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Selective deficits in verbal working memory associated with a known genetic etiology: The neuropsychological profile of Duchenne muscular dystrophy

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Abstract

Forty-one boys diagnosed with Duchenne muscular dystrophy (DMD) were each compared to an unaffected sibling on a battery of neuropsychological tests. Verbal, visuospatial, attention/memory, abstract thinking, and academic achievement skills were tested. Results indicated the boys with DMD performed similarly to their siblings on the majority of measures, indicating intact verbal, visuospatial, long-term memory, and abstract skills. However, the DMD group did significantly more poorly than their siblings on specific measures of story recall, digit span, and auditory comprehension, as well as in all areas of academic achievement (reading, writing, and math). This profile indicates that verbal working memory skills are selectively impaired in DMD, and that that likely contributes to limited academic achievement. The association between the known impact of the genetic mutation on the development of the central nervous system and boys' cognitive profile is discussed.

Keywords

Duchenne muscular dystrophy; Cognitive profile; Dystrophin; Developmental disability; Working memory

INTRODUCTION

Developmental disorders of known genetic etiology offer models for the study of the development of brain–behavior relationships. Subjects can be grouped according to a specific genetic state, and similarities in their shared behavioral phenotype can be inferred to be related to their known underlying etiology. Group differences between those subjects with and without the genetic trait of interest can be established. This “bottom-up” approach has been useful in

characterizing neuropsychological profiles associated with disorders such as Fragile X Syndrome and Williams Syndrome, where select areas of cognitive function have been shown to be preferentially impaired. The current study uses this technique to study the cognitive profile of nonmentally retarded children who have been diagnosed with Duchenne Muscular Dystrophy (DMD).

DMD is known mainly as a genetic disease of muscle, although it also has developmental consequences on the central nervous system. DMD is caused by a mutation of a gene on the X chromosome (Koenig et al., 1987). It occurs in about one in 3200 boys and results in progressive muscular weakness (Emery, 1992). DMD is the most common fatal childhood inherited disorder, and affected individuals rarely live past their mid-twenties. Boys with DMD are also known to be at increased risk of mental retardation, although the majority of boys with DMD are not mentally retarded. There is tremendous individual variation in general intellectual function across affected boys; and, as a group, their mean IQ is about one standard deviation lower than the general population (Bushby et al., 1995; Michalak et al., 1997; Ogasawara, 1989; Rapaport et al., 1991). Notably, boys with DMD have significantly lower Verbal IQ (VIQ) scores than Performance IQ (PIQ) scores (Billard et al., 1992; Dorman et al., 1988; Karagan & Zellweger, 1978; Marsh & Munsat, 1974; Michalak et al., 1997). This has been repeatedly demonstrated and it appears to be a reliable finding across the spectrum of overall intellectual level.

An association between DMD and the development of the central nervous system has only recently become established and provides a potential explanation for the cognitive deficits observed. Specifically, the gene that is mutated in DMD normally makes protein products that localize both to muscle and the central nervous system (as well as other selected tissues). In DMD, however, these protein products are not made (Hoffman & Wang, 1993).

The effects of the mutation on muscle are fairly well characterized (e.g., Michalak & Opas, 1997; Petrof, 1998). The mutation disrupts the gene's production of dystrophin, a protein product. Normally, dystrophin localizes to a glycoprotein complex in the muscle cell membrane and provides structural support (Neve et al., 1996). Without it, muscle cells subject to the force of contraction of normal muscle use develop tears in the cell membrane leading to cellular breakdown and cell death. At birth, boys affected with DMD appear to be physically normal, but as they age they become physically weaker. Most affected males begin to show signs of weakness and have frequent falls by age five, become wheelchair dependent by around age ten, and die (generally due to respiratory failure associated with muscle weakness) by their third decade of life. Females can be carriers and may have a more mild presentation of the disorder.

The effects of the DMD mutation on the brain are not as well understood. In human DMD autopsy tissue and in mouse models of DMD, no brain dystrophin has been found. In normal brain tissue, however, different forms of brain dystrophin have been localized both to specific cell types, as well as to specific brain regions (Gorecki et al., 1992, 1998; Kimura et al., 1997; Lidov et al., 1990; Tian et al., 1996; Uchino et al., 1994a,b). One type is localized specifically to the pyramidal cells of the cerebral cortex and the hippocampus, and does not appear to localize to lower brain structures. Another brain dystrophin has been localized to the Purkinje cells of the cerebellar cortex. Another is specific for glial cells. The different brain dystrophins have some structural overlap with each other and with muscle dystrophin, yet the function of the dystrophin products in the brain is unknown. It is hypothesized that their absence in the brains of boys with DMD is related to the cognitive deficits associated with DMD.

