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THESIS

Myotonic Dystrophy type 1 and Duchenne Muscular Dystrophy  
cognitive profile and behavioral functioning

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## **Abstract**

Duchenne muscular dystrophy (DMD) and myotonic dystrophy type 1 (DM1) are two neuromuscular disorders with a proven correlation between neurological deficits and cognitive deficits. These children have a high prevalence of learning disorders, reading problems in particular, which seems to be caused by deficits in verbal working memory and/or visuospatial functioning. Also a deviating behavior profile with internalizing and attention problems is seen in these children. The aim of the present study was (1) to describe the verbal working memory and visuospatial functioning, and reading skills and behavioral functions of children with DMD and DM1, (2) compare them with normative data and (3) compare DMD and DM1 patients with children with learning disabilities without a evident neurological comorbidity. Three children with myotonic dystrophy type 1 and four children with Duchenne muscular dystrophy in the range of 3 to 11 had undergone a neuropsychological assessment, behaviour questionnaires were completed by the parents. Deviating visuospatial functions were found in DMD and DM1 patients, when comparing them with normative data. With respect to their behavioural profile, DMD patients had more externalising problems compared to the normative data and to children with Verbal Learning Disorders. The data of this study did not correspond with previous studies on DMD and DM1. Limitations and implications for future research are discussed.

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**Literature**

## Chapter 1 Theoretical Background

### §1.1 Introduction

Recent literature (Hendriksen & Vles, 2008; Angeard et al, 2007; Douniol et al, 2009) suggests that certain neuromuscular disorders may also involve brain dysfunction. They found higher prevalence of cognitive, learning and neuropsychiatric disorders in neuromuscular disorders. Furthermore, D'angelo and Bresolin (2007) made a distinction between three types of neuromuscular disorders; (1) Neuromuscular disorders with cognitive deficits and, additional, a known genetic or protein deficit associated with changes of cerebral function, such as Duchenne muscular dystrophy (DMD) and myotonic dystrophy type 1 (DM1). (2) neuromuscular disorders with cognitive deficits and a cerebral abnormality, but without a defined genetic-biochemical abnormality, for example congenital muscular dystrophies and limb girdle muscular dystrophies. (3) neuromuscular disorders without or with very poorly defined cognitive impairment, for instance spinal muscular atrophy and facioscapulohumeral dystrophy. Given the proven correlation between neurological deficits and cognitive deficits, this thesis focuses on DMD and MD1.

Because of the higher prevalence of learning, cognitive and psychiatric disorders in neuromuscular disorders, in this chapter a review of cognition and behavior in learning disorders is described (§ 1.2). Next DMD and DM 1 will be illustrated on the basis of this review (§1.3 and §1.4). After the conclusions of the reviewed literature (§ 1.5), a description is made of the aims of our study, it's research design, and the hypothesis to be tested (§1.6).

### § 1.2 Cognition and behavior in learning disabilities

The cognitive and behavioral profile of learning disabilities will be described in this section in order to create a review that enables an evaluation of DMD and DM1 later in this thesis. This section will start with a definitions of learning disabilities to be able to describe this cognitive and behavioral profile in different sorts of learning disorders.

#### § 1.2.1 Definition of learning disabilities

Learning disabilities are defined as a heterogeneous discrepancy between predicted learning potential and academic performance with a neurobiological nature. To fulfil the definition of learning disorder there should be no sensory or motor impairment, mental retardation, emotional disturbance or environmental, cultural or economic disadvantage as a cause of the learning disorder (Hendriksen et al, 2007). Learning disabilities affect 1 to 2.5 percent of the general population and 10 to 15 percent of all school aged children (Gillberg & Soderstrom, 2003).

The predicted learning potential is determined by the intelligence of a child obtained on well standardized measures, that places a child in a perspective relative to others of similar age within a general population (Baron, 2004, p113). Academic performance is described as the skill levels of arithmetic, reading, spelling and writing (Miyahara et al, 1997; Baron, 2004). These academic skills

can only be acquired when they are preceded by several developmental processes, whereby cognitive functions are crucial. When learning arithmetic the concept numerosity, the number of objects in a set, is important (Butterworth, 2005). Even very young children can discriminate visual arrays on the basis of this numerosity. The development in arithmetic can be seen as an increased understanding of numerosity and its implications, and the ability of manipulating numerosities. Besides numerosity, other cognitive functions are proposed to be important in learning arithmetic, these are working memory, spatial abilities and language skills (Butterworth, 2005). When learning how to read and spell, several cognitive functions are concerned (Hendriksen & Hakvoort, 2010). Visual perception distinguishes spatial shapes from each other. The phonological awareness converts characters into sounds, the sounds are combined to form words, and these words are recognized from a vocabulary memory where words are stored auditory and phonemic. The process described above has to take place rapidly and automatically. Hereby automatic information processing is important (Hendriksen & Hakvoort, 2010). For learning how to write children additionally need visuomotor skills to integrate their visual perception and phonological information processing with fine motor skills (Baron, 2004).

When investigating learning disorders in a child, it should be considered that there is a possible important contribution of behavior (Baron, 2004). Learning disorders frequently occur together with behavioral, social and emotional problems (Hendriksen et al, 2007). The behavioral observation, direct testing, history review and a disposal of didactic knowledge about normal and abnormal brain development should all be taken into account while forming a complete evaluation of the child's behavior (Baron, 2004). To further carry out this evaluation of behavior, the study field of psychology distinguishes internalising behavior and externalising behavior (Mash & Wolfe, 2005). Internalising behavior is defined as behavior that occur within the child, problems in this area include anxiety, depression, somatic complains and withdrawn behavior. Externalising behavior comprehends more acting out behavior, deviating behavior such as aggression and oppositional behavior can occur (Mash & Wolfe, 2005). When describing behavioural problems the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DMS-IV) is often used (American Psychiatric Association, 2000).

### §1.2.2 Subtypes of learning disorders and their cognitive and behavioral profile

After this brief description of learning disabilities and the accompanying relevant concepts, this review will be continued with the evaluation of cognitive and behavioral profiles in learning disorders. Hendriksen et al (2007) distinguished three types of general learning disorders; Verbal learning disorders (VLD), Non verbal learning disorders (NVLD) and Attention with or without Motor function Disabilities (AMD). The cognitive and behavioral profile of these three types of learning disorders will now be further explained. Performances on neurological tests and a description of behavior in these subtypes of learning disorders are shown in tables 1 and 2.

