These differences between the males with fragile X and Down syndrome with regard to functioning on various domains and subdomains highlight the need to carefully examine the profiles of aetiologically homogeneous groups of persons. Concordantly, they highlight the differential performance among aetiological groups with regard to task demands and the need to consider this relationship between aetiology and task demands in evaluating indices of developmental level and behavioural performance.

Knowledge of these distinct patterns of strengths and weaknesses in functioning between the different aetiological groups is essential to planning and implementing interventions. They provide insight about aspects of functioning that are most likely to be sources of difficulty and others that can be used to facilitate learning and performance. For example, multimodal presentations of information may be particularly effective for use with males with fragile X who display relative strengths in simultaneous processing, but especially difficult for children with Down syndrome who show relative weaknesses in simultaneous processing.

In summary, knowledge about the development of aetio logically homogeneous groups of persons is essential to all aspects of work with persons with mental retardation. The data from this study highlights both differences in developmental profiles between persons with fragile X and Down syndrome and discrepancies in evaluations that are related to
baseline measures and task demands. Although the findings differ somewhat with those from previous reports, they reflect patterns that are consistent with previous evidence when issues of matching criteria and task demands are considered.

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