Few studies of brain structure and function in children with DMD have been done. On CT scan, brains of boys with DMD show mild cerebral atrophy (Echenne et al., 1998; Septien et al.,

1991;Yoshioka et al., 1980). Abnormal EEGs have been recorded in some, but not all patients tested (Kozicka et al., 1971). Altered metabolite ratios have been noted in both brains and muscle of boys with DMD using phosphorus-31 magnetic resonance spectroscopy (Tracey et al., 1995). Transcranial stimulation in four boys with DMD suggested possible reduced cortical excitability (Di Lazzaro et al., 1998). Thus, there are no gross brain anomalies in this population, and the level of brain involvement is likely cellular.

The finding of VIQ scores being lower than PIQ scores in boys with DMD is established and has been replicated numerous times. Most studies examining the cognitive profile in DMD have used composite tests of overall function (like IQ scores), and few have examined a range of neuropsychological functions. Nonetheless, some specific cognitive effects have been found to be associated with DMD, although there is some variability across studies. Poor immediate verbal memory has been demonstrated in multiple studies (Anderson et al., 1988;Billard et al., 1992;Karagan & Zellweger, 1978,1980;Marsh et al., 1974;Whelan, 1987), and has been demonstrated across intellectual level (Hinton et al., 2000). Poor attention has also been frequently noted (Cotton et al., 1998;Ogasawara, 1989). Poor long-term verbal memory and poor visual memory have also been observed, yet less consistently (Anderson et al., 1988;Billard et al., 1992;Cotton et al., 1998;Karagan et al., 1980). Additionally, children with DMD have been found to have poor reading skills, and it has been hypothesized to be related to a phonological processing deficit (Billard et al., 1998,1992;Dorman et al., 1988;Leibowitz et al., 1981). Some authors have noted expressive language, and/or fluency, difficulties (Cotton et al., 1998;Karagan et al., 1978;Marsh et al., 1974;Smith et al., 1990;Whelan, 1987). In general, non-verbal skills have appeared to be relative strengths (Anderson et al., 1988;Billard et al., 1992;Whelan, 1987).

Examinations of the cognitive profile associated with DMD have relied on looking at performance within the DMD group (Appleton et al., 1991;Dorman et al., 1988;Karagan & Zellweger, 1978,1980;Leibowitz & Dubowitz, 1981;Marsh & Munsat, 1974), and/or by comparing children with DMD to children with spinal muscular atrophy (SMA), another neuromuscular disorder (Billard et al., 1992,1998;Ogasawara, 1989;Whelan, 1987), and/or by comparison to a group matched on IQ or age characteristics (Anderson et al., 1988;Cotton et al., 1998). Each of these approaches has some methodological limitations. Looking at test performance within the DMD group may be confounded by multiple factors that are associated with the disorder, without being part of the etiology of the disorder, and it may be difficult to tease these out. Further, given the wide variability in general level of function across subjects with DMD, it may be difficult to accurately determine what is a "low" score on a particular test without any standard of reference. Group comparison of DMD boys' performance to that of children with SMA provides a reference to compare to and controls for the effects of physical involvement, but cannot control for numerous familial and environmental factors that might contribute to test performance. Comparison to IQ- or age-matched children does not take into account motor and environmental factors that may contribute to performance. To date, no other group has reported on comparisons of neuropsychological test performance between boys with DMD and their unaffected siblings.

The current study examines neuropsychological function between pairs of boys with DMD and their unaffected sibling. Although innumerable factors likely contribute to test performance, paired comparison of individual probands each matched with an unaffected sibling controls for multiple background factors (both genetic and environmental). In this way, the effect(s) of having a specific mutated gene on the developmental neuropsychology of children with DMD can be tested.

