COGNITIVE SKILLS IN YOUNG BOYS WITH DUCHENNE MUSCULAR DYSTROPHY

By

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A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy,
The City University of New York

2006

UMI Number: 3231986

ProQuest Information and Learning Company
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This manuscript has been read and accepted for the
Graduate Faculty in Psychology in satisfaction of the
dissertation requirements for the degree of Doctor of Philosophy.

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Abstract

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Duchenne muscular dystrophy (DMD) is a genetic disorder that causes progressive, and ultimately fatal, muscular weakness. While known primarily for its devastating motor effects, DMD is also associated with cognitive deficits. These cognitive deficits have been well documented in older children and adolescents with DMD. However, there are little data examining the development of cognitive skills in *young* male children with this disorder. The goal of the current dissertation was to focus directly on the early development of cognitive skills in young boys with DMD. To that end, two studies were conducted. First, early development was assessed indirectly via retrospective parental report in a large sample of children with DMD. Second, cognitive skills were assessed directly in a smaller sample of children with DMD aged three to six. This two-step investigation allowed for the capture of both the global manifestation of early developmental delay and the more detailed explication of cognitive skills as they emerged in young children. In addition to these two research studies, the author presents a hypothesis as to the neural substrates of these cognitive deficits. Many investigators have linked cognitive impairments in DMD to the absence of dystrophin, a protein product which is normally found in multiple tissues throughout the body, but is absent in DMD. The current dissertation advances the hypothesis that it is the absence of

dystrophin in the *cerebellum* which is responsible for the cognitive deficits observed. Specifically, the author contends that brain pathways in the cerebellum (e.g., cerebro-cerebellar loops) which develop without dystrophin may result in altered brain function presenting as cognitive deficits in DMD.

Dedications

This dissertation is dedicated to:

My father,

who instilled in me a love of linguistics, despite my fervent desire to remain uninspired;

My mother,

who eagerly awaited my first words so that we could begin having I-thou conversations;

My in-laws,

who welcomed me as a family member and as a psychologist;

And last but not least, my husband Owen,

If one's name is truly one's destiny (*nomen omen*), then his Hebrew name *Ozer*

(literally, "helper") perfectly captures his role in all of my life's endeavors.

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Introduction

Duchenne muscular dystrophy (DMD) is a genetic disorder caused by a mutation on the X chromosome. DMD is the second most common single gene disorder, occurring in 1/3500 live male births (Emery & Muntoni, 2003). Male children affected with this disease suffer from progressive, and ultimately fatal, muscular weakness. While known primarily for its devastating motor effects, DMD is also associated with cognitive deficits. These cognitive deficits have been studied in older children and adolescents with DMD. However, there are little data examining the development of cognitive skills in *young* male children with this disorder. The current investigation focuses directly on the early development of cognitive skills in young boys with DMD.

The study of the development of cognitive skills in children with a specific genetic disorder offers unique insight into the study of developmental neuropsychology. Typically, children with developmental and behavioral disorders are characterized by clusters of symptoms, often with an unknown etiology. The current investigation offers the inverse: the opportunity to study a group of children with a known genetic etiology, and delineate their early developmental profile. The association of a specific cognitive profile with a known genetic mutation offers the tantalizing possibility that one can reduce neuropsychological differences to the level of the gene. Put differently, DMD presents an opportunity to explore genotype-phenotype relationships using readily available neuropsychological tools.

This investigation employs two methods to explore early cognitive development in children with DMD. First, early development is assessed indirectly (i.e., retrospective parental report) in a large sample of children with DMD. Second, cognitive skills are assessed directly in a smaller sample children aged three to six. This two-step investigation allows for the capture of both the global manifestation of early developmental delay and the more detailed explication of cognitive skills as they emerge in young children. Following the presentation of these two research studies, a third manuscript is included, which presents an innovative approach to understanding the neural substrates of cognition in children with DMD.

Phenotype: Motor presentation

DMD is inherited and present at birth, but it is seldom diagnosed that early. In fact, most children with DMD are not brought to clinical attention until the preschool years (Bushby, Hill, & Steele, 1999). This delay is primarily because, during the first several years of life, skeletal muscle appears to regenerate and compensate for the damage caused by the genetic mutation (Sher, 1990). Eventually, the pace of degeneration outstrips that of regeneration, and children begin to show characteristic symptoms of disease. However, phenotypically, the disease has an insidious onset, and it is not until the disease process has progressed substantially that children begin to show functional deficits.

When finally brought to clinical attention, children with DMD show several hallmarks of the disease (Dubowitz, 1978; Emery et al., 2003). These include frequent falls, difficulty

climbing stairs and abnormalities in gait and posture, such as a waddling or tiptoe gait. Children with this disorder also tend to have difficulty running, jumping, or rising from a sitting position. In particular, boys with DMD display a very characteristic pattern of rising from a prone position; this specific compensatory maneuver was described by the physician William R. Gowers (1879), and has been called the Gower's sign. Boys with DMD also exhibit pseudohypertrophic calves, which look excessively muscular, but are in fact pathognomonic of the disease, resulting from the breakdown of normal muscle and concomitant fatty tissue deposits. Duchenne (1868) wrote that when he first observed the enlarged calves, he did not realize that they were a symptom of disease, rather than health:

> *Je ne prévoyais pas primitivement que cet enfant pût être attaint d'une maladie grave; j'aimais à partager les illusions de la mere qui montrait avec une sorte d'orgueil les membres volumineux de son enfant* (p. 185).
>
> I did not at first perceive that the child had a serious disease. I preferred to share the illusions of the mother who exhibited, with a sort of pride, the large limbs of her child (Brody & Wilkins, 1968) p. 632.

The constellation of symptoms described above generally suggests a diagnosis of muscular dystrophy, which is usually verified by grossly elevated serum creatine kinase levels. The diagnosis of DMD is considered to be definitively confirmed by either a muscle biopsy with immunostaining for dystrophin (which, in the case of DMD, would evidence a complete lack of dystrophin) or a DNA analysis (which would reveal a mutation in the gene for dystrophin). Dystrophin, a protein product normally manufactured for use in multiple tissues throughout the body, has a special role in muscle fibers. Present at the neuromuscular juncture, it is responsible for the structural integrity of the muscle fiber. The absence of dystrophin in skeletal muscle results in the

progressive course of DMD, as the muscles of affected individuals grow weaker over time (for a review, see Blake, Weir, Newey, & Davies, 2002).

Once a definitive diagnosis of DMD has been confirmed, the motor trajectory of the disease is well-known. It begins in infancy, when children with this disorder fail to achieve motor milestones, progressing rapidly through childhood and adolescence, at which point children are generally confined to a wheelchair, and finally young adulthood, when individuals with DMD ultimately succumb to cardiac and respiratory complications.

Despite promising medical advances that have succeeded in lengthening the life span of children with DMD, there is still no cure. Further, for many children recognition of the disorder occurs well after significant muscle damage has occurred, thus hindering earlier intervention. Interestingly, in some cases delayed *language* milestones – not motor milestones – may be the earliest signs of DMD that give rise to clinical concern. Unfortunately, those early indications of DMD often go unnoticed, because most clinicians still do not associate early language impairment with DMD (Mohamed, Appleton, & Nicolaides, 2000). Indeed, with the exception of several case studies (Essex & Roper, 2001; Kaplan, Osborne, & Elias, 1986), this link has never been studied systematically. Given the ubiquitous screening for general milestone attainment, determining how children with DMD present from a cognitive perspective may provide a promising avenue for improving the likelihood of early diagnosis and intervention.

Phenotype: Cognitive presentation

In contrast to the studies which have documented the inevitable decline of motor function in children with DMD, there have been no "natural progression" studies to document the developmental trajectory of cognitive functioning in young children with this disorder. More importantly, there are limited data on cognitive functioning in young children with DMD, especially during the preschool years. Much of the data currently available documents cognitive deficits only in older groups of children and adolescents with this disease. While valuable, these data are of limited prognostic use, and do not inform our knowledge of possible early therapeutic interventions in this population.

Recent meta-analyses by Cotton and colleagues (Cotton, Voudouris, & Greenwood, 2001; Cotton, Voudouris, & Greenwood, 2005) have provided some of the most definitive data to date regarding the cognitive phenotype of older children and adolescents with DMD. Based on their analyses of 32 studies (N=1224), Cotton et al. (2001) concluded that children with DMD are at an increased risk for mental retardation and cognitive deficits; approximately 35% meet criteria for mental retardation. The mean full-scale IQ in the DMD population is 80.2, with a normal distribution. There is a modest but statistically significant discrepancy between the mean Verbal (80.4) and Performance (85.4) intelligence quotients. A further cross sectional analysis of the data (2005) revealed that neither the full-scale IQ scores nor performance IQ scores change with age, even though functional mobility decreases with age. Verbal IQ scores, however, do change with age; the data suggest verbal IQ scores improve linearly with age. There is also some indication in the cross-sectional data of generalized verbal

deficits in younger children as compared to older children, as approximately 40% of the younger children had a VIQ less than or equal to 70, while only 13% of the older adolescents had a VIQ less than or equal to 70 (Cotton et al., 2005).

Based upon the above-described analyses, IQ appears to be normally distributed among individuals with DMD, but the curve is shifted downward. Furthermore, there appears to be evidence to suggest that verbal skills are preferentially affected in young children with DMD, and that verbal skills may improve over time. This stands in stark contrast to the progressive deterioration of the muscular aspect of this disease. While intriguing, it is important to note that these data are based on cross sectional analysis of intelligence scale scores (e.g., Wechsler Intelligence Scales, Stanford-Binet Intelligence Scales) and as such only provide gross estimations of the cognitive phenotype.

Current research, utilizing more specific neuropsychological testing, has focused further on the nature of these verbal deficits. Older children with DMD appear to have difficulty on tests which require immediate repetition of a string of verbal material. For example, deficits have been noted on tests of story recall (Billard et al., 1992; Hinton, De Vivo, Nereo, Goldstein, & Stern, 2000; Hinton, De Vivo, Nereo, Goldstein, & Stern, 2001; Wicksell, Kihlgren, Melin, & Eeg-Olofsson, 2004), sentence repetition (Billard et al., 1992; Hinton, Fee, Goldstein, & De Vivo, 2006), and recall of digits (Billard, Gillet, Barthez, Hommet, & Bertrand, 1998; Hinton et al., 2000; Hinton et al., 2001; Ogasawara, 1989; Ogasawara, 1989; Wicksell et al., 2004). Indeed, one of the most consistent findings when investigating cognition in children with DMD is that scores on the Digit

Span subtest of the Wechsler Intelligence Scales (WIS) are depressed (Anderson, Routh, & Ionasescu, 1988; Billard et al., 1998; Dorman, Hurley, & D'Avignon, 1988; Hinton et al., 2000; Hinton, De Vivo, Fee, Goldstein, & Stern, 2004; Sollee, Latham, Kindlon, & Bresnan, 1985; Ogasawara, 1989; Whelan, 1987; Wicksell et al., 2004). This finding remains consistent regardless of whether children with DMD are compared to normal controls, their siblings, or children with other degenerative muscle diseases. These deficits cannot be attributed to more general delays in the acquisition of language skills, as other areas of language and memory are generally intact (Hinton et al., 2001; Hinton et al., 2006). Moreover, the deficits in Digit Span and Story Memory appear across all intellectual levels (Hinton et al., 2000), while other areas of cognition are generally spared (Hinton et al., 2001). As such, we have identified a specific, circumscribed verbal deficit in children and adolescents with DMD, and called it "limited verbal span." We have hypothesized that it is the core cognitive deficit in DMD, and is responsible for some of the impairments seen in phonological awareness, reading, writing, and arithmetic, which also are found in children with DMD (Billard et al., 1992; Dorman et al., 1988; Hinton et al., 2001; Hinton et al., 2004; Leibowitz & Dubowitz, 1981; Worden & Vignos, 1962).

In contrast to the data regarding verbal deficits in older children and adolescents with DMD, there is relatively little information available regarding early development of language in DMD. This is due, in part, to the difficulty inherent in recruiting a sample of children with a disease that is often not recognized until the preschool years. The majority of studies documenting early verbal impairment consist of a wide age-range of

children (e.g., ages 6-16), with the majority of children age seven and older. For example, the youngest group in Cotton's meta-analysis had a mean age of 7 years, 5 months, and a standard deviation of 1 year, 5 months (Cotton et al., 2005). As such, Cotton and colleagues were not able to describe any changes in verbal skills in young children during crucial time periods in the development of their language abilities.

