Neurocognition and behaviour

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diagnostic work-up and interventions

in

Duchenne and Becker muscular dystrophy

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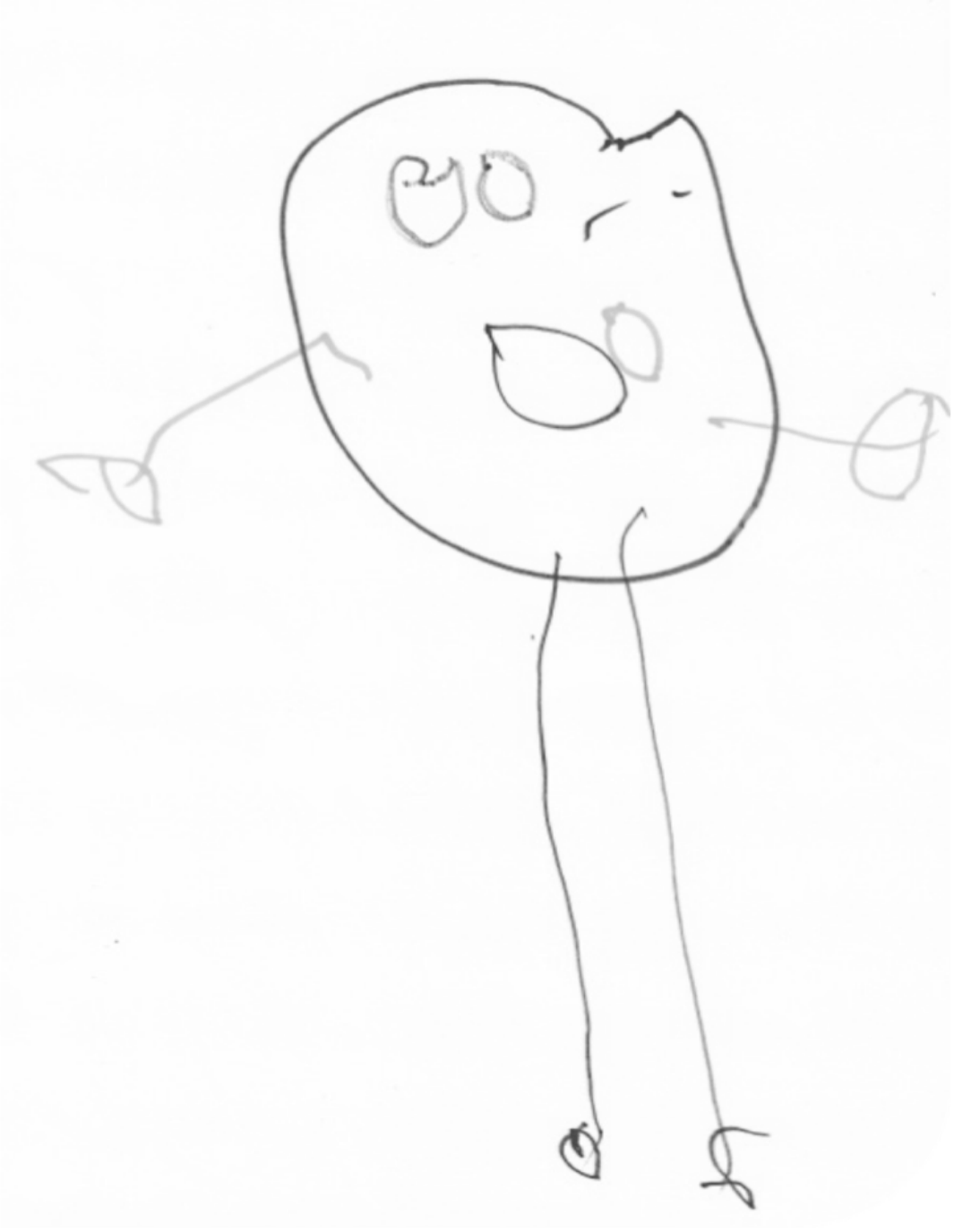

Chapter 1

General introduction

Duchenne (DMD) and Becker muscular dystrophy (BMD) are recessive x-linked (Xp21) neuromuscular disorders caused by mutations in the dystrophin (*DMD*) gene that encodes the dystrophin protein.[1,2] The *DMD* gene consists of 79 exons and contains at least eight independent tissue-specific isoform promoters.[3,4] The full length dystrophin protein (Dp427) for instance is located at the inner part of the muscle fibre membrane (striated muscle) and here it interacts with the dystrophin-associated glycoprotein complex (DCG), which is responsible for the stability of muscle fibres during contraction.[5] In DMD, an absence of the functional full-length dystrophin protein in muscles, results in progressive and severe muscle weakness, respiratory and cardiac complications leading to a life expectancy limited to early adulthood[6,7] In the milder variant, BMD, the full-length dystrophin protein is partially functional resulting in a heterogenous disease course with features such as, incidental muscle cramps and great life expectancy to severe muscle weakness at adolescents with or without cardiomyopathy.[1]

Expression of the full length dystrophin is also found in the brain ($Dp427_B$) were it anchors a subset of $GABA_A$ receptors at the post-synaptic membrane of neurons.[8] It is located in the hippocampus, amygdala and cerebral cortex with a slightly higher expression in the temporal and prefrontal cortex than in parietal and occipital cortex.[8-11] In addition to the full length dystrophin protein (Dp427), many different (shorter) isoforms exist and these are located in the retina (Dp260), in Schwann cells of peripheral nerves (Dp116), in the brain and kidney (Dp140) and an ubiquitously expression (incl. brain) is described for Dp71/Dp40 (see Figure 1.1 for an overview).[8,12]

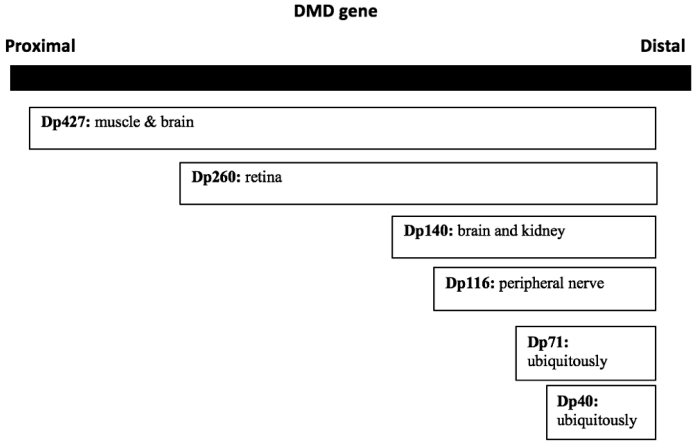

Figure 1.1 *Schematic overview of the DMD gene, the dystrophin isoforms and their expression. The image was based on the references: Doorenweerd (2017), Muntoni (2003), and Waite (2012).*[8,12,18]

The brain isoform Dp140 is linked to microvascular glial cells and is suggested to play a role in transcription factor activity, dendritic development, neuron differentiation and chromatin modification.[8,13] Dp71/Dp40 are found in neurons and glial cells, more specifically Dp71 is found at specialized end-feet of perivascular astrocytes were it anchors aquaporin 4 receptors and Dp40 is localized at presynaptic and post-synaptic membranes in central excitatory synapses.[8,14,15] The expression of the brain isoforms show a clear distinction. $Dp427_B$ has a relatively low expression throughout life, Dp140 is highly expressed during fatal life stages and Dp71 has an intermediate expression at all life stages.[11,16] In contrast to the muscle DGC complex, different brain DCG complexes exists due to the various brain isoforms ($Dp427_B$, Dp140, Dp71/40).[8,17] These brain DCG complexes play a crucial role in brain development and functioning due their roles in neuron differentiation and axon guidance.[11]

Neurocognition and behaviour

In addition to the skeletal muscle pathology, brain-related comorbidities such as neurocognitive and behavioural problems, learning disabilities and epilepsy may be an important part of the disease spectrum of both DMD and BMD. In Duchenne, 30% of patients have a full-scale intelligence quotient (FSIQ) score of approximately one standard deviation below the normal population (IQ <70) with more difficulties in verbal intelligence (VIQ) than performance intelligence (PIQ).[19,20] Moreover, frequent reported cognitive deficiencies are limited verbal span capacity/verbal (working) memory deficiencies and problems with language (receptive and expressive), attention, executive functioning, visuo-spatial abilities and fine-motor skills.[21-26] Longitudinal information on cognitive development is lacking, but the cognitive problems in DMD seem to be non-progressive.[27-31] Furthermore, high prevalence rates of neuro-developmental and behavioural disorders are described for DMD compared to the general population, including attention-deficit hyperactivity disorder (ADHD: 11.7-32%)[32-34], autism spectrum disorders (ASD: 3.1-21%)[33-36], obsessive-compulsive disorder (OCD: 4.8-5.1%) [33,34] and anxiety disorders (27%).[34] High rates of psychosocial problems are also found in DMD (30-50%), although these rates are comparable to those described for other chronic diseases.[37-40] In addition, learning disabilities (LD) including verbal difficulties such as reading disabilities and dyslexia, as well as non-verbal learning disabilities such as math disabilities and dyscalculia frequently occur in DMD.[41-44] For instance, up to 40% of patients with DMD have reading disabilities.[26,41,43,45,46]

In BMD, only five studies focused on cognition, behaviour and learning. In contrast to DMD, it seems that BMD patients have FSIQ scores within the normal range (means reported IQs range from 87.8 to 95.6).[47-49] With respect to cognitive features, previous studies reported more problems in attention, language/speech delays (35.7%), and academics skills such as reading (21%), spelling (32%) and math (26%) in BMD compared to the general population.[48,50] Furthermore, higher prevalence rates of behavioural problems including hyperactive/inattention features (11-36%), autistic features (11.4-17.6%), aggressive behaviour, OCD (1.5-20%), anxiety (21.4-50%) and depression (2.2-8%) have been noticed in BMD.[47,48,50,51] Nevertheless, the reported findings of previous studies were predominantly based on young patients, retrospective cases or unstandardized questionnaires instead of on neurocognitive and behavioural evaluations.

The severity of neurocognitive impairments, behavioural disorders, and learning disabilities in DMD and BMD are likely related to the location of mutation and it effect on the expression of specific brain dystrophin isoforms.[11,32,35,42,49,52-54] In Duchenne, it seems that patients with mutations affecting multiple brain isoforms (i.e. the full-length Dp427B and shorter brain isoforms including Dp140 and/or Dp71) display more severe brain-related comorbidities than patients missing only Dp427B.[11,32,35,42,52-54] In Becker, the role of partial functional brain dystrophin expression on neurocognitive and behavioural functioning is limited. Only the study by Bardoni and colleagues found that a lack of the brain isoform, Dp140, in addition to Dp427B was related to lower general intellectual abilities of patients with BMD.[49] No relation is found between other neurocognitive disfunctions or behavioural disorders and an aberrant expression of the brain isoforms in BMD patients. For both DMD and BMD additional information on the existence of specific dystrophin-associated neurocognitive impairments and behavioural disorders is recommended.

Diagnostic work-up

Improved medical care (e.g. improved ventilation assistance) has increased the life expectancy in DMD, but patients are also confronted with long-lasting or new mental health issues that negatively influence their quality of life.[55] Thereby, improvements in screening and diagnostics of brain-related comorbidities are crucial. Across the lifespan, clinicians should be aware of possible neurocognitive impairments, neurodevelopmental and behavioural disorders, psychosocial problems and learning disabilities.[55] The DMD standards of care recommended that at each visit and

particularly during transition phases, the mental health status of patients should be screened.[55] Further assessment should by applied when screening results display mental health problems.[55] However, until now various methods have been used to evaluate behavioural and psychosocial problems in both DMD and BMD, leading to a variability in prevalence rates. An overview of adequate instruments and their psychometric quality for both populations is lacking.