VLD, such as dyslexia and Specific Language Impairment (SLI), are characterized by deficits in language ability (Hendriksen et al, 2007). Bishop and Snowling (2004) describe these deficits in language for instance as poor oral language, poor literacy skills, difficulties in phonological processing, problems with auditory perception and a lack of fluency. Accompanying cognitive deficits include working memory problems, impairments in motor skills and speed, in particular problems that involve

sequencing, timing and balance (Dick, Leech & Richardson, 2008). When reviewing the behavior of this specific type of learning disorder, VLD shows, compared to the other two subtypes of learning disorder, little behavioral problems (Hendriksen et al, 2007).

NVLD are learning disorders consisting of visual-spatial impairments (Hendriksen et al, 2007). Examples are dyscalculia and Nonverbal Learning Disorder (NLD). Forrest (2004) supplements this description with problems in tactile perceptual, psychomotor and nonverbal problem solving skills. These problem areas combined with strengths in verbal learning, phoneme-grapheme matching, the amount of verbal output and verbal classification, are believed to lead to academic problems, such as mathematic difficulties, and increased rates of psychopathology (Forrest, 2004). This psychopathology is accompanied by internalising problems, such as depression and isolation (Forrest, 2004). Hendriksen et al (2007) confirmed these internalising problems as rated by teachers.

AMD are learning disorders by which the primary diagnosed problems are composed of attention deficit and motor disorders. Examples of this specific subtype are Attention Deficit Hyperactivity Disorder, combined type (ADHD-C), deficits in attention, motor control and perception (DAMP) and developmental coordination disorder (DCD). Two studies (Meister et al, 2001; Westman, Ownby & Smith, 1987) reveal high percentages of the diagnoses AD(H)D in learning disorder population, hereby proving the relevance of this separate type of learning disorder. Besides attention and hyperactivity problems, several studies (Pitcher, Piek & Hay, 2003; Miyahara, Piek & Barrett, 2006) describe fine motor problems and inaccurate drawing in children with ADHD. They suggest that these problems are related to their motor abilities and could not be attributed to their lack of attention and concentration. The study of Hendriksen et al (2007) showed high externalising problems in these AMD children.

Table 1. Performance on neuropsychological tests in learning disorders AMD, VLD and NVLD (Hendriksen et al, 2007)

	Mean (SD)	VLD	NVLD	AMD
Information processing: Sequential	100 (15)	87.48	95.36	86.97
Information processing: Simultaneous	100 (15)	99.59	84.64	95.12
Language	100 (15)	95.00	96.71	96.37
Memory: Immediate	50 (10)	51.77	51.50	51.16
Memory: Delayed	50 (10)	50.18	51.07	48.14
Attention: Accuracy	0 (1)	-0.13	-0.50	-0.42
Attention: Speed	0 (1)	-0.46	-0.56	-0.53
Visual Motor Integration	0 (1)	-0.24	-1.10	-0.66
Reading words	10 (3)	4.21	10.13	8.49
Arithmetic	10 (3)	8.85	6.42	8.63

Table 2. Description of behavioral functioning in learning disorders AMD, VLD and NVLD (Hendriksen et al, 2007).

	Mean (SD)	VLD	NVLD	AMD
Total problems	50 (10)	58.39	59.06	64.66
Internalising	50 (10)	57.67	59.76	58.64
Externalising	50 (10)	54.61	50.76	62.90
Attention scale	50 (10)	62.23	67.53	70.56

Neuroimaging studies show an involvement of different brain areas in specific learning disabilities. In dyslexia, a possible involvement of the frontal and limbic areas and a probable involvement of the parieto-occipital and temporal areas are found (Paramala, Santosh & Ahmed, 2008). Children with SLI seem to have significantly smaller left pars triangularis, a specific region in broca's area, with a rightward asymmetry of the language structures. The degree of left cerebral asymmetry correlates with reading skills and the phonemic analysis of spoken language (Paramala, Santosh & Ahmed, 2008, p 98). In ADHD many brain regions seem to be involved, such as frontal, parieto-occipital and temporal regions, the corpus callosum and cerebellum (Santosh & Ahmed, 2008). The findings in neuroimaging studies are only applicable to large populations, conclusions concerning learning disorders bases on neuroimaging cannot be made for single cases. This involvement of the brain in learning disorders will be discussed later on in the conclusion of this chapter and when forming the hypotheses of the study in this thesis.

### §1.3 Duchenne muscular dystrophy

In this paragraph, DMD will be evaluated on the basis of the review outlined in the previous paragraph, i.e. the cognitive profile, behavioral profile, and the correlating learning disabilities will be discussed. Before evaluating these profiles and learning disabilities, the neuromuscular disorder will be briefly outlined first.

#### §1.3.1. A general description

Duchenne muscular dystrophy (DMD) is the most frequent muscular degenerative disease and the incidence approaches 1 in 3500 male births (Emery, 1991). In general, the transmission is X-linked, which means it is transmitted from mother to son, yet one third of all cases are spontaneous new mutations (Hinton, & Goldstein, 2007). Due to a gene mutation, there is an inhibition of the production of dystrophin, a protein that is normally found in muscles and the brain. Muscle weakness first appears at age 2 to 3, before this age the development seems normal. This muscles weakness will expand from the proximal muscles to the distal muscles, from extensors to flexors and from legs to arms. Eventually respiratory or cardiac failure will result from the muscle weakness, and death will occur (Hinton, & Goldstein, 2007). The inhibition of dystrophin production not only affects the muscles, but also brain function. This neuromuscular disease is associated with lower intellectual functioning; Cotton, Voudouris and Greenwood (2001) describe a total IQ of 80.20, which is more than one



standard deviation below normal scores (mean 100, SD 15). Verbal IQ is significantly lower than Performance IQ (Hinton & Goldstein, 2007).

### §1.3.2 Cognitive profile

#### *Attention*

Hendriksen and Vles (2006) described attentional processes as being weak in DMD. In a study of Wicksell, Kihlgren, Melin & Eeg-Olofsson (2004) attention problems were described as well, but the authors stated that these findings must be interpreted with some caution. A study of Hendriksen (2009) showed attention and concentration problems in 38 % of DMD patients, in comparison to 16 % in the healthy control group.

