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NEUROPSYCHOLOGICAL CHARACTERISTICS OF CHILDREN WITH THE 22q11 DELETION SYNDROME: A DESCRIPTIVE ANALYSIS

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Previous reports of cognitive functioning in children with the 22q11 Deletion Syndrome have reported marked variability in IQ and achievement subtest scores. Studies have begun to explore neuropsychological function in 22q11 DS however results are inconsistent and the profile incomplete. We assessed 40 children ages 5–12 with 22q11 DS. Consistent with past results, visual-spatial memory was significantly lower than verbal memory. Differentially lowered scores were found only in visual attention, working memory and motor function. Contrary with some past results quantitative, verbal ability, and visual spatial memory scores were within 1 SD from the standardization sample mean. Motor behavior, not typically discussed with regard to 22q11 DS school-age children, may be critical to incorporate in neurocognitive studies of children with 22q11 DS. Implications of these findings are considered with regard to past results.

The 22q11 Deletion Syndrome (22q11 DS) results from a meiotic deletion of DNA at the q11.2 site on chromosome 22, occurring in 1 of every 4,000 births (du Montcel, mendizabal, Ayme, Sevy, & Philip, 1996). In over 90% of cases the deletion is not transmitted by either parent (*de novo*; Morrow et al., 1995). The deletion can result in a range of congenital anomalies, from fatal to barely detectable, and perhaps including heart defects, immunologic deficits, craniofacial dysmorphologies, velopharyngeal defects such as overt or submucous cleft palate or inflammation-related pain syndromes (e.g., Ryan et al., 1997). Prior to identification of a single associated deletion, several different clinical labels were used, each reflecting the primary medical disorder of the child, including conotruncal anomaly face syndrome (heart defect with facial dysmorphologies), velo-cardio-facial syndrome (VCFS, velopharyngeal, heart, and facial anomalies), and DiGeorge syndrome (immunologic insufficiency). Although the physical phenotype is heterogeneous, the neuropsychological characteristics are broadly predictable. Researchers have estimated that 90%–100% of children with 22q11 DS are learning disabled (e.g., Lipson et al., 1991; Shprintzen, Goldberg, Young, & Walford, 1981) and display early hypotonia, gross and fine motor dyscoordination, expressive language delay, attentional problems, and behavioral anomalies (Gerdes et al., 1999).

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Initial studies of cognitive functioning in school-age children with 22q11 DS used standard IQ batteries and school-subject achievement tests. Markedly higher verbal than performance IQ scores were reported (e.g., Moss et al., 1995; Swillen et al., 1997) with reading and spelling achievement scores significantly higher than arithmetic scores (e.g., Moss et al., 2000). When full-scale IQs were calculated, they were reported to be in the low-normal to borderline range, attributable to marked subtest score scatter. Rather than global impairment, these results indicated marked variability in the cognitive functioning of children with 22q11 DS.

Recent studies of children with 22q11 DS have begun to use neuropsychological strategies to explore possible sources of their performance deficits. For example, among learning disabled children without the deletion, arithmetic disability was associated with visuospatial deficits (Geary, 1993) and not reading or spelling disability (Rourke, 1991). In particular, short-term visuospatial memory was shown to be associated with arithmetic skill in both normally developing and learning impaired populations (Buchannan, Pavlovic, & Rovert, 1998; Dickey, 1997; Logie, Gilhooly, & Winn, 1994). Wang, Woodin, Kreps-Falk, & Moss (2000) assessed thirty-six 5–12 years old children with VCFS and found that in fact (visual) Spatial Memory and not Number Recall (KABC subtests; Kaufman & Kaufman, 1983) was differentially lowered, with the mean scaled score for spatial memory 1 SD below the standardization sample mean. Bearden et al. (2001) administered a combined battery of tests to 29 children with 22q11 DS ages 5–16 years (mean age 10.3 ± 2.5) including verbal learning/memory tasks, visual learning/memory tasks, WISC-III subtests comprising Verbal Comprehension and Performance Organization subscales, and an achievement test that included word decoding, reading comprehension, numerical operations, and mathematical reasoning. Only the mean scaled score of visual spatial memory (Dot Location subtest, Children's Memory Scale; Cohen, 1997) was more than 1 SD below the standardization sample mean and differed significantly from the verbal memory measure (list-learning task, California Verbal Learning Test; Delis, 1994). It was posited that visuospatial deficits reflected the same functional abnormalities contributing to arithmetic impairments in children with 22q11 DS, in particular right temporal-parietal hemispheric abnormalities (Bearden et al., 2001).