METHODS

Research Participants

Forty-one boys with DMD were studied. All were male, between 6 and 16 years of age, in good general health (other than the diagnosis of DMD), spoke English as their primary language, and were willing to participate. Only participants who had an estimated receptive vocabulary standard score > 70 [as determined by scores on the Peabody Picture Vocabulary Test—Revised (PPVT-R) (Dunn & Dunn, 1981)] were included to ensure the group would be comparable to their unaffected siblings. 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. Participants were recruited from private physicians associated with the Muscular Dystrophy Association clinics in New York, New York [Columbia Presbyterian Medical Center (CPMC) and the Albert Einstein Medical Center]; Atlanta, Georgia (Scottish Rite Children's Medical Center); Hartford, Connecticut (Newington Children's Hospital); and from responses to announcements and mailings sent through the Muscular Dystrophy Association and the Duchenne Parent Project. For those families where more than one boy met the criteria for inclusion, only one affected male was included. The selected proband was chosen randomly; preference for the elder and then the younger boy alternated between families. The ethnic breakdown of this group was: 93% Caucasian, 5% Hispanic, and 2% African American. Twenty of the probands were in a wheelchair at the time of testing.

Forty-one sibling control participants were also recruited. Selection criteria included: one sibling per proband; 6–16 years old; age within 5 years of the proband's age; in good general health; English as primary language; and willingness to participate. Where more than one control participant was available, preference was given first to male gender and then to closeness of age. Twenty-four control participants were male and 17 were female. Twenty-two siblings were older than the proband (13 male and 9 female) and 19 were younger (11 male and 8 female).

Procedures

After giving informed consent, all participants received a battery of neuropsychological tests. Measures were chosen that have a minimal amount of motor demands in order to minimize the potential confounding effects of impaired physical agility. The battery included tests of specific cognitive skills and selected subtests from composite neuropsychological measures. Tests were grouped according to their presumed primary neuropsychological function. Five groups of measures were studied: (1) verbal skills, (2) visuospatial skills, (3) attention/memory skills, (4) abstract/conceptual skills, and (5) academic achievement. For many of the included verbal and visuospatial measures, normative data were not available for older ages. This is due mainly to lack of variability of performance on these tests among older participants; once these skills are learned, most participants are able to reach "ceiling" on the measures. Nevertheless, the measures were included in the test battery to confirm whether or not the participants performed them adequately.

Data were collected at CPMC ($n = 14$ sibling pairs), or in the participants' homes ($n = 27$ sibling pairs). All participants were individually assessed in a quiet room, and each assessment took about 3 h. Participants were given breaks as needed. Testing was done in English. All tests were scored twice (once by the person who administered them and once by a research assistant who had not had direct contact with the participant) to ensure accuracy of the scored data. Discrepancies were resolved by consensus.

Verbal skills—Tests of specific verbal cognitive processes included: Wepman Auditory Discrimination Test (Wepman & Reynolds, 1987), Boston Naming Test (Kaplan et al., 1983), Semantic Verbal Fluency, animal naming (Lezak, 1995), Phonemic Verbal Fluency, “sh” (Lezak, 1995), the Token Test for Children (DiSimoni, 1978), and the Information Subtest from the Wechsler Intelligence Scale for Children-III (WISC-III) (Wechsler, 1991).

Visuospatial skills—Nonmotor tests of visuospatial skills included: Ravens Colored Matrices (Raven et al., 1990), the Gestalt Closure Sub-test from the Kaufman Assessment Battery for Children (K-ABC) (Kaufman & Kaufman, 1983), the Picture Completion Subtest from the WISC-III (Wechsler, 1991), and the Spatial Relations Subtest from the Woodcock-Johnson (WJ) cognitive battery (Woodcock & Johnson, 1977).

Attention/memory—Tests of attention and memory included: Verbal Learning, Visual Learning, Picture Memory and Story Recall Sub-tests from the Wide Range Assessment of Memory and Learning (WRAML) (Sheslow & Adams, 1990), and the Digit Span Subtest from the WISC-III (Wechsler, 1991).

Abstract/conceptual skills—Tests of “higher order” cognitive skills included: the Comprehension and Similarities Subtests from the WISC-III (Wechsler, 1991) and the Children’s Category Test (Boll, 1992).

Academic achievement—Selected tests of reading, (Letter-Word Identification, Word Attack, Passage Comprehension) writing, (Dictation) and math (Applied Problems, Calculation) were administered from the Woodcock-Johnson (WJ) Achievement Battery (Woodcock & Johnson, 1977).

Data Analysis

Individual paired *t* tests were calculated for age, grade, and PPVT-R standard scores to ensure similarity of the groups. Alpha was set at .05. The PPVT-R was included as a measure of vocabulary and single word comprehension, and a general estimate of basic level of verbal function. Socioeconomic and background variables did not require statistical control because participants were from the same family and household.