#### *Language*

Language disorders are a cognitive feature of DMD (D'Angelo & Bresolin, 2006). Speech language delay or specific language impairment may arise even before the onset of muscle weakness (Hendriksen & Vles, 2006). After evaluation of a large number of studies Hinton and Goldstein (2007) concluded that males with DMD have compromised verbal and reading skills and limited immediate verbal (working) memory (p114).

#### *Motor function and sensory perception*

As mentioned in the general description (§ 1.3.1), boys with DMD suffer from motor problems. Hendriksen and Vles (2006) showed that these motor problems varied among the participants in their DMD research group. With respect to perception, no differences in development of boys with DMD are defined in literature.

#### *Visuoperceptual, visuospatial and visuoconstructional function*

The findings of Hinton & Goldstein (2007) suggested normal abilities on visuospatial processing in boys with DMD. Hendriksen and Vles (2006) and D'Angelo and Bresolin (2006) also found relatively strong visuo-motor functioning. However, the results of Wicksell and his coworkers (2004) contradicted these findings; they showed a lower performance on visuospatial tasks of boys with DMD. They also stated DMD boys focussing on details rather than the larger geometric properties, suggesting difficulties with visuospatial constructional abilities (p. 158).

#### *Executive function*

As mentioned above children with DMD suffer from deficits in verbal working memory, cited by Baron (2004) as an executive function. Beside this impaired working memory, Hendriksen and Vles (2006) described the executive functioning in boys with DMD as relatively strong. Hinton and Goldstein (2007) demonstrated that boys with DMD performed similar to their peers on executive functioning tests. In contrast, the study of Wicksell et al (2004) found lower scores on executive functioning tasks.

### *Memory*

Wicksell et al (2004) found that DMD boys performed significantly worse on all aspects of memory; sensory storage, short-term memory, information processing/learning ability and long-term memory, with short-term memory being most affected.

#### §1.3.3 Behavioral profile

Besides various cognitive deficits, behavioral problems are very common in DMD as well. Hinton and Goldstein (2007) described internalising depressive problems and social problems as the mean deviating areas in the behaviour of boys with DMD. Young boys suffer more from social problems, older boys with DMD are more likely to have increased depression and anxiety (Hinton & Goldstein, 2007). It is hypothesized that social difficulties, such as having poor peer relations, arises from the disease itself, while depressive behaviour, such as withdrawing, is a reaction to the progression of the disease (Hinton, & Goldstein, 2007). Reid and Renwick (2001) indicated that adolescents with DM have significant adjustment difficulties. A study of Hendriksen and Vles (2008) revealed a comorbidity of autistic spectrum disorder (3%), ADHD (12%) and obsessive compulsive disorders (4%) in boys with DMD. These three psychiatric disorders were significantly more prevalent in boys with DMD than in the general population (Hendriksen & Vles, 2008).

#### 1.3.4 Learning disabilities

The incidence of learning disabilities is high in boys with DMD (D'Angelo & Bresolin, 2006; Hendriksen and Vles, 2006; Hendriksen and Vles, 2008; Wicksell et al, 2004). Reading problems are significantly more common in males with DMD than in general population (Hendriksen & Vles, 2006). Hendriksen and Vles (2006) also concluded that males with DMD are at a higher risk of developing reading problems, independent of their level of information processing and behavioral functioning. The same authors noted these reading deficits are probably caused by the affected verbal working memory. More specifically, Cyrulnik & Hinton (2008) stated that the impaired working memory has been associated with deficits in the acquisition of phonological knowledge and word vocabulary. Considering that these are important elements in learning how to read, Cyrulnik & Hinton (2008) concluded that it is obvious that boys with DMD suffer from deficits in phonological processing and reading. D'Angelo and Bresolin (2006) stated that poor readings skills do not seem to depend on the motor handicaps in boys with DMD; children with similar neuromuscular disorders do not show the same kind of reading learning problems as boys with DMD. When reviewing the three subtypes of learning disorders of Hendriksen et al. (2007), the cognitive profile of boys with DMD corresponds most with the cognitive profile of a Verbal Learning Disorder.

#### § 1.4 Myotonic dystrophy type 1

In this paragraph DM1 will be evaluated on the basis of the review outlined in § 1.2, meaning the cognitive profile, behavioral profile, and the correlating learning disabilities will be discussed. Before

evaluating these profiles and learning disabilities, the neuromuscular disorder will be briefly evaluated first.

#### § 1.4.1 A general description

Myotonic dystrophy type 1 (DM1) is a genetic neuromuscular disease, with a prevalence of 1 in 20.000 (Emery, 1991). It is an autosomal dominant disease situated on chromosome 19 and caused by multiple repeats of the sequence of DNA bases cytosine, thymine and guanine (CTG). These expanded CTG repeat are situated on the myotonic dystrophy protein kinase gene. The clinical effects of DM1 increases with the extent of these repeats and longer expansions are mainly related to maternal inheritance (D'Angelo & Bresolin, 2006; Schara, Benedikt, & Schoser, 2006). Distinctions are made between three forms of DM1; Congenital, Childhood onset and Adult onset. When evaluating the different types of DM1 in children, congenital DM1 is more severe, and show pre- and postnatal features such as reduced fetal movements, hypotonia, respiratory distress and insufficiency, bilateral facial weakness and difficulties in feeding, sucking, and swallowing (Schara & Schoser, 2006). Later on the child develops more muscle weakness (dystrophy) combined with myotonia (Lieberman & Fischbeck, 2000). The symptoms of Childhood onset DM1 are less severe; Schara and Schoser (2006) describe this subtype of DM1 as having neuromuscular abnormalities, for example weakness of facial and neck muscles, but without the typical facial appearance in the congenital form" (p. 75). Besides physical features, such as a delayed motor development, this neuromuscular disorder also influences intellectual capacities (Douniol et al, 2009). The literature study of Douniol et al (2009) reviews several DM1 studies; Deviating IQ scores are revealed, varying from 69.75 to 80.00, which is in de borderline range. IQ scores decline as the age of onset decreases and the CTG expansion mentioned above, increases. There is no correlation between IQ scores and neuromuscular impairment and the severity of disease (D'Angelo & Bresolin, 2006)

#### §1.4.2 Cognitive profile

##### *Attention*

A study of Angeard et al (2007) revealed poor performances on attention tasks in children with DM1. Later on Douniol et al (2009) also found impaired attention in their cognitive assessment of children with DM1. This will be further discussed in the last subsection "behavior" of this paragraph.