Interventions

Further research on interventions that may limit the influence of brain-related comorbidities in neurocognition and behaviour is necessary and may increase the quality of life of DMD and BMD patients. In the DMD standards of care, recommendations were given on applying known evidence-based interventions to treat behavioural disorders which have been used in populations with other chronic (medical) conditions.[55] They for instance considered psychopharmacological medication to treat moderate to severe symptoms of neurodevelopmental or behavioural disorders. [55] Psychopharmacological medication should be applied according to the prescribing guidelines, although special attention must be given to the DMD patients' medical condition i.e. cardiac status, medical interactions and side effects when it is combined with other existing medication, particularly when patients are older.[55] Stimulant medication is for instance one of the recommended psychopharmacological treatments for DMD patients who have a comorbid ADHD diagnosis.[55] However the safety and effectiveness of this medication has not been evaluated scientifically previously. Furthermore, the DMD standards of care recommended that neuropsychological and educational interventions should be developed and implemented at home and school. However, current literature lacks information on the effectiveness of these interventions for DMD.

Aims and outlines of this thesis

The main aim of this thesis was to provide insights on neurocognition and behaviour, diagnostic work-up and interventions in Duchenne and Becker muscular dystrophy. To achieve this, this thesis addresses the following research questions:

1. Is there a DMD specific dystrophin-associated neurocognitive and behavioural profile?
2. Are cognitive deficits in DMD stable over time?
3. What are the neurocognitive and behavioural features of paediatric and adult males with BMD and are these related to disease severity?
4. Which instruments are valid and reliable to assess behavioural and psychosocial functioning in DMD and BMD?
5. Do males with DMD benefit from psychological (cognitive) interventions such as computerized working memory training?
6. Is stimulant medication i.e. short-acting methylphenidate a safe and effective psychopharmacological treatment for males with DMD and a comorbid ADHD diagnosis?

Outline

Neurocognition and behaviour

- In chapter 2, we evaluate the neurocognitive and behavioural profiles of two neurogenetic disorders, DMD and Neurofibromatosis type 1.
- In chapter 3, we longitudinally assess cognitive functions and explore the role of Dp140 in DMD neurocognitive performance.
- In chapter 4, we describe the neurocognitive and behavioural features of adult males with BMD and correlate these to disease severity.
- In chapter 5, we evaluate the neurocognitive and behavioural profiles of three brothers with BMD with a similar dystrophin gene mutation.

Diagnostic work-up of behavioural and psychosocial assessment

- In chapter 6, we systematically review studies investigating behavioural and psychosocial functioning in DMD and BMD. Our main aims were to give an overview of the instruments used and their psychometric quality.

Interventions

- In chapter 7, we explore the benefits of computerized working memory training in males with DMD and a comorbid learning disability.
- In chapter 8, we evaluate the safety and effectiveness of short acting methylphenidate for males with DMD and a comorbid ADHD diagnosis.

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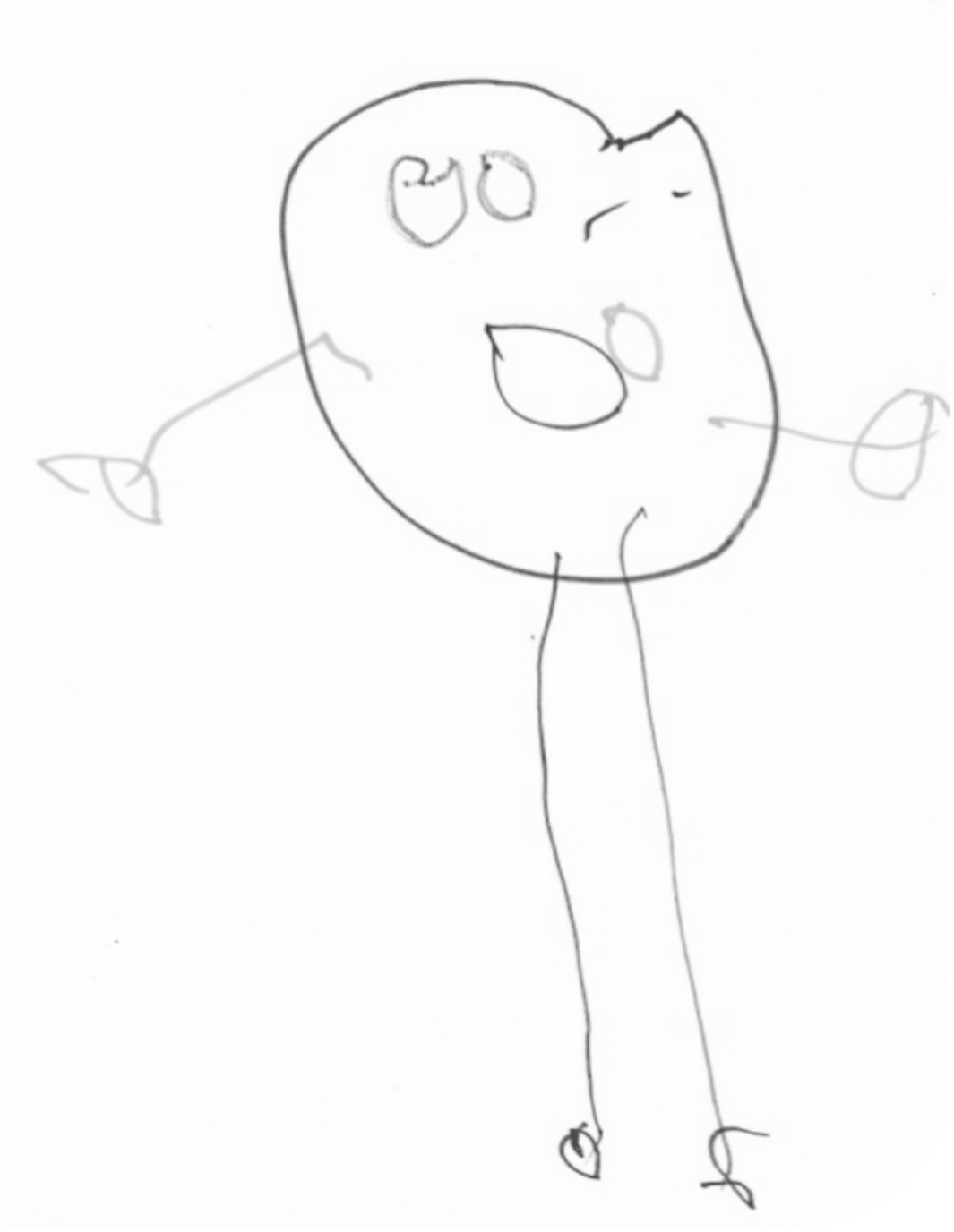

Chapter 2

Cognitive and behavioural functioning in two neurogenetic disorders; how different are these aspects in Duchenne muscular dystrophy and Neurofibromatosis type 1?

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Abstract

The presence of neurocognitive and behavioural problems are common features in various neurogenetic disorders. In Duchenne muscular dystrophy (DMD), these problems have been linked to mutations along the dystrophin gene affecting different brain dystrophin isoforms. However, comparable cognitive and behavioural problems have been found in Neurofibromatosis type 1 (NF1). This study aims to assess disorder specific differences in cognition and behaviour between DMD and NF1. At total of 38 male patients with DMD were aged-matched to 38 male patients with NF1. Patients of both groups underwent neurocognitive assessment for regular clinical care. Intellectual abilities, sequential and simultaneous processing, verbal memory and sustained attention were evaluated. In addition, parents and teachers completed behavioural questionnaires. Males with DMD exhibited low intellectual abilities and sequential processing problems, but these outcomes not significantly differed from males with NF1. Simultaneous processing, verbal memory and sustained attention outcomes were equal for both groups. Outcomes of questionnaires displayed higher rates of aggressive behaviour (13.2%) in DMD, whereas in NF1 higher rates of problems with thinking (15.8%), withdrawn (10.5%) and social behaviour (10.5%) were noticed. In the neurogenetic disorders DMD and NF1, on average overlapping cognitive and behavioural problems are noticed, suggesting that these are not only caused by gene mutations resulting in a lack of one specific protein. Furthermore, due to the variability in severity and overlap of problems in both populations, (re) evaluation and monitoring of cognition and behaviour are important aspects for clinical care.

Introduction

There is growing evidence that gene mutations can cause abnormal brain development that lead to cognitive and behavioural problems in patients with neurogenetic disorders such as Duchenne muscular dystrophy (DMD), Neurofibromatosis type 1, 22q11.2 deletion syndrome, Prader-Willi syndrome, fragile X syndrome and Turner syndrome.[1-6] In DMD, gene mutations result in a loss of the full-length dystrophin protein isoform (Dp427) in muscles (M) and the brain (B).[7,8] A lack of the dystrophin protein $Dp427_M$ is responsible for the progressive muscle weakness in DMD.[9] The isoform $Dp427_B$ and three shorter brain isoforms Dp140, Dp71+Dp40 are believed to be expressed throughout the cerebral cortex with the highest expression in the temporal and frontal cortex, the amygdala and hippocampus.[10-13] The production of one of the brain isoforms (Dp140) is particularly elevated during foetal life stages, suggesting that it may influence brain development.[11]

Patients with Duchenne frequently exhibit cognitive problems, neurodevelopmental-, and behavioural disorders.[3,10,14,15] The full-scale intelligence quotient (FSIQ) in DMD is on average one standard deviation below the population mean.[16] In addition, problems with verbal working memory, attention, executive functioning, learning (e.g. reading, writing, math) have been reported.[14,16-18] The higher rates of neurodevelopmental and behavioural disorders are found for attention-deficit hyperactivity disorders (ADHD; up to 32%), autism spectrum disorders (ASD; up to 21%), obsessive compulsive disorders (OCD up to 5.1%) and anxiety (up to 27%).[14,19-22] The numbers vary due to use of various (screening) instruments. Recent studies have tried to assess whether specific gene mutations affecting the production of brain isoforms can be related to the cognitive problems, neurodevelopmental-, and behavioural disorders of patients with DMD.[10,11,14,21-24] It seems that patients with mutations affecting multiple brain isoforms exhibit more severe problems in cognition and behaviour than patients missing only $Dp427_B$.[19,21,23-26]

Neurofibromatosis type 1 (NF1) is caused by germline mutations in the NF1 gene, resulting in a decreased production of the tumour suppressive protein, neurofibromin.[27] There are a broad number of possible mutations in the large NF1 gene, resulting in variable phenotypes with various neurocutaneous manifestations including (plexiform) neurofibromas, café-au-lait spots, skinfold freckling, but also skeletal and muscular problems (e.g. scoliosis, pseudo-arthrosis, decreased bone strength, reduced muscle strength and motor problems).[27,28] Previous studies in mice have showed that deletions involving exons NF1-23a and NF1-9a result in altered

isoform expression in the brain (i.e. astrocytes) and in the central nervous systems (i.e. in neurons of striatum, cortex and hippocampus).[29] Due to the role of neurofibromin in the brain, human and mice studies have linked a lack of this protein to the cognitive and learning disabilities that are found for NF1.[29-32] Low-average IQ levels are usually shown in NF1 patients, but impairments are also found in visuo-spatial perceptual and visuomotor skills, language, learning (e.g. reading) and executive functions (e.g. attention and working memory).[31-35] In addition, in NF1 higher prevalence rates of ADHD (up to 50%), ASD (14%) and behavioural problems such as anxiety and depression (43%), have been noticed compared to the general population.[31-33,35-40] Due to the large number of unique mutations in NF1, it is complicated to define a distinct cognitive and behavioural profile.[31] However, recent studies have revealed that patients with microdeletions display more pronounced cognitive impairments and learning disabilities than patients with intragenic mutations.[31,41-43]

For neuropsychological diagnostic and treatment purposes we were interested whether patients with different neurogenetic disorders such as DMD and NF1 have specific cognitive and behavioural profiles. Therefore, the current study aimed to assess whether the cognitive and behavioural impairments differ between DMD and NF1.

