Verbal and memory skills in males with Duchenne muscular dystrophy

V J Hinton* PhD;
R J Fee BA, Gertrude H Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, NY;
E M Goldstein MD, Department of Neurology, Scottish Rite Children's Medical Center, Atlanta, GA;
D C De Vivo MD, Departments of Neurology and Pediatrics, College of Physicians and Surgeons, Columbia University, New York, NY, USA.

**Correspondence to first author at* Gertrude H Sergievsky Center and Department of Neurology, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, P & S Box 16, New York, NY 10032, USA.
E-mail: vjh9@columbia.ed

Duchenne muscular dystrophy (DMD) is a progressive pediatric disorder that affects both muscle and brain. Children with DMD have mean IQ scores that are about one standard deviation lower than population means, with lower Verbal IQ than Performance IQ scores. For the present study, verbal skills and verbal memory skills were examined in males with DMD with the Clinical Evaluation of Language Fundamentals, 3rd edition, and the California Verbal Learning Test for Children. Performance of 50 males with DMD (age range 6–14y, mean 9y 4mo [SD 2y 1mo]) was compared to normative values. Two subsets of the probands were also compared with two comparison groups: unaffected siblings (*n*=24; DMD group age range 6–12y, mean 9y 1mo [SD 1y 8mo]; sibling age range 6–15y, mean 9y 11mo [SD 2y 4mo]) and males with cerebral palsy (CP);(*n*=23; DMD group age range 6–9y, mean 7y 8mo [SD 1y 2mo]; CP age range 6–8y, mean 6y 8mo [SD 0y 8mo]). Results demonstrated that although males with DMD performed slightly more poorly than normative values, they performed comparably to the controls on most measures. Consistent deficits were observed only on tests requiring immediate repetition for verbal material (Recalling Sentences, and Concepts and Directions). On other language tasks, including tests of understanding and use of grammar, and understanding of semantic relationships, the males with DMD performed well. Moreover, the males with DMD performed well on multiple indices of verbal recall, and there was no evidence of declarative memory deficits. DMD is a single-gene disorder that is selectively associated with decreased verbal span capacity, but not impaired recall.

See end of paper for list of abbreviations.

The cognitive presentation in Duchenne muscular dystrophy (DMD) is intriguing. Ever since its original characterization by Duchenne,[1] the illness has been known to be associated with 'dull' intellect and 'difficult' speech in some affected individuals, yet most do not have significant cognitive complaints. DMD presents with progressive physical disability and a shortened lifespan. DMD is primarily a disease of muscle, yet it also affects the central nervous system. Individuals with DMD have a genetic mutation that prevents the production of the protein product dystrophin, and of multiple dystrophin isoforms. In muscle, lack of dystrophin results in unstable muscle cell membranes that break down over time, causing progressive weakness. In the brain, a lack of dystrophin isoforms has been documented in the cerebral cortex and cerebellum, in specific cell types (especially pyramidal and Purkinje cells) and in specific cell areas (especially the neuronal postsynaptic densities).[2,3] As a group, children with DMD present with relatively weak verbal and immediate memory skills.[4–8] There is individual variation across factors that contribute to the cognitive phenotype, including intellectual level, age, degree of physical disability, and background environment. The goal of the present study was to explore, in detail, language and verbal memory skills in children with DMD.

A meta-analytical study of IQ scores from 32 published papers examining IQ among a total of 1146 individuals with DMD demonstrated that overall IQ scores are shifted down about one standard deviation from the normative mean.[5] Additionally, by examining aggregate data, the authors demonstrated that Verbal IQ scores were lower than Performance IQ scores.

Studies that have controlled for physical involvement have compared test performance of children with DMD with those with Spinal Muscular Atrophy (SMA) and demonstrated that the children with DMD have poorer verbal, immediate memory, and reading skills than their SMA peers.[4,6–8] Specific findings included lowered scores on Digit Span, Arithmetic, Similarities, Word Repetition, Supraspan, and Reading tests. Other areas, including many measures of basic language skill and nonverbal abilities, were not different between the two groups, highlighting the selective nature of the cognitive profile.[4,8] No measures of long-term memory were included in these studies.