One of the few published data sets on young boys with DMD (under the age of 72 months) is by Smith and colleagues (1990). The sample was comprised of 33 British children with DMD and normal, gender- and age-matched controls. Compared to controls, children with DMD exhibited generalized developmental delay, with severe deficits in motor and speech skills. Smith et al. also reported the presence of behavioral problems in the DMD group only. These data are somewhat at odds with the specificity of findings in older children. They suggest that in younger children with DMD, there may be early generalized developmental delays with concomitant behavioral problems. The hypothesis of generalized delay is also supported by three reported case studies of children (aged 3-4 years) who came to clinical attention for significant language and behavioral problems and were subsequently diagnosed with DMD (Kaplan et al., 1986). Given the paucity of cognitive data among young children with DMD, there is a strong need to replicate the findings and to better characterize the neurocognitive and behavioral profiles of young children diagnosed with DMD. The purpose of this dissertation is to obtain and analyze some much-needed data regarding this population.

Genotype: Genes and dystrophin

At 3000 kb in length, the Duchenne gene is one of the largest genes in the human body, and particularly susceptible to mutation (Koenig et al., 1987). The genetic mutation responsible for DMD disrupts the production of dystrophin, a protein product named for its role in dystrophy (Hoffman, Brown, & Kunkel, 1987). As mentioned previously, dystrophin is normally found in the neuromuscular junction of the skeletal muscle fiber and ensures the structural integrity of the muscle. It is the absence of dystrophin in the skeletal muscle that causes the phenotypical presentation of progressive muscular weakness. However, dystrophin is normally present in multiple tissues throughout the body, including the central nervous system, and in DMD its deficiency is not limited to skeletal muscle tissue. Studies have documented the absence of dystrophin in the cerebral and cerebellar cortices, providing a neural basis for the cognitive deficits in DMD.

There are preliminary data to indicate both structural and functional abnormalities in the brains of individuals with DMD (for review, see Anderson, Head, Rae, & Morley, 2002). On the structural level, CT and MRI studies have documented mild atrophy in children and adolescents with DMD, generally consisting of white matter atrophy (Al-Qudah, Kobayashi, Chuang, Dennis, & Ray, 1990; Echenne et al., 1986). Autopsy studies have also revealed structural abnormalities at the cellular level (Rosman, 1970). These findings were not limited only to mentally retarded individuals with DMD. Thus, there is evidence of structural abnormalities, both at the gross level and at the microscopic level even among individuals with DMD of normal intellectual level.

Some of the most valuable structural data has come from histochemical studies using the *mdx* mouse, a mouse model of DMD. These studies have helped to localize both the cell type and cell area where dystrophin is normally present. In the central nervous system, dystrophin appears to be localized to neurons in the cerebral cortex and the hippocampus, and to the Purkinje cells of the cerebellum (Górecki et al., 1992; Górecki, £ukasiuk, Szklarczyk, & Kaczmarek, 1998; Jung, Pons, Leger, Aunis, & Rendon, 1991; Lidov, Byers, Watkins, & Kunkel, 1990; Lidov, Byers, & Kunkel, 1993; Kimura et al., 1997). Furthermore, staining for dystrophin indicates it is most heavily localized to synaptic areas and it is not found in axonal areas, prompting speculation about its possible role in synaptic transmission. Dystrophin products have been found during normal early brain development, suggesting they may play an important role in neuronal differentiation, migration, synapse formation and/or pruning (Chelly et al., 1990; Kim, Wu, Xu, & Black, 1992; Morris, Simmons, & thi Man, 1995; Sarig et al., 1999). Development of a brain without dystrophin may lead to a brain that is "wired" differently from most, and may in turn lead to alterations in cognitive and behavioral development.

Abnormalities in brain function have been detected in humans and animals with DMD. In children and adolescents with this disorder, functional imaging studies have indicated altered or reduced glucose metabolism in areas normally rich in dystrophin, especially the cerebellum (Lee et al., 2002). In mice, altered glucose metabolism has also been found in the brain (Rae et al., 2002). Furthermore, studies have demonstrated that slices of hippocampal pyramidal neurons from *mdx* mice are more sensitive to hypoxic damage

than slices from control mice, indicating altered function in recovery after insult (Mehler, Haas, Kessler, & Stanton, 1992). Thus, in humans with DMD and in animal models of DMD both hypometabolism and decreased resilience to injury may be functional effects of lack of dystrophin in the brain. These above-mentioned abnormalities in brain structure and function likely underlie the cognitive profile observed in DMD. In mice, lack of dystrophin is associated with poor learning of T-maze or bar pressing tasks (Vaillend, Rendon, Misslin, & Ungerer, 1995). In humans, it is associated with the previously described cognitive deficits.

In sum, brain development lacking dystrophin may result in altered brain function presenting as cognitive deficits in DMD. This hypothesis will be explored in more detail in the third manuscript.

General Summary

The current investigation proposes to study cognitive skills in young boys with a known genetic etiology, DMD. DMD is associated with two phenotypes: progressive motor decline and static (and perhaps even improving) cognitive deficits. In contrast to the motor trajectory, which has been well-characterized, there is a dearth of information regarding the early stages of the cognitive trajectory. This investigation proposes to shed some light on the early development of cognition in young children with DMD using two separate methodologies: an indirect larger study, which examines the attainment of developmental milestones in children with DMD, and a smaller, direct and detailed study, which examines specific cognitive skills in preschool-aged children with this disorder. In

addition to furthering our understanding of the cognitive phenotype of DMD, both studies will also provide invaluable clinical data. The first study will determine whether delays in the attainment of non-motor milestones, such as language development, are an important part of the early clinical picture. The second study will assess adaptive behavior and cognitive skills in detail among children with DMD who are still ambulatory and before motor weakness is pronounced. Both studies will focus on language development, in particular, based on the review of research with older children with DMD. These studies will provide invaluable insight into the early consequences of brain development in the absence of dystrophin and will detail the developmental neuropsychology of DMD.

Part One:

Delayed developmental language milestones in children with Duchenne Muscular Dystrophy

Delayed developmental language milestones in children with Duchenne Muscular Dystrophy

Abstract

Objectives: To document the attainment of developmental milestones in children with Duchenne muscular dystrophy (DMD) and determine whether early delays are associated with later performance on measures of cognition.

Methods: Retrospective parental report was utilized to document the acquisition of ten common developmental milestones in children with DMD (N=130) and their unaffected siblings (N=59). Children completed tests of cognitive functioning.

Results: Parents rated children with DMD as delayed on achieving both language and motor milestones more frequently than their unaffected siblings. Furthermore, those children with DMD who were rated as late *talkers* or late *walkers* performed more poorly on tests of cognitive function than their on-time peers.

Conclusions: In addition to the commonly reported delays in motor milestones, the current study documents delays in the acquisition of language milestones as well. These early delays are associated with significant impairments in later cognitive functioning.

Keywords: Duchenne muscular dystrophy (DMD), developmental milestones, delay, language, motor, cognition.

Duchenne muscular dystrophy (DMD) is an X-linked disorder which occurs in 1/3500 male births (Emery & Muntoni, 2003). It is known primarily as a disease of the muscle, as children present with progressive muscular weakness. The disease is characterized by a lack of dystrophin, a protein product which is normally found in multiple tissues throughout the body (Chelly et al., 1990; Klamut, Gangopadhyay, Worton, & Ray, 1990; Howard et al., 1998; Kim, Wu, Xu, & Black, 1992; Lederfein et al., 1992; Kimura et al., 1997; Górecki, Łukasiuk, Szklarczyk, & Kaczmarek, 1998). Dystrophin has a stabilizing role in skeletal muscle tissue, and the absence of dystrophin in skeletal muscle causes the progressive course of the illness, as the muscles of affected individuals grow weaker over time (for a review see Blake, Weir, Newey, & Davies, 2002). In addition to progressive muscular weakness, some children present with delays in the acquisition of motor milestones (Dubowitz, 1965; Dubowitz, 1978; Emery et al., 2003). What is not yet known, however, is whether other developmental milestones, particularly early indicators of language acquisition, are also delayed more commonly in DMD than in the general population. These language and cognitive manifestations merit further investigation, particularly because some children may have cognitive symptoms that are more pronounced than their motor symptoms during the early course of the disease (Karagan & Zellweger, 1978; Smith, Sibert, & Harper, 1990). For such children, a better understanding of the language and cognitive symptoms of DMD will likely prove useful in the early detection and diagnosis of the disease.

There is ample evidence of cognitive involvement in DMD, although the presentation is much more variable than the motor symptoms of the illness. On average, the mean IQ in

children with DMD is shifted down one standard deviation from the population mean, and Verbal IQ scores are more compromised than Performance IQ scores (Cotton, Voudouris, & Greenwood, 2001). As a result of the downward shift, a number of children with DMD (approximately 35%) score in the mentally retarded range on IQ tests (Cotton et al., 2001). However, no relationship has been documented between levels of muscular degeneration and cognitive impairment (Allen & Rodgin, 1960; Karagan, 1979; Leibowitz & Dubowitz, 1981; Prosser, Murphy, & Thompson, 1969; Zellweger & Hanson, 1967), nor is there a relationship between creatine kinase levels and cognitive impairment (Karagan, 1979). Cognitive impairments do not worsen over time, and in fact, cross sectional data suggest that performance on verbal IQ tests (but not nonverbal tests) may increase with age (Cotton, Voudouris, & Greenwood, 2005; Sollee, Latham, Kindlon, & Bresnan, 1985).

Investigators have differed as to the exact nature of the verbal deficits found in children with DMD (Anderson, Routh, & Ionasescu, 1988; Billard et al., 1992; Cotton, Crowe, & Voudouris, 1998; Wicksell, Kihlgren, Melin, & Eeg-Olofsson, 2004); however, reports consistently demonstrate poor performance on a test of verbal span in which the child must repeat back a series of numbers from memory (Anderson et al., 1988; Billard et al., 1992; Billard, Gillet, Barthez, Hommet, & Bertrand, 1998; Hinton, De Vivo, Nereo, Goldstein, & Stern, 2001; Hinton, De Vivo, Fee, Goldstein, & Stern, 2004; Whelan, 1987; Ogasawara, 1989; Dorman, Hurley, & D'Avignon, 1988). We have argued that these results can best be characterized as a core deficit of limited verbal span or poor immediate verbal memory skills that interferes with general language acquisition and

academic achievement (Hinton, De Vivo, Nereo, Goldstein, & Stern, 2000; Hinton et al., 2001; Hinton et al., 2004). We have attributed these verbal deficits to the absence of dystrophin in the brains of individuals with DMD (for reviews see Anderson, Head, Rae, & Morley, 2002; Mehler, 2000).

Despite the considerable data attesting to specific verbal deficits in children and adolescents with DMD, few studies have focused on early development (< age 5) in this population (Karagan et al., 1978; Marsh & Munsat, 1974). One notable exception is the paper by Smith and colleagues (Smith et al., 1990). Smith et al. investigated early language and motor development in 33 British children with DMD under the age of six and compared them to age-matched controls. These investigators found that children with DMD exhibited general developmental delay and parents reported an increase in behavioral problems. These findings were not accounted for by differences in socio-economic variables between the two groups. These authors did not report on the attainment of early developmental milestones.

A report published in 1985 documented three children who were referred for language delay between 3 and 4 years of age and were later found to have muscular dystrophy (Kaplan, Osborne, & Elias, 1986). The authors highlighted the need for clinicians to consider DMD in the differential diagnosis of children presenting with verbal impairment. We also have had anecdotal reports that for some families delayed language milestones were the initial signs of DMD that gave rise to clinical concern, but this has never been studied systematically. Given the ubiquitous screening for general milestone

attainment, determining how children with DMD present may aid in the early diagnostic process.

The purpose of the current study, therefore, is to examine reports of early developmental milestones in children with DMD. Parental ratings of "on time" or "delayed" with regard to the attainment of developmental milestones in a large group of children with DMD and their unaffected sibling controls are examined. Additionally, these same children's performance at ages 4 to 14 years on neuropsychological tests is examined to determine whether early developmental milestones are associated with later cognitive functioning. The goals of the current study are (1) to document, through retrospective report, the attainment of ten developmental milestones of a large group of children affected with DMD, (2) to compare attainment of milestones between children with DMD and their unaffected siblings; and (3) to examine among the large group of children with DMD whether reports of early delays are associated with performance on tests of neuropsychological functioning. We hypothesize that children with DMD will be reported as having more early language delays than their unaffected siblings or than expected for the general population. We also hypothesize that evidence of early language delays will be associated with lower scores on cognitive tests administered after age four.