Visuospatial memory has proven to be one important area of investigation among children with 22q11 DS. However, neuropsychological characteristics of children with 22q11 DS are notably complex (Moss et al., 2000), and visuospatial memory deficits may not fully account for the variety of deficits evident in children with 22q11 DS. Fifty children with 22q11 DS ages 6–17 (mean age 10.3 ± 3.2) were administered tests of memory (Verbal Learning, Story Memory, and Design Memory subtests from the Wide Range Assessment of Memory Learning) and executive attention (Trail Making), and a standard IQ battery (Woodin et al., 2001). Of the subtest mean scores reported, only math achievement, delayed story recall, Trails B, and the Freedom from Distractibility Index of the WISC-III, a cluster measure of performance on visual attention and working memory tasks, were 1 or more SDs below the standardization sample mean. A striking deficiency in Trails B was found, suggesting impaired mental flexibility and a loss of visual attentional focus when utilizing working memory. In this study, design (visual-spatial) memory was within 1 SD from the mean; nonetheless mean rote verbal memory score (list learning) was significantly higher than either design memory or story recall. (Previously reported verbal/performance IQ differences and reading/math differences also were replicated.) Thus in this sample lowered visual spatial memory scores were accompanied by even more marked impairment on measures of visual attention/executive function ability.

Neuropsychological investigation of the 22q11 DS syndrome is relatively new, reports are still inconsistent, and the profile is incomplete. Visual-spatial memory deficits have been given much consideration but studies do not agree that functioning in this domain is in fact differentially lowered among children with 22q11 DS. One report has hinted that the most severe impairment may be in visual attention and working memory—perhaps a special class of impairment likely to impact functioning in other cognitive areas and on many types of tests. Motor function in school-age children with 22q11 DS has rarely if ever been assessed or discussed despite the frequently reported 10-point IQ difference between verbal and performance scores. Early hypotonia and motor abnormalities are common among children with 22q11 DS before the age of 3 (Gerdes et al., 1999), but whether motor deficits extend into the school years is relatively unexplored in the literature. In addition to clarifying the needs of children with 22q11 DS, more fully characterizing their neuropsychological profiles can provide meaningful links between specific genes and the developing brain, perhaps eventually becoming applicable to a variety of genetic and neuropsychological disorders.

To contribute to past findings we administered IQ and neuropsychological tests similar to those used previously and increased the number of domains assessed. The Stanford Binet IQ battery (S-B; Thorndike, Hagen, & Sattler, 1986) was used to assess verbal, quantitative, and memory abilities. The NEPSY Developmental Neuropsychological Battery for Children (Korkman, Kirk, & Kemp, 1998) was used to asses neuropsychological functioning in language, visual and verbal memory, visual-spatial processing, sensorimotor functioning, and attention and executive function.

We predicted lower mean scaled scores on Quantitative as compared to Vocabulary subtests (S-B). We also predicted lower mean scaled scores for Bead Memory (S-B) as compared to Sentence Recall (S-B). Studies of unaffected populations have demonstrated functionally segregated neural systems in the human cortex for location memory and memory for faces (e.g., Courtney, Ungerleider, Keil, & Haxby, 1996). To begin to explore the relationship between these memory functions in children with 22q11 DS we predicted lower mean scaled scores for Bead Memory as compared to Memory for Faces (NEPSY). Also based on past findings we predicted mean scaled scores greater than 1 SD below the standardization sample mean on tests of arithmetic (Quantitative, S-B), visual-spatial memory (Bead Memory, S-B), visual attention (Visual Attention Omissions, NEPSY), and executive function ability (Auditory Attention Response Set and Tower, NEPSY). Hypotonia and motor delays have been reported in a majority of pre–school-age children with 22q11 DS (e.g., Gerdes et al., 1999) but are relatively unexplored in school-age children with 22q11 DS. Given their early delays we predicted mean scaled scores greater than 1 SD below the standardization sample mean on all tests of motor function, including fine motor dexterity (Finger-Tapping, NEPSY), tactile/kinesthetic awareness (Imitating Hand Positions, NEPSY), and graphomotor control (Visuomotor Precision, NEPSY).

METHOD

Participants

These data are from an ongoing longitudinal study of children with the 22q11 Deletion Syndrome and include 40 children ages 5–12 years. Parents learned of our project through website postings, brochures sent to genetic counselors, doctors' offices, speech and language specialists, and parent support groups. Prior to enrollment in the study all children were confirmed positive for the 22q11 deletion via fluorescence in situ hybridization

(FISH) assay. Potential participants were excluded if they or their parents were not fluent in the English language. All children were unmedicated at the time of testing. The tests and testing procedures were explained to the parents by study staff and to child participants by their parents. Consent forms were sent to parents for review approximately 1 month in advance of scheduled testing. Child verbal assent and parental informed consent was obtained on the first morning of testing prior to the start of assessment procedures.