Materials and methods

Study population

Eligible patients for current study were males with DMD and males with NF1 attending to the outpatient clinic of Kempenhaeghe, the Centre for Neurological Learning Disabilities (CNL), Heeze, the Netherlands, as this Centre is predominantly responsible for the neuropsychological care of these patients in the Netherlands. The inclusion criteria comprised of having a previously genetical confirmed mutation of the dystrophin gene for DMD patients or a previously genetical confirmed mutation of the neurofibromin gene for NF1 patients, an age between 6-16 years, an adequate proficiency in Dutch, normal hearing, absence of severe visual impairment and no physical immobility of upper extremities (the reliability of the cognitive tests may be reduced by impairments in hearing, vision and physical immobility of upper extremities). Exclusion criteria were: epilepsy, symptomatic optic pathway glioma, brain tumours, or hydrocephalus. NF1 males with focal abnormal signal intensity (FASI) were not excluded because no equivocal relation is found between the presence of FASI and cognitive, developmental impairments and learning disabilities.[44,45] Each eligible male

patient with DMD was matched on age (restriction within 1 year) to an age equivalent male with NF1. The age range of participants (6-16 years) was chosen to allow for the administration of the cognitive test and behavioural questionnaires, standardized for the Dutch population. Ethical approval was granted by the local Medical Ethical Committee of Kempenhaeghe. The study was conducted in accordance with the 18th World Medical Assembly, Helsinki 194.

Study procedure

DMD and NF1 patients received an extensive neuropsychological assessment between October 2008 and August 2019 to evaluate their cognitive and behavioural functioning as part of regular clinical care at CNL. Cognitive assessment evaluated intellectual abilities (full scale intelligence, verbal intelligence and performance intelligence), processing speed, sequential processing (verbal span capacity and working memory), simultaneous processing (visuospatial functioning), verbal memory (immediate recall, delayed recall, recognition) and sustained visual- and auditory attention. Behavioural functioning was screened using questionnaires for parents and teachers. All collected cognitive and behavioural data were extracted from the patient files for current retrospective study. Demographic (i.e. age, educational level, gender), disease-related characteristics (i.e. genetic mutation, ambulation, comorbid learning disabilities, neurodevelopmental or behavioural DSM classified diagnoses, use of stimulant medication such as methylphenidate (MPH), use of corticosteroids, somatic comorbidities, vision or hearing problems and immobility of upper extremities), sociodemographic characteristics of parents and information on problems during pregnancy and delivery were extracted from the patient files. The comorbid learning disabilities extracted from the patient files included dyslexia and dyscalculia. In addition, learning difficulties such as problems with reading, writing, math, automatization or spelling that did not fulfil the criteria for dyslexia and dyscalculia were extracted from the files. The neurodevelopmental and behavioural DSM-IV/DSM-5 that were obtained from the patient files included ADHD, ASD, OCD, developmental coordination disorder (DCD), anxiety, depression and tic disorders. All cognitive, behavioural and learning comorbidities were previously diagnosed by a health or medical professional. The educational status of patients was categorized as regular or special education. Parents educational status was indicated using the Dutch Verhage categories[46] and was used to estimate the sociodemographic status of patients. The Verhage categories were combined into (1) low level (i.e. <6 years of primary education, finished primary education, <2 years low-level secondary education, finished low-level secondary education), (2) middle level (i.e. finished average-level secondary

education) and (3) high level (i.e. finished high level secondary education, university degree).[46]

Neuropsychological assessment

Cognition

The Wechsler Intelligence Scale for Children Third edition (WISC-III)[47] measured Full-Scale Intelligence Quotient (FSIQ), Verbal Intelligence (VIQ), Performance Intelligence (PIQ), Verbal Comprehension, Perceptual Organization and Processing Speed. Raw scores of the WISC-III were converted to age-related norm scores (mean=100, SD=15).[47] The Kaufmann Assessment Battery for Children-II (KABC-II) was used to assess sequential processing (verbal span and auditory working memory) and simultaneous processing (visuospatial functioning).[48] Sequential processing was based on the subtests Number recall and Word Order. Simultaneous processing was based on the subtests Rover and depending on age the subtests Triangles (6 years) or Block Counting (7-16 years). Raw scores of the subtests were converted to age-related scaled scores (mean=100, SD=15).[48] Verbal memory of immediate recall, delayed recall and recognition was tested using the Rey auditory learning task (15-word test).[49] Scores of the 15-word test were computed to (1) a sum of correct responses given during the five consecutive trials (total immediate recall score), (2) total correct response during the delayed trial (delayed recall score) and (3) sum of correct recognition responses (recognition score).[49] Sustained visual attention was measured using the Bourdon Vos.[50] The Test of Everyday Attention for Children, Second Edition (TEA-Ch)[51], subtest Score! was used to measure sustained auditory attention. Teach-Ch raw scores were converted to scaled scores (mean=10, SD=3).[51]

Behaviour

Behavioural functioning was screened using two informant rating instruments, the Child Behaviour Checklist for Children (CBCL) and the Teacher report Form (TRF).[52] Both instruments evaluated behaviour based on eight syndrome scales (anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviour and aggressive behaviour). Two broadband scales on internalizing symptoms (made up of withdrawn, somatic complaints and anxious/depressed scales), externalizing symptoms (made up of rule-breaking behaviour and aggressive behaviour), and a total problem scale score were calculated using the syndrome scale scores. In line with the manual, a cut-off value (clinical range score) of $T \geq 70$ was used to indicate the clinical range of the eight

syndrome scales, and T≥64 was applied to indicate the clinical range of internalizing, externalizing symptoms and a total problem score.[52]

Statistical analysis

Age-matching (restriction within 1 year) was randomly performed by case control matching of SPSS. Demographic and disease-related characteristics were presented as mean (SD), or absolute number and proportion. Stochastic regression imputation was applied in case of incomplete variables of cognitive and behavioural data.[53] The imputed values were drawn using predictive mean matching.[53] Differences between the DMD and NF1 group on demographic and disease-related parameters as well as cognitive and behavioural outcomes were tested using the independent samples t-test, X^2 tests, Fisher exact test, or Mann-Whitney-U tests, as appropriate. Effect sizes (quantified as Cohen's d) were calculated to indicate the strength of differences of the cognitive and behavioural outcomes.[54] Effect sizes were defined as: 0.20-0.50=small, 0.50-0.80=medium and ≥0.80=large.[54] Multivariate analyses (MANOVA) examined differences between the groups on cognitive and behavioural outcomes corrected for the covariates age, comorbid diagnoses of patients (i.e. learning, neurodevelopmental, or behavioural disorders), use of stimulant medication (MPH), use of steroids, educational status of patients and family history of learning and behavioural problems. Preliminary assumptions associated with all test statistics, such a normality and multivariate normality, homogeneity of variance, homogeneity of variance-covariance matrices, linearity and multicollinearity were examined using a variety of methods including visual inspection of histograms, boxplots, scatterplots, inspection of skewness, kurtosis, Shapiro-Wilk test, Levene's test and Box's M test (p≥.001).[55] Cognitive outcomes i.e. age-related norm scores were converted to z-scores (mean =0, SD=1). Behavioural outcomes were also evaluated using the clinical cut-off value of T-score ≥63.[52] All statistical analyses were carried out using IBM SPSS version 24.0 for MAC OS X.

Results

Participant characteristics

Data of 50 patients with DMD were available. Twelve patients were excluded because of age (n=7 were <6 years and n=2 were >16 years old) or having epilepsy (n=3). In total 38 patients with DMD were age-matched with 38 males with NF1. Demographic and disease-related characteristics of both groups are displayed in Table 2.1.

Table 2.1 *Participant characteristics.*

	DMD (N=38)	NF1 (N=38)	p
Demographic characteristics			
Mean age in years (SD)	9.6 (2.6)	9.7 (2.6)	.839
Education of participants (%)			.000**
Regular education	6 (15.8)	23 (60.5)	
Special education	32 (84.2)	15 (39.4)	
Educational levels of parents (%)			
Mother:			.522
Low level	6 (17.1)	4 (10.5)	
Middle level	14 (40.0)	17 (56.7)	
High level	15 (42.9)	9 (30.0)	
Father:			.570
Low level	4 (10.5)	2 (7.1)	
Middle level	6 (19.4)	10 (35.7)	
High level	21 (67.7)	16 (57.1)	
Family history learning and behavioural problems (%)			.002*
ADHD	4 (10.8)	9 (24.3)	
ASS	1 (2.7)	4 (10.8)	
Dyslexia	6 (16.2)	13 (35.1)	
Learning difficulties	3 (8.1)	3 (8.1)	
Pregnancy & delivery problems (%)			.229
Hypoxia	1 (2.6)	0	
Premature birth (34 to ≤ 37 wk)	4 (10.4)	1 (2.6)	
C-section	1 (2.5)	2 (5.3)	
Intrauterine growth problems	2 (5.3)	2 (5.3)	
Pre-eclampsia	1 (2.6)	0	
Disease-related characteristics			
Wheelchair dependence (%)			.000**
Permanent	16 (44.4)	0	
Intermittent	5 (13.9)	0	
Never	15 (41.7)	0	
Medication use (%)			
Steroids (prednisone)	31 (81.6)	0	.000**
Stimulants (MPH)	4 (10.5)	9 (23.7)	.222
Sleep problems (%)			.133
Falling asleep	8 (21.6)	15 (39.5)	
Staying asleep	0	0	
Comorbid diagnoses (%)			.491
ADHD	7 (18.2)	16 (41.6)	.025*
ADD	3 (7.9)	4 (10.5)	1.000
ASD	10 (26.3)	4 (10.5)	.076
Depression	1 (2.6)	0	1.000
Anxiety	2 (5.3)	0	.493
Tics	1 (2.6)	1 (2.6)	1.000
Dyslexia	1 (2.6)	4 (10.5)	.358
Dyscalculia	3 (7.9)	0	.240
DCD	0	11 (28.9)	.005*

Results are mean (SD) or median (range) for continuous variables, and frequencies (%) for categorical variables. Verhage categories are defined as low level (i.e. <6 years of primary education, finished primary education, <2 years low-level secondary education, finished low-level secondary education), middle level (i.e. finished average-level secondary education), and high level (i.e. finished high level secondary education, university degree).[41] wk=weeks. Reasons for C-section were: N=1 pelvic presentation, N=1 C-section at 38 weeks because of intrauterine growth problems, and N=1 emergency C-section but reason was not documented. Reports on family history of learning and behavioural problems are based on 1st, 2nd, and 3rd family degree. * p<.05 (two-sided); ** p<.01 (two-sided).

