COGNITION IN DUCHENNE MUSCULAR DYSTROPHY

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ABSTRACT

Duchenne muscular dystrophy (DMD) is a genetic neuromuscular disease characterized by a lack of dystrophin – a protein – in mainly skeletal muscle cell membranes. The disorder, affecting 1:3500 male births, is of a progressive nature, causing degeneration and death of the muscles. Though the spectrum of intellectual functioning in DMD ranges from above normal to severely retarded, there seems to be a particular profile of cognitive deficits associated with the disorder. The current descriptive case control study, which forms part of a larger study based at Red Cross War Memorial Children's Hospital, seeks to describe the neurocognitive phenotype of a cohort of South African boys with DMD. The sample consisted of 10 DMD boys and 8 suitably matched controls; ages ranged from 7 to 15 years. Based on previous international studies, a neuropsychological test battery was constructed to measure the following domains: General intellectual ability; Performance IQ; attention/concentration; memory; visuoconstructional ability; executive function; and reading ability. Results indicate that South African DMD boys have normal intellectual abilities; long-delayed recall also seems to be intact. Impairments have been found in attention visuospatial short-delayed recall, cognitive flexibility, phonological processing, and sequential information processing. Apart from some of the results that were inconclusive, the data show that the neuropsychological profile of this South African sample as determined thus far, matches that seen in previous international studies.

BACKGROUND

Duchenne muscular dystrophy (DMD) is a neuromuscular disease characterized by a lack of dystrophin – a protein – in mainly skeletal muscle cell membranes (Felisari et al., 2000). Originally described in 1861 by a French neurologist, Guillaume Benjamin Amand Duchenne, the incidence of the disease is about 1:3500 male births (Muscular Dystrophy Foundation of South Africa, 2000). DMD is thus the most prevalent neuromuscular illness, and affects all sociocultural groups. Being part of the muscular dystrophy spectrum, it fits the following criteria: (i) it is a primary myopathy, (ii) it has a genetic basis, (iii) it has a progressive course, and (iv) there is eventual degeneration and death of muscles (Nelson, 2004).

DMD is an X-linked recessive trait, which is the reason why it is symptomatically manifest mainly in boys (Nelson, 2004). Most individuals inherit the disorder from their mothers; only 30% of all DMD patients result from new (spontaneous) genetic mutations. For approximately the first 2 years after birth, DMD children are hardly symptomatic, although poor head control may be the first sign of hypotonia in infancy. By age 5 or 6 years, symptoms can usually be observed. Most boys remain ambulant until an average age of about 10 years, by which time they need to be confined to a wheelchair. From time of diagnosis, patients need to be monitored and medically checked regularly, especially their cardiac and respiratory systems. Quality of life may be improved by regular physiotherapy and constant monitoring of diet. Steroids may also be administered to boost strength. Unfortunately there is no way to treat or slow down the progression of DMD. Death usually occurs by age 18 (Nelson, 2004).

When Duchenne originally described the disorder in 1861, one of the features he included was intellectual impairment. Although intellectual impairment seems to occur in most patients, most are still able to function reasonably well in mainstream schools. Only a few patients are profoundly mentally retarded, but it is noteworthy that there is no correlation between intellectual impairment and severity of the disease (Nelson, 2004).

Brain, Molecules, and Genetics

Many scientists have tried, by means of histology, to find evidence for deformities in the brain that correlate with intellectual impairment in DMD. Some studies have found neuronal irregularities such as, Purkinje cell loss, cortical atrophy, and ventricular dilation in DMD patients, while others have found no differences between DMD patients and healthy individuals in terms of the physical make-up of the brain (Anderson, Head, Rae, & Morley, 2002). Overall, therefore, the literature indicates that there is still no histological evidence showing any consistent peculiarities for DMD patients.

Electrophysiological studies, however, seem to be inconsistent in showing brain abnormalities in DMD patients, therefore findings still remain controversial (Anderson et al., 2002). However, most consistent abnormality, 14 and 6/s positive spikes on the electroencephalograph, is also found in conditions such as migraines and vegetative seizures, where the brain is not functioning normally.

Because DMD is a genetic disorder, there is in the literature much discussion about the relationships between DMD-associated genetic anomalies, the absence of dystrophin, and cognitive impairment (Anderson et al., 2002). Variance in the cognitive profile of patients is now believed to be partly due to different genetic mutations. More specifically, distal deletions, more than proximal ones, are correlated with mental retardation in DMD. In particular, dystrophin isoforms Dp71 and Dp140, which are coded on the distal parts of the dystrophin gene, may be instrumental in the cognitive dysfunction observed in some DMD patients. The Dp71 and Dp140 proteins are expressed in the brain i.e. they are also found in the brain. Mutations in their sequences could mean dysfunctional proteins and therefore impaired cognition (Bardoni et al., 2000; Bushby et al., 1995; Moizard et al., 1998, 2000).

Previous Research into the Cognitive Profile of DMD Patients

Most studies assessing intellectual ability in DMD have employed measures such as the Wechsler Intelligence Scales (WIS; The Psychological Corporation, 1997; Wechsler, 1999). These studies consistently find that full scale IQ is significantly lower in DMD patients, compared to age-matched typically developing individuals, by an average of one standard deviation (Cotton, Voudouris, & Greenwood, 2001; Lebowitz & Dubowitz, 1981).

Additionally, early studies (e.g., Karagan & Zellweger, 1978) suggested that Verbal IQ (VIQ) was significantly more impaired than Performance IQ (PIQ) in DMD, particularly in younger boys. A meta-analytic review that included 1224 DMD boys between the ages 2 and 27 years, however, showed no overall difference between PIQ and VIQ. The meta-analysis did note the interesting trend that the VIQ-PIQ discrepancy significantly decreased with age. Subsequent studies have confirmed that the reason for this declining discrepancy is not that PIQ declines with age as muscles become weaker; rather, PIQ remains relatively constant (at about 1 SD below the population mean, or in the range commonly described as low average) while VIQ increases with age, peaking in the early teen years (Cotton et al., 2001, 2005).