To investigate whether any of the general neuropsychological areas differed between the proband and sibling control groups, group by measure multivariate analyses of variance (MANOVA) were run. Because the sibling group included girls as well as boys, gender was included as a covariate in all of the area analyses. For the verbal and visuospatial area group comparisons, age was also entered as a covariate because for many of the measures standard scores are not available, so raw data were analyzed. For the attention/memory, conceptualization/executive function, and academic achievement group comparisons, standardized scores were analyzed.

Multiple paired *t* tests were also run on each measure to ensure that comparisons were made between participants within a family. The Bonferroni correction was applied to set an alpha that was appropriate for the large number of individual analyses. For each test, alpha was stringently set at .003, taking into account all of the 20 test measures analyzed (or $.05/20 \sim .003$). Individual *p* values that were equal to or less than .003 were considered to reflect definite between group differences.

RESULTS

Description of Sample

Demographic information for the different participant groups is presented in Table 1. Comparison of the proband and matched sibling groups using paired *t* tests confirmed that the groups did not differ with respect to age, grade, or single word comprehension.

Figure 1 shows the distribution of PPVT-R scores for both probands and their siblings. For inclusion in the current study, only participants who scored above a standard score of 70 were chosen, to ensure comparability of the two groups on other more demanding cognitive tests. As such, the distribution of probands scores is not intended to represent the DMD population distribution. Further, the likelihood of finding significant between-group differences due solely to general level of function is diminished, and the possibility of finding between-group differences in selective cognitive skills is enhanced.

Note that the sibling scores are skewed toward the higher end of the distribution, likely reflecting some sample bias. Sample bias may be due to recruitment procedures, as only probands who had unaffected siblings were included (which may be a select group), and families who agree to participate in studies often reflect higher socioeconomic and educational backgrounds than the general population.

Description of Test Performance

Neuropsychological test performance data and between-group comparisons are presented in Table 2.

Verbal skills—Comparison of the two groups' raw scores on the verbal tests, controlling for gender and age, was not significant (omnibus $F = 1.62$, n.s.) indicating that the DMD boys, as a group, did not perform differently on the verbal measures than their unaffected siblings.

Paired *t* tests of raw scores on the verbal tests indicated that the boys with DMD and their siblings performed similarly on tests of auditory discrimination, naming, semantic and phonemic fluency. On the Token Test for Children, however, the DMD group performed more poorly than their sibling controls ($t = 3.21$, $p \leq .003$).

The DMD group's mean score on the Token Test was lower than that of their siblings, yet was still well within normal limits. Because the Token Test is comprised of five parts, each with an increasingly complex auditory and cognitive demand, *post-hoc* analyses of the individual parts were performed to determine where the boys with DMD were differing from their siblings. Results indicated that the boys with DMD had a trend to make more errors than their siblings on sections four and five ($t = 2.14, 2.34$; $p = .04, .02$, respectively), and their performance was not significantly different from their siblings on the other sections. The finding that the errors were not randomly dispersed across the sections suggests that the boys with DMD are less likely to have generalized hearing and/or attentional deficits. Rather, their performance decreased as the auditory load increased, suggesting that they may have selective difficulty with auditory and/or syntactic comprehension.

Visuospatial skills—Comparison of the two groups' raw scores on the visuospatial tests, controlling for gender and age, was not significant (omnibus $F = 1.18$, n.s.) indicating that the DMD boys, as a group, did not perform differently on the visuospatial measures than their unaffected siblings.

Paired *t* tests of raw scores on the visuospatial tests indicated that the boys with DMD and their siblings performed similarly on tests of gestalt closure, picture completion, and spatial

relations. There was a trend for the DMD group to perform more poorly than their sibling controls on the Ravens Coloured Matrices ($t = 2.79, p = .008$), yet this finding did not meet our stringent criteria of significance.

Attention/memory—Comparison of the two groups' scaled scores on the tests of attention and memory, controlling for gender, was significant (omnibus $F = 4.21, p \leq .003$) indicating that the DMD boys, as a group, do significantly more poorly on tests of attention and memory than their unaffected siblings.

Paired t tests of scaled scores on the attention and memory tests indicated that the boys with DMD and their siblings performed similarly on tests of verbal learning, visual learning, and picture memory. In contrast, the boys with DMD scored significantly more poorly on the tests of story recall ($t = 3.85, p \leq .003$) and digit span ($t = 4.11, p \leq .003$).

Because the visual and verbal learning tests involve four trials, delayed recall and an experimental recognition component, more detailed exploratory analyses were run. No significant differences were found between the DMD group and their siblings on any of the test components.