Comparisons with unaffected siblings to control for environmental background have also shown poorer verbal, immediate memory, and academic skills.[9,10] Specifically, children with DMD did poorly on Digit Span, Comprehension, Story Memory, and Token Test when compared with their sibling controls, in addition to having lower reading and arithmetic skills. However, the main finding was that most cognitive areas remained strong. Performance on tests of basic receptive vocabulary, naming, category fluency, and factual knowledge did not differ between the groups, clearly demonstrating that many basic language skills are not compromised. Likewise, children with DMD performed similarly to their siblings on a range of 'higher-order' tests of 'executive function'. Similarly, there was no evidence of visual spatial impairment among the males with DMD, including intact spatial learning and memory. Further, and surprisingly, there was no evidence of poor verbal declarative memory on a list-learning task, even though story recall was deficient. This was contrary to our expectations and seemingly uncharacteristic, given the areas that are compromised in DMD.

The present study builds on previous work. The repeated finding of Verbal deficits (fueled primarily by lowered verbal IQ and poor reading scores) provided the basis for studying language skills in greater depth. Additionally, our unexpected finding of good performance on a verbal memory test made us choose to re-examine the skill with a more detailed measure that could examine learning characteristics more thoroughly.

The current hypothesis to be tested is that rote verbal recall and most language skills will not be impaired, yet tests requiring immediate verbal repetition will be. Data will be examined in three ways: (1) within a large group of children with DMD, (2) comparing males with DMD with their unaffected siblings to control for environmental factors, and (3) comparing males with DMD to males with cerebral palsy (CP) to control for sex, central nervous system involvement, and motor disability.

Method

PARTICIPANTS

DMD probands

Fifty males with DMD were studied. All were between 6 and 14 years of age, in otherwise good general health, spoke English as their primary language, and were willing to participate. Diagnosis of DMD was based on clinical onset of progressive weakness before 5 years of age, elevated serum creatine kinase levels, and either molecular assessment of mutation in the DMD gene or muscle biopsy that was deficient in dystrophin and compatible with DMD.

Probands versus siblings

Where possible, one healthy sibling without DMD living in the same household was also recruited for each proband. Selection criteria included the following: 6 to 16 years old; age within 5 years of the proband's age; in good general health; English as primary language; and willingness to participate. A total of 24 siblings from separate families met these criteria and participated. Twelve control participants were male and 12 participants were female. Ten siblings were older than the proband and 14 participants were younger. Twelve of the 24 sibling pairs had participated in our earlier studies.[9]

DMD versus CP

Because of the presumed contributing effects of having a developmental motor disability on behavior, data from 23 males diagnosed with CP were included as a comparison sample. Children were matched to DMD probands on age and receptive vocabulary scores. All of the children with CP were enrolled in a study examining the cognitive outcome of children born at very-low birthweight (i.e., less than 1500g).[11,12] Each child received a standardized and reliable neurological evaluation[13] from an experienced pediatric neurologist, who made a diagnosis of CP.

The children with CP were between 6 and 8 years old. This restricted age range was due to the design of the low-birthweight study. To ensure comparability of the groups, only probands who were between 6 and 9 years old were selected from the group of 50 males with DMD. Then, each male with DMD was matched to an eligible male with CP. For each pair of males, standard scores on the Peabody Picture Vocabulary Tests – III (PPVT - III)[14] were within five points and age was within 3 years. All participants were ambulatory at the time of participation and all were from separate families. Maternal levels of education were comparable between the groups, with all mothers having completed high school and about one-third of each group having attended some graduate school. Most participants in each group were Caucasian (DMD, 22/23; CP, 17/23), yet the CP group had more African Americans (DMD, 1/23; CP, 6/23).

PROCEDURE

The present study was approved by the Columbia University Institutional Review Board. Before data collection, parents of all participants provided written informed consent and all participants gave verbal assent.

MEASURES

As a measure of receptive vocabulary, participants were individually administered the PPVT-III.[14]

To investigate language skills, all participants received seven subtests (Sentence Structure, Word Structure, Concepts and Directions, Formulated Sentences, Word Classes, Recalling Sentences, and Listening to Paragraphs) from the Clinical Evaluation of Language Fundamentals, 3rd edition (CELF-3).[15] Standardized scaled score conversions were available for all ages on five of the subtests. However, for the other two (Sentence Structure and Word Structure) no scaled score conversions were provided for children more than 8 years old. Data were therefore analyzed as raw scores with age entered as a covariate for the between-group comparisons.