The Wechsler intelligence tests may not be the ideal instruments to measure general intellectual functioning in DMD, given the verbal emphasis of the tests and clinical and research observations of language-based disorders in DMD individuals (e.g., Dorman, Hurley, & D'Avignon, 1988). Thus, Wicksell et al. (2004) used a nonverbal measure of general intellectually ability (Raven's Coloured Progressive Matrices; RCPM; Raven, Raven, & Court, 1998) in a study with DMD boys. Their results indicated that the general intellectual ability of their DMD sample was similar to that of their control group.

Because of the variability of clinical presentation within the DMD population, a key question is whether measures of overall intelligence, or general intellectual ability, are sufficient to capture individual variations in cognitive functioning within the population. Therefore, some researchers have moved towards examining whether DMD is associated with a pattern of particular cognitive deficits, regardless of IQ (Wicksell et al., 2004). For instance, Bresolin et al. (1994) found that DMD boys showed a consistent pattern of impairments on short-term memory tasks, regardless of whether their IQ scores were in the retarded range or not. Wicksell et al. (2004) replicated that result, and also showed that DMD individuals performed significantly more poorly than did typically developing children on tests of sensory storage and executive functioning.

The consensus from multiple studies, however, is that language is the most marked domain of cognitive impairment in DMD. For instance, Smith, Sibert, and Harper (1990), while investigating the differences in early development (< 72 months) between DMD boys and normal boys, found that the DMD group performed significantly more poorly on tests of expressive language, verbal comprehension, and receptive vocabulary. Importantly, maternal

intelligence and home environment were of no consequence in this study. Other studies of language functioning in DMD have found that auditory comprehension and reading ability (particularly non-word reading) are compromised, again regardless of IQ or overall information processing skills (Billard, Gillet, Barthez, Homet, & Bertrand, 1998; Hendriksen & Vles, 2006; Hinton, De Vivo, Nereo, Goldstein, & Stern, 2000; Lebowitz & Dubowitz, 1981).

Present Study

The scholarship in this area, especially more recent studies, provides strong evidence for specific cognitive deficits in DMD. The aim of this study, as part of a bigger one at the Red Cross War Memorial Hospital (RXH), is to describe the neurocognitive phenotype of a cohort of South African boys with DMD. Furthermore, this study also seeks to improve on most previous neuropsychological investigations of DMD by administering a carefully selected and comprehensive battery of tests that will provide not just an IQ measurement but a profile of cognitive strengths and weaknesses within the disorder. The battery used here closely resembles that used by Wicksell et al. (2004) in terms of the tested domains: general intellectual ability, PIQ, attention/concentration, learning and memory, visuoconstruction, executive function, and reading.

METHODS

Participants

The RXH runs a Neuromuscular Service that caters in part for patients with DMD. Patients suspected to have the disorder are screened genetically and if the genetic test is negative, a muscle biopsy is done to ascertain the diagnosis. A database has been created for boys with DMD, and the participants were obtained from the database.

As patients came in for consultation, they received a verbal breakdown of the study and were asked if they wished to take part. Some families were given the consent forms to take home with them. I, as the one to administer the neuropsychological battery, was present at some of the clinics for the families to familiarize themselves with me. Some families did not attend the clinic during this initial stage, but they were contacted by one of the doctors involved in

the larger study at the hospital. The doctor also called all the families to set up appointments for the testing. My task was to call the families closer to the appointment date to confirm and reschedule where necessary.

Eleven boys with DMD were recruited in this way and included in the study. One of these was eventually excluded from the analysis because he had outlying results on most of the tests. The reason for his outlier status may have to do with the fact that he was the only DMD boy in this sample from a high socio-economic background. Each remaining DMD boy and his family helped to recruit a control participant who was matched as closely as possible for age (maximum of 6 months difference), sex, and socioeconomic status (from the same neighbourhood). Only 8 of the 10 were successful in their recruitment attempts, although two came with girls. The demographic characteristics of both the DMD participants and their typically developing (TD) counterparts are shown in Table 1. None of the participants had a history of psychiatric diagnosis or treatment, head injury with loss of consciousness or any other neurological problems. One participant in the DMD group had been previously diagnosed with Attention-Deficit Hyperactivity Disorder (ADHD).

All of the experimental procedures were approved by the Red Cross War Memorial Children's Hospital Research Committee, and by the University of Cape Town Research Ethics Committee of the Psychology Department.

Measures

The literature on DMD indicates that researchers have been focussing their attention on no more than a few areas of cognition. The most comprehensive study to date is one by Wicksell et al. (2004). As mentioned earlier, the present study employed a carefully selected and comprehensive battery of neuropsychological tests. This battery assessed seven domains of cognition: general intellectual ability, performance IQ (PIQ), attention/concentration, learning and memory, visuoconstruction, executive functions, and reading ability. For participants who preferred to be tested in Afrikaans and Xhosa, translators were present to administer translated versions of tests where they were available, and to translate tests without translated versions.

General intellectual ability was measured using the *Raven's Coloured Progressive Matrices* (*RCPM*; Raven et al., 1998). This test assesses nonverbal, logical reasoning, and is considered a reasonably culture-fair test (Strauss, Sherman, & Spreen, 2006). It consists of 36 items divided into 3 sets; difficulty increases from one item to the next within sets, and also from one set to the next. The matrices are printed in colour to appeal to children (Lezak, Howieson, & Loring, 2004). In South Africa, the RCPM is often used in clinical practice and educational settings; isiXhosa norms have been developed (Knoetze, Bass, & Steele, 2005).