Of the DMD group, 21 males (55.3%) had mutations affecting Dp140 production (i.e. mutations corrupting the Dp140 promoter, the Dp140 translation start site or were located downstream of exon 50 as the Dp140 ATG start-site is located in exon 51). Ten males (26.3%) had mutations not affecting Dp140 production (i.e. deletions or duplications upstream of intron 44). Dystrophin expression was undefinable of five males (13.2%) with deletions or duplication breakpoints between intron 44 and exon 51.[24] No information on deletions or duplications was available in the electronic patient files of two males (5.3%). Of the NF1 group, none of the patients had microdeletions.

Disease-related characteristics are displayed in Table 2.1. The majority of the DMD group (81.6%) used prednisone steroids, six (15.6%) used deflazacort and one (2.6%) had no corticosteroid treatment, because it severely affected his emotional status. The prevalence rates of comorbid diagnoses in neurodevelopmental and behavioural disorders differed between the DMD and NF1 group (see Table 2.1). ASD diagnoses were more often found for the DMD group (23.4%) compared to the NF1 group (13%), whereas the rate of ADHD diagnoses is higher for the NF1 group (41.6%) than for the DMD group (18.2%, see Table 2.1). Diagnoses of learning disorders such as dyslexia and dyscalculia were found in both groups. Furthermore, n=11 males with DMD (28.6%) and n=18 (46.8%) males with NF1 exhibited learning disabilities in reading, writing, mathematics, spelling and automatization that not fulfil the diagnostic criteria for dyslexia or dyscalculia. Within the NF1 group nine used MPH, whereas in the DMD group four males used MPH (see Table 2.1).

Cognitive outcomes

Intellectual abilities

Of the DMD group, the mean FSIQ was 86.4 (SD=11.9), mean Verbal IQ was 89.6 (SD=12.0) and mean Performance IQ was 85.3 (SD=12.0). These two latest outcomes indicated no discrepancy between VIQ and PIQ for the DMD group. Additionally, their overall mean score of Verbal Comprehension was 91.5 (SD=9.5), mean Perceptual Reasoning was 84.9 (SD=8.6) and mean Processing Speed was 89.5 (SD=16.2). Of the NF1 group, the overall mean FSIQ was 91.5 (SD=15.4), mean Verbal IQ was 93.9 (SD=14.4) and mean Performance IQ was 89.9 (SD=17.0), signifying no discrepancy between VIQ and PIQ. The overall mean of the NF1 group for Verbal Comprehension was 95.5 (SD=15.0), mean Perceptual Reasoning was 89.4 (SD=14.5) and mean Processing Speed was 94.0 (SD=17.3). As shown in Table 2.2, no significant differences were found on all IQ measures between the DMD and NF1 group.

Table 2.2 *Wechsler Intelligence Scale for Children-III outcomes of the DMD and the NF1 group.*

	Mean (SD) DMD group (N=38)	Mean (SD) NF1 group (N=38)	Test-statistic value	p	Effect size	95% CI	
						Lower	Upper
FSIQ	-0.91 (0.79)	-0.57 (1.03)	-1.626	.108	-0.4	-0.76	0.07
VIQ	-0.69 (0.81)	-0.41 (0.96)	-1.387	.170	-0.3	-0.69	0.12
PIQ	-0.98 (0.80)	-0.67 (1.13)	-1.370	.175	-0.3	-0.76	0.14
VC	-0.57 (0.63)	-0.30 (1.00)	-1.411	.163	-0.3	-0.65	0.11
PO	-1.00 (0.58)	-0.71 (0.96)	-1.654	.103	-0.4	-0.72	0.00
PS	-0.77 (1.12)	-0.40 (1.15)	-1.402	.165	-0.3	-0.67	0.06

Z-scores are mean (SD), Test statistic values are t-values, Effect size = Cohen's d, 95% CI=95% Confidence Interval. FSIQ=Full-scale intelligence quotient, VIQ=Verbal intelligence quotient, PIQ=Performance intelligence quotient, VC=Verbal Comprehension, PO=Perceptual Organization, PS=Processing speed.

WISC distribution of FSIQ of the two groups are displayed in Figure 2.1. Of the DMD group, four males (10.5%) had a FSIQ score of ≤70, thirteen males (34.2%) scored between 70-85, seventeen (44.7%) fell within the range 85-100, three (7.9%) scored between 100-115 and one (2.6%) had a FSIQ score ≥115 (see Figure 2.1). Of the NF1 group, four (10.5%) scored below ≤70, six males (15.8%) had a FSIQ score between 70-85, nineteen (50.0%) fell within the range 85-100, six (15.8%) had a FSIQ score between 100-115 and three (7.9%) had FSIQ score ≥115 (see Figure 2.1). The sociodemographic status (measured by educational status (ES) of parents) of both groups were not correlated to the FSIQ outcomes (ES mothers of DMD group *rs*=.16, *p*>.05, ES fathers of DMD group *rs*=.19, *p*>.05, ES mothers NF1 group, *rs*=.13, *p*>.05 and ES fathers NF1 group, *rs*=.26, *p*>.05).

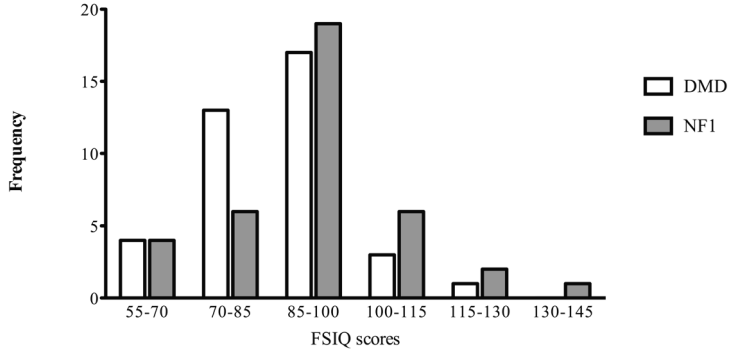

Figure 2.1 *Frequencies of the Wechsler full-scale intelligence quotient scores of the DMD (N=38) and NF1 group (n=38).* FSIQ=full-scale intelligence quotient, DMD=Duchenne muscular dystrophy, NF1= Neurofibromatosis type 1.

Sequential and simultaneous processing

Results showed that mean sequential processing of the DMD group was 81.9 (SD=12.5) and of the NF1 group mean sequential processing was 80.6 (SD=7.9). Mean simultaneous processing of the DMD group was 95.6 (SD=14.3) and of the NF1 group mean simultaneous processing was 97.5 (SD=12.0). No significant difference was found between the groups on sequential processing and simultaneous processing (see Table 2.3).

Table 2.3 *Cognitive outcomes of (working) memory, attention, and visuospatial abilities of the DMD and NF1 group.*

Cognitive domains	DMD (N=38)	NF1 (N=38)	Test-statistic value	p	Effect size	95% CI	
						Lower	Upper
SEQ	-1.21 (0.84)	-1.29 (0.53)	0.536	.594	0.1	-0.23	0.41
SIM	-0.30 (0.96)	-0.17 (0.80)	-0.620	.537	-0.1	-0.53	0.28
SVAS	-0.55 (1.01)	-0.70 (1.04)	0.619	.538	0.1	-0.32	0.61
SVAA	-0.65 (1.27)	-0.51 (1.36)	-0.468	.641	-0.1	-0.74	0.46
SAU	-0.66 (1.08)	-0.85 (1.05)	0.767	.445	0.2	-0.30	0.67
IR	-0.27 (1.17)	-0.24 (1.64)	-0.075	.941	-0.0	-0.67	0.63
DR	-0.38 (1.14)	-0.54 (1.35)	0.542	.589	0.1	-0.42	0.73
RC*	28.5 (24-30)	29 (21-30)	-0.890	.374	NA	NA	NA

Z-scores are mean (SD) except of * outcomes are raw median (range) scores, Test-statistic values are t-values, except of * is z-value, Effect size=Cohen's d, 95% CI=95% Confidence Interval. SEQ=Sequential processing, SIM=Simultaneous processing, SVAS=Sustained Visual Attention Speed, SVAA=Sustained Visual Attention Accuracy, SAU=Sustained Auditory Attention, IR=Immediate Recall, DR=Delayed Recall, RC=Recognition, DMD=Duchenne muscular dystrophy, NF1=Neurofibromatosis type 1, NA=not applicable.

See Figure 2.2 for visualization of differences between the DMD and NF1 group on outcomes of sequential and simultaneous processing. Both groups had lower sequential processing than simultaneous processing outcomes (DMD group, $p<.001$ and NF1 group, $p<.001$). No significant correlation was found between the lower sequential outcomes and FSIQ outcomes of the DMD population ($r=0.23$, $p>.05$) and NF1 population ($r=0.05$, $p>.05$). Simultaneous processing outcomes were moderate but significantly correlated with FSIQ in the DMD group ($r=0.39$, $p<.05$), but not in the NF1 group ($r=0.08$, $p>.05$).

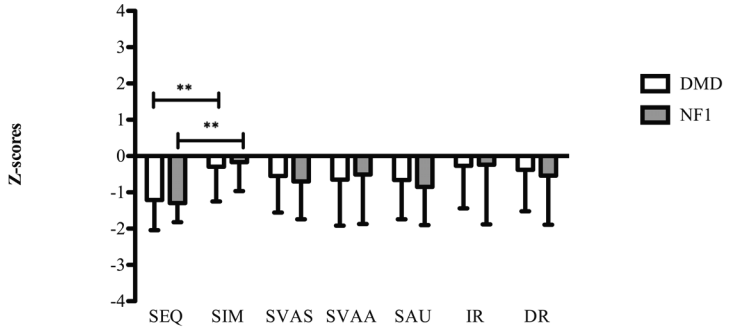

Figure 2.2 *Mean (SD) outcomes of the DMD group (N=38) and NF1 (N=38) group.* SEQ=Sequential processing, SIM=Simultaneous processing, SVAS=Sustained Visual Attention Speed, SVAA=Sustained Visual Attention Accuracy, SAU=Sustained Auditory Attention, IR=immediate recall, DR=delayed recall, DMD=Duchenne muscular dystrophy, NF1=Neurofibromatosis type 1. ** p<.001 (two-sided).

Verbal memory

On verbal memory i.e. immediate recall, delayed recall and recognition no significant differences were found between the groups (see Table 2.3). The outcomes on immediate and delayed recall of both groups are visualized in Figure 2.2. Only immediate recall of the NF1 group was significantly correlated with total FSIQ (r=0.55, p<.001) and no correlation was found for the DMD group (r=0.06, p>.05).

Sustained attention

On visual sustained attention results showed no significant differences between the DMD and the NF1 group on speed or accuracy (see Table 2.3). Mean sustained auditory attention was also not significantly different between the groups (see Table 2.3). See Figure 2.2 for visualization of differences between the DMD and NF1 group on outcomes of sustained visual and auditory attention. All sustained attention measures were not significantly correlated with the FSIQ outcomes of the DMD and NF1 group.

A multivariate analysis was run to determine the effect of the covariates, age, comorbid diagnoses of patients (i.e. learning, neurodevelopmental, or behavioural disorders), use of stimulant medication (MPH), use of steroids, educational status of patients and family history of learning and behavioural problems on all cognitive outcomes of both groups. Results showed again non-significant differences between the groups on intellectual abilities, sequential and simultaneous processing, verbal memory, sustained visual and auditory attention after controlling for the influence of the covariates on the cognitive outcomes (see Table 2.4).