To investigate verbal memory skills, children were administered the California Verbal Learning Test – Children's Version (CVLT-C).[16] The CVLT-C assesses strategies and processes used to learn and recall everyday verbal material. Children learn a 15-item list with items from different semantic categories. The main outcome measure is the total number of items recalled across five trials. Additionally, short-term and long-term recall, recognition, learning strategies, and serial position effects are measured. Because of the large number of data points derived from the CVLT-C data, exploratory analyses were performed on 10 additional indices, and α was adjusted with the Bonferroni correction to 0.005 (e.g., 0.05/10).

STATISTICAL ANALYSIS

DMD versus normative values

To evaluate the overall performance on language and memory measures, raw data from 50 males with DMD were converted to age-scaled standardized scores, and the distribution of scores across the group was examined. To test whether the data were normally distributed, one-sample Kolmogorov–Smirnov tests were run. To determine whether standardized scores differed from the expected population mean, one-sample *t*-tests were run. For those children who were older than 8 years at the time of testing ($n=34$), no scaled scores for two CELF subtests (Word Structure and Sentence Structure) were computed.

Family pairs and disability pairs

Two sets of analyses were done on select groups of children to determine whether performance was comparable on tests of verbal and memory skills. To examine the similarity of the groups, paired *t*-tests (comparing probands versus siblings,

and probands versus children with CP) were calculated for age and PPVT-III scores. For the first set of analyses, socioeconomic and background variables were controlled by design because comparison children were from the same family and household as the probands. For the second set of analyses, sex and physical variables were controlled by design because comparison children were males with motor impairment (CP).

To examine language skills, two two-group by seven-measure multivariate analyses of covariance (MANCOVAs) with age entered as a covariate were run on the raw data from the CELF subtest. Significant main effects were followed by pairwise comparisons.

To examine verbal memory skills, paired *t*-tests were run on the main outcome measure of total recall across the five learning trials. Additional exploratory comparisons of CCVLT indices were made with paired *t*-tests and adjusted α values.

Results

DMD versus normative data

Performance of the 50 children with DMD on the receptive vocabulary test (PPVT-III) was normally distributed (Kolmogrov–Smirnov $Z=0.65$, not significant). Scores ranged from 67 to 137 and the group mean (103.8; [SD 16.1]) did not differ significantly from the population mean (100; [SD 15]; $t=1.28$, not significant; Table I).

On the more complex language tests of the CELF, scores from the 50 males with DMD were also normally distributed on the five subtests for which standardized scores were available for all participants (Table II). When compared with normative data, the children with DMD performed significantly below the expected mean on each of the five subtests (Table II). The range of scores was great, yet aggregate mean values placed the males with DMD 1 to 3 scaled score points below the expected values of 10, with poorest performance observed on Recalling Sentences, Formulated Sentences, and Concepts and Directions. For the two subtests with a limited sample size (e.g., with participants less than 8 years old; $n=16$) mean scaled scores did not differ significantly from normative values.

On the CVLT-C, the data were normally distributed and the 50 males with DMD scored similarly to the standardization sample on the main outcome measure (Table II).

Probands versus siblings

Comparison of 24 probands and their unaffected siblings with the use of paired *t*-tests confirmed that the groups did not differ with regard to age or estimated Verbal IQ (Table I).

The two groups differed significantly in their language skills as demonstrated by performance on the CELF-3 (Table III). The two-group by seven-measure MANCOVA with age entered as a covariate was significant (omnibus $F[7,39])=3.10$, $p=0.01$). Between-group pairwise comparisons indicated differences on only two subtests: Concepts and Directions

Table I: Participant characteristics

Characteristic	*Probands*		*Sibling pairs*			*Disability pairs*		
	Males with DMD (n=50)	*One-sample t statistic*	*Males with DMD (n=24)*	*Control siblings (n=24)*	*Paired t statistic*	*Males with DMD (n=23)*	*Males with CP (n=23)*	*Paired t statistic*
Age range; mean (SD), y:m	6–14 9:4 (2:1)	–	6–12 9:1 (1:8)	6–15 9:11 (2:4)	1.37	6–9 7:8 (1:2)	6–8 6:8 (0:8)	7.09[a]
PPVT SS range; mean (SD)	67–137 103.8 (16.1)	1.65	70–137 105.1 (16.1)	76–145 110.1 (17.2)	1.99	66–124 99.5 (14.3)	68–120 98.0 (14.8)	3.24[a]

[a]Significant finding ($p<0.05$) on between-group paired *t*-tests. DMD, Duchenne muscular dystrophy; PPVT SS, Peabody Picture Vocabulary Test Standard Score. For probands, no significant difference was found between scores on PPVT SS and expected value of 100.