The *Wechsler Abbreviated Scale of Intelligence* (*WASI*; Wechsler, 1999) was used to determine the PIQ of the participants. The Block Design (BD) and the Matrix Reasoning (MR) are the PIQ subtests. The BD subtest consists of 13 items. Examinees are given blocks (with red, white, and red and white sides) with which they are to make a two dimensional design shown to them. The tasks are timed. As this is a construction test, it was also used to assess the visuoconstructional abilities of the participants (Lezak et al., 2004). The MR test measures visual information processing and abstract reasoning skills. This exercise is similar to the RCPM. There are two practice and 35 test items on this test. The advantage of using the PIQ (and RCPM) is that they do not depend on language for completion (Wechsler, 1999). In South Africa, the WASI is often used in clinical settings, but there are no published research studies featuring the use of the instrument in South African populations. There are however, studies published on other Wechsler scales e.g. Nell, (1999).

Attention/concentration was measured by the Sequences and Numbers subtests of the *Children's Memory Scale* (*CMS*; Cohen, 1997), was the third domain that was assessed. The CMS allows for the calculation of an attention/concentration index (A/C index). This index is a measure of processing speed, working memory, and the ability to sustain and direct attention. The A/C index is calculated from performance on the Sequences and Numbers subtests. In the Sequences subtest, the items test one's ability to mentally manipulate and sequence auditory-verbal information. All items are timed. The Numbers subtest requires respondents to repeat (both forward and backward) random number sequences of increasing length.

For the domain of learning and memory, three tests were used in this assessment. First is the *Rey Auditory-Verbal Learning Test (RAVLT)*, which is a test of verbal learning and memory (Lezak et al., 2004; Strauss et al., 2006). In the RAVLT, a list of 15 words is read to each

respondent; he must immediately say any words he remembers from the list in any order (immediate recall). The same list is read four more times, and after each time the respondent is asked to say the words remembered. After the fifth trial, a second list of words is read and those words must be remembered. Participants are then asked to say any words they remember from the first list again; this is a measure of short-delay free recall. After 25-30 minutes (a delay filled by other tests in the battery), the participant is asked to say the words they can remember from the first list (long-delay free recall). As a further test of learning and memory, participants are then asked to complete a word recognition task for the words on the main list (Lezak et al., 2004). In this test, there are many potential dependent variables, but the three chosen for this study are Total (sum of trials one to five), Trial 5 (immediate recall after main list is read for the fifth time), and the long-delay free recall variables. These were chosen because they have been reported to be the most reliable (Strauss et al., 2006).

The second test in this domain is the Story Memory Test (SMT) of the *Senior South African Individual Scale - Revised* (*SSAIS-R*; Van Eeden, 1991) which measures verbal-auditory memory. The SSAIS is a standardized intelligence test; the SMT is a verbal subtest. A short story was read to each participant; he was then asked to retell the story, not necessarily verbatim but including essential details, immediately and 25-30 minutes later (short- and long-delay).

The third test in this domain, the *Rey-Osterrieth Complex Figure Test (Rey-O),* is a rich source of information on visuospatial skills, visuoconstruction ability, visual memory and executive functioning (Strauss et al., 2006). The Rey-O is among the top ten neuropsychological tests administered and it is not culturally biased. Each participant was given a piece of paper with the complex figure on the top half of the page and was asked to copy it onto the bottom half of the page (for picture of complex figure used see Lezak et al., 2004, p. 537). This process gives a measure of the visuoconstructional abilities of the participant. To measure visual memory, the participants were asked to draw the Rey-O from memory immediately after drawing the copy (short-delay), and 25-30 minutes later (long-delay). The Rey-O is often used in clinical settings, but there are no published research studies featuring the use of the instrument in South African populations.

The next neuropsychological domain tested was executive functioning. The *Trail Making Test* (*TMT*; Reitan, 1992) allows for analysis of scanning and visuomotor tracking, attention,

speed, and cognitive flexibility. The test consists of two parts, Trails A and Trails B. In Trails A, each participant was required to connect consecutively numbered circles. In Trails B, they had to connect consecutively numbered and lettered circles, alternating between the two sequences. The trails were to be made as fast as possible without lifting the pencil from the paper (Lezak et al., 2004). The TMT is a reliable and popular, the fourth most used test of executive functioning (Strauss et al., 2006). Its use has been reported in South Africa (Rosin & Levett, 1989).

The second test within this domain was the *Tower of London* (*TOL;* Culbertson & Zillmer, 2001)*.* It measures executive planning efficiency and problem solving ability. The TOL uses two wooden boards, one for the examiner and one for the participant, with three upright sticks, and three coloured balls (red, green, and blue). The examiner places the balls in a predetermined position and the participant rearranges the balls on their board from a standard start position, in as few moves as possible, to match the arrangement on the examiner's board. There are 10 test items which are progressively more difficult. Participants have a maximum of 2 minutes in which to complete each item while adhering to two rules: only one ball can be moved at a time, and each stick can hold a maximum number of balls which may not be exceeded (Lezak et al., 2004). Seven scores may be obtained from this test, but in this study, I only used these two as outcome variables: Total Move Score (TMS) and Total Correct Score (TCS). The TMS is the primary measure of executive planning, while the TCS clarifies an individual's planning and problem solving abilities (Culbertson & Zillmer, 2001). There are no published research studies featuring the use of this instrument in South African populations.

The final test of executive functioning is the *Verbal Fluency Test* (Strauss et al., 2006). It assesses response generation, working memory, speed, and semantic memory. For this study we tested both phonemic fluency and category fluency. Under phonemic (letter) fluency, the participants being tested in English were asked to say as many words as they could, beginning with a target letter within one minute. Afrikaans and Xhosa participants used a different set of three target letters. For category fluency the participants had to say the names of as many animals as possible within one minute.