Methods

Participants

One-hundred and thirty children with DMD and fifty-nine unaffected sibling controls participated in a large-scale study investigating cognitive skills in boys with muscular

dystrophy. Diagnosis of muscular dystrophy was based on clinical onset of progressive weakness before five years of age, and either molecular assessment of mutation in the DMD gene, or muscle biopsy that was deficient in dystrophin and compatible with DMD. Siblings were within five years of age of the proband. When more than one comparison child was available, preference was given first to male gender and then to closeness in age. Children with DMD were between the ages of 4 and 14, with a mean age of 9.00 years (SD=2.52), and sibling controls ranged from 3 to 16, with a mean age of 9.85 years (SD=3.61). Approximately one third of the probands (38%) were in a wheelchair at the time of assessment, and none of the sibling controls were wheelchair-bound. Racial composition of the sample was predominantly Caucasian (88%), with an additional 7% reported to be Hispanic, 3% reported to be African-American, and 2% reported to be Indian.

Participants for this study were recruited through the Muscular Dystrophy Association (MDA) clinics of Columbia Presbyterian Hospital, New York and Children's Healthcare of Atlanta at Scottish Rite Children's Medical Center. Additionally, newsletters with a description of the study were sent to Parent Project Muscular Dystrophy (PPMD), regional MDA clinics, and parent support groups. Interested individuals returned the response form directly to the investigator.

This study was approved by the Columbia University and New York Presbyterian Hospital Institutional Review Board, by the Queens College of the City University of

New York Institutional Review Board, and by the Children's Healthcare of Atlanta at Scottish Rite Children's Medical Center Institutional Review Board.

Measures: Parent questionnaires

As part of several ongoing studies, parents completed a developmental milestone questionnaire; they were asked to indicate whether their child was "on-time" or "late" for ten developmental milestones listed. These included when the child first began to: smile, sit, crawl, stand, walk, say single words, construct complete sentences, read, and become bowel and bladder trained. In addition, parents had the option of recording the month at which their child achieved each milestone.

Parents also completed the Child Behavior Checklist (Achenbach, 1991), a 118-item questionnaire which lists a variety of behaviors. Parents were asked to rate the frequency with which their child engaged in these behaviors on a three point scale ("never," "sometimes," or "often/always"). Scores were compared to published norms according to each child's age and a standardized score was computed.

Measures: Children's battery

Children enrolled participated in different neuropsychological studies involving a number of measures of language, memory, and visuo-spatial skills. Measures included in the battery required minimal motor involvement. Some of the test measures have been described in detail elsewhere (Hinton et al., 2001). This paper will report results from two tests used across batteries to ensure the largest sample size: the Peabody Picture

Vocabulary Test – 3rd edition (Dunn & Dunn, 1997) and the Raven's Colored Progressive Matrices (Raven, Raven, & Court, 1993). Both tests were scored twice to ensure consistency; discrepancies were resolved by consensus.

The Peabody Picture Vocabulary Test (PPVT-III) is primarily a measure of receptive vocabulary. Children hear a single word and are required to indicate which of the four pictures on the page most closely corresponds to the word. Children's raw scores are standardized according to age-matched normative values. Scores on the PPVT are strongly correlated with scores on the Wechsler Intelligence Scale for Children – Third Edition (range .82 to .92).

The Raven's Coloured Progressive Matrices (RCPM) is a non-verbal measure of visuo-spatial skills, conceptualization, and reasoning. Children attempt to find the missing piece of the pattern from an array of different puzzle-like choices. The RCPM is also a measure of general intellectual functioning, and scores on the RCPM are associated with the Wechsler Intelligence and Stanford-Binet scales (r=.7) (Spreen & Strauss, 1998).

Procedure

After obtaining written informed consent from the parent and verbal assent from the child, parents completed questionnaires while their children were administered the complete battery of neuropsychological tests. Testing was done in English. Most testing was completed at the Columbia Presbyterian Medical Center. In some cases, however,

children were tested in their home, in a quiet room. The entire battery of tests took approximately three hours, and the children took breaks as necessary.

Analyses

Based upon the retrospective history of early developmental milestones provided by the parents, children were classified as either "on time" or "late" in achieving developmental milestones. In the event that the parent did not indicate whether their child was on time or late, but recorded the month at which their child achieved each milestone, the data were converted to "on-time" or "late" by determining whether the child achieved the milestone within the same period or after 90% of the general population did. Norms for the general population were based on the Denver Developmental Screening Test (Frankenburg & Dodds, 1967), with the exception of bowel and bladder control norms which were extracted from Copeland and Kimmel (Copeland & Kimmel, 1989). In the event that a parent both endorsed "on time" or "late" and recorded the month, preference was given to the on-time/late variable; however, these data were checked for accuracy. Due to the variable manner in which parents responded to items on this questionnaire, the total number of responses for each developmental milestone is different. As such, data are presented as percentages, and the lowest number of responses (n = 130) was used as the total N.

<u>Analysis #1: DMD children only</u>

To determine the percentage of children with DMD (n = 130) reported to be "on time" vs. "late" for each developmental milestone, a frequency count was used.

Analysis #2: DMD vs. Sibling Controls

In order to determine whether the likelihood of delay for each developmental milestone was equivalent between the probands and their siblings, chi-square analyses were performed only on those probands with unaffected siblings controls (n = 59). The null hypothesis predicted an equal likelihood of delay among children with DMD and their siblings as reported by their parents. Alpha was set at .005 in order to account for the multiple comparisons (.05 / 10 = .005).

Analysis #3: DMD children only

In order to determine whether early delay was associated with later cognitive functioning, two variables with the largest chi-square values were chosen: when the child first began to walk and construct complete sentences (hereafter referred to as "walk" and "sentence"). These variables were chosen due to their discriminative ability among the sibling pairs and, for the current analysis, applied to the larger group of DMD probands only. A series of independent sample t-tests were performed among DMD children in order to determine whether delay on the above-mentioned two variables was related to performance on the PPPVT-III, RCPM, and parental report on the CBCL. The null hypotheses were that there would be no differences in test scores between children rated "delayed" or "on time" on early milestones.

Results

Analysis #1: DMD children only

The percentage of children with DMD reported to be “on time” vs. “late” for each developmental milestone can be found in table 1. Data show variable ranges of responses across items. Only 3% of the children with DMD were rated “late” on developing their smile, while 67% were rated “late” on beginning to walk independently. For most items, between 30 and 50 percent of the group were rated “late” (see Table 1).

Analysis #2: DMD vs. Sibling Controls

Results of chi-square analyses revealed that children with DMD were rated as “late” more often than their unaffected siblings on most, but not all, developmental milestones (see table 2). Specifically, parents reported that their children with DMD were more often late in motor milestones such as sitting ($X^2 = 28.37$, $p < .001$), crawling ($X^2 = 40.53$, $p < .001$), standing ($X^2 = 44.79$, $p < .001$) and walking (70% vs. 2%, $X^2 = 52.14$, $p < .001$) than their siblings. Furthermore, a greater percentage of children with DMD than siblings were also rated as delayed on language milestones. More children with DMD were reportedly late in speaking their first word ($X^2 = 24.12$, $p < .001$) and in speaking in full sentences (49% vs. 4%, $X^2 = 29.73$, $p < .001$) than their siblings. No between group differences were observed on other aspects of development, such as when their children first smiled, or when they achieved bowel or bladder control (see Table 2).

Analysis #3: DMD children only

a. Late vs. on-time in constructing complete sentences: Results of independent samples t-tests reveal that children with DMD whose parents rated them as “late” in constructing complete sentences were more likely to perform poorly on

measures of single-word vocabulary [mean (SD): late = 94.29 (22.26), on-time = 107.00 (17.07); t= 3.75, p < .001] and visuo-spatial reasoning [mean (SD): late = 90.87 (25.26), on-time = 101.62 (13.21); t = 3.17, p = .002] than children with DMD who were on time in this regard. There was no significant difference in behavioral difficulties between the two groups of children with DMD.

b. Late vs. on-time in walking: Children with DMD who were rated as delayed on walking performed significantly more poorly on a measure of visuo-spatial reasoning [mean (SD): late = 94.35 (22.08), on-time = 103.07 (12.12); t = 2.38, p = .02]; however, there was no relationship between delayed walking and performance on a measure of single-word vocabulary. Furthermore, children with DMD who rated as delayed on walking did not exhibit later behavioral issues when compared to children with DMD who achieved this milestone on time.

Discussion

Results of the current investigation indicate that children with DMD are more likely than their siblings to be rated as delayed on most language and motor milestones. Consistent with previous reports of motor delay, children with DMD tend to be delayed in sitting, crawling, standing and walking. The current investigation also documented delays in language milestones; children with DMD are more likely than their siblings to exhibit delays in speaking their first word and in constructing sentences. Not all aspects of development were rated as delayed. For example, parents reported that children with DMD and their siblings were equally capable of mastering bladder and bowel control at similar ages. The selectivity of these findings indicates that reports of delay among affected children cannot be attributed solely to a bias in reporting.

The second goal of this study was to examine, in more detail, the relationship between early developmental delay and cognitive functioning among children with DMD. To that end, children with DMD who were rated as delayed in walking and talking were compared, on specific neuropsychological measures, to children with the same diagnosis who had achieved those milestones on time. Measures of vocabulary and visuo-spatial reasoning served as estimates of general intellectual functioning. Results of this investigation revealed that late talkers performed significantly more poorly on these measures of intellectual functioning. It is important to emphasize that these findings, while statistically robust, represented subtle differences in performance. For example, children with DMD who were reported to be late talkers scored slightly below average (mean standardized score of 95) on the test of vocabulary, while those who were on time in learning to speak scored slightly above average (mean standardized score of 107). These findings were statistically significant at the $p < .001$ level. There were no significant differences between the two groups on reports of behavior.

A similar analysis was performed on children who had been rated as delayed in walking; in contrast to late talkers, it was hypothesized that late walkers would not exhibit cognitive delays or behavioral problems. Unexpectedly, however, late walkers did significantly more poorly on the test of reasoning than their on-time peers. While the reason for this finding is unclear, it not uncommon to observe impaired motor skills associated with cognitive disorders (Diamond, 2000). For example, children with specific language impairment often present with poor motor skills (Powell & Bishop,

1992; Sommers, 1988; Bishop, 2002; Hill, Bishop, & Nimmo-Smith, 1998; Hill, 2001). It can be conjectured that the same part of the brain that is responsible for learning coordinated movement (i.e., cerebellum) also contributes to cognitive functioning in this disorder. Tentative support for this hypothesis is offered by a recent PET scan study in which children with DMD exhibited reduced glucose metabolism in areas normally rich in dystrophin, namely, the cerebellum (Lee et al., 2002).

The current study employed retrospective parental report as the primary method of investigating the attainment of developmental milestones in a large group of children with DMD and their siblings. Although the investigators are mindful of the potential drawbacks associated with the use of retrospective parental report in ascertaining timing of developmental milestones (Donoghue & Shakespeare, 1967; Glascoe & Dworkin, 1995; Hart, Bax, & Jenkins, 1978; Majnemer & Rosenblatt, 1994; McGraw & Molloy, 1941; Mednick & Shaffer, 1963; Treharne, 1992; Goldstein, 1985; Ewert & Green, 1957; Pyles, Stolz, & Macfarlane, 1935), several features of the experimental design of the current study serve to increase the likelihood of accurate parental report. The investigators chose to focus on broad categories such as “on-time” and “late” in order to increase the likelihood of accurate parental report. The fact that the control group consisted of siblings also enhanced the investigators’ confidence in the accuracy of parental report, because the accuracy of the parent likely remained consistent between siblings. Indeed, there is substantial support for the hypothesis that most parents are capable of judging whether their child’s development is on par with other children of the same age, even when they are poor, uneducated or lack parenting experience (Glascoe,

1997; Glascoe, 2003; Pulsifer, Hoon, Palmer, Gopalan, & Capute, 1994; Glascoe, 1991; Glascoe et al., 1995; Glascoe, 1997; Glascoe, 2000).

The use of siblings as controls is, in fact, one of the strengths of the current experimental design. This method of control helps account for genetic, familial and socio-economic variables, and, thus, permits detection of subtle neuropsychological deficits unique to children with this disorder. Previously published data have demonstrated subtle, yet statistically robust, differences in neuropsychological test performance between children with DMD and their unaffected siblings (Hinton et al., 2001). Some of the cognitive deficits observed might not ordinarily suggest a need for clinical intervention, but, when compared to their siblings, their significance is highlighted.