Table II: Duchenne muscular dystrophy probands

Test	*Sample size*	*K–S Z-score*	*Range*	*Mean (SD)*	*t-test*
Sentence Structure	16	–	3–15	9.1 (4.4)	0.78
Concepts and Directions	50	0.96	3–16	7.8 (3.6)	4.74[a]
Word Class	50	0.60	3–14	8.5 (3.1)	3.56[a]
Word Structure	16	–	5–15	8.9 (3.1)	1.47
Formulated Sentences	50	1.0	3–13	7.6 (2.7)	6.59[a]
Recalling Sentences	50	0.70	3–13	7.6 (2.9)	6.02[a]
Listening to Paragraphs	50	0.83	3–14	8.8 (3.2)	2.77[a]
CVLT-C Trials 1–5	50	0.84	28–74	47.0 (11.19)	1.83

Data are presented as scaled scores on Clinical Evaluations of Language Fundamentals, 3rd edition (CELF-3) and *T* score on California Verbal Learning Test – Children's Version (CVLT-C). Note that data for two subtests, Sentence Structure and Word Structure, do not represent full samples because scaled scores were not available for all participants because of age constraints for score conversion. K–S, Kolmogorov–Smirnov test of normal distribution. One-sample *t*-tests were run comparing with expected values of 10 on CELF-3 tests and 50 on CVLT-C. [a]Significant finding ($p<0.05$).

(mean difference=4.23, $F[1,47]=7.13$, $p=0.011$) and Recalling Sentences (mean difference=11.40, $F[1,47]=8.72$, $p=0.005$).

No difference was found between the two groups on verbal list learning (Table IV). The males with DMD and their siblings performed comparably on the CVLT-C main outcome measure, as well as across all the exploratory indices of recall and learning.

DMD VERSUS CP

Despite matching the pairs of DMD and CP males to be within 3 years of age and within 5 points on the PPVT-IIII standard score, comparison of the two groups using paired *t*-tests indicated that the groups differed, yet the actual group differences were slight (Table I). As a group, the children with DMD were 1 year older and had mean receptive vocabulary scores that were only 1.5 standard points higher than the children with CP (PPVT-III standard score: DMD, mean 99.5 [SD 14]; CP, mean 98 [SD 15]).

The DMD and CP groups differed significantly in their language skills as demonstrated by performance on the CELF-3 (Table III). The two-group by seven-measure MANCOVA with age entered as a covariate was significant (omnibus $F[7,37]=3.43$, $p=0.006$). Only one pairwise between-group difference was significant: Recalling Sentences (mean difference=14.97, $F[1,45]=10.63$, $p=0.002$); children with DMD scored below the children with CP.

No difference in memory was found between the two groups on the CVLT-C (Table V). The males with DMD performed comparably to their siblings and the males with CP on the main outcome measure of recall and across all the additional CVLT-C indices.

Discussion

The results of the present study more thoroughly characterize the selectivity of verbal skill deficits among children with DMD. Although language skills in the group with DMD were depressed relative to the normative sample, when the participants with DMD are compared with control participants of comparable age, receptive vocabulary, and either family background or physical impairment, most language skills do not differ between the groups. On an array of complex language skills, including grammar acquisition and use, language production, verbal reasoning, and grasping relations among verbal concepts, the participants with DMD performed as well as their comparison groups. Further, on an array of verbal memory measures, including short-term and long-term recall, learning slope and recognition memory,

Table III: CELF-3[15] group comparisons

Test	*Sibling pairs (n=24) F(7,39)=3.10[a]*			*Disability pairs (n=23) F(7,37)=0.43[a]*		
	Mean difference	*SEM*	*Univariate F(1,47)*	*Mean difference*	*SEM*	*Univariate F(1,45)*
Sentence Structure	0.20	0.50	0.15	0.18	1.16	0.02
Concepts and Directions	4.23	1.58	7.13[a]	3.72	2.46	2.28
Word Class	1.03	1.47	0.49	0.74	2.11	0.12
Word Structure	1.54	1.57	0.95	0.98	1.61	0.38
Formulated Sentences	4.88	2.51	3.76	4.41	2.76	2.55
Recalling Sentences	11.40	3.86	8.72[a]	14.97	4.59	10.63[a]
Listening to Paragraphs	0.93	0.61	2.34	0.41	0.63	0.41

[a]Significant finding ($p<0.05$). Data are presented as group difference of adjusted marginal means for raw scores on Clinical Evaluations of Language Fundamentals, 3rd edition (CELF-3). SEM, standard error of mean.