##### *Language*

In the development of children with DM1 language and speech delays are seen (Douniol et al, 2009; Schara, Benedikt, & Schoser, 2006). These problems were revealed in the written language skills, even when IQ scores were within the normal range (Douniol et al, 2009). On the other hand a study of Ekstrom, Hakenas-Plate, Tulinius, & Wentz (2009) showed a relative strength in language comprehension. They also found receptive language was more developed than expressive language.

### *Motor function and sensory perception*

A delayed motor development can be a symptom of DM1 (Douniol et al, 2009; Schara & Schoser, 2006). Douniol et al (2009) also mentioned hypotonia and motor coordination impairments, D'Angelo and Bresolin (2006) described disabilities in visual perception as a common cognitive deficit in DM1.

### *Visuoperceptual, visuospatial and visuoconstructional function*

Visual spatial deficits are common in children with DM1 (Douniol et al, 2009; Schara & Schoser, 2006; D'Angelo & Brosolin, 2006). The study of Angeard et al (2007) revealed severe deficits in visuospatial and visuoconstructive skills and the authors stated that these results are similar to results from previously conducted studies.

### *Executive function*

Douniol et al (2009) speculated about the involvement of verbal working memory in DM 1 patients. It is hypothesized that cognitive impairment in children with DM1 may be linked to a potential deficit in executive functioning (Angeard et al, 2007, D'Angelo & Bresolin, 2006). Further research on specific executive functions is necessary before statements in this matter are made.

### *Memory*

In several studies (Angeard et al, 2007; Douniol et al, 2009) memory deficits are mentioned as common in DM1 patients. D'Angelo & Bresolin, (2006) specified these memory deficits as impairments in visual memory and verbal short and long-term memory.

### §1.4.3 Behavioral profile

Douniol et al (2009) reviewed two studies regarding the behavior in children suffering from DM1 (N respectively 14 and 24). They found 29 to 42 % scoring within the clinical range for total problems on the Child Behaviour Checklist (CBCL). 40 % had internalising problems, 6 to 8 % had externalizing problems within the clinical range. When evaluating the separate subdomains of the CBCL, children with DM1 had significantly high scores on withdrawing, social problems and attention problems. 56 to 63 % of the populations had at least one axis 1 DSM-IV diagnosis. The most frequently reported diagnosis was ADHD (30%). Anxiety disorder was the second most frequent diagnose (19 to 25%). A study of Ekstrom reviewed in the same article (Douniol et al, 2009) showed another distribution of psychiatric diagnoses, only 11% of their research group (N = 18) had ADHD, 16.7% was diagnosed with an autistic disorder. D'Angelo and Bresolin (2006) described DM1 patient as having a homogeneous personality profile, with statistically significant differences for avoidance, obsessive-compulsive passive-aggressive, and schizotypic traits (p. 22). Depression was also frequently observed but this seemed to be secondary to the emotional reactions caused by their physical impairments and restrictions. Reviewing the psychopathology of these children, D'Angelo and Bresolin (2006), described ADHD and anxiety disorder as most frequent diagnoses.

#### §1.4.4 Learning disabilities

Learning disorders are rather frequent in children with DM1. When reviewing several studies, Douniol et al (2009) found two thirds of their DM1 population having a learning disorder. Learning disorders were found to be frequent, even in children without a mental retardation (22 - 66%) (Cohen et al, 2006). As mentioned earlier in this thesis, learning disabilities affect the written language skills, in particular spelling and reading impairments, despite of normal word identification (Douniol et al, 2009). Because no phonological dysfunction was found, Cohen et al (2006) suggested that other brain deficits may be involved, such as working memory. Douniol et al (2009) speculated about the involvement of verbal working memory in the reading and spelling problems in DM 1 patients as well. Furthermore they explained that these difficulties in spelling and reading are probably increased by oral motor dysfunction and impaired facial expression of children with DM1, but could also be explained by visual spatial deficits and a motor coordination disorder. Cohen et al (2006) hypothesised the involvement of the visual-spatial orientation, because of the disharmonious IQ profile they found, with a lower performance IQ. When reviewing the three subtypes of learning disorders of Hendriksen et al. (2007), the cognitive profile of children with DMD corresponds most with the cognitive profile of a Verbal Learning Disorder.

#### § 1.5 Conclusion

After reviewing literature on DMD and DM1 it can be concluded that learning disorders occur in both neuromuscular disorders and particularly consist of reading problems and corresponds most with the cognitive profile of a Verbal Learning Disorder. The literature listed in previous paragraphs gives several reasons for these reading problems. In children with DMD the reading problems seem to be caused by an impaired verbal working memory. Furthermore it is stated that the reading problems do not seem to be caused by the motor handicaps or visuospatial dysfunction of children with DMD (Cyrulnik & Hinton, 2008; D'Angelo and Bresolin, 2006; Hendriksen and Vles, 2006). Considering reading problems in children with DM1, the involvement of verbal working memory is hypothesized as well. In contrast to DMD, the reading problems in DM1 could also be explained by visuospatial deficits (Cohen et al, 2006; Douniol et al, 2009). Summarising, when trying to explain the reading disabilities in DMD and DM1, two possible cognitive functions arise, verbal working memory and visuospatial functioning. The current study will look more closely at reading, and the possible accompanying cognitive deficits.

Besides reading problems and cognitive impairments, children with DMD and DM1 both have deviating behavioral profiles. Children with DMD and DM1 both show internalizing problems, social problems, withdrawal and depression (Hinton & Goldstein, 2007; Douniol et al, 2009). The comorbidity of ADHD and autism is present in both neuromuscular disorders and in both significantly higher than in the general population. Therefore the behavior of children with DMD and DM1 will be evaluated in this study as well.