Reading ability was the final domain tested. The first test of reading ability that was administered is the *Neale Analysis of Reading Ability – Revised* (*Neale*; Doctor & Chandler,

1986). This test is useful in determining the nature and cause of reading difficulties. It is an oral test administered individually. The Neale is made up of three parallel tests, A, B, and C, but in this study we only used the first one. Each one is made up of six passages forming a continuous scale. The Neale provides scores for speed, accuracy of word recognition, and comprehension. It is commonly used to assess reading problems in South Africa.

The second test of reading ability was the *Non-word Reading Test* from the *Phonological Assessment Battery* (*PhAB*; Frederickson, Frith, & Reason, 1997). This test is used to see what specific reading deficits the child has. It consists of one practice card and two test cards. For each of the test cards there are 10 words which have been made up and have no meaning. These words are presented to the child and he is required to correctly read these words.

Procedure

Testing was conducted in designated rooms at the hospital. On arrival, the parents and the participants were told about the testing session and what to expect. For those who had not received the consent form, it was presented and they were given time to go through and sign it (see Appendices B and C). Some demographic information was collected about the participants and their families. Testing ideally should have been done with family members outside the room, but some children wanted their mothers in the room with them. In such cases the family member sat behind the participant. While the testing proceeded, parents filled out behaviour questionnaires on the participants.

The test battery was administered in a sequence that allowed for the administration of the delayed recall measures (see Appendix A). English and Afrikaans participants followed the same sequence while the Xhosa sequence was a little different due to the unavailability of Xhosa versions of the RAVLT, SMT, and the reading tests.

The battery was designed to take a maximum of 2 hours to administer. Some participants chose to take breaks during the session, an allowance that had been made. The choice to discontinue the testing due to any discomfort was also available to participants and many of the participants took (comparison between two people on last test, non-word reading test).

After the testing session was concluded, we had an informal discussion about the different tests. For instance, some participants found the TOL particularly interesting and we would talk it, along with other reflections they had. Money was then given to families to cover transport costs. Some family members had a few questions, so these were also addressed after the testing, before they said goodbye.

RESULTS

Data Analysis

The initial analysis of the test scores was done using a one-way ANOVA on each test, but this report is focussed on the results obtained from an ANCOVA (analysis of covariance). The covariate in this study was age; this because many of the tests have previous reports of older children performing better than younger ones (e.g., Culbertson & Zillmer, 2001; Knoetze et al., 2005). Three of the older DMD participants were unable to recruit TD controls; therefore any differences between DMD and TD participants could be masked in the ANOVA. All tests were run at the 5% significance level.

Effect sizes reported were calculated to give the *Cohen's d* effect size. Howell (2007) gives an interpretation guide for this effect size: $d \geq 0.2$ – small effect; $d \geq 0.5$ – moderate effect; $d \geq 0.8$ – large effect. The results of all the tests are shown in Table 2.

General intellectual ability

Assessment of this domain reveals that there is no significant difference between the DMD and TD participants ($p = 0.189$). Therefore both groups have similar intelligence. However, the effect size points to a moderate effect ($d = 0.661$) suggesting that the lower performance of the DMD participants, though not significantly lower, is considerably explained by their condition. On average, both groups performed within one standard deviation above the mean for published isiXhosa norms (Knoetze et al., 2005); this is true even for the ANCOVA-adjusted means. DMD participants' performance is ranked between the 50th and 75th percentiles, while TD children ranked between the 75th and 90th percentiles.

Performance IQ

PIQ was not significantly lower in DMD boys ($p = 0.456$), and the same applies to the PIQ subtests, i.e. Block Design and Matrix Reasoning. The PIQ effect size is one of those that decreased, from large in the ANOVA to moderate in the ANCOVA, suggesting that across the age span, DMD boys have a PIQ similar to that of normally developing children.

Attention/Concentration

The analysis shows that there is no difference between the two groups with respect to the A/C index ($p = 0.101$). However, the DMD boys performed significantly worse than the TD controls on both the Sequences and the Numbers-Backward tests ($p = 0.006$ and $p = 0.038$ respectively). The overall Numbers subtest was also marginally significant in favour of the TD children ($p = 0.058$); probably driven by the poor performance on the Numbers-Backward supplementary test. All the effect sizes recorded within this domain were large ($d > 1.4$) besides the Numbers-Forward, suggesting that DMD are still at a disadvantage compared to TD controls in their attention and concentration abilities.

Learning and Memory

The effect sizes in this domain generally indicate that the DMD participants performed worse than the controls ($0.36 > d > 1.255$). The RAVLT Total was marginally significant ($p = 0.059$), pointing to a difference between the two groups in the verbal-auditory acquisition of words; with the DMD participants being at a disadvantage. However, by the time trial 5 is completed, they perform more like the controls ($p = 0.318$).

For short-delay recall, the DMD participants performed similarly to the controls ($p = 0.547$) on the verbal-auditory measure (SMT) whereas their performance on the visuospatial task (Rey-O: immediate) was significantly worse ($p = 0.03$). None of the long-delay measures showed significant differences between the two groups.

Visuoconstruction

None of the tests in this domain yielded significant results, but both of them suggest a tendency toward significance. For the Rey-O, $p = 0.051$). The block design test did not have such a small p-value but it had a large effect ($d = 1.164$). The adjusted means for the two groups, DMD = 6.114 and TD = 16.062, also point to an important difference between the two groups. The large variance of scores in the DMD group could be the reason for the lack of statistical difference between the two groups; this applies to other tests too.

Executive Functions

In this domain, unexpected results were obtained from the TOL – the DMD participants performed slightly better than the controls. The primary measure of executive planning as measured by this test, the TMS, was not significant, but the TCS, another measure of planning and problem solving tended to significance ($p = 0.057$) in favour of the DMD boys. On the other hand, the other tests of executive function provided evidence for impairment in DMD. The DMD participants performed significantly worse than the TD controls on both the Trails A and B ($p = 0.014$ and $p = 0.002$, respectively). The Trails B showed a very large effect size ($d = -2.655$) meaning that the DMD boys have poor cognitive flexibility. The TD group also performed significantly better on the phonemic fluency task ($p = 0.021$), while the category fluency task showed an insignificant difference between groups ($p = 0.347$) and a moderate effect size ($d = 0.586$).