Table IV: CVLT-C[16] group comparisons

Test	*Sibling pairs*			*Disability pairs*		
	Males with DMD (n=24)	*Control siblings (n=24)*	*Paired t statistic*	*Males with DMD (n=23)*	*Males with CP (n=23)*	*Paired t statistic*
Trials 1–5	51.35 (12.50)	52.10 (11.86)	0.29	47.48 (10.85)	45.26 (12.31)	0.74
Trial 1						
Recall	0.30 (1.21)	0.28 (0.95)	0.10	–0.15 (1.11)	–0.19 (0.97)	0.21
Long Delay	–0.10 (1.09)	0.25 (0.80)	1.25	–0.57 (1.20)	–0.98 (1.20)	1.26
Learning Slope	–0.32 (2.020)	0.25 (0.91)	1.36	0.00 (1.02)	–0.59 (0.97)	2.03
Semantic Clustering	–0.37 (0.96)	–0.08 (1.14)	1.06	0.04 (1.32)	0.04 (1.62)	0.00
Serial Cluster	0.63 (1.16)	–0.02 (0.91)	1.79	0.35 (1.14)	–0.43 (0.68)	2.91
Primacy Recall	0.37 (1.67)	–0.02 (0.86)	0.92	–0.53 (1.32)	–0.39 (1.36)	0.33
Middle Recall	–0.11 (1.25)	–0.05 (1.11)	0.21	0.39 (1.40)	0.28 (1.15)	0.28
Recency Recall	0.23 (0.94)	0.04 (0.93)	0.67	0.18 (1.12)	0.35 (1.31)	0.43
Recognition	0.43 (0.82)	0.25 (0.79)	0.70	0.13 (1.34)	–0.19 (1.00)	0.84
Discriminability	0.47 (1.02)	0.42 (0.82)	0.18	0.26 (1.20)	–0.19 (1.43)	1.35

Data are scaled scores on California Verbal Learning Test – Children's Version (CVLT-C) and are presented as mean (SD). Data for main outcome measure, Trials 1–5, are presented as a *T* score. Data for all exploratory analyses are presented as *Z* scores. DMD, Duchenne muscular dystrophy. For exploratory analyses, no paired *t* between-group difference was significant at Bonferroni adjusted α of 0.005.

the children with DMD performed comparably to both the standardization sample and their comparison groups.

The data from 50 children with DMD represent a wide range of ability and have a normal distribution, reflecting the heterogeneity of performance among participants with DMD. The sample was a convenience sample and may not reflect the performance of all children with DMD, yet no exclusionary criteria (other than willingness to participate) were applied to the group. The finding of lowered mean scaled scores of about 1.5 to 2.5 in comparison with normative values on the CELF-3 is similar to that reported when examining Verbal IQ scores among children with DMD.[5] It is notable that when compared to their unaffected siblings or children with CP, the findings are more specific, suggesting a circumscribed area of weakness for males with DMD.

The participants with DMD performed significantly more poorly on the Recalling Sentences subtest of the CELF-3 than either their siblings or the group with CP. That this difference was observed even in the DMD–CP comparison is perhaps most telling, given that the children with CP had lower receptive vocabulary scores than the children with DMD, yet those with DMD still performed significantly more poorly on Recalling Sentences. In the DMD–sibling comparisons, poorer performance was also found on Concepts and Directions. Accurate performance on both tests requires listening to and replicating a specific sequence of verbal information. These data support the hypothesis that children with DMD have compromised immediate recall for increasing spans of verbal information.