To summarize, a significant proportion of children with DMD exhibit delays in language milestones, in addition to the commonly reported delays in motor skills. Our experience with this population indicates that early delays in the acquisition of language are frequently an important part of the early clinical picture for DMD, but they have not yet been consistently documented. To the best of our knowledge, this is the first study to systematically document delayed language milestones in a large group of children with DMD. The current study also found that delayed language milestones, and to a lesser extent delayed motor milestones, are associated with poor later cognitive outcome among children with DMD. These findings are significant for several reasons: Early delays in the development of language and motor skills (i.e., before the onset of significant motor weakness) demonstrate that poor performance on measures of cognition cannot be

attributed solely to muscle fatigue, emotional reactions to DMD, or the loss of educational opportunities due to limited ambulation. Moreover, early delay implicates an underlying central nervous system component to DMD. Finally, the current findings underscore the need for early intervention services in this population. The initiation of early intervention may help limit later learning problems, potentially enhancing the quality of life for a group of children who face adversity in the form of enormous physical and emotional challenges.

Acknowledgments: Sponsored by the NICHD (1R29HD34155-01) and NIMDS and the Muscular Dystrophy Association (PI: V.J. Hinton).

Table 1: Percentage of children with DMD rated as "on time" or "late" for each developmental milestone*

MILESTONE	ON TIME (%)	LATE (%)
Smile	97	3
Sit	64	36
Crawl	47	50
Stand	43	53
Walk	33	67
Speak	62	38
Sentence	57	43
Bowel trained	60	40
Bladder trained	59	40
Read	51	47

*Percentages have been rounded up and may not equal 100% in all cases

Table 2: Comparison of children with DMD and sibling controls on developmental milestones: Percentage late for each milestone as per parental report

MILESTONE	PROBAND: % LATE	CONTROL: % LATE	CHI-SQUARE	P VALUE
Smile	3%	2%	.34	n.s.
Sit	38%	0%	28.37	$p < .001$
Crawl	60%	6%	40.53	$p < .001$
Stand	56%	0%	44.79	$p < .001$
Walk	70%	2%	52.14	$p < .001$
Speak	42%	4%	24.12	$p < .001$
Sentence	49%	4%	29.73	$p < .001$
Bowel trained	28%	8%	7.77	n.s.
Bladder trained	25%	10%	5.97	n.s.
Read	94%	6%	25.89	$p < .001$

Key: n.s. = not significant

Part Two:

Global cognitive delays in young children with Duchenne muscular dystrophy (DMD)

Abstract

Objectives: To examine adaptive behavior and cognitive skills in young children with Duchenne Muscular Dystrophy (DMD), a genetic disorder that causes progressive muscular weakness and concomitant cognitive deficits. Previous studies have documented specific language deficits in older children with DMD, but there are limited data on younger children. *Methods:* Thirty-one children with DMD who were between three and six years old and 20 unaffected family control children were recruited. Parents completed questionnaires relating to development and adaptive functioning, while children completed neuropsychological testing. *Results:* Paired t-tests indicate that children with DMD are rated as delayed relative to familial controls on measures of adaptive functioning, as assessed by the Vineland Adaptive Behavior Scales. Furthermore, children with DMD exhibit impairments on multiple measures of cognition, including measures of receptive language, expressive language, visuo-spatial skills, fine-motor skills, and attention/memory skills. Across all domains examined, the young children with DMD performed more poorly than their familial controls. *Discussion:* Young children with DMD exhibit deficits in multiple areas of functioning. These deficits are more generalized than those reported in older children with this disorder. Dystrophin, a missing protein product, is hypothesized to be responsible for these cognitive and behavioral impairments.

Keywords (6): dystrophin, development, preschool, language, genetic, neuroscience.

Duchenne muscular dystrophy (DMD) is a genetic disorder caused by a mutation on the X chromosome. DMD is the second most common single gene disorder, occurring in 1/3500 live male births (Emery & Muntoni, 2003). Male children affected with this disease suffer from progressive, and ultimately fatal, muscular weakness. While known primarily for its devastating motor effects, DMD is also associated with cognitive deficits. These cognitive deficits have been studied in older children and adolescents with DMD. However, there are little data examining the development of cognitive skills in *young* male children with this disorder. The current investigation focuses directly on the early development of cognitive skills in young boys with DMD.

The study of the development of cognitive skills in children with a specific genetic disorder offers unique insight into the study of developmental neuropsychology. Typically, children with developmental and behavioral disorders are characterized by clusters of symptoms, often with an unknown etiology. The current investigation offers the inverse: the opportunity to study a group of children with a known genetic etiology, and delineate their early developmental profile. The association of a specific cognitive profile with a known genetic mutation offers the tantalizing possibility that one can reduce neuropsychological differences to the level of the gene. Put differently, DMD presents an opportunity to explore genotype-phenotype relationships using readily available neuropsychological tools.

The cognitive deficits documented in older children and adolescents with DMD appear to be mainly circumscribed to verbal skills. Across studies, verbal intelligence scores are

significantly lower than performance intelligence scores (Cotton, Voudouris, & Greenwood, 2001). Other areas of cognitive functioning, such as visuo-spatial skills, long-term memory, and abstract reasoning skills do not appear to be affected (Hinton, De Vivo, Nereo, Goldstein, & Stern, 2001; Cotton, Crowe, & Voudouris, 1998; Karagan, Richman, & Sorensen, 1980; Wicksell, Kihlgren, Melin, & Eeg-Olofsson, 2004).

While there is a general consensus among investigators that verbal skills are preferentially affected in older children and adolescents with DMD, the nature of this deficit remains unclear. We have previously characterized this deficit as one of *limited verbal span*, based upon evidence which indicates that these children have considerable difficulty with immediate repetition of verbal material, and in particular, when the verbal information increases in length and complexity. When asked to recall numbers, sentences, or stories, for example, children with DMD consistently perform more poorly than their matched controls (Anderson, Routh, & Ionasescu, 1988; Billard et al., 1992; Billard, Gillet, Barthez, Hommet, & Bertrand, 1998; Dorman, Hurley, & D'Avignon, 1988; Hinton, De Vivo, Nereo, Goldstein, & Stern, 2000; Hinton et al., 2001; Hinton, De Vivo, Fee, Goldstein, & Stern, 2004; Ogasawara, 1989; Whelan, 1987; Wicksell et al., 2004). These findings appear across all intellectual levels, regardless of cognitive functioning (Hinton et al., 2000), and are not due to more general impairments in language and memory (Hinton, Fee, Goldstein, & De Vivo, 2006). Whether *limited verbal span* is an “attentional” or language issue is unclear, but most likely both skills contribute. We have further hypothesized that *limited verbal span* may be the core deficit in DMD, and as deficits in verbal span have been linked to impairments in the acquisition

of phonological knowledge and single-word vocabulary (Adams & Gathercole, 2000; Gathercole, Hitch, Service, & Martin, 1997), this core deficit may also help to explain impairments seen in phonological awareness, reading, and writing, which also are found in children with DMD (Billard et al., 1992; Dorman et al., 1988; Hinton et al., 2001; Hinton et al., 2004; Leibowitz & Dubowitz, 1981; Worden & Vignos, 1962).

In comparison to the data regarding verbal deficits in older children and adolescents with DMD, there is relatively little information available regarding early development of language in DMD. Several case studies have reported young children (e.g., ages 3-6) who came to clinical attention for significant language and behavioral problems and were subsequently diagnosed with DMD (Essex & Roper, 2001; Kaplan, Osborne, & Elias, 1986; Mohamed, Appleton, & Nicolaides, 2000). One of the few published data sets on young children with DMD (under the age of 72 months) is by Smith and colleagues (1990). The sample was comprised of 33 British children with DMD and normal, gender- and age-matched controls. Compared to controls, children with DMD exhibited generalized developmental delay, with severe deficits in motor and speech skills. Smith et al. also reported the presence of behavioral problems in the DMD group only. These data are somewhat at odds with the specificity of findings in older children. They suggest that in younger children with DMD, there may be early generalized developmental delays with concomitant behavioral problems, or that Smith's sample is very different from other groups in phenotypic characteristics as well as age. Given the paucity of data among young children with DMD, there is a strong need to replicate the findings and to help better characterize the cognitive and behavioral profiles of young children diagnosed

with DMD. Moreover, in young children, delayed cognitive skills likely impact upon adaptive behavior and an evaluation of daily life skills is warranted.

The purpose of the current study was to explore adaptive behavior and cognitive skills of young children with DMD and to replicate the findings of early, generalized delay as documented by Smith et al. (1990). Adaptive behavior and cognitive skills were individually assessed in 3 to 6 year-old children with DMD and unaffected family controls to determine whether the selective or generalized deficits are associated with diagnosis of DMD. The following three hypotheses were evaluated: 1. Parents will rate young children with DMD as having poorer adaptive behavior skills than their unaffected controls. 2. Children with DMD will perform more poorly on tests of cognitive functioning than their familial controls. 3. Young children with DMD will exhibit more generalized deficits than those reported in older children with DMD.

Methods

Participants

Thirty-one young boys with muscular dystrophy who were between the ages of 3 and 6 were recruited (mean age = 5.10 years, SD=1.08). Inclusion criteria included diagnosis of muscular dystrophy, good general health, ability to complete all test measures, English as the primary language, and willingness to participate. All probands were ambulatory at the time of assessment. Of the 31 boys, two met criteria for a more mild form of the disorder, known as Becker's muscular dystrophy.

Controls were recruited for each boy with DMD when possible. Controls consisted of male or female family members. Inclusion criteria consisted of proximity in age to the affected child (i.e., within four years), good general health, ability to complete all test measures, English as the primary language, and willingness to participate. Twenty subjects were recruited, consisting predominantly of siblings (n=17). When more than one sibling was available, preference was given first to male gender and then to closeness in age. When no sibling was available, cousins (n=3) were recruited. Controls ranged in age from 3 to 9, with a mean age of 5.10 years (SD=1.74). Among the controls, 9 were older (6 males and 3 females) and 9 (4 males and 5 females) were younger. Two controls were fraternal twins (1 male, 1 female).

The majority of probands and controls had not yet entered first grade; they were in preschool, pre-kindergarten, or kindergarten. The majority of young children with DMD were receiving therapeutic services; physical (86%), occupational (77%), and speech (59%). In contrast, a smaller percentage of controls were receiving speech therapy services (13%).

Racial composition of the sample was predominantly Caucasian (92%), with an additional 6% reported to be Hispanic; 2% did not categorize their racial affiliation. Responses to questions about socio-economic information indicated that the sample was composed of well-educated families. Most mothers had completed a Bachelor's degree, and the average family income was approximately $75,000.

Procedure

Participants for this study were recruited through the Muscular Dystrophy Association (MDA) clinics of Columbia Presbyterian Hospital, New York, and Children's Healthcare of Atlanta, at Scottish Rite, Atlanta, Georgia. Additionally, newsletters with a description of the study were sent to Parent Project Muscular Dystrophy (PPMD), regional MDA clinics, and parent support groups. Interested individuals returned the response form directly to the investigator. This study was approved by the Columbia University and New York Presbyterian Hospital Institutional Review Board, by the Queens College of the City University of New York Institutional Review Board, and by the Children's Healthcare of Atlanta at Scottish Rite Children's Medical Center Institutional Review Board.

Written informed consent was provided by all parents prior to their children's participation. Children who were capable of doing so gave verbal assent prior to their participation. Parents completed the questionnaires while their children were being tested. Testing was done in English. Most children were tested at home (n=28); however, some children came to the medical centers in New York (n=11) or Georgia (n=12). The entire battery of tests took approximately four hours to administer, and testing was generally divided into two separate sessions of two hours each, so as not to over-burden the children.

Although testers were not blind to the child's diagnosis, every effort was made to ensure that test administration was standardized for both probands and controls. All tests were

scored twice to ensure reliability of the data; discrepancies were resolved by consensus. To ensure that there was no evidence of hearing loss, a brief hearing screen was attempted with all research subjects. About ½ the sample objected to the placement of the headphones on their head, or did not comply with the instructions. In those cases, medical records were reviewed and parents were interviewed to confirm that there was no suspicion of any auditory impairment.

Measures: Parent battery

Parents completed a developmental history form that queried about general health characteristics, schooling, and demographic information. In addition, parents completed the Vineland Adaptive Behavior Questionnaire (Sparrow, Balla, & Cicchetti, 1984), a semi-structured interview designed to measure adaptive behavior. The questionnaire generates scores in four different areas of functioning, including Communication, Socialization, Daily Living Skills, and Motor Skills, as well as a summary Adaptive Behavior Composite score, as an estimate of everyday living skills.

Measures: Children's battery

The following battery was composed of tests which have a minimal amount of motor demand, with the exception of tests specifically designed to measure fine-motor skills. The battery included tests of specific cognitive skills and select subtests from composite neuropsychological measures. Tests were grouped according to their presumed primary neuropsychological function. Five groups of measures were studied: (1) Receptive

language skills, (2) expressive language skills, (3) visuo-spatial skills, (4) fine-motor skills, and (5) attention/memory skills.