Reading

Unfortunately, due to participants choosing to abort the testing sessions prematurely, there was no data to statistically analyze in this domain. There was only one DMD boy who went through the reading tasks. Three controls did the Neale, but only one did the non-word reading task (see Figure 1).

DISCUSSION

The aim of this study was to describe the neurocognitive profile of South African DMD boys. Results suggest that, on average, DMD boys are not mentally retarded; they have average intellectual capabilities, comparable to typically developing children. Boys with DMD definitely have attention, and short-delay memory impairments for visuospatial material. Other deficient cognitive processes are: cognitive flexibility, phonological processing, and sequential information processing. Although many of the tests showed insignificant differences between the DMD and control participants, a number of the probabilities returned and effect sizes calculated, point to some very important differences between the two groups. The search for specific impairments in DMD boys is supported by the fact that performance within cognitive domains is varied and therefore needs to be probed further.

The results from the RCPM demonstrate that the DMD boys have similar intellectual abilities with the controls. This is in keeping with previous research using the same measure of intellectual ability (Wicksell et al., 2004). Another study using this test also yielded results showing similarities between DMD boys and other children (Cotton, Crowe, & Voudouris, 1998). Most significantly, however, is that the DMD boys performed within a normal range as determined by local isiXhosa norms (Knoetze et al., 2005). This means that boys with DMD are able to engage in logical and abstract reasoning. However, the effect size shows that DMD boys are still at a slight disadvantage. Performance in this domain could explain why many DMD boys can function in mainstream schools.

In a meta-analytic study by Cotton et al. (2005), nonverbal intelligence was reported to be significantly depressed in DMD individuals. The findings in this study contradict that conclusion. Both groups of participants performed significantly worse than published international averages; it was in the borderline impaired range, but there was no difference between the two groups. The results of the PIQ test tie in well with those of the RCPM above in that they are both measures of nonverbal logical reasoning and both show the performance of DMD participants to be equivalent to that of controls. However, the performance of both groups on the subtests of nonverbal intelligence falling into the borderline impaired range is disturbing. It could be that the low socioeconomic and educational backgrounds of the children are strongly affecting their performance. Otherwise, all the participants could be impaired in this regard. The large effect size as shown by the BD, coupled with the near-

significant findings of the Rey-O (copy), suggest that it is very likely that DMD individuals have impaired visuocontructional abilities. This contradicts findings reported by Cotton et al. (1998), and Hinton et al. (2000), who stated that visuo-spatial/constructional abilities were normal in DMD boys. However findings in this research are in line with those of Wicksell and colleagues (2004), who also found impairments in visuospatial abilities. I found that the struggle in this area of cognition could be observed through an apparent "focus on details rather than the geometric properties" of the diagram; an observation also made my Wicksell et al. (2004, p. 158). Therefore, further investigation is needed in this domain. Future analyses could employ the organizational scoring for the Rey-O to assist in detection of visuoconstructional impairments.

Some of the data indicate that DMD boys have normal attention, processing speed, and working memory. However, most tests that measure these areas of cognition give strong evidence for impairment in verbal-auditory working memory and attention. The performance on the Sequences subtest, in particular, indicates that DMD participants have difficulty with sequential recall. These findings are congruent with the work done by Anderson, Routh and Ionasescu (1988). These researchers attributed this difficulty to an inability to sustain attention. Hendriksen and Vles (2006) found that the difficulty with sequential information is because of a low information processing speed of sequential data.

The marginal significance of the measures for learning suggests that verbal-auditory learning in DMD boys is slower; this piece of data is in line with past research (Hinton et al., 2000). The current study also supports previous findings that showing that long-delayed recall is intact in DMD boys (Wicksell et al., 2004). The results on short-delayed recall were unexpected in that verbal-auditory memory in DMD boys was similar to that of TD children. Usually DMD boys perform worse than normal children on these tasks (Bresolin et al., 1994; Hinton et al., 2000; Wicksell et al., 2004). It is possible that the story that was read was not suitable to the sample assessed, i.e. not culture-fair, thus the very poor performance observed in both groups. Hinton et al., (2000) stated that visuospatial abilities in DMD are not impaired but the findings of this study contradict that. It can therefore be concluded that DMD boys have impaired short-term memory regardless of the mode through which information is presented, and this is keeping with research (Bresolin et al., 1994; Wicksell, et al., 2004).

In this study, measures of executive planning and problem solving ability showed that DMD individuals are not compromised in this regard; they actually suggest that on some executive function measures, they could be better off than normal children. These findings contradict past research using the same measures (Wicksell et al., 2004), and are probably due to small sample size. The assessment of other executive functions led findings similar to those found by Wicksell et al. (2004), i.e. poor performance by DMD participants. The poor performance of DMD participants on the Trails, A and B, again points to an inability to sustain attention. The need to process visual information and coordinate it with motor actions is necessary in this task. The processing of sequential information may also be affecting the performance of these tasks. However it is noteworthy that the physical disability of DMD boys is also likely to affect the speed to task completion. This study shows that cognitive flexibility is also highly impaired in DMD boys. The slow response generation in the phonemic fluency task could be a result of difficulties with phonological processing that have previously been found in DMD boys (Billard et al., 1998).

The little data collected from the tests of reading ability was not sufficient for group comparisons. One serious limitation in this study was the small sample size. As in other studies, the DMD group showed a lot of variance in scores. This is likely to have clouded the results. Increasing sample size in future research will better control for the variability.