Because the Digit Span Subtest is comprised of two parts, digits forwards and digits backwards, each with a somewhat different cognitive demand, *post-hoc* analyses of individuals' maximum forward and backward span were performed. Results indicated that the boys with DMD had a significantly shorter backward digit span than their siblings (Probands 3.56 ± 1.76 ; Controls 4.97 ± 2.15 ; $t = 3.46, p \leq .003$). Further, there was a trend for DMD subjects to also have a shorter forward digit span than their siblings (Pro-bands 7.32 ± 1.75 ; Controls 8.34 ± 2.89 ; $t = 2.62, p = .012$).

Abstract/conceptual skills—Comparison of the two groups' scaled scores on the tests of abstract thinking, controlling for gender, was approaching significance (omnibus $F = 3.83, p = .01$) indicating that the DMD boys, as a group, may not have as good conceptual abilities as their siblings.

Paired t tests of scaled scores on the concept formation tests indicated that the boys with DMD and their siblings performed similarly on tests of verbal similarities and non-verbal categorization. However, the boys with DMD scored significantly more poorly on the WISC-III Comprehension Subtest ($t = 3.75, p \leq .003$).

Academic achievement—Comparison of the two groups' standard scores on the tests of academic achievement, controlling for gender, was significant (omnibus $F = 4.98, p \leq .003$) indicating that the DMD boys, as a group, are not as proficient in their academic skills as their siblings.

Paired t tests of scaled scores on the academic tests indicated that the boys with DMD performed significantly more poorly than their siblings on tests of reading ($t = 4.72, p \leq .003$), math ($t = 6.65, p \leq .003$), and writing ($t = 7.01, p \leq .003$).

DISCUSSION

Taken together, these data present convincing evidence of a specific cognitive profile associated with DMD. As a group, boys affected with DMD did significantly more poorly than their unaffected siblings in the areas of attention/memory and academic function. There was also an observed trend for the DMD group to do more poorly on tests of abstract thinking than

their siblings. Notably, on tests of specific verbal and visuospatial skills, the DMD group performed similarly to their sibling controls.

Evaluation of the individual tests that were significantly different between groups gives more insight into the specific nature of the cognitive profile. The boys with DMD had more difficulty than their siblings on Story Memory and Digit Span (particularly backward span) suggesting that their immediate verbal working memory may become taxed more readily than that of their siblings. Interestingly, the DMD group did well on measures of visual and verbal learning, indicating their attention to the material, rote memorization and long-term storage, recall, and recognition abilities are intact. Likewise, the DMD group's performance on the Picture Memory Subtest did not significantly differ from their siblings, suggesting that their visual working memory is stronger than their verbal working memory.

The DMD subjects also performed significantly more poorly than their siblings on the Token Test for Children and the Comprehension Subtest of the WISC-III. Both of these tests require ability to attend to and comprehend relatively complex verbal material. The DMD group had no difficulty on other measures of verbal or conceptual skills, suggesting that their poor performance on the Token and Comprehension Tests cannot be generalized to poor verbal or abstract thinking skills. Further, the pattern of errors on the Token Test was not random, suggesting poor performance is less likely due to inattention than to difficulty with auditory load.

Taken together, the profile of weakness for the DMD group (as determined by their performance on Story Memory, Digit Span, Comprehension and the Token Test) may best be characterized as reflecting poor verbal working memory. In a model of working memory originated by Baddeley and Hitch (1974), verbal working memory has been proposed to be mediated by a phonological loop. The loop is specialized to hold verbal information over a short period of time, and is comprised of a phonological store and a rehearsal process. The model has been studied developmentally by Gathercole and others and has been implicated in language learning (Baddeley et al., 1998). We propose that the nature of the cognitive profile observed in the DMD group may stem from limited space in the phonological store, and possibly poor rehearsal ability. Thus, subjects with DMD had more difficulty than their siblings remembering stories, repeating back digits, and following long verbal statements, because of an inability to hold all of the phonological information in their immediate store.

This might well account for the findings of lower general verbal IQ associated with DMD in other studies. The current data support and extend previous findings of cognitive profiles in DMD, but are more specific. Three published studies comparing boys with DMD to subjects with SMA found evidence of verbal working memory deficits in the DMD group (Billard et al., 1992; Ogasawara, 1989; Whelan, 1987). Whelan reported decreased immediate memory in the DMD group (Whelan, 1987). Ogasawara found boys with DMD to have decreased digit span and supra span (Ogasawara, 1989). And Billard found that subjects with DMD performed more poorly on tests of auditory selective attention, syntactic comprehension, and verbal and visual memory (Billard et al., 1992).