Verbal skills: Receptive and expressive language skills

The receptive composite score consisted of the Peabody Picture Vocabulary Test (PPVT-III) (Dunn & Dunn, 1997), and three subtests from the Clinical Evaluation of Language Fundamentals – Preschool Version (CELF-P) (Wiig, Secord, & Semel, 1992), which form the Receptive Language score (Linguistic Concepts, Sentence Structure, and Basic Concepts).

The expressive composite score consisted of the Expressive Vocabulary Test (EVT) (Williams, 1997), and three subtests from the CELF-P (Wiig et al., 1992), which form the Expressive Language score (Recalling Sentences, Formulating Labels, and Word Structure).

Visual-spatial skills

The visual-spatial composite score consisted of the Matching subtest from the Wide Range Assessment of Visual Motor Abilities (WRAVMA) (Adams & Sheslow, 1995), and Picture Completion from the Wechsler Preschool and Primary Scale of Intelligence – Revised (WPPSI-R) (Wechsler, 1989) or the Wechsler Intelligence Scale for Children – Third Edition (WISC-III) (Wechsler, 1991).

Fine-motor skills

Fine-motor skills were assessed using the Pegboard subtest of the WRAVMA (Adams et al., 1995).

Attention/Memory skills

The composite score for attention/memory skills consisted of two subtests from the NEPSY: A Developmental Neuropsychological Assessment (Korkman, Kirk, & Kemp, 1997): Visual Attention and Narrative Memory.

Analyses

For the purpose of the current analyses, only children with familial controls were included (n=20). The selected proband group consisted of 20 boys with DMD. The control group consisted of a mixed gender group of males (n=11) and females (n=9). Multiple exploratory analyses were run to determine whether gender contributed to control group data.

Paired t-tests were run between the proband and control groups to ensure similarity of age. Socioeconomic variables did not require statistical control because participants were from similar socioeconomic backgrounds.

To determine whether parents rate young children with DMD as having poorer adaptive behavior skills than their unaffected controls, paired t-tests were utilized. The dependent variables consisted of scores on four subtests of the Vineland: Communication,

Socialization, Daily Living Skills, and Motor Skills. The null hypothesis that children in both groups would have similar adaptive functioning in all domains was tested. Alpha was set at .01 in order to account for multiple comparisons (.05/4 = .01).

To determine whether children with DMD perform more poorly on tests of cognitive function than their controls, paired t-tests were used. Five composite scores served as the dependent variables: (1) Receptive language skills, (2) expressive language skills, (3) visuo-spatial skills, (4) fine-motor skills, and (5) attention/memory skills. The null hypothesis that the two groups would perform similarly across all test measures was tested. The domain-wise alpha was set at $p < .05$. The Bonferroni correction was utilized (.05/number of specific subtests) to correct for multiple comparisons within each domain and examine specific subtest differences. Individual t-values that were equal or less than Bonferroni-corrected alpha were considered to reflect definite between group differences.

Results

Sample Descriptives

Examination of performance of the control children comparing boy and girl controls across measures using multiple exploratory t-tests confirmed that there were no significant between-gender differences on any measure.

Age was comparable between the proband and control groups ($t = .43$, n.s.). Socioeconomic and demographic variables were controlled for by design.

Adaptive Behavior

According to parental report, children with DMD display significant delays in adaptive behavior skills. These delays are observed across domains when compared to their unaffected family members (see Table 1). Paired analyses indicate that children with DMD are delayed relative to familial controls in all four areas of functioning, including communication daily living, socialization, and motor skills. In general, children with DMD were rated about one standard deviation lower than their controls across the scales with the biggest differences being observed on the communication and motor scales.

Neuropsychological Test Data

Children with DMD perform significantly more poorly than their unaffected family members on multiple measures of cognition (see Table 2). Paired analyses demonstrated that the boys with DMD performed more poorly than their controls on measures of receptive language, expressive language, visuo-spatial skills, fine-motor skills, and attention/memory skills. Thus, the profile appears to be one of global cognitive delay, with the probands scoring approximately one standard deviation below their familial controls.

Discussion

The results of the current study indicate that young children with DMD exhibit impairments in multiple areas of cognitive and adaptive functioning, as confirmed both by parental report and neuropsychological test data. Parents report generalized deficits in adaptive functioning in their affected children. Children with DMD reportedly have

difficulty in behaviors relating to self-sufficiency in language skills, motor skills, personal care, and social skills. The children's skills were, on average, approximately one standard deviation below that expected from the normal population and from their familial controls.

Neuropsychological test data also showed generalized deficits across domains in young children with DMD. Specifically, when compared to familial controls of comparable age, young children with DMD performed significantly more poorly on tests of receptive and expressive language, visual-spatial skills, fine-motor skills, and attention/memory skills. Similar to the adaptive behavior findings, children with DMD scored approximately one standard deviation below their controls. No clear pattern of relative strengths or weaknesses was seen. It is interesting to note, however, that despite significant between-group differences on all measures, children with DMD generally scored in the low-average to average ranges. Unaffected family members scored in the average to high-average ranges. As such, although group performance was shifted down, individual performance of some children with DMD might well have escaped attention had they not been compared to well-matched controls. A visual presentation of the performance of individual sibling pairs on one of the composite scores (e.g., expressive language) is presented in Figure 1. This figure demonstrates that, despite variability in their test scores, probands generally perform more poorly than their sibling controls.

The results of the current study are in concordance with the previously published, albeit limited, data on cognitive deficits in young children with DMD. Smith et al. (1990)

found generalized developmental delays, with the most severe impairments in language and motor skills. The delays reported in Smith's sample are more severe than those reported in the current study; sampling differences may be responsible for the discrepant findings. The current findings of generalized delay are also consistent with the case studies mentioned previously (Essex et al., 2001; Kaplan et al., 1986; Mohamed et al., 2000), in which preschool children initially referred for language and behavioral delays were subsequently diagnosed with DMD.

The results of the current study are consistent with prior cross-sectional studies which have found more severe language deficits in "younger" children with DMD, as compared to "older" children with DMD (Miller, Tunnecliffe, & Douglas, 1985; Sollee, Latham, Kindlon, & Bresnan, 1985), notwithstanding the fact that the "younger" children in previous samples (e.g., mean age 13.5 years for Miller et al., 1985 and mean age 7.7 years for Sollee et al., 1985) are considerably older than the young children in the current sample. The results of the current study also complement the cross-sectional findings of Cotton et al. (2005). According to a recent meta-analysis by Cotton and colleagues, young children with DMD (e.g., mean age 7 years, 5 months) exhibit significant verbal impairments; verbal skills consistently improve with age in children and adolescents with DMD, with the oldest children outperforming those in all other age groups.

The current study is particularly valuable for examining cognition in a proscribed age range (e.g., three to six), allowing for a more fine-tuned analysis of language skills as they emerge. Other studies investigating cognition in DMD have utilized wide age-

ranges, which may mask more subtle differences in the emergence of language. In addition, the current investigation extends prior findings by showing the functional impact in adaptive skills for these children, implicating real-life consequences. Finally, the use of familial controls allows the investigators to control for socio-economic variables, such as educational access, parenting style, social supports, and other environmental factors.

The findings of generalized deficits in young children with DMD are at odds with the specificity of findings in older children and adolescents with this disorder. DMD affects multiple areas of cognition, yet these deficits appear to become more narrowly defined, and thus more specific, over time as the children mature. Longitudinal data from children with early language impairments indicate that it is not unusual for these types of deficits to become less severe, or in fact, resolve completely over the course of the preschool years (Bishop & Edmundson, 1987; Scarborough & Dobrich, 1990; Silva, 1980). Other investigators (Aram & Nation, 1975) have hypothesized that "the younger a child with a developmental language disorder, the more generalized is its effect, while as children become older, their language improves and the areas of deficiency become more specific" (p.239). Thus, the current findings of generalized deficits may be indicative of the integrative nature of development. A longitudinal study, following young, preschool-aged children with DMD over time is necessary to address the mechanism by which generalized cognitive impairments resolve into a specific language deficit. Our lab is currently following children identified in this study and investigating their language and reading skills as they emerge.

One potential drawback of the current study is that it consisted of a sample of convenience. Given that there are currently no population-based studies which report upon the incidence of cognitive impairment in children with DMD, it is impossible at this time to determine whether the current sample over-represents cognitive impairments in this population. The other potential drawback to the current study – the small sample size – is less of a concern because the strength of the effect sizes suggests that a lack of power was not at issue.

The cognitive deficits observed in children and adolescents with DMD may be attributed to the lack of dystrophin, a protein product normally found in multiple tissues throughout the body. The genetic mutation responsible for DMD disrupts the production of dystrophin (Hoffman, Brown, & Kunkel, 1987). Dystrophin is normally found in the neuromuscular junction of skeletal muscle fiber and ensures the structural integrity of the muscle (Blake, Weir, Newey, & Davies, 2002). It is the absence of dystrophin in the skeletal muscle that causes the phenotypical presentation of progressive muscular weakness. However, dystrophin is also normally present in multiple tissues throughout the body, including the central nervous system, and in DMD its deficiency is not limited to skeletal muscle tissue (Lidov, Byers, Watkins, & Kunkel, 1990; Lidov, Byers, & Kunkel, 1993). Studies have documented the absence of dystrophin in the cerebral and cerebellar cortices of individuals diagnosed with DMD (Kim, Wu, & Black, 1995; Uchino et al., 1994a; Uchino et al., 1994b), providing a neural basis for the cognitive deficits in DMD. Development of a brain without dystrophin may lead to a brain that is

"wired" differently from most, and may in turn lead to alterations in cognitive and behavioral development.

In summary, the current study examines adaptive behavior and cognitive deficits in a sample of children with a known genetic disorder. In contrast to the profile of specific verbal deficits reported in older children with DMD, young children with this disorder appear to exhibit generalized deficits in multiple areas of cognition and adaptive functioning. The current study helps elucidate genotype-phenotype associations that are seen early in the disorder; however, it is not known how these generalized cognitive deficits evolve into more specific language impairments as children mature. It is hoped that future studies will help characterize the developmental trajectory in children with this disorder. The association of a specific cognitive profile with a genetic disorder is unique, and DMD offers a unique opportunity to examine such gene-cognition relationships.

Acknowledgments: Sponsored by the NICHD (1R29HD34155-01) and NIMDS and the Muscular Dystrophy Association (PI: V.J. Hinton).

Table 1

Differences in adaptive functioning according to parental report

Vineland Domain	Probands	Controls	t-value	Effect size
	Mean (SD)	Mean (SD)		
Communication	81.47 (16.57)	107.26 (15.37)	t = 4.90[a]	r = .76
Daily living skills	78.68 (19.18)	99.00 (16.87)	t = 3.55[a]	r = .64
Socialization	89.11 (16.48)	105.79 (15.52)	t = 3.90[a]	r = .68
Motor skills	69.50 (20.97)	94.25 (14.67)	t = 3.40[a]	r = .79

[a] $p < .01$.