Another big limitation in this study was the attrition of the sample. Some members of both groups did not complete all the tests. This was largely due to the length of the testing session. Shortening sessions and having multiple ones might yield better results. Previous studies have managed to test participants in their homes (e.g., Cotton et al., 1998); this may be a step worth taking to ensure that participants are in a comfortable environment, and to avoid inconveniencing families that would need to transport physically disabled children.

Future research should do better job of using executive function tests that go along with empirically derived EF domains; viz. shifting, updating, and inhibition (Miyake et al., 2000). Executive functioning is a category that includes a lot of different tests and a lot of different functions and researchers need to increase precision in describing this and other cognitive functions.

In conclusion, in this study I have described that South African DMD boys have normal intellectual abilities; long-delayed recall also seems to be intact. Impairments have been found in attention visuospatial short-delayed recall, cognitive flexibility, phonological processing, and sequential information processing. All other domain and sub domains need to be investigated further in order to get more conclusive results. Otherwise, so far, the local profile is largely similar to that found internationally. Despite few limitations, this research is the beginning of the process of enabling clinicians in South Africa to identify the children with DMD who are at risk of developing any learning difficulties, therefore allowing for early, better, and more holistic interventions relevant to their needs.

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APPENDICES

Appendix A

Sequence of Test Administration

For English and Afrikaans participants:

      CMS: Sequences

      NEPSY: Finger Tapping Test

      Rey-O (copy and immediate recall)

      Story Memory Test (SMT) (immediate recall)

      Trail Making Test

      Tower of London

      Raven's Coloured Progressive Matrices

      Rey-O (delayed recall)

      SMT (delayed recall)

      Verbal Fluency

      RAVLT (learning)

      CMS: Numbers

      WASI: Block Design; Matrix Reasoning

      RAVLT (delayed recall and recognition)

      Neale Analysis of Reading

      PhAB non-word reading test

For Xhosa participants:

      CMS: Sequences

      NEPSY: Finger Tapping Test

      Rey-O (copy and immediate recall)

      Trail Making Test

      Tower of London

      RAVLT (learning)

      Rey-O (delayed recall)

      Raven's Coloured Progressive Matrices

      CMS: Numbers

      Verbal Fluency

      RAVLT (delayed recall and recognition)

      WASI: Block Design; Matrix Reasoning

Appendix B

Information Leaflet and Consent Form for Duchenne Muscular Dystrophy Project

Principal investigator: **Dr K Donald**
School of Adolescent and Child Health
Red Cross Children's Hospital
Rondebosch, Cape Town
Contact number: (083) 4194188

Your child is being invited to take part in a research project and we would like to ask for your consent. Please take some time to read the information presented here which will explain the details of the project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you understand what the research entails and how you and your child may be involved. Your child's participation is entirely voluntary. If you or your child is at all uncomfortable with the process you may contact myself (Dr K Donald) or Dr M Blockman. You are also free to withdraw at any stage, even if you do agree to take part.

This study has been approved by the Committee for Human Research at the University of Cape Town and will be conducted according to the ethical guidelines and principles of the International Declaration of Helsinki, South African Guidelines for Good Clinical Practice and Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

Some research overseas has shown that children with Duchenne Muscular Dystrophy have an increased risk of learning difficulties. A few studies have shown that a deletion on a specific part of the dystrophin gene is associated with an even higher risk of having learning problems.

We wish to look at whether this is true for South African boys with Duchenne muscular dystrophy. If we are able to identify a subgroup of boys who are at higher risk of having intellectual difficulties, we will be able to target these children for more intensive developmental follow up and educational support from an early age.

What would participation in this study involve?

All children who we think are likely to have Duchenne muscular dystrophy are offered gene testing (a simple blood test) as a routine part of their care. This is so that we can confirm the diagnosis and counsel you as parents about the likelihood of the problem occurring in children you may have in the future.

Although developmental assessment is offered to children under school age we have not to date offered formal psychometric testing of your child's intellectual development. With your permission we would like your child to undertake these tests. They are tests of intelligence and learning. In addition we would like you to complete a questionniare about aspects of your child's behaviour. The tests will take approximately 2 hours and will be arranged at your convenience at Red Cross Hospital. If your child is of school age, the testing will be performed by a postgraduate psychology student (supervised by Dr Kevin Thomas, senior

lecturer in the department of Psychology, University of Cape Town.) If your child is not yet at school Dr Kirsty Donald will perform the tests.

Participation is entirely voluntary. If you decide that your child should not participate in this study, it will not affect the way we treat your child. He will continue to receive the same standard of care that he presently experiences.

We will also be testing children from similar socio-economic backgrounds without Duchenne Muscular Dystrophy to make a comparison. These children will be chosen from your neighbourhood or from your child's school. We may ask for your help in recruiting these children.

Will you benefit from taking part in this research?

The results of the tests will be available to yourselves in full and should we discover any particular problems, we hope to be able to offer more informed advice about choice of schooling in pre-school children and the need for support for specific learning difficulties in children of school-going age.

Who will have access to your child's records?

All information collected will be treated as confidential and protected. If it is used in a publication or thesis, the identity of the participant will remain anonymous. The only people who will have access to the information collected will be Dr Kirsty Donald and Dr Kevin Thomas. As part of the study the research records may need to be reviewed by auditors or the Research Ethics Committee.

Will you be paid to take part in the study and are there any costs involved?

No, you will not be paid to take part in the study, but transport for yourself and your child will be paid for visits during the study.

Is there anything else you should know or do?

Please don't hesitate to contact Dr Kirsty Donald at telephone (083) 4194188 should you have any further queries or encounter any problems

You can contact the Committee for Human Research at 021-4066338 (Health sciences faculty, Research Ethics Committee, Room E52-24 Groote Schuur Hospital, Old Main Building, Observatory, 7925) if you have any concerns or complaints that have not been adequately addressed by your study doctor

CONSENT

By signing below, I………………………………………..give consent for my child …………………………………..to take part in the research study entitled: *Intellectual functioning and Duchenne Muscular Dystrophy: Intellegence testing and correlation with genetic diagnosis*

I declare that:

I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.