Procedures

All tests were conducted by a licensed clinical psychologist or by one of four specially trained neuropsychological testers with a minimum 2 years' child testing and treatment experience at the doctoral training level and supervised by a licensed clinical psychologist. All tests were completed on two consecutive mornings. To control for circadian effects all test sessions were completed by 1 P.M. Parents waited immediately outside the testing room for their children and were available to the children whenever breaks were needed. Breaks were provided according to the needs of the child; imposed breaks were taken every 50 minutes for children who did not request them sooner.

The Stanford-Binet Intelligence Scale, 4th Ed. (S-B; Thorndike et al., 1987) is comprised of 15 subtests that assess four general areas of cognitive function, including Verbal Reasoning, Visual Reasoning, Quantitative Reasoning, and Short-Term Memory. The method and content of the S-B subtests are based three decades of research, and the standardization samples are large and up to date. Four subtests from this battery assessed cognitive functions included in the hypotheses: arithmetic ability (Quantitative), verbal ability (Vocabulary), visual-spatial memory (Bead Memory), and verbal memory (Memory for Sentences). The NEPSY Developmental Neuropsychological Battery (Korkman et al., 1998) was comprehensively standardized using 1,000 American school-children and assesses language, memory, visuospatial function, sensorimotor function, attention, and executive function. NEPSY subtests that assess areas previously reported to be impaired in children with 22q11 DS include Memory for Names (verbal memory), Visual Attention Omissions (visual inattention), Auditory Attention Response Set (working memory), and Tower (executive ability). Three NEPSY subtests assess different aspects of seusorimotor function, including Finger Tapping, Imitating Hand Positions, and Visuomotor Precision. Table 1 provides brief descriptions of each subtest analyzed.

Data Scoring and Analysis

All data were scored by the tester and re-scored by a licensed psychologist. Verbal/performance domain score differences previously reported and variability in test results across studies of children with 22q11 DS suggested the possibility of wide intra-subtest score scatter. To consider the validity of domain and composite scores for these analyses each participant's subtest score range was calculated. The spread of S-B subtest scores ranged from 2 to 11 with a mean difference of 5.96 (SD ± 1.93; nearly 2 SDs between lowest and highest subtest scores). The spread of NEPSY subtest scores ranged from 5 to 14 with a mean difference of 9.93 (SD ± 2.75; over 3 standard deviations between lowest and highest subtest scaled score). For every participant, the statistical difference between lowest and highest NEPSY scores was significant ($p < .05$, NEPSY Manual,

Table 1 Description of Stanford-Binet and NEPSY Subtests Analyzed.

Subtest	Task Description
Stanford-Binet	
Vocabulary	Define the meaning of everyday words
Quantitative	Match numbers, add, subtract, multiply, compute math problems
Bead Memory	View, retain, and replicate from memory bead arrangement patterns
Memory for Sentences	Immediately recall sentences of increasing length and complexity
NEPSY	
Memory for Names	Learn names associated with cartoon line drawings of children faces
Memory for Faces	Identify photos of children's faces seen during exposure trial
Visual Attention	Visually scan and mark single and dual targets (timed)
Omissions	Number of targets missed
Commissions	Number of non-targets marked
Auditory Attention	Select correct color cube(s) according to 1 per sec. verbal cues
Single Rule	Respond to only one color word
Response Set	Retain and respond to three color words while applying novel rule set
Tower	Re-arrange balls on pegs to match display following task rules
Finger Tapping	Tap fingers in simple and sequenced patterns (timed)
Imitating Hand Positions	Imitate hand positions modeled by tester
Visuomotor Precision	Guide pencil line within narrow winding boundaries (timed)

Table B.1; Korkman et al., 1998); differences between lowest and highest scaled scores were found both within and across domain categories. Because scatter of this magnitude invalidates summary scores, domain and composite scores were not used in these analyses.

It was noted during scoring that NEPSY global Visual Attention scores improved as a result of faster completion time regardless of the number of omissions or commissions committed. Visual Attention Omission and Commission scores were calculated using age-appropriate standardization sample standard deviations provided in the NEPSY manual.

A widely used benchmark of notably lowered performance on individual subtests from a standardized battery is >1 standard deviation below the standardization sample mean (e.g., Delis, Kaplan, & Kramer, 2001; Spreen & Strauss, 1998). Normally distributed group scores greater than one standard deviation below the standardization sample mean indicate a sample mean at or below 16th percentile. For comparability to past studies of children with 22q11 DS we adopted this benchmark as well.

Variations in cell sizes are indicated by stated degrees of freedom or table cell size notations. It should be noted that in the Response Set segment of the Auditory Attention subtest, a task largely dependent on working memory, two children (females, ages 5.5 and 5.7) were unable to learn the rule set (hear red, select yellow; hear yellow, select red; hear blue, select blue) and received no score. An additional four children (two females, 5.5 and 6.4: two males, 5.5 and 7.2) easily demonstrated in the sample items that they learned the rule set. However, once the task began they seemed to lose the rule set, responded incorrectly or randomly with no correct responses, and stopped responding mid-way through. For the purpose of these analyses, these four children were given a scaled score of 1 (scaled score equivalent of "no hits") for Response Set.