Because of the proven correlation between the neurological disorder, in this case known genetic or protein deficits associated with changes in the cerebral functioning, and the learning disorder, the term

neurological learning disorder is used in this thesis (D'Angelo & Bresolin, 2006). In paragraph 1.2.2 neuroimaging studies in learning disorders without neurological comorbidity show differences in the brain as well. However this involvement is only seen in large populations, not, as in DMD and DM1, in single cases. Because of this more clearly indicated neurological basis of neurological learning disorders, it can be hypothesised that the cognitive and behavioral deficits in these disorders are more explicit as well. This association will be further explored in this thesis

Summarizing, in the current study children with DMD and DM1 will be evaluated on the four functions described above, meaning reading skills, verbal working memory, visuospatial functioning and behaviour, and compared with normative data. In addition, the relation of the neurological learning disorders and learning disorders without a neurological comorbidity will be investigated.

## §1.6 A description of aims of study, research design and hypotheses

### § 1.6.1 Aims of study

The study has three aims: (1) to describe the specific neurocognitive functioning, reading skills and behavioral functions of children with Duchenne muscular dystrophy. (2) To compare the performance of children with Duchenne muscular dystrophy and myotonic dystrophy type 1 to normative data. (3) To compare children with a proven neurological learning disability, i.e. myotonic dystrophy type 1 and Duchenne muscular dystrophy, and children with a learning disability without an evident neurological comorbidity.

### §1.6.2 Research design

First a descriptive analysis will be performed in which of the groups DMD and DM1 are evaluated on verbal working memory and visuospatial abilities, reading skills and behavioral functions. This is followed by two comparative analyses (Hinkle, Wiersma, Jurs, 2003). The first analysis will compare the scores of children with DMD and DM1 with normative data. The second comparison study will compare children with a proven neurological learning disorder, in this DMD and DM1, and children with a learning disorder without an evident neurological comorbidity. These two comparison studies will emphasize verbal working memory, visuospatial functioning, reading skills and behavioral functions as well.

### §1.6.3 Hypotheses

Hypothesis 1: In comparison with normative data, children with DMD have significant deficits in verbal working memory and reading skills and have significantly more internalising behavioral problems.

Hypothesis 2: When comparing children with DMD and children with a learning disability without an evident neurological comorbidity, children with DMD have poorer verbal working memory and reading skills and more internalising behavioral problems.

Hypothesis 3: In comparison with normative data, children with DM1 have significant deficits in verbal working memory, visuospatial functioning and reading skills and have significantly more internalising behavioral problems.

Hypothesis 4: When comparing children with DM1 and children with a learning disability without an evident neurological comorbidity, children with DM1 have poorer verbal working memory, visuospatial functioning and reading skills and more internalising behavioral problems. Table 3 gives an overview of the expected differences concerning these hypothesis.

Table 3. Overview hypotheses

	DMD		DM1	
	Normative data comparison	Learning disabilities comparison	Normative data comparison	Learning disabilities comparison
Verbal working memory	1a. Difference	2a. Difference	3a. Difference	4a. Difference
Visuospatial	1b. No difference	2b. No difference	3b. Difference	4b. Difference
Reading skills	1c. Difference	2c. Difference	3c. Difference	4c. Difference
Internalising behavior	1d. Difference	2d. Difference	3d. Difference	4d. Difference

## Chapter 2 Method

### § 2.1. Procedure

All children referred to the centre for neurological learning disorders (CNL), Kempenhaeghe Heeze in the period September 2008-2010 were included in the first analysis. The children have undergone multidisciplinary assessment in this tertiary outpatient clinic for children with complex learning problems as comorbidity due to neurological disorders, such as neuromuscular disorders, neurofibromatosis or spina bifida. The assessment protocol consisted of a neurological examination, an evaluation of the general health and a psychological assessment. This assessment consisted of a history taking with parents, a battery of neuropsychological tests and (behaviour) questionnaires completed by parents. When a child was diagnosed with learning, mental or behavioural disorder, these diagnoses were based on the diagnostic criteria of the DSM-IV (American Psychiatric Association, 2000). Some learning disorders are not described in this manual, for example DAMP is a compound diagnose of two DSM-IV diagnoses DCD and ADHD. NLD is not mentioned in the DSM-IV at all, and therefore in this study diagnosed according to the criteria of Rourke (Rourke, van der Vlugt & Rourke, 2002).

### § 2.2 Participants

For the first part of the study, a descriptive study of DMD and DM1, the entire neurological learning disorder research group consisted of 117 children (74 boys; 43 girls). The mean age of the neurological learning disorder research group was 9.73, with a range from 3 to 20 years (SD 3.74). Only seven children were diagnosed with DMD or DM1 (all boys) and therefore could be selected from the database for further analyses, this was 6 percent of the entire database. Three children with myotonic dystrophy type 1 had a mean age of 6.25 with a range from 3 to 9 years (SD 3.20). Four children with Duchenne muscular dystrophy had a mean age of 7.33 with a range from 4 to 11 years (SD 3.51).

To give an impression of the neuromuscular research group, a general description of the seven children is provided. Table 4 gives an overview of intelligence and information processing in DMD and DM1 patients. In DMD the mean Total IQ was 83.50, which is more than one standard deviation below average. The intelligence profile of the DMD patient in this study is harmonious, The information processing profile of the DMD children is disharmonious, sequential processing (for a description of this measure see below in § 2.3) is low and simultaneous processing is average. In DM1 total IQ is 83.00, which is again more than one standard deviations below average. The intelligence profile is harmonious. Sequential information processing is low average, simultaneous information processing is average, the information processing profile is still harmonious.



Table 4. Intelligence and information processing for the seven DMD and DM1 patients

	Test: Mean (SD)	DMD: N per test	DMD: Mean (SD)	DM1: N per test	DM1: Mean (SD)
<b>Intelligence</b>					
Total IQ	100 (15)	2	83.50 (16.26)	2	83.00 (1.41)
Verbal IQ	100 (15)	3	92.00 (16.09)	2	90.50 (0.71)
Performance IQ	100 (15)	3	85.67 (4.04)	2	79.00 (1.41)
<b>Information processing</b>					
Sequential information processing	100 (15)	3	85.67 (20.01)	3	88.00 (0.00)
Simultaneous information processing	100 (15)	3	100.00 (6.08)	3	98.67 (11.59)

### § 2.3 Measures

The battery of neuropsychological tests intended to measure cognitive and academic functions, including verbal working memory, visuospatial functioning and the child's reading skills. Behavioral profile was examined by questionnaires sent to patients prior to the assessment. In the composition of this neuropsychological battery and behavioral assessment, the administered tests in the study of Hendriksen et al (2007) were taken into account.