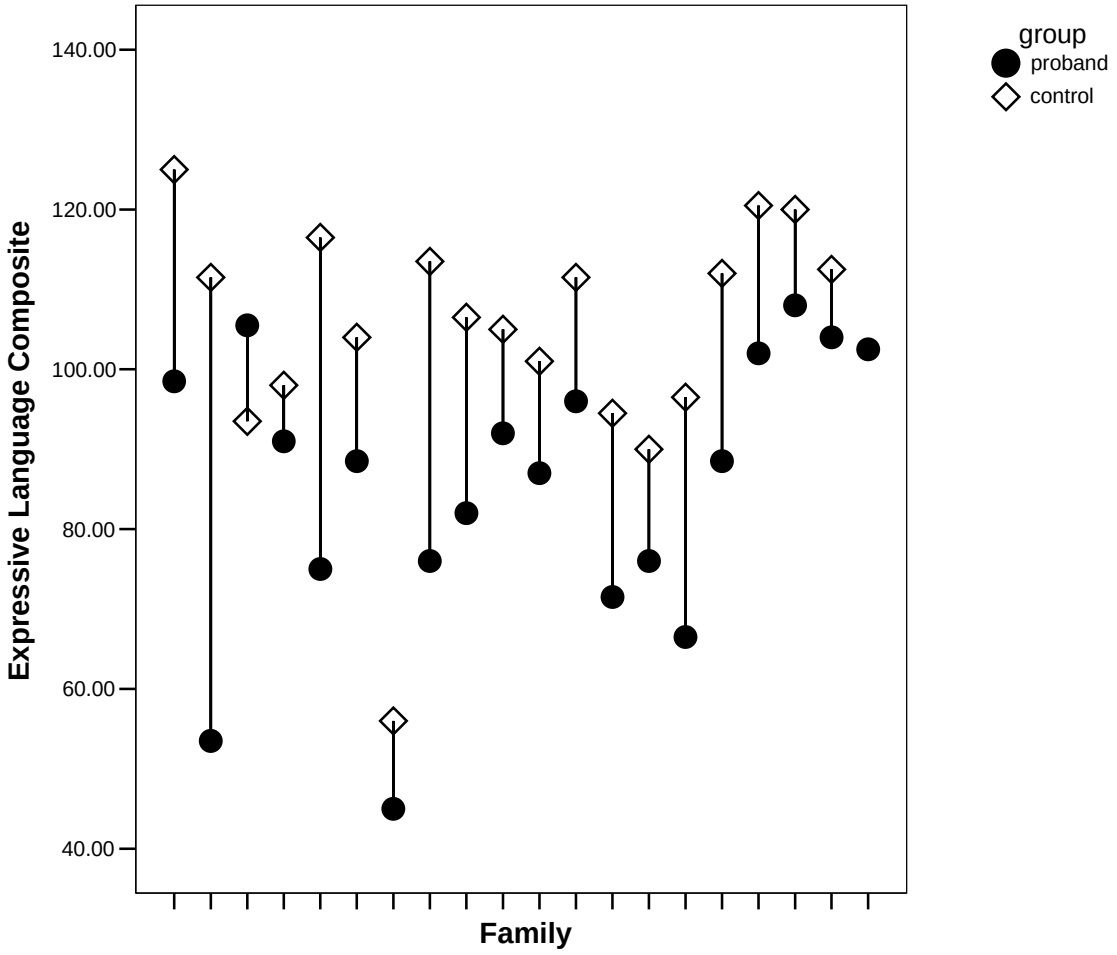
Table 2

Differences in cognitive functioning according to neuropsychological test data

Cognitive Domain	Probands	Controls	t-value	Effect size
	Mean (SD)	Mean (SD)		
Receptive language	92.13 (19.79)	106.55 (14.90)	t = 3.77[b]	r = .66
Expressive language	84.55 (17.32)	104.63 (15.39)	t = 5.85 [b]	r = .81
Visuo-spatial skills	90.74 (13.36)	107.45 (13.34)	t = 4.18[b]	r= .71
Fine-motor skills	86.63 (11.52)	102.13 (10.96)	t = 4.44[b]	r = .71
Attention/memory skills	84.56 (12.63)	106.06 (11.67)	t = 6.72[b]	r = .86

[b] $p < .05$

Figure 1: The majority of probands do worse than their siblings on measures of expressive language.



Part Three:

Duchenne muscular dystrophy: A cerebellar disorder?

Abstract

Duchenne muscular dystrophy (DMD) is a genetic disorder caused by a mutation on the X chromosome. The primary result of the mutation is progressive, and ultimately fatal, muscular weakness. However, in addition to progressive muscle weakness, children with DMD often exhibit cognitive deficits. These deficits have been linked to the absence of dystrophin, a protein product which is normally found in multiple tissues throughout the body. We argue that it is the absence of dystrophin in the *cerebellum* which is responsible for the cognitive deficits observed. Specifically, it is our contention that brain pathways in the cerebellum (e.g., cerebro-cerebellar loops) which develop without dystrophin may result in altered brain function presenting as cognitive deficits in DMD. In the current paper, we begin by reviewing data that document structural and functional abnormalities in the brains of individuals with DMD and *mdx* mice. Following a brief review of the cognitive deficits associated with DMD, we present neuroimaging and neuropsychological evidence to indicate that the cerebellum is involved in the same aspects of cognition that are impaired in children with DMD. Finally, we argue that children with DMD display the types of deficits that one would predict given a cerebellar injury, both in terms of the type of deficit and the quality of deficit.

Keywords: Duchenne muscular dystrophy, dystrophin, development, dyslexia, cerebellum.

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked disorder that causes progressive muscular weakness and is associated with cognitive deficits. The disorder is caused by a mutation in a gene on the X chromosome that disrupts the production of dystrophin, a protein product normally found in the neuromuscular junction. The resulting absence of dystrophin causes structural and signaling defects, which ultimately result in the breakdown of muscle fiber. Children and adolescents with DMD exhibit a gradual deterioration in muscle strength and function. Young men with DMD eventually succumb to cardiac and respiratory complications.

Studies have documented that dystrophin normally is present in multiple tissues, including the central nervous system throughout the cerebral and cerebellar cortices. The absence of dystrophin during brain development in individuals with DMD likely underlies the cognitive deficits observed. In the current paper, we hypothesize that the absence of dystrophin specifically disrupts the efficiency of the cerebro-cerebellar pathways, resulting in the cognitive deficits observed in DMD. Put simply, we argue that DMD is a cerebellar disorder.

Dystrophin and the brain: Possible neural substrates of cognitive deficits

Dystrophin is absent in the muscles of individuals with DMD, and its absence in muscle fiber is pathognomonic of the disease. Less well known is the fact that dystrophin is also absent in the central nervous system (CNS) in those individuals affected with DMD. In fact, since brain-type dystrophin is normally as abundant as muscle-type dystrophin

(Lederfein et al., 1992), its absence likely reflects a significant alteration in brain structure. These alterations in brain structure impact brain function, and likely underlie the cognitive deficits seen in children with DMD. We begin by presenting evidence that DMD is associated with altered brain structure and function.

Some of the most valuable localization data to date has been collected from the *mdx* mouse, a knock-out mouse model of DMD. Immunohistochemical studies of normal mouse brain have demonstrated that dystrophin is localized to the cerebral cortex, the hippocampus, and the cerebellum. In the *mdx* mouse brain, however, these areas are lacking in dystrophin (Lidov, Byers, Watkins, & Kunkel, 1990; Lidov, Byers, & Kunkel, 1993; Huard & Tremblay, 1992; Kim, Wu, Xu, & Black, 1992). Further, among these three brain areas, dystrophin is normally most abundant in the cerebellum (Lidov et al., 1990). Dystrophin also localizes to certain cell types and cell areas. In both the cerebral cortex and cerebellum, dystrophin normally localizes to neurons (Chelly et al., 1990; Lidov et al., 1990). Within the cerebellum, it localizes specifically to Purkinje cells, and does not localize to other structures or processes (i.e., granule cells, stellate cells, basket cells, etc.) (Huard et al., 1992; Lidov et al., 1990; Lidov et al., 1993). A more detailed analysis reveals that dystrophin is highly enriched at post-synaptic structures, thus prompting speculation that is involved in synaptic functioning (Lidov et al., 1990; Tian et al., 1996; Kim et al., 1992; Kamakura et al., 1994; Górecki, Łukasiuk, Szklarczyk, & Kaczmarek, 1998). Furthermore, there is evidence to suggest that within the post-synaptic densities, dystrophin normally co-localizes with the $GABA_A$ receptors (Knuesel et al., 1999).

The cellular data described above have been partially verified in human studies. Autopsy studies have documented the absence of dystrophin in the post-synaptic densities of the cerebral cortex in individuals diagnosed with DMD (Kim, Wu, & Black, 1995). The normally "highly enriched" dystrophin proteins found in a control brain were "undetectable" in the brain of a boy with DMD (Kim et al., 1995). In another series of autopsy studies, patients with DMD and known "intellectual disturbances" were examined: the investigators found a complete absence of dystrophin in cerebral and cerebellar neurons (Uchino et al., 1994a; Uchino et al., 1994b). In addition to these cellular anomalies, limited autopsy data have also revealed disordered connections and architectural anomalies (Rosman, 1970). Structural MRI imaging has revealed mild atrophy in some individuals with DMD (Al-Qudah, Kobayashi, Chuang, Dennis, & Ray, 1990). Thus, there is evidence to indicate altered brain structure in humans with DMD, both on the cellular level and on the gross structural level.

In both mice and humans, dystrophin expression appears to be developmentally regulated. In mice, for example, dystrophin isoforms are involved in many different types of developing tissue, and that activity seems to increase before birth (Sarig et al., 1999). Kim et al. (1992) found differences in the expression of dystrophin and its isoforms during development in mice, with the brain-type dystrophin exhibiting dramatic increases from day 7 to day 10 of development (Kim et al., 1992). This is in contrast to the muscle-type dystrophin, which appears to plateau much more rapidly in the fetal mouse (Chelly et al., 1990). Similarly, Sogos and colleagues (2002) have documented

the presence of dystrophin very early in human fetal development, and noted an increase in its expression until approximately week 15. Morris and colleagues, using post-mortem brain tissue samples from an adult (60 year-old) and fetus (3.5 months), found that there are dramatic decreases in dystrophin isoforms after birth (Morris, Simmons, & thi Man, 1995).

In addition to structural abnormalities, there is evidence to indicate altered brain functioning in humans and animals with DMD (for a review, see (Anderson, Head, Rae, & Morley, 2002). In humans, DMD is associated with metabolic abnormalities of the brain (Tracey et al., 1995). Furthermore, reduced glucose metabolism has been found in areas normally rich in dystrophin, including the cerebellum, medial temporal structures, sensorimotor area, and temporal neocortex (Lee et al., 2002). In *mdx* mice, similar functional brain abnormalities have been reported: *mdx* mice exhibit impairments in glucose metabolism and other metabolic abnormalities (Rae et al., 2002a; Tracey, Dunn, & Radda, 1996). Of interest is that functional abnormalities have been detected on the cellular level in brain tissue slices of *mdx* mice. Specifically, following hypoxic injury, pyramidal neurons in hippocampal slices prepared from the *mdx* mouse are less likely to recover when compared to slices prepared from the control mice (Mehler, Haas, Kessler, & Stanton, 1992). Thus, the dystrophin-deficient brain appears to be less resilient to adverse environmental influences than the normally developed brain.

Of mdx mice and mazes

The structural and functional deficits documented above have been hypothesized to underlie the cognitive deficits seen in mice and humans. *Mdx* mice, for example, exhibit memory impairments on tasks such as the T-maze (Vaillend, Rendon, Misslin, & Ungerer, 1995). These learning and memory deficits have been described as "specific" rather than "global," and relate to the *mdx* mouse's ability to retain novel information (Vaillend et al., 1995). Furthermore, the experimenters argue that these cognitive deficits cannot be attributed solely to motor or emotional variables, as young mdx mice (<6 months) do not exhibit impaired motor function or coordination (Vaillend et al., 1995). Other aspects of learning and visuo-spatial skills do not appear to be impaired in *mdx* mice (Sesay, Errington, Levita, & Bliss, 1996).

Cognitive deficits in DMD

Duchenne himself, when characterizing the disorder, commented on the cognitive deficits apparent in some children with DMD, observing that they presented with "*intelligence obtuse*" (Duchenne, 1868). However, the children he observed appeared to have a wide range of intellectual functioning, ranging from idiocy to precocity (e.g., "*facultés intellectuelles très-développées,*" "*son intelligence était précoce*"). Duchenne's observations based on case studies were supported by early experimental research investigating the cognitive deficits in DMD (primarily assessing general IQ levels). Considerable data now indicate that the mean IQ in children with DMD is significantly lower than in the normal population, and a meta-analysis reveals that it is on average one standard deviation below the mean (Cotton, Voudouris, & Greenwood, 2001). These

scores appear to be normally distributed, and, as Duchenne observed in the 1800's, there is considerable variability in the presentation of children with this disorder (Cotton et al., 2001).

We have previously argued that there is a core cognitive deficit in DMD, and we have referred to it as "limited verbal span" (Hinton, De Vivo, Fee, Goldstein, & Stern, 2004). Research indicates that children with DMD have difficulty on tests which require attention to and repetition of verbal material. For example, deficits have been noted on tests of story recall (Billard et al., 1992; Hinton, De Vivo, Nereo, Goldstein, & Stern, 2000; Hinton, De Vivo, Nereo, Goldstein, & Stern, 2001; Wicksell, Kihlgren, Melin, & Eeg-Olofsson, 2004), sentence repetition (Billard et al., 1992; Hinton, Fee, Goldstein, & De Vivo, 2006), and recall of digits (Billard, Gillet, Barthez, Hommet, & Bertrand, 1998; Hinton et al., 2000; Hinton et al., 2001; Ogasawara, 1989; Wicksell et al., 2004). Indeed, one of the most consistent findings when investigating cognition in children with DMD is that scores on the Digit Span subtest of the Wechsler Intelligence Scales (WIS) are depressed (Anderson, Routh, & Ionasescu, 1988; Billard et al., 1998; Dorman, Hurley, & D'Avignon, 1988; Hinton et al., 2000; Hinton et al., 2004; Sollee, Latham, Kindlon, & Bresnan, 1985; Ogasawara, 1989; Whelan, 1987; Wicksell et al., 2004; Hinton et al., 2001). This finding remains consistent regardless of whether children with DMD are compared to normal controls, their siblings, or children with other degenerative muscle diseases. These deficits cannot be attributed to more general delays in the acquisition of language skills, as other areas of language and memory are intact (Hinton et al., 2001;

Hinton et al., 2006). The verbal deficits appear across all intellectual levels (Hinton et al., 2000), while other areas of cognition are generally spared (Hinton et al., 2001).