Data were entered and maintained in a Statview database and analyzed using Statview Version 3.0 for PC or SAS Version 6.0 for PC. For comparability to the NEPSY, S-B

scores were transformed to scaled scores with mean = 10, SD = 3; for reference original S-B scores (mean = 50, SD = 8) were also tabled. Unpaired *t*-tests were used in preliminary analyses for gender comparisons. The Kolmogorov-Smirnov one-sample test (Daniel, 1991; Kolmogorov, 1933) was used to examine distribution normality for each of the subtests reported. Paired *t*-tests were used to examine hypothesized differences between verbal and quantitative performance and between visual and verbal memory ability. For all secondary (unplanned) analyses $p \leq .01$ to control for Type I error. These included correlation, simple and multiple regression analyses.

RESULTS

Forty children ages 5.2–12.9 confirmed positive for the 22q11.2 Deletion Syndrome (23 females, 17 males; mean age 7.7, SD ± 2.4) were included in these analyses. Demographic characteristics of the sample are shown in Table 2. Preliminary *t*-test comparisons of mean scaled scores for the subtests to be analyzed revealed no significant differences between males and females and the genders were combined.

The score distributions for each subtest were examined for bimodality and tested for normality using the Kolmogorov-Smirnov one-sample test ($p \leq .05$). The distributions of all S-B and NEPSY subtest scores included in these analyses were unimodal and normally distributed.

Paired *t*-test was used to examine the hypothesis that Quantitative (QNT) score mean was lower than Vocabulary (VOC) score mean. Contrary to previous findings no difference was apparent (mean difference = .32, $t(37) = .76$, $p = .40$). We examined other measures of verbal ability to determine whether they might better capture the expected difference. S-B QNT and Comprehension (CMP) subtest means also did not differ (mean difference = .76, $t(36) = 1.84$, $p = .07$), and the difference obtained was in the opposite direction of that predicted. No differences were apparent between S-B QNT

Table 2 Social, Clinical, and Academic Demographics of Children with 22q11 DS.*

Female	58% (23)
Parent Education (SES)**	
12–15 Years	77% (62/80)
≥16 Years	23% (18/80)
Caucasian	92% (37)
22q11 DS FISH*** Positive	100% (40)
Mean Age of Detection	37.0 months (±2.6)****
Early Hypotonia with/Motor Delays < Age 3	92% (37)
Walking Mean Age (SD)	17.6 months (±5.4)
Permanent Hearing Loss (Hearing Aid Corrected)	7% (3)
Speech/Language Therapy	83% (33)
Occupational Therapy	68% (27)
Physical Therapy	38% (15)
Regular Education Classroom	18% (7)
Main-streamed Inclusion Classroom	55% (22)
Special Education Classroom	25% (10)
Home-Schooled	2% (1)

Note. *N = 40, **Hollingshead Index of Social Position (Hollingshead & Redlich, 1958), ***fluorescence in situ hybridization assay, ****2 outliers confirmed positive at 10.6 and 12.8 years not included in the mean (SD) calculation.

and NEPSY verbal ability subtests, including Instruction Comprehension (mean difference = .03, $t(36) = .06$, $p = .96$) or Phonological Processing (mean difference = .20, $t(37) = .57$, $p = .57$).

Paired *t*-tests were also used to test performance differences on memory tests. As suggested by past studies mean scores for Bead Memory (BDM) were found to be significantly lower than those for Sentence Memory (SNM; mean difference = –1.47, 95% C.I. = –2.69/–.25, $t(35) = -2.45$, $p = .02$). The difference in mean scaled scores of BDM and Memory for Faces approached but did not reach significance in the predicted direction (mean difference = –1.02, $t(38) = -1.66$, $p = .10$).

The means, SDs, score ranges, and percent of children scoring above the mean on S-B and NEPSY subtests were calculated (Tables 3 and 4). Consistent with past reports mean scaled scores more than 1 SD below the standardization sample mean (<7.0) included Visual Attention Omissions (VOM) (visual inattention) and Auditory Attention Response

Table 3 Stanford-Binet Subtest Means, SDs, Ranges, % Above the Mean, and Cell Sizes.*