Table 2.4 *Multivariate analyses of cognitive outcomes of the DMD and NF1 group.*

	DMD (n=38)			NF1 (n=38)			p
	Mean	95% CI		Mean	95% CI		
		Lower	Upper		Lower	Upper	
Cognitive outcomes							
FSIQ	-0.52	-1.01	-0.03	-0.93	-1.40	-0.45	.359
VIQ	-0.22	-0.68	0.25	-0.87	-1.32	-0.41	.121
PIQ	-0.72	-1.26	-0.19	-0.91	-1.43	-0.39	.698
VC	-0.27	-0.70	0.16	-0.55	-0.97	-0.13	.470
PO	-0.88	-1.33	-0.43	-0.80	-1.20	-0.36	.841
PS	-0.60	-1.22	-0.03	-0.52	-1.13	0.09	.883
SEQ	-1.22	-1.60	-0.84	-1.28	-1.65	-0.91	.854
SIM	-0.15	-0.64	0.33	-0.33	-0.80	0.15	.691
SVAS	-0.84	-1.39	-0.30	-0.47	-1.00	0.62	.447
SVAA	-0.26	-0.95	0.44	-0.92	-1.60	-0.24	.290
SAU	-1.18	-1.74	-0.61	-0.25	-0.81	0.30	.073
IR	-0.06	-0.81	0.30	-0.47	-1.21	0.27	.548
DR	-0.16	-0.85	0.53	-0.64	-1.32	0.03	.433

Cognitive outcomes are means of z-scores corrected for the covariates age, the presence of comorbidities (learning, neurodevelopmental or behavioural disorders), use of stimulant medication (MPH), use of steroids, educational status of patients, and family history of learning and behavioural problems. 95% CI=95% Confidence Interval. FSIQ=Full-Scale Intelligence quotient, VIQ=Verbal Intelligence quotient, PIQ=Performance intelligence quotient, VC=Verbal Comprehension, PO=Perceptual Organization, PS=Processing speed, SEQ=Sequential processing, SIM=Simultaneous processing, SVAS=Sustained Visual Attention Speed, SVAA=Sustained Visual Attention Accuracy, SAU=Sustained Auditory Attention, IR=immediate recall, DR=delayed recall, DMD=Duchenne muscular dystrophy, NF1=Neurofibromatosis type 1. * p<.05 (two-sided).

Behavioural reports of parents and teachers

Outcomes of the behavioural reports of the DMD and NF1 group are displayed in Table 2.5. Parents of the DMD group reported that 23.7-28.9% of the males had internalizing or externalizing problems, whereas according to teachers 13.2% displayed internalizing and externalizing problems. Aggressive behaviour was the most frequent observed behavioural problem in DMD (13.2%) according to parents (CBCL) responses. These five DMD males that displayed aggressive behaviour were aged between 7,1-14,4 years. Problems with thinking and withdrawn were also reported by parents of the DMD group. Results further showed differences in the prevalence rates of behavioural problems reported by parents (CBCL) compared to those reported by teachers (TRF), with limited behavioural problems documented by teachers. Parents of the NF1 group, reported that 18.4-15.8% of the males had internalizing and externalizing problems, which is approximately comparable to the responses of teachers (15.8% internalizing and 15.8 % externalizing). In particular, problems with thinking and withdrawn were documented by parents of the NF1 group, whereas teachers rated more social problems.

Table 2.5 *Behavioral reports of parents and teachers of the DMD and NF1 group.*

	DMD (n=38)					NF1 (n=38)							
Questionnaires with scales	Mean (SD)	Median	Min	Max	Clinical range (%)	Mean (SD)	Median	Min	Max	Clinical range (%)	Definition of clinical range	*p*	Effect size
CBCL													
Anxiety/Depression	56.0 (6.6)	53	50	78	1 (2.6)	55.0 (7.9)	51	50	84	2 (5.3)	≥70	.120	
Withdrawn	60.5 (7.9)	60	50	82	4 (10.5)	59.9 (8.8)	58	50	88	4 (10.5)	≥70	.562	
Somatic complaints	58.3 (7.1)	57.3	50	76	3 (7.9)	58.3 (7.0)	57	50	72	2 (5.3)	≥70	.754	
Social problems	60.1 (6.9)	59.7	50	83	1 (2.6)	60.0 (7.1)	60	50	75	3 (7.9)	≥70	.925	
Thought problems	59.6 (7.5)	59.7	50	77	4 (10.5)	62.3 (7.5)	62.6	50	75	6 (15.8)	≥70	.096	
Attention problems	59.7 (6.2)	59	50	75	3 (7.9)	61.5 (6.3)	61	50	71	2 (5.3)	≥70	.155	
Rule-Breaking	56.7 (6.1)	55.5	50	71	1 (2.6)	55.2 (5.9)	53	50	73	2 (5.3)	≥70	.244	
Aggression	62.1 (9.3)	60.9	50	83	5 (13.2)	59.4 (7.7)	59	50	87	1 (2.6)	≥70	.256	
Intern. Prob.	57.2 (8.9)	57	34	75	9 (23.7)	55.1 (9.7)	53.2	41	78	7 (18.4)	≥63	.333#	0.3
Extern. Prob.	57.8 (11.0)	58.2	33	75	11 (28.9)	55.4 (10.0)	57.2	33	78	6 (15.8)	≥63	.335#	0.2
Total Prob.	59.9 (9.4)	60.2	41	77	12 (31.6)	58.8 (10.1)	59.3	34	78	11 (28.9)	≥63	.609#	0.1
TRF													
Anxiety/Depression	56.7 (5.1)	55.9	50	68	0	57.6 (5.9)	57.2	50	76	1 (2.6)	≥70	.460	
Withdrawn	58.2 (6.4)	57.3	50	77	2 (5.3)	58.6 (5.8)	57.2	50	81	1 (2.6)	≥70	.512	
Somatic complaints	52.4 (3.3)	50.2	50	62	0	53.5 (4.6)	51.2	50	67	0	≥70	.533	
Social problems	59.9 (4.8)	60.9	50	70	0	62.0 (7.8)	62	50	81	4 (10.5)	≥70	.240	
Thought problems	57.0 (5.8)	56.8	50	72	1 (2.6))	56.8 (6.8)	57	50	79	2 (5.3)	≥70	.740	
Attention problems	57.4 (6.1)	57	50	79	2 (5.3)	56.8 (5.5)	55.4	50	72	1 (2.6))	≥70	.621	
Rule-Breaking	54.7 (3.9)	54.9	50	68	0	54.8 (5.0)	53.7	50	68	0	≥70	.649	
Aggression	59.4 (5.7)	58.9	50	75	2 (5.3)	57.6 (6.1)	57.3	50	78	1 (2.6)	≥70	.156	
Intern. Prob.	55.9 (7.2)	56.1	38	71	5 (13.2)	58.0 (6.1)	57.6	45	75	6 (15.8)	≥63	.166#	-0.3
Extern. Prob.	57.1 (6.8)	56.6	41	73	5 (13.2)	55.0 (7.5)	55.5	41	74	6 (15.8)	≥63	.212#	0.3
Total Prob.	57.5 (6.0)	57	40	73	5 (13.2)	57.9 (6.2)	57.8	49	72	7 (18.4)	≥63	.776#	-0.1

CBCL=Child Behavior Checklist, TRF=Teacher Report Form, DMD=Duchenne muscular dystrophy, NF1=Neurofibromatosis type 1, Inter. prob.=score of total internalizing problems, Extern. Prob.=score of total externalizing problems, Total prob.=total problems score. Differences between the DMD and NF1 group were assessed using Mann-Whitney U-tests, except for # which are analyzed using Independent sample *t*-test.

Again, a difference in rates was found between parents (CBCL) and teachers (TRF) responses for the NF1 group. No significant differences were found between the DMD and the NF1 group on all subscales, the broadband scales internalizing- and externalizing problems and total problem scores (see Table 2.5).

A multivariate analysis was run to determine the effect of the covariates, age, comorbid diagnoses of patients (i.e. learning, neurodevelopmental, or behavioural disorders), use of stimulant medication (MPH) or steroids, educational status of patients and family history of learning and behavioural problems on the CBCL and TRF broadband internalizing- and externalizing scales and the total problem scores. Results showed that the broadband internalizing scale of the CBCL was significantly higher for the DMD than for the NF1 group after controlling for the covariates (see Table 2.6). No differences were found between the groups on the internalizing TRF scale score, externalizing CBCL and TRF scale scores and the total problem scores of the CBCL and TRF (see Table 2.6).

Table 2.6 *Multivariate analyses of behavioural reports of parents and teachers of the DMD and NF1 group.*

	DMD (n=38)			NF1 (n=38)			
	Mean	95% CI		Mean	95% CI		p
Questionnaires		Lower	Upper		Lower	Upper	
CBCL int.	61.2	56.3	66.1	51.6	46.8	56.4	.031*
CBCL ext.	60.1	54.3	65.9	53.6	47.9	59.3	.216
CBCL total	61.8	56.6	67.0	57.2	52.2	62.3	.328
TRF int.	58.2	54.5	61.9	55.8	52.1	59.4	.465
TRF ext.	57.4	53.5	61.3	54.9	51.1	58.7	.478
TRF total	58.1	54.6	61.5	57.3	53.9	60.7	.798

Behavioural outcomes are means of z-scores corrected for the covariates age, the presence of comorbidities (learning, neurodevelopmental or behavioural disorders), use of stimulant medication (MPH), use of steroids, educational status of patients, and family history of learning and behavioural problems. 95% CI=95% Confidence Interval. CBCL int.=CBCL total internalizing problems scale score, CBCL ext.=CBCL total externalizing problems scale score, CBCL total=CBCL total problem score, TRF int.=TRF total internalizing problems scale score, TRF ext.=TRF total externalizing problems scale score, TRF total=TRF total problem score, DMD=Duchenne muscular dystrophy, NF1=Neurofibromatosis type 1. * $p<.05$ (two-sided).

Discussion

Cognitive- and behavioural problems are well known comorbidities in the neurogenetic disorders, DMD and NF1. A lack of protein expression in the brain may be responsible for the development of these brain-related comorbidities in both disorders. Genotype-phenotype studies have investigated whether certain gene mutations result in specific

and more severe phenotypes. In DMD, studies showed more severe cognitive and behavioural impairments in patients with mutations affecting the full-length and shorter brain isoforms, whereas in NF1 studies revealed more pronounced impairments in cognition, behaviour and learning in patients with microdeletions. Since in both neurogenetic disorders, different proteins are involved, we hypothesized that the cognitive and behavioural profiles of patients with DMD differ from patients with NF1. Surprisingly, no statistical significant differences were found between the groups on cognitive outcomes even after controlling for the covariates (age, comorbid diagnoses of patients (i.e. learning, neurodevelopmental, or behavioural disorders), use of stimulant medication (MPH), use of steroids, educational status of patients and family history of learning and behavioural problems). Results of reported behavioural problems by parents and teachers also displayed no significant differences between the DMD and NF1 group. Though, after controlling for covariates the multivariate results proved that there may be a significant difference between the groups on internalizing behavioural parent reports, reflecting more problems in de DMD group. This is contrary to previous literature showing that rates of depression, anxiety and psychosocial difficulties in DMD are not significantly worse due to disease characteristics compared to individuals with other chronic diseases.[56-58]

Cognitive outcomes

The intelligence quotients of our total DMD group were in general in accordance with previous data, with an overall mean FSIQ that was approximately one standard deviation below the population mean.[16,59,60] No discrepancy between verbal IQ and performance IQ was found within our DMD group. This may likely be due to the large number of patients with distal mutations (55.3%) in our study, of which is known that they exhibit lower intellectual abilities in general.[60] Despite that our DMD group exhibit more difficulties on all intellectual tasks, their performances were not significantly lower compared to the NF1 group. However, the IQ distribution levels revealed that our DMD males predominantly fell within the low to low-average range, whereas the NF1 males performed low to normal. Higher rates of mental retardation (FSIQ<70) have been described previously for DMD (30%) than for NF1 (4-8%), with most NF1 patients falling in the low-average to normal range.[31,59] The IQ of our NF1 group was comparable to previous findings (IQ mean of 90)[4], which is on average comparable to the general population. Though, a variation in scores was noticed in our NF1 group, underscoring the heterogeneity in IQ in NF1.[33] We found no correlation between the social-demographic status of the patients and their IQ levels.