I have had a chance to ask questions and all my questions have been adequately answered

I understand that taking part in this study is voluntary and I have not been pressurised to take part

I may choose to leave the study at any time and will not be penalized or prejudiced in any way.

Signed at (place)…………………………………….on (date)……………………..

……………………………………………..   ……………………………………………..
Signature of guardian/parent   **Signature of witness**
RELATION TO CHILD: …………………………….

Appendix C

Information Leaflet and Consent Form for Duchenne Muscular Dystrophy Project (Controls)

Principal investigator: **Dr K Donald**
School of Adolescent and Child Health
Red Cross Children's Hospital
Rondebosch, Cape Town
Contact number: (083) 4194188

Your child is being invited to take part in a research project and we would like to ask for your consent. Please take some time to read the information presented here which will explain the details of the project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you understand what the research entails and how you and your child may be involved. Your child's participation is entirely voluntary. If you or your child is at all uncomfortable with the process you may contact myself (Dr K Donald) or Dr M Blockman. You are also free to withdraw at any stage, even if you do agree to take part.

This study has been approved by the Committee for Human Research at the University of Cape Town and will be conducted according to the ethical guidelines and principles of the International Declaration of Helsinki, South African Guidelines for Good Clinical Practice and Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

Some research overseas has shown that children with Duchenne Muscular Dystrophy have an increased risk of learning difficulties. A few studies have shown that a deletion on a specific part of the dystrophin gene is associated with an even higher risk of having learning problems.

We wish to look at whether this is true for South African boys with Duchenne muscular dystrophy. If we are able to identify a subgroup of boys who are at higher risk of having intellectual difficulties, we will be able to target these children for more intensive developmental follow up and educational support from an early age. In order for us to do this we need to test boys who do not have Duchenne Muscular Dystrophy and compare them with the boys in our clinic who do.

What would participation involve?

With your permission we would like your child to undertake these tests. They are tests of intelligence and learning. In addition we would like you to complete a questionnaire about aspects of your child's behaviour. The tests will take approximately 2 hours and will be arranged at your convenience at Red Cross Hospital. Your transport money will be reimbursed. If your child is of school age, the testing will be performed by a postgraduate psychology student (supervised by Dr Kevin Thomas, senior lecturer in the department of Psychology, University of Cape Town). If your child is not yet at school Dr Kirsty Donald will perform the tests.

Will you benefit from taking part in this research?

The results of the tests will be available to yourselves in full and should we discover any particular problems, we hope to be able to offer more informed advice about choice of schooling in pre-school children and the need for support for specific learning difficulties in children of school-going age.

Who will have access to your child's records?

All information collected will be treated as confidential and protected. If it is used in a publication or thesis, the identity of the participant will remain anonymous. The only people who will have access to the information collected will be Dr Kirsty Donald and Mr Kevin Thomas. As part of the study the research records may need to be reviewed by auditors or the research ethical committee.

Will you be paid to take part in the study and are there any costs involved?

No, you will not be paid to take part in the study, but transport for yourself and your child will be paid for visits during the study.

Is there anything else you should know or do?

Please don't hesitate to contact Dr Kirsty Donald at telephone (083) 4194188 on above number should you have any further queries or encounter any problems

You can contact the Committee for Human Research at 021-4066338 (Health sciences faculty, Research Ethics Committee, Room E52-24 Groote Schuur Hospital, Old Main Building, Observatory, 7925) if you have any concerns or complaints that have not been adequately addressed by your study doctor

CONSENT

By signing below, I…………………………………………..give consent for my child …………………………………..to take part in the research study entitled: *Intellectual functioning and Duchenne Muscular Dystrophy: Intellegence testing and correlation with genetic diagnosis*

I declare that:

I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.

I have had a chance to ask questions and all my questions have been adequately answered

I understand that taking part in this study is voluntary and I have not been pressurised to take part

I may choose to leave the study at any time

Signed at (place)…………………………………………….on (date)……………………..

………………………………………….   …………………………………………..
Signature of guardian/parent   **Signature of witness**
RELATION TO CHILD: ………………

TABLES AND FIGURES

Table 1

Demographic Characteristics of the Participants

		DMD (*n* = 10)	TD (*n* = 8)
Sex			
	Male	10	6
	Female	0	2
Age			
	Range (years-months)	7-6 to 16-7	7-2 to 14-7
	Mean (SD)	12.0 (2.8)	11.2 (2.4)
Education (years)			
	Mean (SD)	3.7 (2.45)	3.6 (2.06)
Home Language			
	English	2	2
	Afrikaans	5	4
	Xhosa	3	2
Language of Testing[a]			
	English	7	5
	Afrikaans	2	2
	Xhosa	1	1

[a]Two of the participants with home languages of Afrikaans preferred to be tested in English because they attended English-medium schools.