Subtest	Mean (SD)**	Range	SS ≥ 10	(*n*)
Vocabulary	8.5 (2.5) [46.1/6.7]	4–15	30%	(40)
Quantitative	8.7 (2.4) [46.5/6.3]	4–14	32%	(38)
Bead Memory	7.5 (2.7) [43.3/7.1]	1–14	16%	(39)
Sentence Memory	9.0 (2.3) [47.2/6.1]	4–14	32%	(37)
Comprehension	8.1 (2.2) [44.8/5.9]	4–13	23%	(39)
Visual Reasoning	8.5 (3.3) [47.4/6.1]	5–14	36%	(39)
Pattern Analysis	7.9 (2.3) [44.5/6.1]	3–12	22%	(36)
Digit Memory	9.2 (2.1) [47.9/5.5]	6–12	44%	(16)***

Note. *ages 5.2–12.9, $N = 40$, **original S-B means/SDs in [ ], mean = 50, SD = 8, ***Digit Memory subtest entry level is typically 8+ years

Table 4 NEPSY Subtest Means, SDs, Ranges, % Above the Mean, and Cell Sizes.*

Subtest	Mean (SD)	Range	SS ≥ 10	(*n*)
Memory for Names	8.5 (3.2)	2–14	45%	(39)
Memory for Faces	8.6 (3.2)	2–15	45%	(40)
Narrative Memory	7.5 (3.0)	1–15	27%	(40)
Visual Attention (global)	8.3 (2.5)	2–13	40%	(40)
Omissions	6.5 (2.8)	1–11	17%	(40)
Commissions	9.2 (2.2)	4–12	50%	(40)
Auditory Attention	8.3 (2.7)	3–13	41%	(33)
Single Rule	8.6 (2.8)	3–13	46%	(39)
Response Set	6.8 (3.7)	1–13	29%	(37)
Tower	8.0 (3.0)	3–15	32%	(40)
Finger Tapping	6.8 (4.2)	1–13	35%	(39)
Imitating Hand Positions	6.5 (3.0)	1–13	13%	(39)
Visuomotor Precision	5.6 (2.5)	1–11	7%	(40)
Instruction Comprehension	8.7 (2.7)	1–14	41%	(40)
Phonological Processing	8.5 (2.7)	3–15	40%	(40)
Speeded Naming	7.9 (3.9)	1–17	28%	(39)
Arrows	8.3 (2.8)	2–13	37%	(32)
Design Copying	7.2 (2.7)	2–12	25%	(40)

Note. *ages 5.2–12.9, $N = 40$

Set (ARS; inability to maintain and apply a rule set). Additionally, mean scaled scores for the three motor subtests administered were all greater that 1 SD below the mean, including Finger-Tapping (FTP; simple motor dexterity), Imitating Hand Positions (IHP; tactile/kinesthetic awareness), and Visuomotor Precision (VMP; graphomotor control). Contrary to two studies (Bearden et al., 2001; Wang et al., 2000) and consistent with one (Woodin et al., 2001), BDM mean scaled score was within 1 SD from the mean. Contrary to past findings mean scaled score for Quantitative (QNT) was also within 1 SD from the standardization sample mean. Contrary to our predictions Tower mean scaled score was not greater than 1 SD below the standardization sample mean.

Secondary Analyses

Findings in the primary analyses that diverged from the predictions raised several questions regarding impairment in children with 22q11 DS, and we addressed these in secondary analyses. To control for Type I error alpha was set to $p \leq .01$. Sample age was used to examine the unexpected finding of no difference between quantitative and verbal measures. It was noted that difficulty with S-B QNT items appeared linked to an increase in the level of abstraction and mental flexibility necessary to solve them (discussed on page XX). The sample here analyzed included children from a more restricted age range (5–12) and lower mean age (7.7 ± 2.4) than in past studies (e.g., Woodin et al., 2001, ages 6–17, mean age 10.3 ± 3.2). If 22q11 DS math failures were partly attributable to the level of abstraction and mental flexibility required, test age might be inversely associated with S-B QNT scores. Using simple linear regression analysis we attempted to predict QNT scores from test age. The slope of the regression line was significantly less than zero indicating that as participant age increased QNT scores tended to decrease (slope = –.45; 95% C.I. = –.75/–.15; $t_{36} = -3.0$; $p = .005$; $Y = 12.2 - .45X$; $r^2 = 20\%$). While test age accounted for a relatively small percentage of variation in Quantitative test scores, this result may indicate that significant differences between measured quantitative and verbal ability are more likely to occur among older samples of children with 22q11 DS.

Associations between participant age and subtest scores were considered from another perspective. Associations with age are not expected among age-normed tests. Positive associations between age and subtest means in a deficient range might suggest that deficits reflect developmental delay rather than impairment. Simple linear regressions were used to predict performance score on the basis of test age for those functions found to be deficient (>1 SD below standardization sample mean). No significant associations between test age and lowered mean scores were found ($p \leq .01$). (FT: slope = 0.30, $r^2 = 3\%$, $t_{37} = 1.0$, $p = .31$; IHP: slope = –0.18, $r^2 = 2\%$, $t_{37} = -.85$, $p = .40$; VMP: slope = –0.03, $r^2 < 1\%$, $t_{38} = -0.16$, $p = .87$; VOM: slope = –0.10, $t_{38} = -0.52$, $r^2 < 1\%$, $p = .61$; ARS: slope = 0.56, $t_{35} = 2.25$, $r^2 = 13\%$, $p = .04$) In this cross-sectional sample, there was no evidence of developmental improvement in areas of lowered performance.