Deficits in verbal span and working memory have long been documented as consistent cognitive features of DMD, but similar characteristics have been described for NF1.[15,18,33,60-63] Within the present study both groups equally displayed lower sequential processing outcomes that were likely independent of IQ. Both especially exhibit difficulties in recalling information that increase in load in sequential order. On delayed memory and recognition memory, both groups performed comparable and approximately normal. These findings emphasize that males with DMD often display a limited verbal short-term memory and span capacity in the recall of specific sequence information, but not in consolidation or retrieval.[61] Seeing the influence of limited verbal capacity on language development, attentional processes and learning it is important that the verbal memory problems are indicated at an early age. Particularly as it is shown that short-term memory and verbal span capacity are more powerful predictors for academic attainment of reading, writing and math than IQ.[60-62,64,65] Furthermore, patients with delays in verbal span capacity seem not to grow out their deficit[63], underscoring that early diagnosis and treatment of cognitive and academic problems should be part of regular clinical care of both neurogenetic disorders.[,66,67] In terms of psychological interventions clinicians may address tools that enhance or stimulate the learning of verbal auditory information, such as remedial teaching at school.[66] Cognitive training for instance working memory training seems also a beneficial tool for children with short-term memory problems and learning disabilities[68,69], and it efficacy for patients with DMD and NF1 with comorbid learning disabilities should be investigated in future studies.

With respect to processing speed and visuospatial abilities (simultaneous processing), we found comparable outcomes for both groups. In DMD, most studies reported normal visuospatial abilities, but for NF1 the visuospatial disabilities are known cognitive features.[15,31,70,71] A possible explanation for the absence of visuospatial disabilities in our NF1 group may depend on the less sensitive cognitive tasks that we used in current study. For NF1 regular clinical care at CNL, patients underwent various visuospatial and visuomotor tests, however certain tests that are part of the NF1 protocol (i.e. Rey-Osterrieth Complex Figure test) are not collected for patients with DMD. This limited our possibility in comparing visuospatial outcomes in which patients with NF1 display great deficits.[4] Furthermore, we solely evaluated the cognitive profiles of males with NF1 and females were excluded, as the population of DMD predominantly involves men. However, gender in NF1 strongly influences phenotype expression and it is suggested that the clinical heterogeneity in NF1 likely results from an interplay between genomic determinants such as gender and neurofibromin functioning in specific tissue.[72] This mechanism should be addressed in future studies

investigating cognitive profiles in NF1, as most previous studies assessed cognition and behaviour in samples consisting of both sexes.

On sustained deficits in visual as well as auditory attention we found no differences between our groups. Within both neurogenetic disorders attention deficits are frequently reported, but to date most DMD and NF1 studies reference the prevalence rates of AD(H)D as a marker of presence of attention problems, with little to no use of direct neurocognitive measures of attention. Only three previous DMD study used a cognitive attention task to estimate attention[15,18,73], whereas two other studies used a processing speed task or verbal memory task.[70,71] Studies addressing attention deficits solely based on ADHD prevalence rates should be interpreted with caution, because evidence is growing on the distinction between patients with ADHD with predominantly behavioural features (hyperactive/impulsive) and patients with the cognitive phenotype (inattention).[33] Each type is suggested to have its own type of impairments, developmental trajectories and underlying neurobiology, which requires differentiation in diagnosis as well as in treatment.[33]

We noticed that 55.3% of our DMD group, had distal mutations abolishing the production of Dp140 and it is suggested that these males have more severe cognitive impairments.[23,24,26] Additional post-hoc analyses checked whether the DMD males with mutations affecting Dp140 production (Dp140-, N=10), DMD males with intact Dp140 (Dp140+, N=21) and males with NF1 (N=38) differed. After applying Bonferroni correction we found a trend (p=.60) for the group Dp140- indicating that these patients performed less well on processing speed compared to the other two groups (Dp140+ and NF1). It may be considered that in neurogenetic disorders not all cognitive functions are fully attributable to the genotype, but environmental and perinatal factors including maternal factors (e.g. stress, malnutrition, hypertension, substance (abuse) and fatal factors (hypoxia, low birth weight, prematurity) may be contributable and determinative for the phenotypes of patients as well.[74]

Behavioural outcomes

On average, males of both groups fell below the clinical cut off values on all syndrome scales, the broadband scales and the total scale scores of the CBCL and the TRF, representing that parents and teachers reported no significant elevated behavioural problems. More detailed analyses on abnormal ranges of the groups showed that parents and teachers of males with DMD more often reported aggressive behavioural problems. Prednisone is the standard prescription to stabilize muscle strength, extend

ambulation and stand abilities in DMD and it is known that boys who take steroids exhibit more externalizing behavioural problems i.e. aggressive behaviour than boys taking no steroids. This may explain the higher rates of aggressive behaviour in our DMD group. However, results on the relation steroid use and higher incidences of externalizing behavioural problems are equivocal.[58,75,76] Furthermore, DMD patients deal with physical milestones during the disease course, which may induce aggressive behaviour as well. For instance, our males were aged between 7-14 years and this is the age-range at which patients with DMD are confronted with loss of ambulation.

Within the NF1 group, parents more often reported difficulties in thinking and withdrawn, whereas teachers often reported social problems. It is interesting that the behavioural problems reported by parents and teachers of both groups differed in rates, with higher incidences reported by parents. In DMD, it is known that parent ratings are higher probably due to the parents perception of the magnitude of problems belonging to the illness and the increased parental stress resulting from difficult parent-child interactions.[77,78] Our findings emphasize that screening of behavioural problems should be done by evaluating different perspectives (i.e. parents, teachers, patients and clinicians) on patients functioning.[79] This is particularly important in neurogenetic disorders due to the presence of more than one cognitive or behavioural comorbidity and their overlap in symptoms. Furthermore, the CBCL may be no suitable instrument for screening behavioural problems, which we previously described in our systematic review.[79] For clinicians it is important to know that results of the CBCL should be interpreted with caution and no definite diagnoses should be made solely on the basis of this instrument, as the symptom items of the CBCL subscales have no conceptual link with diagnostic criteria of behavioural disorders.[80] In addition, insufficient psychometric properties have been found recently for the CBCL especially for patients with DMD.[79] This may explain why some of the anomalies such as the lack of social problems in our DMD sample are not found, while 25% of them had a diagnosis of ASD. Due to our recent sensitivity findings of CBCL, the neuropsychological diagnostic work-up of patients with DMD is currently adapted in our Centre.

Neurophysiology in relation to cognition and behaviour in DMD and NF1

In both neurogenetic disorders, the affected proteins (i.e. dystrophin in DMD and neurofibromin in NF1) are expressed in a wide variety of nervous tissues including neurons and glial cells (e.g. astrocytes, oligodendrocytes) in the brain.[7,10,30,81-83] A loss of the affected proteins result in functional and structural alterations of neurons and glial cells particularly located in corticostratial circuits and the hippocampus.[7,30,81,82,84] For

instance, by interacting with other components of the dystrophin-glycoprotein complex (DGC), such as syntrophin, the brain variant of the full-length dystrophin protein isoform ($Dp427_B$) links to inhibitory γ-aminobutyric acid type A ($GABA_A$) receptors at the postsynaptic neural membrane.[7,85] A lack of dystrophin results in a decreased density of $GABA_A$ receptor clustering of receptor subunits at inhibitory synapses.[84,85] Aberrant anchoring of $GABA_A$ receptors causes an increased extrasynaptic expression of $GABA_A$ receptors, which triggers a disruption of calcium homeostasis and makes cells vulnerable to necrosis.[86,87] Dystrophin deficiency also induces altered excitatory synapse functions and organizations i.e. abnormal enhanced NMDA receptor activation.[10] In NF1, the decreased production of neurofibromin causes reduced Ras signalling molecule, leading to increased GABAenergic inhibition in the hippocampus due to impaired long-term potentiation.[30,82] Furthermore, neurofibromin is localized at excitatory synapses postsynaptically where it interacts with the NMDA receptor.[30,82] Overall, in both disorders neuronal alterations in $GABA_A$ and glutamate functions are found and these have been linked to the presence of neurocognitive deficits.[7,10,30,81-83] It is tempting to speculate that due to the comparable neuronal defects we found no differences between the DMD and NF1 group. Though in DMD an increased excitation is described whereas in NF1 an increased inhibition is found, respectively. Further research should elucidate whether this dissimilarity effects the presence and severity of cognitive deficits. Another possible aetiology for the cognitive (and also learning) abnormalities in DMD and NF1 are glial dysfunctions (e.g. astrocyte abnormalities), but their contributory role needs further investigation.[7,30] The proposed mechanisms that may underlie the cognitive phenotype in DMD are versatile. In addition, neuroimaging studies revealed individual variability in brain structures, networks, perfusion and metabolism.[88] Future studies should link the cognitive outcomes to genetics (i.e. dystrophin isoform expression and neurophysiology) and neuroimaging, to better determine the factors involved in the presence and severity of the DMD cognitive phenotype.[88]

Limitations and future perspectives

Unfortunately, not all collected data of the groups could be evaluated as other standard protocols have been used for regular clinical care for DMD and NF1 in our outpatient clinic. Therefore, academic skills for instance reading, writing and math that are often impaired in both groups were not assessed in current study. Due to the differences in neuropsychological batteries certain data were missing for which we applied stochastic regression imputation, but this does not take patients physical abilities into account. Furthermore, all participants of the present study were referred to the outpatient clinic

Centre CNL, and these patients frequently have more (severe) learning, cognitive or behavioural than other patients with DMD or NF1, making our results likely less generalizable. Although, most prevalence rates of comorbid neurodevelopmental diagnoses and certain cognitive outcomes were in line with those reported by previous DMD and NF1 literature. In addition, we included participants aged 6-16 years to allow for the administration of the cognitive test and behavioural questionnaires, standardized for the Dutch population. However, cognitive and behavioural functions undergo major changes throughout childhood development, making mean group comparisons with large distributions of performances of young children (i.e. aged 6-7) and older children (15-16 years) difficult. Future studies should evaluate large samples size in which performances of different age groups can be evaluated. Nevertheless, our findings emphasize that comorbidities in cognition, behaviour and learning difficulties may arise in both neurogenetic disorders. Early cognitive and behavioural (re)evaluations are required and should be part of standards of care, in order to facilitate treatment as early as possible when necessary. Future longitudinal studies in DMD and NF1 should evaluate whether patients further grow in or out of their cognitive, behavioural and learning comorbidities. A nice addition to the NF1 literature would be to evaluate genotypes-phenotypes in severity and impact of cognitive, behavioural and learning comorbidities. These analyses could not be carried out in current study, since none of the NF1 patients had microdeletions.