The finding that many language skills are intact in children with DMD (when appropriate comparisons are made) is supported by other research. Single-word comprehension has been shown to be strong,[8,9,17] as has single word expression or picture naming,[6,9] although it is lower in younger children with DMD.[18] Some studies have demonstrated impaired verbal fluency,[8,17,19,20] whereas others do not;[6,9] the differences are probably due in part to impaired letter or phonemic fluency and intact category or semantic fluency. Tests of syntactic comprehension have shown compromised skills in some studies[9,17] but not in others[6] (although we have argued that poor performance was due less to not understanding grammatical rules than to the verbal load of the tasks, thus implicating immediate verbal span[9]).

Interestingly, on the verbal memory test, the children with DMD did not have difficulty. The results were conclusive for the main outcome measure; the children's scores did not differ from normative values or either of the comparison groups. Moreover, across the 10 exploratory analyses of scores derived from the CVLT-C, there also were no between-group differences. On indices of short-term, long-term, and recognition recall, as well as learning styles and strategies, there was no evidence of impaired performance when compared with either family or disability-matched controls.

This finding replicates our previous results of intact verbal memory, using a new measure and newly recruited participants. As before when we studied 41 children with DMD compared with 41 sibling controls on a similar verbal learning test, we found no between-group difference.[9] These results are in apparent contrast to two published studies that concluded that children with DMD had memory deficits.[19,20] Wicksell et al.[20] concluded that the DMD group 'performed significantly worse on all aspects of memory' than normal controls, yet careful exploration of their data show that performance on a list-learning task was not different between the groups. Rather, their findings were influenced mainly by the large effects of decreased performance on story memory, comparable to our previous findings.[9,21] Anderson et al.[19] found that lowered IQ scores accounted for the lower overall performance on a memory task but not for the poor recall associated with the first items presented. However, they had no comparison group. Analysis of the present CVLT-C data demonstrate no between-group difference for either the family or disability pairs on recall from the primary, middle, or recent items on the list. Thus, the present data do not replicate the serial position effect. The present data do suggest a trend for the children with DMD to be more prone to recalling items using serial order rather than semantic meaning, which is considered a less efficient and more immature learning strategy. However, these findings did not reach significance.

The finding of intact list learning in DMD is also surprising in light of the anatomical data implicating a role for the hippocampus-mediated memory in DMD. Neuropathological studies have demonstrated that dystrophin isoforms are missing from hippocampal areas.[22,23] Additionally, hippocampal brain slices from the *mdx* mouse (a model for DMD) have been shown to have reduced functional capacity in some situations.[24] Vailliend et al.[25] have offered evidence that long-term potentiation associated with learning is disrupted in the *mdx* mouse, affecting memory consolidation. However, the present data do not support the hypothesis of grossly impaired hippocampal function among the males with DMD and normal intellectual level.

We propose that the present findings offer more support for our theory that children with DMD have limited capacity for verbal span but are not impaired in consolidation or retrieval. In the present study the males with DMD had difficulty on Sentence Recall and Concepts and Directions, whereas our previous work showed them to have difficulty on Digit Span, Comprehension, and Story Memory; however, neither study found impaired declarative memory. According to a model of verbal memory proposed by Baddeley,[26] verbal information is acquired in a phonological loop, rehearsed, and then consolidated with time. We suggest that a diagnosis of DMD somehow constrains the immediate storage capacity of the phonological loop, such that slightly less verbal information can be processed when initially heard. This model allows that children with DMD learn as well as their peers, and can manipulate information or extract relevant details as well as their peers, when they are provided with the opportunity to rehearse the information mentally. However, they may not be as proficient on initial presentation of long statements or instructions, because of limited space in the phonological loop. Missing dystrophin in the synapses of selective brain neurons may make it harder to process large verbal loads. The consequences of such impairment could be wide ranging, interfering with both early language acquisition (and expression) and academic achievement.[10] Moreover, such an impairment could account for the lower Verbal IQ scores on tests that have structured administration guidelines and do not permit the repetition of instructions. Nonetheless, the remediation for such an impairment may be relatively straightforward: speaking more simply, using shorter sentences, repeating information, and presenting information with contextual cues or visual stimuli may all be means of

enhancing the learning and life of a child with DMD.

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List of abbreviations

CELF-3	Clinical Evaluation of Language Fundamentals, 3rd edn.
CVLT-C	California Verbal Learning Test for Children
DMD	Duchenne muscular dystrophy
K–S	Kolmogorov–Smirnov
MANCOVA	Multivariate analysis of covariance
PPVT–III	Peabody Picture Vocabulary Test, 3rd edn.