Thus, children with DMD are at increased risk of having poor verbal working memory skills. However, because of the great variability in performance in the DMD group, this does not mean that every child with DMD will have deficient working memory abilities; rather, the likelihood of their having this as an area of cognitive weaknesses is significantly increased. This can be visually demonstrated by looking at performance of individual sibling pairs on two tests—one that does not require verbal working memory and one that does. Standard scores on the Information and Digit Span Subtests for individual DMD subjects paired with their own sibling control are presented in Figure 2. Note that for Figure 2a, there is great variability among

the sibling pairs on the Information Subtest; 16 of the probands performed better than their siblings and 22 performed worse, consistent with random variation (Chi-square = .95, n.s.). In contrast, Figure 2b demonstrates that pairing of standard scores on the Digit Span Subtest indicates that 31 of the probands did worse than their sibling control, which is significantly different from random chance (Chi-square = 16.89, $p = .000$). Yet, most proband's scores still fall within normal limits, and would not be characterized as "deficient." Probands across the IQ range show weaker performance in Digit Span than their unaffected siblings.

The children in the DMD group also performed more poorly than their unaffected siblings on measures of academic achievement in reading, math, and dictation. This has been noted in other studies as well, with reading deficits being the most well characterized. Numerous potential factors may have contributed to the observed between-group differences on the measures of academic achievement. It is possible that the DMD group's poorer performance is a result of potentially different schooling opportunities given to children with physical limitations. However, this explanation seems unlikely to account for the magnitude of the differences, as 18 of the sibling pairs attended the same school (many went to different schools because of their age difference), and the majority of DMD subjects were in regular class placements (71%). The sample of children in the current study all live at home, and most have had access to interventions when necessary. It is also possible that physical limitations may affect test performance in the DMD group. Yet, this explanation also seems unlikely as the measures chosen involved no or few motor demands. Further, DMD subjects have been shown to do more poorly on specific cognitive tests relative to disability-matched peers. Another similar concern is that increased fatigue among boys with DMD may compromise school performance over time. The demands of the school setting, including basic tasks such as writing, become more effortful with increased age for the child with DMD. Yet, cross-sectional analysis of the DMD group's academic achievement scores across grades indicated that there is no consistent drop with age (omnibus $F = 1.11$, n.s.), suggesting that their overall poorer performance is not directly related to age-associated fatigue. Another possibility is that the children's reactive responses to their illness may have impaired their cognitive skills. That is, if the children with DMD are showing greater signs of depression than their unaffected siblings, their cognitive skills may be compromised. However, there was no evidence of increased depressive symptoms in the DMD group. This was determined by comparing responses of the two groups on a self-administered depression questionnaire [the Children's Depression Inventory (Kovacs, 1992)] and on a parent behavior questionnaire [the Achenbach Child Behavior Checklist (Achenbach, 1991)] (Hinton et al., manuscript in preparation).

The most likely explanation for the observed academic difficulties is that the complex demands of academic learning rely heavily on verbal working memory abilities. In boys with DMD, working memory skills are selectively compromised. Specifically, it is hypothesized that brain dystrophin products contribute to the optimal brain function underlying working memory skills. Since the brains of children with DMD have developed without specific dystrophin products, they likely function slightly differently from brains (like those of their siblings) that developed with the dystrophin products. These current data argue that boys with DMD may benefit from early school interventions designed to avoid taxing their verbal working memory skills.

How the dystrophin products normally found in the brain may augment verbal working memory skills is unknown. It has been suggested that they may play a stabilizing role similar to their function in the muscle cell, possibly contributing to the integrity of individual synapses. Dystrophin products localized to neurons are only found in the soma and dendrites (not the axon) and tend to aggregate at the postsynaptic densities, suggesting a possible role in synaptic function (Dorbani-Mamine et al., 1998; Jancsik & Hajos, 1998; Kim et al., 1992; Lidov et al., 1990; Uchino et al., 1994a). Further, dystrophin products in the central nervous system are

found more in the cerebral and cerebellar cortices than in lower brain structures (Gorecki et al., 1998,1992;Kimura et al., 1997;Lidov et al., 1990;Tian et al., 1996;Uchino et al., 1994a,b), and various theories of the neuroanatomical basis of working memory and/or attention have localized these abilities to cortical areas (Baddeley, 1986;Goldman-Rakic, 1988;Mesulam, 1990;Posner & Peterson, 1990). Future neurobiological work examining the role of dystrophin in the development of the brain may offer greater insight into the neurological basis of verbal working memory.