Areas of differentially lowered ability in this sample of children with 22q11 DS included visual attention (VOM), working memory (ARS), fine motor dexterity (FTP), kinesthetic processing (IHP), and fine motor control (VMP). To examine the possible influence of lowered ability in these areas on other subtests noted to require one or more of these functions we examined their associations. One subtest, NEPSY Comprehension of Instructions, required the acquisition, organization, and active maintenance of auditorially perceived (verbal) information (working memory, ARS) for responding. Subtests requiring visual attention (discrimination of visual displays, VOM) included S-B BDM and

Table 5 Summary of Simultaneous Regression Predicting Bead Memory Performance from Visual Attention Omissions and Imitating Hand Positions.*

Variable	B	β	SE β	*p*
Visual Attention Omissions	.420	.456	.140	.001
Imitating Hand Positions	.170	.206	.126	[.187]

Note. *ages 5.2–12.9, $N = 38$

Pattern Analysis, and NEPSY Memory for Names (differentiating simple cartoon drawings of children's faces for association with names). No non-motor subtest required repetitive finger movements (FTP). Three subtests required manipulation and accurate placement of small objects utilizing both kinesthetic processing (IHP) and fine motor control (VSP): S-B BDM (large beads) and Pattern Analysis (small blocks), and NEPSY Design Copying (pencil).

Single-order correlations ($p \leq .01$) were found for four of the five considered subtests with one or more identified areas of deficit: S-B BDM (IHP $r = .40$; VOM $r = .41$), S-B Pattern Analysis (VSP $r = .42$), NEPSY Memory for Names (VOM $r = .45$), and NEPSY Comprehension (ARS $r = .48$). (Mean subtest inter-correlation for NEPSY standardization sample = .12, NEPSY Manual, Table E1, pages 362–365, Korkman et al., 1998.) Three simple regression models for predicting Pattern Analysis, Memory for Names and Comprehension scores, and a multiple regression model for predicting Bead Memory score were constructed according to these single-order associations. All four regression analyses were statistically significant though the strength of associations tended to be weak: As Visual Motor Precision scores increased Pattern Analysis scores tended to increase (slope = .38; 95% C.I. = .09/.66; $t_{34} = 2.7$; $p = .01$; $Y = 5.8 + .38X$; $r^2 = 18\%$); as Visual Attention Omissions scores increased (improved) performance on Memory for Names tended to increase (slope = .51; 95% C.I. = .18/.84; $t_{37} = 3.1$; $p = .004$; $Y = 5.2 + .51X$; $r^2 = 21\%$); as Auditory Attention Response Set scores increased Comprehension of Instructions scores increased (slope = .36; 95% C.I = .13/.59; $t_{35} = 3.2$; $p = .003$; $Y = 6.4 + .36X$; $r^2 = 23\%$). The final model attempted to predict Bead Memory score from Imitating Hand Positions and Visual Attention Omissions scores (Table 5). Kinesthetic awareness/fine motor control was less associated than the single-order correlation suggested, whereas the influence of visual attentional ability was moderately predictive (slope = .42; 95% C.I. = .13/.71; $t_{35} = 3.0$; $p = .001$, $r^2 = 33\%$). Possible implications of these associations will be considered below.

DISCUSSION

IQ and neuropsychological batteries were administered to 40 children with 22q11 DS ages 5.2–12.9, and performance scores were evaluated and compared with previous reports of cognitive and neuropsychological performance in this population. Several findings were consistent with past results. A significant difference was found between measures of visual spatial and verbal memory, and scores in a deficient range were found on tests of visual attention and working memory. Visual spatial memory ability within a normal range was consistent with one previous report. In addition impairment was indicated on all three types of motor behavior assessed including fine motor dexterity, kinesthetic awareness, and visual motor precision.