The Kaufman Assessment Battery for Children, second edition (KABC-II) measures information processing and distinguishes two forms of processing, sequential and simultaneous. In this thesis only sequential information processing is used to assess verbal working memory (mean 100; SD 15). The standard scores were based on United States norms (Kaufman & Kaufman, 2004).

The Beery Developmental Test of Visual Motor Integration (VMI) measures visual spatial and motor functioning. This test investigates the integration of visual perceptual and fine motor abilities and consists of three subtests that increase in difficulty (mean = 0; SD = 1). In the visual motor integration test the child has to copy 24 geometric forms. The calculation of standard scores were based on United State norms (Beery & Beery, 2006).

Dutch Tempo tests assess academic performance and exists of three separate tests. In the Tempo Test Reading - Words, the child has to correctly read out as many words as possible in one minute (scores in learning productivity quotient (LRQ)). In the Tempo Test Reading - Sentences, the child has to read as many words of a story as possible. After one minute the child has to explain what the story is about. (Vos, 2002; Vos & Kooistra, 2000).

To evaluate the behavioral and neuropsychiatric functioning of the child, parents completed a behavioral questionnaire, the Child Behaviour Checklist (CBCL). In this questionnaire, parents answer questions about the skills and behavior of their child. T-scores are calculated for three scales, Total problems, externalising problems and internalising problems and several subscales such as attentions problems and somatic complaints (mean = 50; SD = 10) (Verhulst, van der Ende & Koot, 1996).

## § 2.4 Data Analysis

When describing intelligence, cognitive functions, reading skills and behavior Descriptive variables were used. To compare children with DMD and DM1 with normative data, and with children with a learning disability without a neurological comorbidity, one sample T-tests were used (Pallant, 2005). Due to the small sample size, a normal distribution cannot be demonstrated. Yet a normal distribution is legitimate to assume, therefore one sample T-tests can be used as statistic analysis. The performances of the children with learning disabilities without a neurological comorbidity have been retrieved from a research study of Hendriksen et al (2007).

## Chapter 3 Results

### § 3.1 Performance of DMD patients on neuropsychological and behavioral measures

The performance of children with DMD on neuropsychological tests and behavioral measurements are shown in table 5. The mean scores of the three subtypes of learning disorders (Hendriksen et al, 2007) are noted in this table as well.

Table 5. Performance on neuropsychological tests and behavioural measurements for DMD patients

	N per test: DMD/VLD NVLD/AMD	DMD: Mean (SD)	VLD: Mean (SD)	NVLD: Mean (SD)	AMD: Mean (SD)
<b>Cognition</b>					
Verbal working memory	3/71/14/104	85.67 (20.01)	87.48 (11.42)	95.36 (10.40)	86.97 (12.06)
Visual motor integration	3/152/18/109	-1.07 (0.40)	-0.24 (0.80)	-1.10 (0.66)	-0.66 (0.72)
<b>Academics</b>					
Reading sentences	2	81.50 (26.16)	-	-	-
Reading words	2	75.00 (35.36)	-	-	-
<b>Behavior</b>					
Total problems	2/95/17/111	58.00 (0.00)	58.39 (11.41)	59.06 (13.54)	64.66 (8.85)
Internalising problems	2/95/17/112	50.50 (2.12)	57.67 (11.61)	59.76 (14.29)	58.64 (10.33)
Externalising problems	2/95/17/112	59.50 (0.71)	54.61 (11.84)	50.76 (13.04)	62.90 (11.28)
Attention problems	2/95/17/112	62.00 (7.07)	62.23 (8.39)	67.53 (12.40)	70.56 (7.97)

Table 6 reports the results of the comparative analyses with DMD patients. When reviewing the cognitive functions, verbal working memory did not differ significantly when compared with normative data or compared with the three learning disorder subtypes. Visual motor integration was significantly lower in DMD patients compared to normative data, but when comparing visual motor integration of DMD patients with the three learning disorder subtypes, no significant differences were found. With regard to the academics, reading performance of two boys with DMD did not significantly differ from normative data. Reading performance could not be compared with the three learning disorder subtypes, because of the performance of DMD patients was measured in LRQ and the performances of the learning disorder subtypes were measured in standardized scores. Therefore it was statistically impossible to compare these measurements with each other.

The results of the comparative analyses of children with DMD with respect to behavior are shown in table 6 as well. When reviewing total problems, the comparison with normative data and the three learning disorder subtypes could not be calculated because the standard deviation was 0. There were no significant differences found when comparing internalising problems of DMD patients with normative data or the three learning disorder subtypes. Externalising problems were significantly higher in children with DMD compared to normative data and the learning disorder subtype NVLD. Externalising problems did not significantly differ from the other two learning disorder subtypes. No

significant differences were found when comparing the attention scale of DMD patients with normative data or the three learning disorder subtypes.

Table 6. Results of the comparison studies of DMD patients

	t: compared with normative data	t: compared with VLD	t: compared with NVLD	t: compared with AMD
<b>Cognition</b>				
Verbal working memory	-1.24	-0.16	-0.84	-0.11
Visual motor integration	-4.59 *	-3.55	0.13	-1.74
<b>Academics</b>				
Reading sentences	-1.00	-	-	-
Reading words	-1.00	-	-	-
<b>Behavior</b>				
Total problems	a	a	a	a
Internalising problems	0.33	-4.78	-6.17	-5.43
Externalising problems	19.00 *	9.78	17.48 *	-6.80
Attention problems	2.40	-0.05	-1.11	-1.71

a. t cannot be computed because the standard deviation is 0.

\*  $P < 0.05$

### § 3.2 Performance of DM1 patients on neuropsychological and behavioral measures

The performance of children with DM1 on neuropsychological tests and behavioral measurements are shown in table 7. The mean scores of the three subtypes of learning disorders (Hendriksen et al, 2007) are noted as well.