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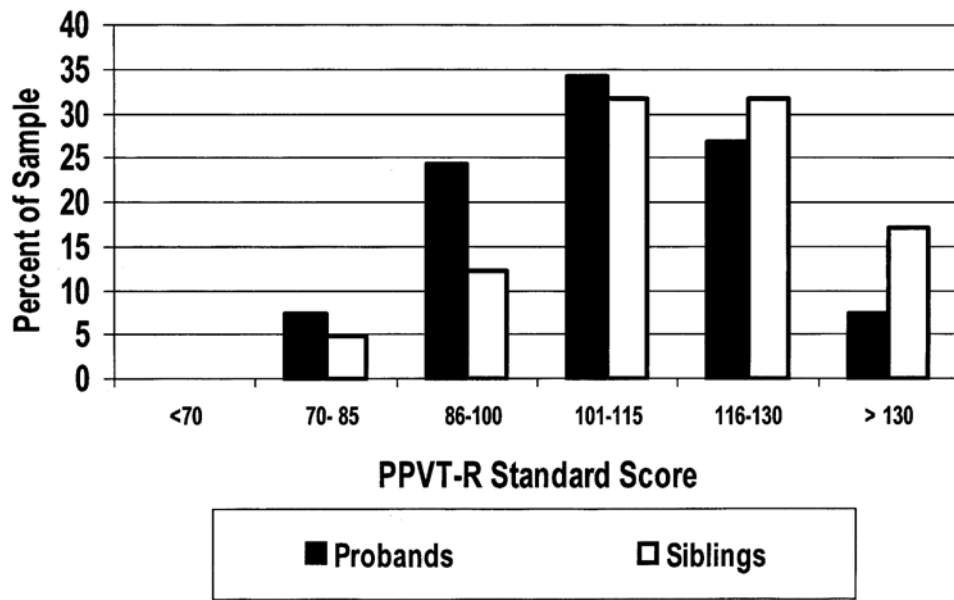


Fig 1. Distribution of proband and sibling scores on the PPVT-R. Only participants with standard scores > 70 were included in this study to ensure a minimum vocabulary.