Deficits in verbal span have been linked to impairments in the acquisition of phonological knowledge and single-word vocabulary (Adams & Gathercole, 2000; Gathercole, Hitch, Service, & Martin, 1997). Thus, it comes as no surprise that children with DMD also exhibit deficits in phonological processing and reading (Billard et al., 1992; Billard et al., 1998; Dorman et al., 1988; Hendriksen & Vles, 2006; Hinton et al., 2001; Hinton et al., 2004; Leibowitz & Dubowitz, 1981; Worden & Vignos, 1962). Indeed, when compared to children with another fatal and progressive muscular disorder, spinal muscular atrophy (SMA), on measures of academic achievement, 40% of children with DMD were not yet fluent readers, whereas all children with SMA were fluent readers (Billard et al., 1992).

When compared to their unaffected siblings, children with DMD consistently perform more poorly on tests of phonological awareness and phonological memory (Hinton, Cyrulnik, & Fee, 2005). Dorman and colleagues (1988) examined reading and phonological processing skills in a cohort of older children with DMD and found that they had significant difficulty on a test of phonological manipulation called “sound deletion” (e.g., say “stand” without the “t” sound), in which they had to isolate a particular sound. Qualitative analyses revealed that the children with DMD were particularly impaired on this task, often deleting adjacent phonemes, or struggling to reconstitute the word after deleting the target sound (Dorman et al., 1988). Indeed, even

when children with DMD are compared to control children who are equivalent in terms of their reading age, children with DMD make more phonological errors when reading non-words (Billard et al., 1998). Thus it appears that children with DMD present with a form of developmental dyslexia, with a particular impairment in phonological processing (Hinton et al., 2004). These types of deficits are consistent with what one would predict given their verbal span limitations.

The cerebellum: Structure and function

Structurally, the cerebellum is one of the most elegantly designed regions of the brain. Although its name derives from Latin for *little cerebrum*, this "little" structure contains a staggering number of neurons. "The total number of cells in the cerebellar cortex exceeds four times the number of cells in the cerebral cortex" (Andersen, Korbo, & Pakkenberg, 1992). These neurons are arranged in a three-cell layer -- the molecular, Purkinje cell and granule cell layer. Neurons from these layers form self-contained units, each consisting of one Purkinje cell and associated molecular and granule cell neurons. Known as "cerebellar cortical modules," these modular circuits are arranged in an orderly array throughout the entire cerebellum, resulting in a lattice-like configuration (O'Hearn & Molliver, 2001). These modular circuits have been conceptualized as the modern equivalent of micro-chips, capable of processing large amounts of information (Leiner, Leiner, & Dow, 1991; Leiner, Leiner, & Dow, 1995). The primary member of this module is the Purkinje cell neuron, which analyzes most of the incoming information, and is responsible for all of the output from the module (O'Hearn et al., 2001). As the

Purkinje cell is the primary output neuron, developmental anomalies in the structure of the Purkinje cell will likely result in widespread disruptions to signaling efficiency.

Functionally, the cerebellum is divided into three distinct regions with corresponding sets of connections. We will focus primarily on the *cerebro-cerebellar* loops, which connect the lateral parts of the cerebellar hemisphere with the cerebral cortex, and are traditionally responsible for the coordination of movement (Ghez, 1991). From an evolutionary perspective, the lateral parts of the cerebellum (along with the dentate nucleus), have enlarged significantly in humans, and some have argued that these structural changes represents a functional expansion of the cerebro-cerebellar loops (Leiner et al., 1991; Leiner, Leiner, & Dow, 1993).

There is anatomical and physiological evidence to suggest that the cerebro-cerebellar loops are much more extensive than previously thought (Leiner et al., 1993; Schmahmann, 1991; Schmahmann, 1996). The cerebellum receives input from multiple association areas of the cerebral cortex (including frontal, temporal and parietal areas) via the pontine nuclei which project to the cortex of the cerebellum (i.e., mossy fibers). The cerebellum also receives information from the association areas via the red nucleus and the inferior olive (i.e., climbing fibers). Indeed, the "cerebellum receives not only visual, auditory, and somatosensory information from posterior lobes of the cerebral cortex, and not only motor information from the frontal lobe, but also highly-processed multisensory information from some association areas" p. 120 (Leiner et al., 1991). Furthermore, the cerebellum can influence cerebral activity by projecting back to these areas through via

the dentate nucleus (specifically, the phylogenetically newer part, the neodentate) and the thalamus. In fact, projections have been traced from the cerebellum to the dorsolateral prefrontal cortex that are separate from those cerebello-thalamocortical projections which innervate the motor cortex (Middleton & Strick, 1994). It seems that both the primary motor cortex and the dorsolateral prefrontal cortex receive different projections from distinct groups of Purkinje cells in the cerebellum. These projections appear to be part of "closed-loop circuits" which indicate that there are separate motor and non-motor channels between the cerebellum and the cerebral cortex which remain distinct as they traverse the brain (Kelly & Strick, 2003).

Several investigators have argued that the role of the cerebellum is not limited to the coordination of motor information, but that it extends to the coordination of certain types of cognitive information as well. The manner in which the cerebellum achieves this goal varies according to the theoretical perspective: automatization/skill learning perspective (Leiner, Leiner, & Dow, 1986; Leiner et al., 1991; Leiner et al., 1993), dynamics learning (Ito, 1993), the internal model hypothesis and the cerebellar microcomplexes (Ito, 2005; Ito, 1997), the dysmetria of thought hypothesis (Schmahmann, 1991; Schmahmann, 1996; Schmahmann, 2004), timing mechanisms (Ivry, 1997), and attentional and anticipatory mechanisms (Akshoomoff, Courchesne, & Townsend, 1997; Courchesne et al., 1994; Courchesne & Allen, 1997). Although the theoretical perspective may differ, all of the above theories agree that the cerebellum is responsible for the optimization and enhancement of cognitive performance in certain domains. The cerebro-cerebellar loops

are perhaps responsible for “skilled mental performance” in the same way that other loops are responsible for “skilled motor performance” (Leiner et al., 1986).

If, indeed, the cerebellum is responsible for “skilled mental performance,” it follows logically that damage to the cerebellum will result in sub-optimal performance (and not necessarily frank deficits). Put differently, if our hypothesis regarding the disruption of cerebro-cerebellar circuits in DMD is correct, we should expect to see a pattern of sub-optimal performance on cognitive tasks in children with this disorder. In fact, we do indeed observe this pattern in our sample of children with DMD. They generally score within the normal range on standardized tests. It is only when compared to controls that the weaker performance of children with DMD becomes apparent (e.g., (Hinton et al., 2001). Thus, there appears to be some preliminary evidence to support our contention that disruptions of the cerebro-cerebellar loops underlie the cognitive phenotype of DMD. In the following sections, we present further evidence to indicate that the cerebellum is involved in cognitive functioning in certain domains (e.g., verbal working memory, phonological processing and reading).

The cerebellum & verbal working memory: Evidence from neuroimaging

Cerebellar activation has been documented in numerous verbal tasks, and more importantly, is consistently activated in verbal working memory tasks (Jonides et al., 1998; Jonides et al., 1997; Honey, Bullmore, & Sharma, 2000; Crottaz-Herbette, Anagnoson, & Menon, 2004; Glabus et al., 2003; Schumacher et al., 1996; Chen & Desmond, 2005; Fiez et al., 1996; Paulesu, Frith, & Frackowiak, 1993; Cabeza et al.,

1997; Awh et al., 1996; Smith, Jonides, & Koeppe, 1996). The cerebellum does not appear to be involved in spatial working memory tasks (Smith et al., 1996), indicating a dissociation between the two types of working memory. Cerebellar activation appears in verbal working memory tasks regardless of input modality (Schumacher et al., 1996), and increases in response to task difficulty (Jonides et al., 1997). Cerebellar activation also cannot be attributed solely to speech production or to a motor response, as this is generally controlled for by the experimental design (i.e., subtraction or parametric methods). Thus, across methodologies, there appears to be a growing consensus that the cerebellum is part of the network of brain regions mediating verbal working memory.

In a review of 275 PET and fMRI studies on cognition, Cabeza and Nyberg note that the cerebellum is active in verbal working memory tasks, especially when phonological processing is involved (2000). There is no consensus as to what aspect of phonological processing is mediated by the cerebellum; some argue for encoding (Ravizza et al., 2006; Chein & Fiez, 2001), others for articulatory control processes and phonological storage (Desmond, 2001; Chen et al., 2005; Awh et al., 1996; Desmond, Gabrieli, Wagner, Ginier, & Glover, 1997), yet there is general agreement that the cerebellum is actively involved in processing phonological material.

<u>The cerebellum & verbal working memory: Evidence from neuropsychological studies</u>

Neuroimaging studies demonstrate that the cerebellum is active when an individual engages in a verbal working memory task. Neuropsychological studies of patients with cerebellar injury suggest that the cerebellum is not only active, but also necessary, for verbal working memory. Imaging studies document the brain areas recruited to

participate in a cognitive process, while neuropsychological studies demonstrate that damage to the area results in deficits in the cognitive process. Interestingly, damage to the cerebellum appears to disrupt general language production in children, but specific language skills in adults. This is consistent with studies which demonstrate more diffuse neural representation of language in young children (for example, see (Booth et al., 1999).

Mutism and subsequent dysarthria (MSD) is common in young children following resection of cerebellar tumors, but rarely appears in adults who undergo similar procedures (van Dongen, Catsman-Berrevoets, & van Mourik, 1994). The pattern of language deficits exhibited by these children has sometimes been called “cerebellar” mutism, and generally resolves, in some cases to dysarthria (Pollack, Polinko, Albright, Towbin, & Fitz, 1995; Van Calenbergh, De Laar, Plets, Goffin, & Casaer, 1995). During post-surgical recovery children often exhibit abnormal voice quality, and peculiar alterations in tone, pitch, and loudness, in addition to bizarre behavioral abnormalities (Pollack, 1997; Pollack, 2001; Pollack et al., 1995).

Recent evidence suggests that MSD is not simply a disorder of muscular control and timing but is associated with a constellation of language impairments. After surgery, children exhibit deficits in naming, comprehension, and processing complex language (Riva & Giorgi, 2000). Another study documented impairments on measures of visual-spatial skills, expressive language, story recall, and sequencing and planning in children with cerebellar tumor resection who had not received radiation or chemotherapy

(Levisohn, Cronin-Golomb, & Schmahmann, 2000). Some investigators believe that language impairments in MSD are due to the destruction of dentate nuclei projections (Pollack et al., 1995), or perhaps to a more general disruption in cerebro-cerebellar pathways (Cole, 1994; Desmond, 2001; Pollack, 2001; Silveri, Leggio, & Molinari, 1994). In either case, these studies point to an important role for the cerebellum in the maintenance of language in children.

In adults, damage to the cerebellum appears to disrupt more specific aspects of language processing, namely verbal working memory. In a recent study investigating working memory, patients with cerebellar damage exhibited deficits on measures of verbal, but not spatial, working memory; these deficits could not solely be accounted for by speech output problems (Ravizza et al., 2006). Furthermore, symptom severity was associated with performance on the verbal, but not spatial, memory task (Ravizza et al., 2006). When these patients were tested on measures of rehearsal (e.g., articulatory suppression and word-length effect), no significant impairments in these normal effects were found, indicating that rehearsal processes were intact. As such, Ravizza and colleagues (2006) hypothesized that the cerebellum mediates phonological encoding. Justus and colleagues (2005) reached a similar conclusion, when they tested adult patients with cerebellar damage on a verbal working memory task. They reported a reduced phonological similarity effect, indicating that the normal effect of similar phonemes on recall was reduced in cerebellar patients. This study provides evidence for a non-articulatory role for the cerebellum, perhaps for the phonological short-term store (Justus, Ravizza, Fiez, & Ivry, 2005).

Silveri and colleagues (Silveri, Di Betta, Filippini, Leggio, & Molinari, 1998) present a case study of an 18-year-old Italian patient with a right cerebellar tumor. Silveri et al. utilized a battery sensitive to verbal working memory; specifically, measures designed to dissociate among different aspects of the phonological loop (e.g., phonological similarity effect, word-length effect, articulatory suppression effect, recency effect, auditory vs. visual presentation of stimuli). The results of this patient's testing indicate that he suffered from a deficit in the rehearsal process, specifically the "phonological output buffer," however, he displayed an intact phonological short-term storage system (Silveri et al., 1998). Silveri and colleagues hypothesize that the right cerebellum may be involved in the rehearsal process, particularly covert speech planning.