Table 7. Performance on neuropsychological tests and behavioural measurements for DM1 patients

	N per test: DM1/VLD NVLD/AMD	DM1: Mean (SD)	VLD: Mean (SD)	NVLD: Mean (SD)	AMD: Mean (SD)
<b>Cognition</b>					
Verbal working memory	3/71/14/104	88.00 (0.00)	87.48 (11.42)	95.36 (10.40)	86.97 (12.06)
Visual motor integration	3/152/18/109	-0.66 (0.18)	-0.24 (0.80)	-1.10 (0.66)	-0.66 (0.72)
<b>Academics</b>					
Reading sentences	2	51.00 (1.41)	-	-	-
Reading words	2	68.50 (6.36)	-	-	-
<b>Behavior</b>					
Total problems	2/95/17/111	54.50 (2.12)	58.39 (11.41)	59.06 (13.54)	64.66 (8.85)
Internalising problems	2/95/17/112	56.00 (2.83)	57.67 (11.61)	59.76 (14.29)	58.64 (10.33)
Externalising problems	2/95/17/112	48.50 (3.54)	54.61 (11.84)	50.76 (13.04)	62.90 (11.28)
Attention problems	2/95/17/112	63.50 (3.54)	62.23 (8.39)	67.53 (12.40)	70.56 (7.97)

Table 8 reports the results of the comparison studies of DMD patients. With regard to the cognitive functions, verbal working memory of DM patients could not be compared with normative data and the three learning disorder subtypes, because the standard deviation was 0. The visual motor coordination of children with DM1 was significantly lower than normative data. Significant differences could not be found when comparing the visual motor integration with the three learning disorder subtypes. When reviewing reading performance, DM1 patients scored significantly lower on reading sentences compared to normative data. This significance was not found in reading words. As mentioned earlier reading performance could not be compared with the three learning disorder subtypes because of a difference in measurements

With relation to behavior, comparison studies of children with DM1 are shown in table 8 as well. When comparing measurements of total problems, internalising problems, externalising problems and the attention scale of DM1 patients with normative data, no significant differences were found. When a comparison with the three learning disorder subtypes is made, no significant differences on behavior were found as well.

Table 8. Results of the comparison studies of DM1 patients

	t: compared with general mean	t: compared with VLD	t: compared with NVLD	t: compared with AMD
<b>Cognition</b>				
Verbal working memory	a	a	a	a
Visual motor integration	-6.43 *	-4.12	4.14	-0.06
<b>Academics</b>				
Reading sentences	-49.00 *	-	-	-
Reading words	-7.00	-	-	-
<b>Behavior</b>				
Total problems	3.00	-2.59	-3.04	-6.77
Internalising problems	3.00	-0.84	-1.88	-1.32
Externalising problems	-0.60	-2.44	-0.90	-5.76
Attention problems	5.40	0.51	-1,61	-2,82

a. t cannot be computed because the standard deviation is 0.

\*  $P < 0,05$

**Chapter 4 Discussion**

The aim of this study was to examine the cognitive functions verbal working memory and visuospatial functioning, and reading skills and behavior in children with DMD and DM1. The sample consisted of seven boys, four boys with DMD and three boys with DM1. This gender distribution is partly in accordance with literature, that describe DMD only occurs in males and DM1 does not depend on gender (Angeard et al, 2007; Douniol et al, 2009; Hinton & Goldstein, 2007). In the following paragraphs the results will be discussed on the basis of the formulated hypothesis and literature of DMD and DM1. The comparison of current findings with the hypotheses formulated in §1.6.3 are shown in table 9.

Table 9. Comparison of current findings with the hypotheses

	DMD		DM1	
	Normative data comparison	Learning disabilities comparison	Normative data comparison	Learning disabilities comparison
Verbal working memory	1a. Difference	2a. Difference	3a. Difference	4a. Difference
Visuospatial	1b. No difference	2b. No difference	3b. Difference	4b. Difference
Reading skills	1c. Difference	2c. Difference	3c. Difference	4c. Difference
Internalising behavior	1d. Difference	2d. Difference	3d. Difference	4d. Difference

  

	Confirmed
	Not confirmed
	Not calculated

§ 4.1 Cognition, reading and behavior in DMD patients

The only difference found, when comparing DMD patients with the normative data, was a lower level of visual motor integration. These findings do not confirm previous research. The normal verbal working memory found in this study is in contrast with the conclusions of Hinton and Goldstein (2007) after evaluating a large number of studies. The deviating visuospatial functioning found in this study is also not confirmed by the findings of Hendriksen & Vles (2006), D’Angelo & Bresolin (2006) and Hinton and Goldstein (2007), they all observed normal to strong visuospatial functioning in children with DMD. On the other hand the visuospatial deficits in this study do correspond with the findings of Wicksell et al (2004). The reading performance in this study did not differ from normative data. This contradicts previous findings, since literature suggests deviating reading skills (Cyrulnik & Hinton, 2008; D’Angelo and Bresolin, 2006; Hendriksen and Vles, 2006). Therefore hypotheses 1a, 1b and 1c cannot be confirmed.

Children with DMD showed more externalising problems than normative data and no deviating internalising and attention problems. These findings are opposite to previous findings, as literature

mainly indicates more internalizing and attention problems in children with DMD (Hinton & Goldstein, 2007). Because internalising problems showed no difference hypothesis 1d is not supported.

Because no differences were found when comparing verbal working memory in DMD patients with the three subtypes of learning disorders, hypothesis 2a cannot be supported. As expected visual motor integration was not different in DMD and the three subtypes of learning disorders. This confirms hypothesis 2b. Hypothesis 2c could not be investigated because of statistical limitations. Children with DMD showed more externalising problems than children with NVLD. This could be explained by the low level of externalising problem in NVLD (Hendriksen et al., 2007). A difference in internalizing problems could not be found, therefore hypothesis 2d cannot be supported.

Overall, no evident consistent verbal working memory impairments, reading difficulties or internalising behavioral problems are found in the studied sample, in contrast with the results of other studies on DMD and the hypotheses (Cyrułnik & Hinton, 2008; D'Angelo and Bresolin, 2006; Hendriksen and Vles, 2006; Hinton & Goldstein, 2007). Furthermore, there were no differences when comparing DMD patients with the three subtypes of learning disorders, which was partly unexpected. Later on (§ 4.3) possible reasons for these deviating results are discussed.