Testers' qualitative notes supported the quantitative findings. With regard to visual attention, only a few children appeared impulsive during the scanning task although many seemed unable to visually match target items in both ordered and random displays. Their scanning lacked strategy and they frequently re-examined items while missing an abundance of targets. The Response Set segment of the Auditory Attention task was difficult for most of the children regardless of their final score. They appeared taxed, anxious, or overwhelmed, actively sought encouragement and support, and at times entirely lost the novel instruction set, slipping back into the more automatic response (red for red, yellow for yellow). Participants' hand movements were visibly dyscoordinated, clumsy, and inaccurate, and they appeared unable to regulate movement force and direction. When modeling the tester's hand positions it was common for children across the age range to be unaware of their postural errors. When attempting to guide a pencil through a winding trail, pencil lines were weak, poorly controlled, and very slow or very haphazard; an immature pencil grip was typical for the 5- and 6-year-olds. Overall, the children in this sample were warm, personable, eager to succeed, and proud of their accomplishments. Nonetheless, between subtests most children required attentional re-direction, encouragement to maintain focus, and frequent reminders of task and testing goals.

Contrary to past findings differences between quantitative and verbal skills were not observed, and quantitative scores were not greater than 1 SD below the standardization sample mean. Consideration of subtest items supported the notion that S-B QNT item difficulty, scaled to challenge ability across the age range, was linked to increasing demands on abstraction and mental flexibility. The first 12 items required the participant to match, count, order, or add (dots on dice). Children through age 6.5 scored at the mean by completing only these items. The next 6 items were solved with pictures (e.g., seven apples are shown as the child is asked, "If you give three away how many are left?") and children through age 9.5 scored at the mean by solving these. Not until item 19 is a problem presented that required mental manipulation of recalled number concepts (e.g., what is the smallest whole number that can be divided by 3 and 6?). It seemed reasonable to suspect that underlying deficits in abstraction and working memory could lower test performance among older children whose scores were the result of errors on (abstract) items not attempted by younger children. The small but significant inverse association between age and quantitative performance in this relatively young sample may be indirect evidence of this effect. It is likely that abstraction ability should be directly measured, studied, and described in children with 22q11 DS, as well as experimentally controlled and considered in studies of their academic, cognitive, and neuropsychological status.

Consistent with past results short-term visual spatial memory was found to be significantly worse than sentence recall. However different from two previous reports and consistent with one, mean visual spatial memory score was not greater than 1 SD below the standardization sample mean in this group of children. Differentially lowered visual-spatial memory scores previously reported among children with 22q11 DS were obtained using a monochrome dot location task (e.g., Bearden et al., 2001), whereas scores within 1 SD from the mean on visual-spatial memory were reported in a study that used a design memory task (Woodin et al., 2001). The S-B Bead Memory task used colorful plastic shapes (blue, red, or white cones, balls, or disks). Compared to a monochromatic dot location task, perhaps the S-B task enhanced performance by increasing interest level and thus perhaps attention and persistence. Exploratory regression analysis estimated that 33% of the variance of visual-spatial memory performance in this sample was accounted for by visual attentional ability. If interest level heightens visual attention, test that use attractive

materials may improve children's visual spatial memory ability. If so, this raises questions regarding the role of attention in the development of visual spatial memory function, and perhaps broader issues regarding brain networks and the interaction of persistence, visual attention, and visual memory function. To address these, studies specially designed to experimentally control the hypothesized functions are required.

Differentially lowered scores greater than 1 SD from the standardization sample mean on tests of visual attention and working memory are consistent with past studies that showed performance 1 or more SDs below the mean only on Trails B, a subtest that requires visual attention, mental flexibility, and working memory (Woodin et al., 2001). Tower subtest mean within 1 SD from the standardization sample mean was perhaps inconsistent with lowered Response Set scores (working memory). However, past studies have noted floor and ceiling effects on Tower tests for adults (Humes, Welsh, Retzlaff, & Cookson, 1997) and similar effects may have influenced these results as well. Solutions for the first four items could be solved through simple matching and without mental visualization of response options. Children ages 5 to 7 achieve a score within 1 SD from the mean by completing only these items. Subsequent items progress in difficulty but are dependent on the child perceiving essentially one concept—the notion of temporary placement. Once a child discovers this, the mid-level items (though not the three most difficult ones) are relatively simple. These task attributes could account for both floor and ceiling effects and other tests of executive function are needed.

Secondary analyses were completed to examine whether lowered scores on measures of attention, executive function, and motor dexterity might be associated with performance on subtests in other (conceptually segregated) domains. Although the results perhaps are not surprising, they provide a statistical demonstration of the influence of visual attention and executive function on performance in the other domains examined. In future studies, it will be important to statistically control for impairment in visual attention and working memory when examining other domain functions in children with 22q11 DS.

Motor performance was consistently lowered in this sample. Lowered mean scores were found in all areas of motor ability assessed. Motor impairment was not correlated with age and thus did not appear to reflect developmental delay, although this issue should also be examined in longitudinal data. Motor deficits previously reported among pre-school children (e.g., Gerdes et al., 1999) appear to continue into early and middle childhood among children with 22q11 DS.