Although the conclusion drawn by Silveri et al. (1998) is not consistent with those drawn by Ravizza et al. (2006) and Justus et al. (2005), the hypotheses are not mutually exclusive, and all indicate cerebellar involvement in phonological processing. The studies differ in methodology (e.g., case vs. group study), etiology (e.g., tumor vs. stroke) and location (e.g., right vs. left cerebellum), which may have differential effects on different aspects of phonological processing. Furthermore, there may be different areas of the cerebellum which are involved in storage and rehearsal. In fact, there is neuroimaging evidence to suggest that the frontal/superior aspects of the cerebellum are involved in articulatory processes, while the parietal/inferior aspects of the cerebellum are involved in phonological storage (Chen et al., 2005).

Data from “natural experiments” (i.e., children and adults with acquired lesions in the area of interest) highlight two important points regarding language/verbal working memory processes when cerebro-cerebellar pathways are disrupted: In patients with acute cerebellar lesions, deficits in verbal working memory appear to be both *subtle* and *transient*. For example, in the case of cerebellar damage in children, language deficits normally resolve soon after surgery and, in most cases, are no longer apparent after four months (Pollack et al., 1995; van Dongen et al., 1994). Similarly, the deficit in verbal working memory in the Italian adolescent resolved within a few months after surgery. In adults with cerebellar damage, the deficits in verbal span are often subtle. Ravizza et al. (2006) observes: “the patients’ verbal spans were quite good and fell within the normal range based on standardized norms … the deficit here was apparent in comparison to age- and education-matched control participants” (p. 310).

This is similar to the cognitive deficits seen in DMD, which are also both *subtle* and *transient*. As noted before, among individuals with DMD, performance on certain verbal working memory tasks often falls within the low-average to average range. Similar to Ravizza et al. (2006), the cognitive deficits in many children with DMD only become apparent when compared to well-matched controls. Furthermore, cross-sectional data suggests that verbal skills may improve with age in children with DMD (Cotton, Voudouris, & Greenwood, 2005). However, these likely reflect modest gains, as children with DMD do not usually “recover” from their verbal deficits in the same way that children with cerebellar injury do. This may be attributed to the lack of plasticity that is

frequently seen in developmental language disorders as compared to acquired language disorders.

The cerebellum & reading: Evidence from neuroimaging

While considerably less plentiful than imaging data of verbal working memory, recent structural and functional imaging studies have implicated the cerebellum in reading and developmental reading disorders. Structural imaging studies have demonstrated an increased incidence of cerebellar abnormalities (e.g., symmetries) in individuals with reading disorders (Eckert et al., 2003; Leonard et al., 2001; Rae et al., 2002b). The degree of symmetry has been linked to performance on tests of phonological processing (Rae et al., 2002b). Furthermore, cerebellar abnormalities contribute significantly to discriminatory analyses which differentiate among subtypes of dyslexia (Leonard et al., 2001). Indeed, the cerebellum "is one of the most consistent locations for structural differences between dyslexic and control participants in imaging studies" p. 482 (Eckert et al., 2003).

Several functional imaging studies have documented cerebellar activation during component processes of reading, such as phonological processing (Paulesu et al., 1996; Xu et al., 2001; Zatorre, Meyer, Gjedde, & Evans, 1996) and single-word identification (Fiez, Balota, Raichle, & Petersen, 1999; Herbster, Mintum, Nebes, & Becker, 1997; Mechelli, Gorno-Tempini, & Price, 2003; Price et al., 1994); however, very few investigators comment upon this activation. An elegantly designed study by Fulbright and colleagues (1999) specifically investigated the role of the cerebellum in the different

component processes of reading. Specifically, a series of tasks were designed to investigate the role of the cerebellum in orthographic analysis, phonological analysis (word rhyme) and lexical semantic processing. Fulbright et al. (1999) found that cerebellar activation increased as cognitive demands involved in reading increase. Furthermore, different areas were engaged by the cerebellum in phonological processing as compared to lexical-semantic processing. The cerebellar activation in this study could not be attributed to motor control or strictly to covert articulation as the motor components were accounted for using a subtraction paradigm, and input (e.g., same/different judgment task) and output (e.g., yes/no button press) demands were kept constant across tasks.

The findings of cerebellar activation in reading are consistent with a putative role of the cerebellum in the optimization of certain cognitive skills. Other investigators have hypothesized that the cerebellum is generally responsible for the "skilled manipulation of symbols" (Leiner et al., 1991), a description which seems to perfectly capture the experience of fluent reading. This is consistent with theoretical models of reading which have suggested that for reading to develop successfully, many of the component skills involved must be mastered to the point of automaticity (Kitz & Tarver, 1989; LaBerge & Samuels, 1974; Shaywitz, 1998).

<u>The cerebellum & reading deficits: Evidence from neuropsychological studies</u>

A group of researchers from the United Kingdom have proposed that the deficits associated with dyslexia are due to cerebellar involvement (for an historical overview of

their research, the reader is referred to (Nicolson & Fawcett, 1999). Fawcett, Nicolson and Dean (1996) tested children with dyslexia on measures of cerebellar functioning. They report that the dyslexic children exhibited significant impairments on all of the cerebellar tests, both compared to age-matched controls and reading-matched controls (Fawcett, Nicolson, & Dean, 1996). Moreover, the effect sizes associated with cerebellar impairment were greater than those associated with reading impairment. Finally, all dyslexic children, to various extents, exhibited impairments on these tasks, indicating that these results were not just representative of a few dyslexic children (Fawcett et al., 1996).

These findings were subsequently replicated in a later study (Fawcett & Nicolson, 1999). Dyslexic children exhibited deficits on several cerebellar tests (e.g., balance, posture and muscle tone), and the degree of severity was similar to the that exhibited on tests of spelling and reading (Fawcett et al., 1999). A closer inspection of the data revealed that not only were these findings consistent at the group level, but they even were consistent when reduced to the individual level (i.e., a majority of dyslexic children showed signs of cerebellar dysfunction) (Fawcett et al., 1999).

Nicolson, Fawcett and colleagues present an intriguing perspective on dyslexia and reading difficulties, one which implicates cerebellar involvement. They posit that a developmental disorder of the cerebellum or cerebro-cerebellar loops is responsible for the reading difficulties in children with dyslexia (Nicolson, Fawcett, & Dean, 2001). In particular, they suggest that early cerebellar dysfunction may cause mild motor and articulation difficulties; these articulation difficulties may prevent the acquisition of the

phonological code, or may prevent its implementation in an automatic manner (this deficit may be reflected in impaired verbal working memory); phonological processing difficulties, in turn, may lead to the difficulties in the acquisition of fluent reading (Nicolson et al., 2001). While perhaps not mainstream, this theory neatly accounts for the various manifestations of dyslexia, and offers a plausible account of the manner in which cerebellar abnormalities may cause impairments in both phonological processing and reading. Furthermore, this theory offers a heuristic model for conceptualizing the reading difficulties seen in children with DMD. Their putative developmental description seems to perfectly describe the association of deficits seen in DMD children.

It is important to note that, while this section has focused on the "cerebellar deficit hypothesis," every theory of dyslexia must account for the manner in which children normally acquire language and reading in a rapid and effortless fashion. Reading becomes automatic, nay obligatory, in most normal children and adults. Indeed, there appears to be general consensus that the acquisition of fluent reading involves mastery of a particular skill or subset of skills to the point of automaticity (Bruck, 1992; Chall, 1987; Felton, Naylor, & Wood, 1990; Kitz et al., 1989; LaBerge et al., 1974; Shaywitz, 1998; van Daal & van der Leij, 1999; van der Leij & van Daal, 1999). Theories of dyslexia which attribute reading impairments to basic deficits in temporal processing (Anderson, Brown, & Tallal, 1993; Tallal, Miller, & Fitch, 1993), emphasize that the core deficit involves difficulty processing <u>rapidly</u> changing stimuli. The efficiency with which children analyze fast and transient stimuli (on the order of tens of milliseconds) appears to be impaired in dyslexia (Anderson et al., 1993; Tallal et al., 1993). Thus, across

theoretical perspectives, there is general agreement that efficiency and automaticity are paramount in the acquisition of reading skills. If, as we have argued, the cerebellum is responsible for helping to automatize cognitive skills, it stands as the perfect neural substrate to assist in this process.

Summary

We have argued that DMD is a "cerebellar" disorder. In the current paper, we have presented evidence to support our contention that disruptions of the cerebro-cerebellar pathways best account for the profile of cognitive deficits seen in children with DMD (e.g., limited verbal span, difficulty with phonological processing and reading). We reviewed neuroimaging evidence suggesting that the cerebellum is involved in these same aspects of cognition and that damage to the cerebellum disrupts functioning in these domains. Although there are numerous other areas of the brain that are traditionally implicated in these types of deficits (and which may also play a role in DMD), we contend that the cerebro-cerebellar loops hypothesis provides the most parsimonious explanation for the cognitive effects associated with the disease. In fact, the hypothesis that disruptions of the cerebro-cerebellar loops cause cognitive deficits in children with a motor disorder is consistent with opinions that motor and cognitive development are closely interrelated (Diamond, 2000).

We have also argued, as have others, that the cerebellum serves to coordinate cognition in the same way that it operates to coordinate motor skills and learning; it helps to automatize and optimize performance in certain cognitive domains. Thus, damage to the

cerebellum will likely result in sub-optimal performance and these decrements in performance may escape detection if not studied carefully. We have shown that children with DMD display the types of deficits that one would predict given a cerebellar injury, both in terms of the type of deficit and the quality of the deficit.

Finally, we have argued that these deficits are due to the genetic mutation in DMD, which disrupts the production of dystrophin. Brain pathways in the cerebellum develop without dystrophin, a crucial protein product. As dystrophin may be responsible for synaptic function, and especially for the formation of synapses early on in development, the lack of dystrophin in the fetal brain may lead to the disruption of synapse formation. Disordered connections may result in inefficient signaling and transmission of information, especially in the domain of language. Indeed, microscopic cortical abnormalities have been implicated in language and reading disorders in some of the earliest studies investigating the neuro-anatomical locus of language disorders (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985; Cohen, Campbell, & Yaghmai, 1989; Humphreys, Kaufmann, & Galaburda, 1990), and many investigators believe that the lack of plasticity seen in developmental language disorders may be due to an inefficiently wired brain (Bishop, 2000).

As evidenced by the findings described above, DMD provides a unique window into the relationship between neuroanatomical structure and cognitive function. It offers investigators the opportunity to study brain development that occurs without the presence of a necessary protein, which is the result of a mutation on a single-gene. In short, DMD

facilitates a rare opportunity for us to traverse the continuum from genotype to cognitive phenotype.

Conclusion

Neuropsychologists are, at heart, reductionists. We believe that cognitive skills can be localized to structures in the brain. We also believe that alterations in brain structure can compromise the integrity of brain functioning, which, in turn, can cause observable changes in behavior and cognition that may be measured using neuropsychological tests. The unique perspective of the neuropsychologist was the animating force behind this dissertation, which has sought to describe cognitive deficits in a population of children with a genetic disorder and to attribute those deficits to a particular brain structure. Taking this approach to its logical conclusion, this dissertation has extended the causal chain by studying children with a single-gene disorder and hypothesizing that a mutation in a single gene is responsible for the alterations in brain structure and function, and ultimately, cognition.

There are those who believe that attributing cognitive deficits to a genetic mutation implies a certain sense of fatalism about those cognitive deficits. On the contrary, the findings of the current investigation should in fact impart a sense of hope to parents of children with DMD. The global cognitive deficits exhibited by the younger children tested in this sample stand in stark contrast to previous studies of older children with DMD, which have reported only selective cognitive deficits. This dichotomy suggests that children may improve over time and that some non-genetic variable (i.e., environmental factor) is facilitating this remediation. Put differently, although brain structure and function can affect cognition and behavior, the converse holds equally true as well – i.e., behavior and cognition can affect brain structure and function (Kujala et al.,

2001; Small, Flores, & Noll, 1998; Temple et al., 2003). The links in the causal chain are not static, one-way associations; rather, they are dynamic and reciprocal brain-behavior relationships. In the end, however, the true promise of this research lies not only in the specific findings as they relate to children with DMD, but in the tantalizing possibility that through the study of single-gene disorders one can reduce neuropsychological differences to the level of the gene.

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Conclusion

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