#### § 4.2 Cognition, reading and behavior in DM1

The only difference found, when comparing DMD patients with the normative data, was a lower level of visual motor integration. These findings do not confirm previous research. When evaluating this study on children with DM1, differences in verbal working memory could not be investigated because of statistical limitations. Therefore hypothesis 3a cannot be examined. When the mean score of verbal working memory is interpret without statistical analysis, it is somewhat lower than normative data. As expected, the level of visual motor integration was, compared to the normative data, lower in DM1 patients, this is in accordance with literature (Douniol et al, 2009; Schara & Schoser, 2006) and confirms hypothesis 3b. The level reading of sentences was lower in DM1 patients than the normative data, but the reading of words was not. These results are partly in line with other studies reporting overall reading problems in children with DM1 (Cohen et al, 2006; Douniol et al, 2009). Hypothesis 3c can therefore not be confirmed.

No differences were found in behaviour. This is not conform the literature, which suggests more internalising and attention problems in children with DM1 (Douniol et al, 2009; D'Angelo and Bresolin, 2006; Schara & Schoser, 2006). Consequently hypothesis 3d cannot be endorsed.

When comparing DM1 patients with the three subtypes of learning disorders, verbal working memory could not be investigated because of statistical limitations. Thus hypothesis 4a cannot be examined.

When the mean score of verbal working memory is interpret without statistical analysis, it is somewhat lower than NVLD. This seems to be in accordance with literature that suggest relatively high verbal working memory in NVLD (Hendriksen et al, 2007).

Children with DM1 show, in contrast with the hypotheses, no deviations in visual motor integration and behavior compared to the three learning disorders. Therefore hypothesis 4b and 4d cannot be supported. Hypothesis 4c could not be investigated because of statistical limitations.

In conclusion, in this study verbal working memory, reading skills and internalising behavior are not found to be different, this is not in accordance with other studies on DM1 and the hypotheses (Cohen et al, 2006; Douniol et al, 2009; D'Angelo and Bresolin; Schara & Schoser, 2006). Supplementary, children with DM1 did not differ from the three learning disorder subtypes, which was again unexpected. In the following paragraph, possible limitations of this research will be mentioned.

#### § 4.3 Limitations

As mentioned in the prior two paragraphs, the data of this study do not correspond with previous studies on DMD and DM1. Also the intelligence profile of the DMD patient was harmonious, which is in contrast with literature that indicates a lower verbal IQ (Hinton & Goldstein, 2007). Several theoretical and methodological issues need to be considered.

An important limitation of the current study is the small sample size, four children with DMD and three children with DM1. A small sample size makes it difficult to obtain significant results, apart from the actual differences in data in these comparison studies. This line of reasoning considering small sample size, can therefore be an explanation for the very few significant differences found in this research. A larger sample size may lead to more meaningful results.

Secondly, due to the small sample size in this research, on certain variables the same scores were measured in each participant, leading to a standard deviation of 0. Therefore some statistic analyses could not be executed. When increasing the sample size, the change of the standard deviation being precisely 0, decreases. Future research on cognition, reading and behavior in children with DMD and DM1 should consist of a larger sample size.

Heterogeneity of the research group is another important limitation of this study as well. As Hinton and Golstein (2007) stated, the cognitive results of boys with DMD depends on psychical presentation of the disease, overall level of intelligence, environmental background and age variables. In DM1 cognitive functioning is influenced by the form of DM1; congenital of childhood onset, the number of CTG repeats and the form of inheritance, maternal or paternal (Douniol, et al, 2009). The variables were not all known in the literature reviews and in the research group of this study.

Finally, the representativeness of the research group can be questioned. The results in this research may be influenced by the referral bias. The sample in this research may, for example, differ from the total population DMD and DM1 concerning the experienced problems, thus the research population in this study could over represent those with cognitive, behavioral or learning deficits. Furthermore, the age of the research group in this study was relatively young, mean age in DMD and DM1 was 6.87. This young age may have influenced the results, since, for example, certain cognitive functions are still developing or will develop at an older age. It could also be possible that the cognitive, behavioral and learning problems reviewed in literature on DMD and DM1, does not find expression at such young age, which could be an explanation of the few differences found in this study. When reviewing the comparison with learning disorders without a neurological comorbidity, the mean age in the study of Hendriksen et al (2007) was 10.03. The age could not be manipulated, because there was no disposal of the raw data. The age difference between the two comparison groups may have influenced the



comparison study as well. Because of the referral bias and age of the research group, an aselect randomisation cannot be assumed, which restricts generalisation of the present findings. Furthermore, it is thought that the present sample is not representative for the whole population DMD and DM1, because of the small sample size, referral bias, age of the research group and the fact that the features of the sample in this research do not correspond to other studies.

#### § 4.4 Implications for the future

In conclusion, there are limitations of the study in this thesis, hereby meaning the small sample size and the not assumed aselect randomization, caused by age and referral bias. Future research should consist of an increased sample size, to make sure the statistical analyses give information about the research population, instead of being merely a result of statistical rules. It should also be taken into account, when performing research on referred children, results may never be generalised to the total population, because the absence of aselect randomisation. As a solution to the referral bias, non-referred children with DMD and DM1 should be included in the study as well. In future studies the age distribution should be more widespread, so that the influence of age is minimized .

Furthermore, for the future, being in the receipt of the cognitive, academic and behavioral data on children with DMD and DM1, it should be interesting to execute seven separate case studies. As mentioned above, the information acquired on this research may not seem to be very useful for population analyses, but it can give valuable information about the clinical aspects of these rare neuromuscular disorders, also in relation to literature. When evaluating scores of these single cases, the statistical treats of the tests, for example the standard error, can be used to calculate score intervals. These intervals give information about measurements of a patient in contrast to the test mean, and therefore can be useful when evaluation a single case. The on literature based hypotheses formed in this research, can be examined in these single case studies as well.

#### § 4.5 Conclusion

In the present study the verbal working memory and visuospatial functioning, and reading skills and behavioral functions of children with DMD and DM1 are described. These functions are compared with normative data and compared with children with learning disabilities without a evident neurological comorbidity. Deviating visuospatial functions are found in DMD and DM1 patients, when comparing them with normative data. With respect to the behavioral profile, DMD patients have more externalising problems compared to the normative data and to children with Verbal Learning Disorders. The data of this study do not correspond with previous studies on DMD and DM1. There are several theoretical and methodological limitations, such as the small sample size and the absence of aselect randomization. Implications for future research are made.

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