Table 2: Summary of Statistical results for Test Battery

Domains and tests	n (DMD:TD)	DMD M	DMD SD	TD M	TD SD	DMD Adjusted M	TD means M	MS error	F	p	ANCOVA Effect size (Cohen's d)	ANOVA Effect size
General Intellectual ability												
- RCPM	10:08	22.727	5.764	23.750	5.418	21.462	24.297	18.407	1.896	0.189	0.661	0.344
Performance IQ	05:07	77.000	21.317	78.857	10.511	71.998	76.859	91.929	0.606	0.456	0.507	0.916
- Block design	05:07	16.167	20.154	14.714	11.221	6.114	16.062	73.012	3.194	0.108	1.164	0.822
- Matrix reasoning	05:07	15.167	9.239	11.571	5.653	11.704	12.355	45.241	0.022	0.885	0.097	-0.177
Attention/Concentration Index	04:06	74.000	17.464	80.333	7.421	68.319	79.287	57.697	3.553	0.101	1.444	1.821
- Sequences	08:08	31.222	18.254	38.000	9.304	25.142	39.983	76.022	10.949	0.006	1.702	0.896
- Numbers	05:06	11.000	2.683	11.000	2.280	9.329	11.559	2.173	4.871	0.058	1.513	0.546
~Forward	06:07	7.143	1.574	6.857	1.069	6.801	7.028	1.565	0.098	0.760	0.182	-0.102
~ Backward	05:06	3.333	2.805	4.167	1.835	1.866	4.612	2.598	6.170	0.038	1.703	0.968
Learning and Memory - verbal/auditory learning												
~ RAVLT trial 5	07:07	9.125	4.051	9.714	3.861	7.880	10.263	14.553	1.096	0.318	0.625	0.335
~ RAVLT total	07:07	35.625	12.839	40.571	13.477	29.735	43.122	113.712	4.422	0.059	1.255	0.713
- short-delay recall												
~ verbal-auditory: SMT	07:06	12.750	9.067	11.167	7.574	9.660	12.063	44.624	0.388	0.547	0.360	0.103
~ visuospatial: Rey-O	09:08	8.350	4.014	12.938	5.876	7.445	13.249	23.095	5.870	0.030	1.208	1.062
- long-delay recall												
~ verbal-auditory: SMT	05:06	12.667	9.374	9.833	8.256	7.585	11.346	48.438	0.562	0.475	0.540	0.062
RAVLT	04:06	9.000	3.162	9.833	4.167	8.244	9.671	15.081	0.247	0.635	0.367	0.529
~ visuospatial: Rey-O	07:08	10.188	4.891	13.625	7.809	9.403	13.898	48.153	1.186	0.298	0.648	0.594

Table 2 (continued)

Domains and tests		n (DMD:TD)	DMD M	SD	TD M	SD	DMD Adjusted M	TD means M	MS error	F	p	ANCOVA Effect size (Cohen's d)	ANOVA
Visuoconstruction													
- Rey-O (copy)		09:08	21.550	9.260	26.563	7.971	19.637	27.658	56.586	4.575	0.051	1.066	0.687
- Block design		05:07	16.167	20.154	14.714	11.221	6.114	16.062	73.012	3.194	0.108	1.164	0.822
Executive functions													
- Tower of London													
~ TMS		08:08	89.111	18.306	82.750	15.078	88.725	82.525	326.182	0.407	0.534	-0.343	-0.330
~ TCS		08:08	99.778	16.954	86.500	10.623	102.278	85.722	216.509	4.374	0.057	-1.125	-1.047
- Trail Making Test	part A	08:08	134.333	100.071	91.875	62.084	163.568	73.932	3640.921	8.011	0.014	-1.486	-0.643
	part B	06:07	234.143	94.691	186.286	57.227	286.125	167.750	1987.530	16.866	0.002	-2.655	-1.399
Verbal Fluency	letters	07:07	8.143	4.776	13.714	4.889	7.231	14.626	21.201	7.238	0.021	1.606	1.153
	animals	07:07	11.857	4.180	12.286	2.430	11.140	13.003	10.106	0.964	0.347	0.586	0.125
Reading													
- Neale													
~ Accuracy		01:03	40.000	0.000	38.333	3.786							
~ Comprehension		01:03	18.000	0.000	12.000	2.646							
- PhAB non-words		01:01	12.000		11.000								

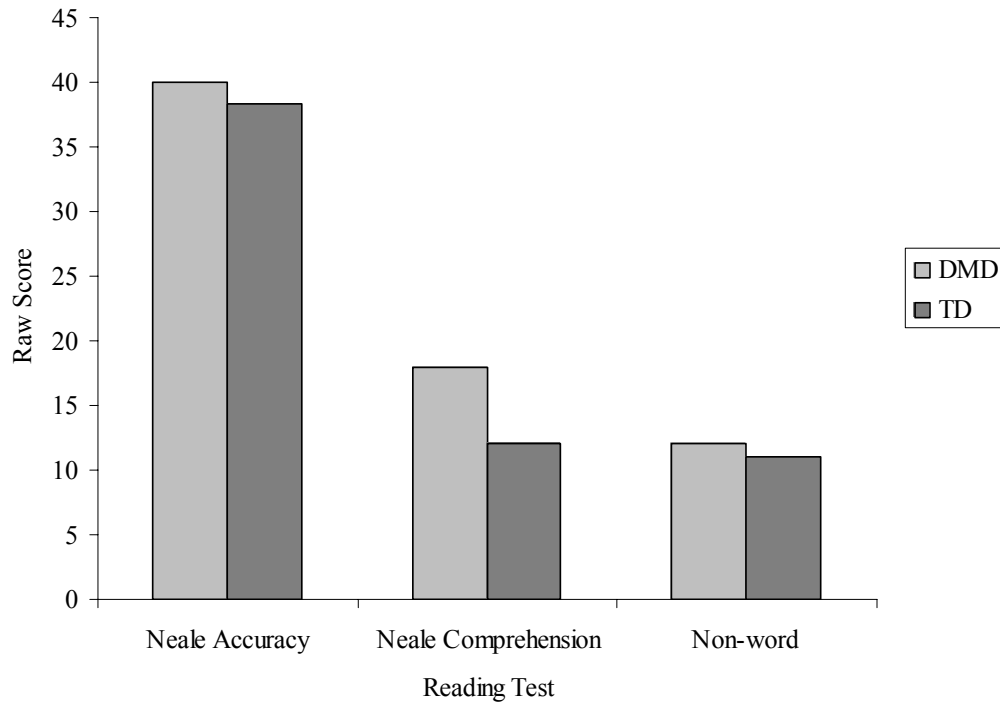*Note.* Data shown in the table are, unless otherwise noted, from the analyses of covariance (ANCOVAs).

Figure 1: Graph showing Reading test scores for DMD and TD children