Conclusion

The cognitive features of patients with DMD considerably overlap with those of male patients with NF1. It suggests that brain-related comorbidities in cognition are not only caused by gene mutations resulting in a lack of one specific protein, but also depend on other protein interactions and on neuronal and glial functional and structural alterations. Some differences in clinical features were noticed between the DMD and NF1 group, for instance the IQ levels of the DMD group were more distributed to the left compared to the NF1 group. With regard to behavioural features, aggressive behaviour was more often reported by parents and teachers of the DMD group, whereas in NF1 parents and teachers frequently reported problems with thinking, withdrawn and social behaviour. Clinicians should keep in mind that in both disorders one or more comorbidities may occur, that symptoms may overlap and that the severity of symptoms may variate between patients. This underscores that (re) evaluations and monitoring of cognitive development and behavioural functioning is required in both neurogenetic disorders. Possible cognitive or behavioural implications

for treatment in both disorders could be for instance remedial teaching, cognitive (working memory) training, social training, psycho-education for patients, parents and teachers and neuropsychopharmacology.

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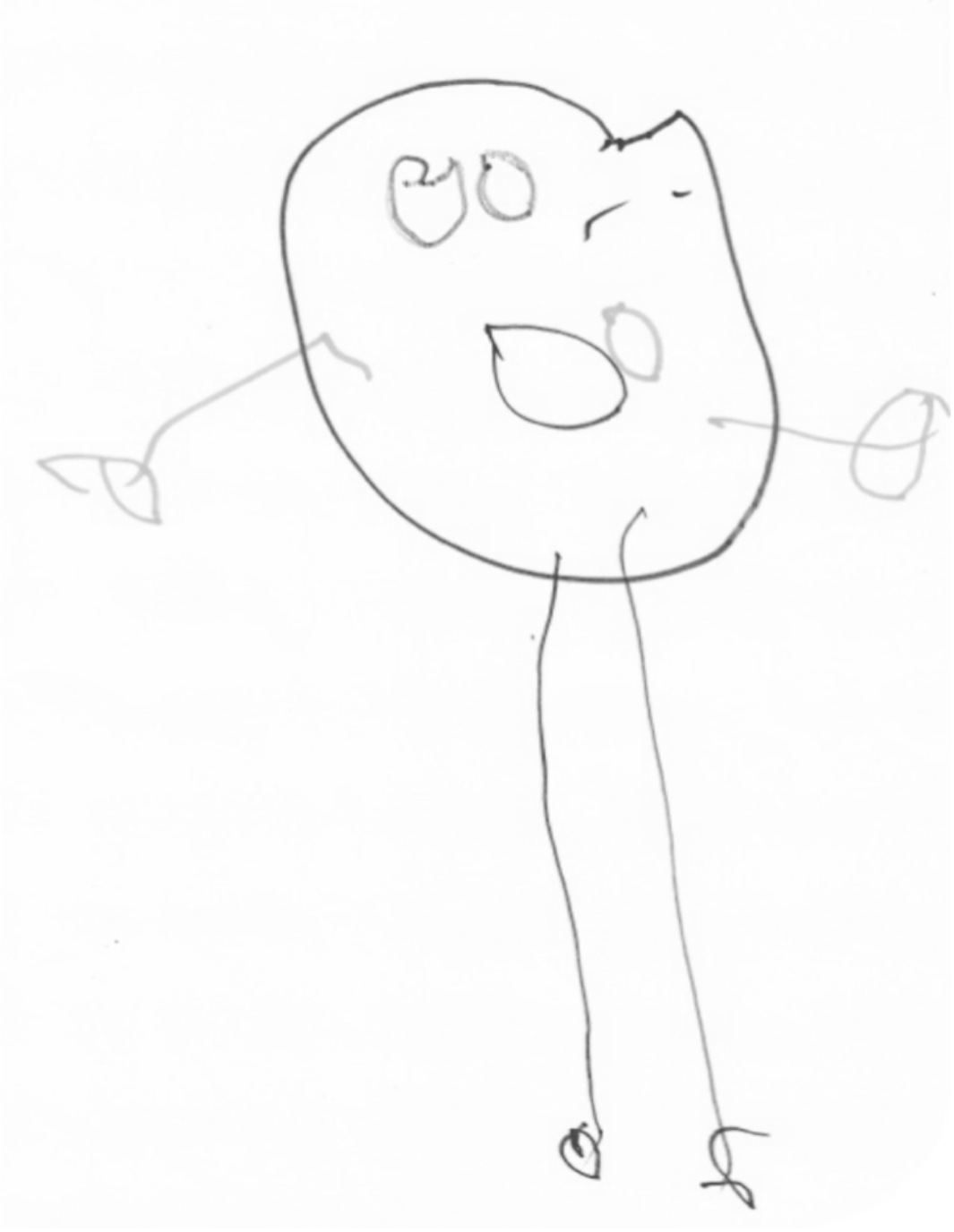

Chapter 3

Longitudinal follow-up of verbal span and processing speed in Duchenne muscular dystrophy

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Abstract

Neurocognitive deficits are frequently described in Duchenne muscular dystrophy (DMD), but it is unknown how these progress over time. Our aim was to longitudinally assess verbal span capacity and information processing speed in DMD and to explore a genotype-phenotype relation. Verbal span and processing speed scores were available of 28 males with DMD on two time-points, with a mean time interval of 28.34 months (SD=16.09). The cohort contained of six patients missing only dystrophin isoform Dp427, sixteen missing Dp427 and Dp140, and six were undeterminable. A lower verbal span capacity was found at the first and second assessment, whereas processing speed was normal at both time-points. Post-hoc analyses suggested lower scores on verbal span and processing speed for patients missing Dp427 and Dp140. In DMD, a developmental stagnation in verbal span capacity, irrespective of normal processing speed, is detected through longitudinal follow-up. This appears more pronounced in patients missing Dp427 and Dp140.

Introduction

The X-linked neuromuscular disease, Duchenne muscular dystrophy (DMD) is characterized by severe and progressive muscle weakness due to mutations in the dystrophin-encoding (*DMD*) gene. Mutations in the *DMD* gene result in a lack of expression of the full-length dystrophin isoform (Dp427) in muscles (M) and the brain (B).[1] In addition to the full-length isoform, shorter brain isoforms exist including Dp140, Dp71, and Dp40. A disturbed expression of the brain isoforms (Dp427B, Dp140, Dp71 + Dp40) may be related to the presence of neurocognitive problems in DMD.[1-6] It is proposed that the different isoforms are part of dystrophin-glycoprotein-like complexed (DGC-like) in either neurons or glia cells, depending on the dystrophin isoform.[7] This complex can contain for example β-dystrobrevin, ε-sarcoglycan, dystroglycan, γ-syntrophins, neuronal nitrix oxide, GABA-A receptors or Acquaporin 4 receptors.[1,7] However, little is known of the exact function of dystrophins in the brain, nor what happens to these DGC-like components in absence of dystrophin.

Previous studies have shown that males with DMD exhibit a specific neurocognitive profile in that the mean full-scale intelligence quotient (FSIQ) is approximately one standard deviation below the population mean.[8] A lower verbal intelligence has in particular been described, whereas performance intelligence often seems preserved.[7] In addition to the lower intellectual abilities, it is found that males with DMD exhibit cognitive impairments in verbal (working) memory, attention, executive functions, and academic achievement (reading, writing, and mathematics).[9-13] The verbal memory deficits on “short-term memory” or “ verbal span capacity” have consistently been found as core neurocognitive deficits in DMD and are expressed by a limited immediate recall of forward digits, words, stories, or sentence repetition.[9,14-17] Interestingly, these verbal memory problems do not rely on the lower verbal intellectual abilities and are not caused by general impairments in language and memory.[13,16,18] A decreased ability in retaining verbal information within short-term memory stores (i.e. the phonological loop) appears to be responsible for the poor academic achievement on reading, writing, and mathematics in males with DMD.[11,14,16] In addition, their limited verbal capacity for retaining information in the phonological loop may explain their ineffectual proficiency on initial presentations of long statements or instructions.[15,19] Despite the important role of verbal span capacity on academic skills and learning, it is unknown whether males with DMD further grow out of their verbal deficit, or whether it remains unchanged over time. The present study builds on previous evidence of limited verbal span capacity in DMD and provides the first longitudinal analyses on verbal span. An information processing speed task that does not rely on verbal memory was added as a

control variable. As a result, the developmental pathways of both neurocognitive functions could be assessed. In addition, the present study further explores the relation between disturbed expression of brain isoform Dp140 and neurocognitive problems i.e. verbal span capacity and information processing speed in DMD.

Materials and methods

Participants

We included males with DMD who were seen for research purposes at the Leiden University Medical Centre (LUMC) or for clinical purposes at the outpatient clinical Centre for Neurological Learning disabilities (CNL) of Kempenhaeghe between 2010 and 2018. Males were included if they met the following criteria: (1) had a proven mutation of the *DMD* gene which was previously genetically confirmed, (2) had neurocognitive data on verbal span capacity and information processing speed at two time points (i.e. first and second neurocognitive assessment) (3) were aged between six and sixteen years, and (4) had an adequate proficiency in Dutch. The age range of participants was chosen to allow for the administration of the cognitive test and behavioral questionnaires, standardized for the Dutch population. Exclusion criteria were: (1) a follow-up assessment within a period of six months or less and (2) physical immobility of upper extremities (hand and arm function) that could affect information processing speed scores. Ethical approval was granted by the local Medical Ethical Committees of both institutes and written informed consents were obtained.

Study procedure

The institutes LUMC and CNL used the same cognitive tasks to evaluate verbal span capacity and information processing speed during the first and second neurocognitive assessments. These tasks were administered by a researcher of LUMC (ND) and by psychologists of CNL, who were all trained by the same clinical neuropsychologist (JH). The neurocognitive data and additional baseline participant characteristics i.e. demographic (age, educational level, estimated intelligence quotient score) and disease-related parameters (genetic mutation, wheelchair bound, comorbid neuropsychiatric and developmental diagnoses, and use of medication in particular methylphenidate and corticosteroids) were extracted from research files of LUMC or from the electronic patient files of CNL. Comorbidities extracted from the files were: attention-deficit (hyperactivity) disorders (ADHD or ADD), autism spectrum disorders (ASD), dyslexia, and dyscalculia. For this study, education was dichotomized in regular

schooling or adapted education. All participants were further divided in three groups to explore associations between Dp140 expression and neurocognitive data on verbal span and information processing speed. Males with mutations not affecting Dp140 production (i.e. deletions or duplications upstream of intron 44) were considered Dp140+.[20] If males had mutations abolishing Dp140 production (i.e. mutations corrupting the Dp140 promoter, the Dp140 translation start site or located downstream of exon 50 (the Dp140 ATG start-site is located in exon 51) they were considered Dp140-.[20] Males with deletions or duplication breakpoints between intron 44 and exon 51 were assigned to a third group 'undefinable' and were left out of the subgroup comparison.[20] In the current study, only one male had a mutation downstream of exon 56 affecting promoter site Dp116, and none had a mutation downstream of exon 63 affecting the promoter site Dp71.