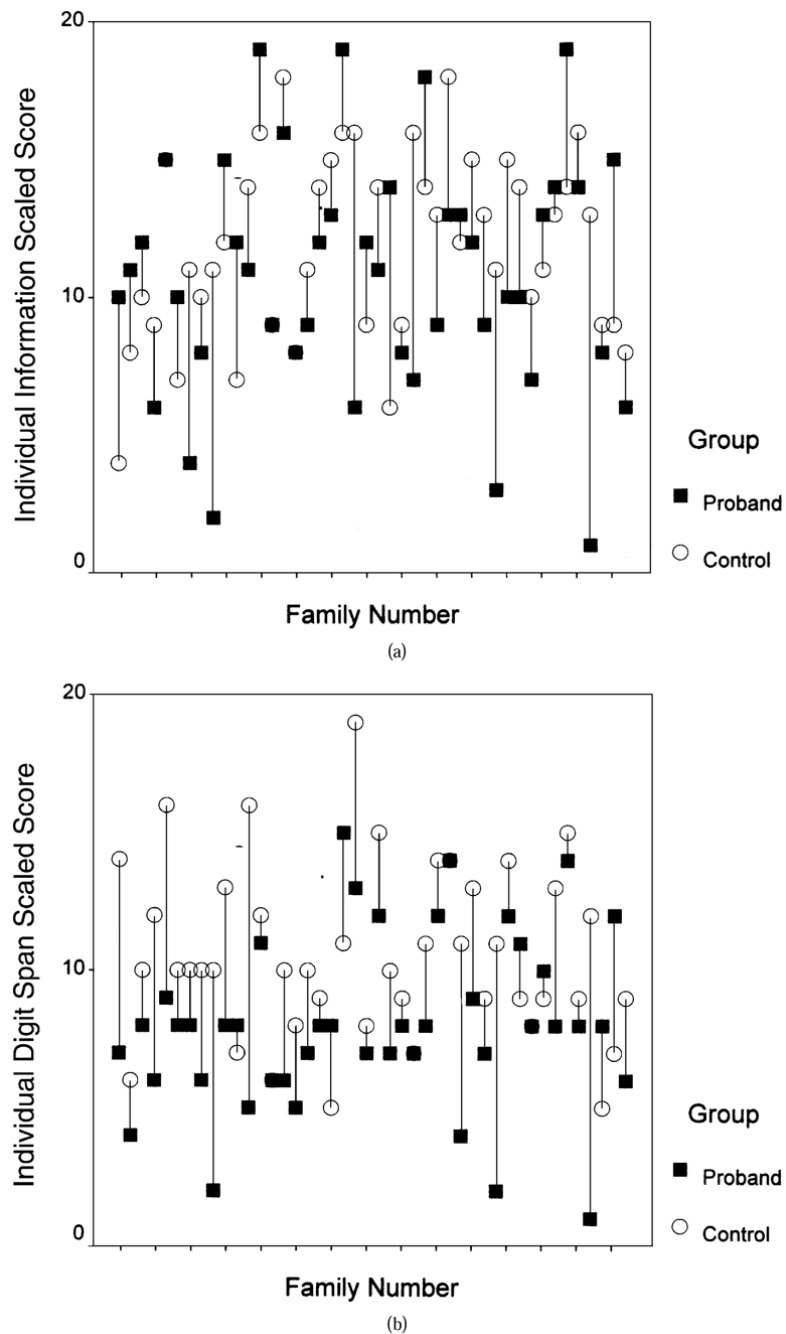


Fig 2. (a,b) Scaled scores on the WISC-III Information and Digit Span Subtests for individual DMD subjects each paired with his own sibling control. Note that for Figure 2a there is great variability among sibling pairs on the Information subtest, while Figure 2b demonstrates on the Digit Span Subtest the majority of probands did worse than their siblings, yet still scored within normal limits.

Table 1

Subject characteristics

41 Matched pairs	Proband Mean \pm SD	Sibling Mean \pm SD	Statistic^a
Age	9.85 \pm 2.12	10.45 \pm 3.19	$t = 1.25$, n.s.
Grade	4.27 \pm 2.36	5.17 \pm 3.23	$t = 1.44$, n.s.
PPVT standard score	108.73 \pm 16.79	113.39 \pm 17.69	$t = 1.87$, n.s.

^a n.s.: not significant.

Table 2

Specific skills

Test	Proband Mean \pm SD	Sibling Mean \pm SD	Statistic
Verbal skills			$F = 1.16$
Wepman Auditory Discrimination	26.26 \pm 2.32	26.84 \pm 2.26	$t = 1.39$
Semantic Fluency–Animals	17.61 \pm 4.52	18.56 \pm 7.27	$t = 0.81$
Phonemic Fluency–“sh”	4.60 \pm 2.64	5.63 \pm 2.96	$t = 2.01$
Information Scaled Score	11.32 \pm 3.90	11.95 \pm 3.44	$t = 0.96$
Token Test for Children	52.15 \pm 6.36	55.68 \pm 5.02	$t = 3.21^a$
Visuospatial skills			$F = 1.18$
Ravens Coloured Matrices	26.24 \pm 6.34	28.61 \pm 6.36	$t = 2.79$
Gestalt Closure	19.29 \pm 2.57	20.27 \pm 6.15	$t = 0.98$
Picture Completion	17.37 \pm 4.41	19.51 \pm 4.56	$t = 2.63$
Spatial Relations	38.37 \pm 8.21	42.17 \pm 7.56	$t = 2.66$
Attention/memory			$F = 4.21^a$
Verbal Learning	11.17 \pm 3.06	11.55 \pm 2.63	$t = 0.69$
Visual Learning	11.07 \pm 2.90	11.32 \pm 2.56	$t = 0.43$
Story Memory	8.60 \pm 2.78	10.75 \pm 2.54	$t = 3.85^a$
Picture Memory	9.67 \pm 2.90	10.97 \pm 2.54	$t = 2.25$
Digit Span	8.39 \pm 2.90	10.54 \pm 3.23	$t = 4.11^a$
Conceptualization			$F = 3.83$
Similarities	10.88 \pm 2.92	11.34 \pm 3.34	$t = 0.91$
Comprehension	8.66 \pm 3.02	10.98 \pm 3.31	$t = 3.75^a$
Children’s Category Test	47.52 \pm 10.68	51.83 \pm 9.78	$t = 1.87$
Academic achievement			$F = 4.98^a$
Read	95.55 \pm 17.14	106.26 \pm 13.29	$t = 4.72^a$
Math	89.16 \pm 19.03	106.61 \pm 16.74	$t = 6.65^a$
Write	93.08 \pm 18.03	109.42 \pm 15.11	$t = 7.01^a$

^a $p \leq .003$