Motor functioning in children with 22q11 DS merits more recognition and should be incorporated into the study and interpretation of their cognitive and neuropsychological performance. For example, performance IQs (e.g., Wechsler Intelligence Scales) include scores from timed and untimed subtests dependent on graphomotor control and fine motor coordination. Past findings of 10 or more IQ point differences between verbal and performance IQ scores may be partly attributable to tactile/kinesthetic processing and graphomotor control impairment in children with 22q11 DS. Our exploratory analyses suggested one possible direct influence of motor impairment on the completion of a block design test and there may be more. Many cognitive, neuropsychological, and neurocognitive tests utilize materials that require manipulation and completion under timed conditions.

With regard to etiology, motor impairment and learning disorders have been found to co-occur (e.g., Berninger & Rutberg, 1992; Waber & Bernstein, 1994), perhaps suggesting a shared source of impairment for functions often considered "segregated." As an example, evidence now suggests that the cerebellum—commonly associated only with the development of motor ability—may be functionally intertwined during development

with basal ganglia and dorsal lateral prefrontal cortex (C/BG/DLPFC; Diamond, 2000). Among children with 22q11 DS, a recent brain-imaging study revealed volumetric anomalies in the head of the caudate (Sugama et al., 2000), the primary output structure of the DLPFC (e.g., Selemon & Goldman-Rakic, 1988). Thus this model may be specifically useful for the further study of attention, working memory, and motor deficits identified in this sample of children with 22q11 DS. C/BG/DLPFC seems to become most activated when tasks are challenging versus easy, novel versus familiar, changing versus fixed, and timed versus untimed (Diamond, 2000). Relatively few neuropsychological tests for children provide a means to quantify or control for these aspects of performance within functional domains. Tasks that tap a fuller array of functions governed by C/BG/DLPFC networks may provide one approach for further considering the primary sources of neuropsychological impairment in children with 22q11 DS.

These data represent a first step in more fully delineating the cognitive strengths and weaknesses of children with the 22q11 Deletion Syndrome. However, as suggested above, additional measures are needed to fully capture the types of deficits that characterize the cognitive development of children with the 22q11 Deletion Syndrome. When more data have been collected, formal profile analyses will be critical for defining a neurocognitive phenotype associated with the 22q11 Deletion Syndrome.

Limitations

Past results were replicated and corroborated with alternate tests of comparable abilities, explanations of inconsistencies were offered, and areas of notably lowered performance not previously incorporated in neuropsychological studies of children with 22q11 DS were discussed. However, the findings suggested areas of impairment not completely or directly captured by the measures used. Lowered test score means for attention and working memory were quantitatively apparent only on selected aspects of the subtests provided by the NEPSY battery. Global Visual Attention and global Auditory Attention scores were within 1 SD from the standardization sample mean. Only indirect evidence of lowered abstract ability was found and no NEPSY subtest seemed to directly capture this important aspect of cognitive function. Response Set (ARS) appeared to be a good measure of working memory, however, because two children could not learn the rule set and four children became overwhelmed by the task during completion; other tests with lower gradients are needed for characterizing working memory in this population.

We selected the NEPSY for its coverage of neuropsychological domains, and it provided broad comparative results. However, this replication of visual attention and working memory impairment requires more focused and detailed evaluation of these domains. We attempted to explore the influence of identified areas of deficit on performance in other domains. Purer tests that assess components of visual attention, auditory working memory, aspects of motor behavior, and abstraction ability are necessary for the neuropsychological characterization of children with 22q11 DS.

Examining associations between test results and school performance would have enhanced the interpretation of these data. However, preliminary review of school records revealed wide variability in grading strategies for remediated children (e.g., grading on the basis of altered tests, individual improvement, or special distributions). Moreover, all children in this sample were provided with remediation at some point during development (see Table 2), but this factor could not be controlled quantitatively due to marked variation in type, quality, frequency, and consistency.

The age range of children in sample was relatively broad. Our observations have suggested that in this population the patterns of neurocognitive strengths and weaknesses shift with age. Future studies will be needed to accurately characterize the neurocognitive phenotype of children with the 22q11 Deletion Syndrome at various points of development.

Several of the analyses here reported relied on comparisons to standardization sample means, which limits the conclusions that can be drawn. In future studies, it would be additionally informative to compare the performance of children with 22q11 DS to a control sample of children with learning disabilities who are without the 22q11 deletion. With regard to the NEPSY, parent education (≤ 11 yrs.—10%; 12–15 yrs.—60%; ≥ 16 yrs.—30%) was approximated by our sample; however, none of our parents had less than a high school education (see Table 2). Also, unlike the standardization groups, this sample included mostly White children (93%) as compared to 68% White, 15% African American, 11% Hispanic, and 6% other in the NEPSY standardization sample. Whether these findings apply to non-White children with 22q11 DS of parents of lower educational level (< 12 years) requires further study.

AUTHOR NOTE

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