Neurocognitive assessment

Intelligence quotient scores (IQ) were estimated by standardized scores (mean=100, SD=15) of the Peabody Picture Vocabulary Test - third edition - Netherlands (PPVT-III-NL)[21] during the first neurocognitive assessment. This non-motor test can be applied to estimate general intellectual functioning in a wide age range and has previously been used in DMD.[10,19] Verbal span capacity was assessed by the forward Number Recall subtest of the Kaufman Assessment Battery for Children - second edition (KABC-II).[22] Raw scores were converted to standardized scaled scores (mean=10, SD=3) based on age-adjusted norm data as specified in the test manual, with higher scores reflecting better performance.[22] The Symbol Search subtest of the Wechsler Intelligence Scale for Children - third edition(WISC-II)[23] was used to assess information processing speed. Raw scores were converted to standardized scaled scores (mean=10 and SD=3) based on age-adjusted norm data as specified in the test manual, with higher scores reflecting better performance.[23] Current study only assessed the abovementioned cognitive tasks since the neurocognitive test battery of LUMC was administered for research purposes and consisted of a limited number of tasks, whereas the test batteries of CNL were based on individual request for help based on good clinical practice.

Statistical methods

Participant characteristics were represented as mean and standard deviation, or absolute number and proportion. One sample t-tests were used to compare results of the total sample to norm values. Differences between the following groups: (1) research population of LUMC and clinical population of CNL, and (2) the subgroups DMD_Dp140+ and DMD_Dp140- were tested, using the independent samples *t*-test,

Mann-Whitney-U tests, and Fisher exact tests, as appropriate. Normal distributions were examined by visual inspection of histograms and normal probability plots. The raw and scaled scores of the 28 males with DMD were used to evaluate longitudinal data on verbal span capacity and information processing speed. Both scores were used to assess the developmental pathways i.e. unchanged raw scores and decreasing scaled scores (developmental stagnation), increasing raw scores and stable scaled scores (expected development), increasing raw and scaled scores (growing out of deficit), or decreasing raw and scaled scores (growing into deficit). Paired t-tests were used to test for differences between the first and second neurocognitive assessment within the total sample. To further evaluate individual clinical differences, z-scores of +2.0 SD or -2.0 SD were considered as significant changes and results were presented as absolute number and proportion.[24] Furthermore, change (longitudinal) scores were computed by subtracting the scaled scores of the second assessment from the first assessment for each cognitive task. We used linear regression analyses to test whether age, individual differences in time between measurements in months, and use of stimulation medication had significant effects on the cognitive change scores. For post-hoc analyses, Mann-Whitney- U tests were used to explore differences on neurocognitive data (scaled scores) between the subgroups Dp140+ and Dp140-. All statistical analyses were carried out using SPSS version 24.0 for MAC OS X. Results were considered significant if $p<.05$ (two-sided) for all analyses.

Results

Participant characteristics

Out of the total 75 number of patients identified, 28 DMD males met the inclusion/exclusion criteria of whom 11 participants of the LUMC research study and 17 patients of the CNL clinical population were included (see Figure 3.1). Differences in participant characteristics between the research and clinical population consisted of the research participants being significantly older ($p=.004$) and with a significantly longer time between the first and second neurocognitive assessment ($p=.015$, see Supplementary Table S3.1). No significant differences were observed for any of the demographic characteristics such as educational level and estimated IQ scores, nor on disease related characteristics such as wheelchair bound, comorbid neuropsychiatric or developmental diagnoses, and use of corticosteroids or methylphenidate medication (see Supplementary Table S3.1). Patient characteristics of the included participants (n=28) are displayed in Table 3.1. During the first neurocognitive assessment 13 males

(46.4%) of the total sample had no comorbid neuropsychiatric or developmental diagnoses, seven males (25%) had a diagnosis of ADHD, two males (7.1%) had ADD, two males (7.1%) had ADD with dyslexia, three males (10.7%) had ASD, and one male (3.6%) had solely dyslexia. The mean time between the first and second neurocognitive assessment of the total sample was 28.34 months (SD=16.09, range 7.33-57.76).

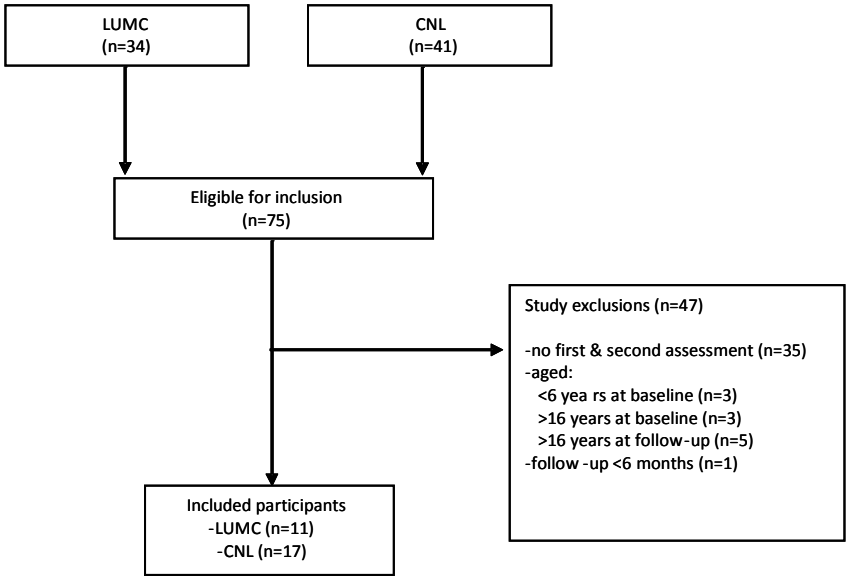

Figure 3.1 *Flowchart of inclusion.*

Neurocognitive outcomes of DMD versus norm values

The estimated IQ scores of the 28 males with DMD ranged between 71-129 and their IQ mean (103.7, SD=13.7; see Table 3.1) was not significantly different in relative to the population mean (100, SD=15, $p>.05$). On verbal span capacity, a significantly lower mean scaled score was found when compared to the expected norm value of 10 on both the first (mean=7.6, SD=2.6, $p<.001$) and second neurocognitive assessment (mean=6.7, SD=3.1, $p<.001$). On information processing speed the total mean scaled score of the 28 males with DMD was not significantly different with respect to the norm value of 10 on their first (mean=9.1, SD=3.4, $p>.05$) or second neurocognitive assessment (mean=8.6, SD=4.3, $p>.05$).

Table 3.1 *Patient characteristics of the total DMD sample and of subgroups.*

	Total cohort (n=28)	Subgroups			
		DMD_Dp140+ (n=6)	DMD_Dp140- (n=16)	Test statistic value	*p*-value
Demographic characteristics					
Mean age in years (SD)	8.7 (2.2)	8.28 (1.2)	9.05 (2.4)	-0.442	.658
Education (%)					
Regular school	14 (60.9)	4 (80)	7 (50)	1.360	.338
Adapted education	9 (39.1)	1 (20)	7 (50)		
PPVT-III-NL score (n)	20	4	11		
Mean PPVT-III-NL (SD)	103.7 (13.7)	108.0 (7.7)	99.8 (15.3)	-0.654	.513
Disease-related characteristics					
Wheelchair dependency (%)	8 (29.6)	2 (33.3)	4 (26.7)	0.093	1.000
Comorbidity present at assessment (%)	15 (53.6)	4 (66.7)	8 (50)	0.489	.646
Medication use (%)					
Corticosteroids	23 (82.1)	6 (100)	14 (87.5)	0.825	1.000
Methylphenidate	9 (32.1)	2 (33.3)	5 (31.3)	0.009	1.000

Results are mean (SD) for continuous variables or frequency (%). Test statistic values are z-values for continuous variables, and X^2 or Fisher exact values for categorical variables, PPVT-III-NL=Peabody Picture Vocabulary Test- III-NL, unknown patient group is excluded from the subgroup analysis (n=6), DMD_Dp140+= males able to express Dp140, DMD_Dp140-=males unable to express Dp140.

Longitudinal neurocognitive data in DMD

Verbal span

The longitudinal raw scores on verbal span capacity of the 28 males with DMD showed no significant mean difference between the first and second neurocognitive assessment (see Table 3.2), even though an increase due to development would have been expected. See Figure 3.2 for visualization of individual trajectories of raw scores. In line with this, the longitudinal scaled scores showed a decrease over time on verbal span capacity (see Table 3.2), with a significant lower mean scaled score at the second neurocognitive assessment compared to the first neurocognitive assessment. Figure 3.3 depicts the visualization of the decreased scaled scores.

Table 3.2 *Longitudinal neurocognitive data of the 28 males with DMD.*

					95% CI	
	First assessment (mean; SD)	Second assessment (mean; SD)	Test statistic value	*p*-value	Lower	Upper
Verbal span capacity						
Raw score (range: 3-16)	9.0 (2.7)	8.5 (2.2)	1.520	.140	-.200	1.343
Scaled score (range: 1-14)	7.6 (2.6)	6.7 (3.1)	-2.393	.024*	-1.725	-.132
Information processing speed						
Mean raw score (range: 3-59)	22.2 (8.3)	25.6 (10.9)	1.746	.093	-.605	7.420
Mean scaled score (range 1-16)	9.3 (3.3)	8.6 (4.3)	-0.895	.379	-2.44	.961

Mean and standard deviations, Test statistic values are t-values of the paired t-test, 95% CI=95% Confidence Interval, * p<.05 (two-sided)

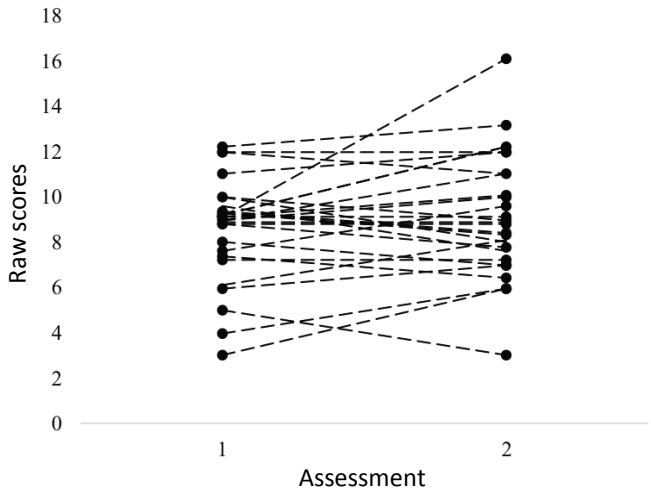

Figure 3.2 *Raw scores of verbal span capacity.*

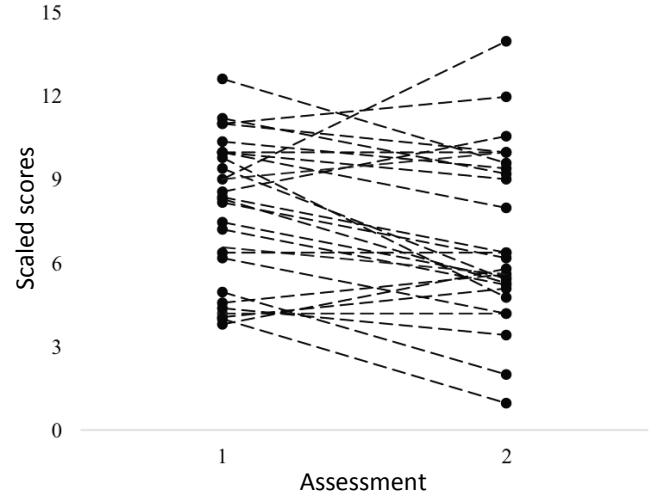

Figure 3.3 *Scaled scores of verbal span capacity.*

When assessing the scores of the 28 males individually, the z-scores of the second assessment did not decreased or increased more than 2SD compared to their first performance, indicating that none grown further in or out their possible span deficit. Regression analyses showed no significant effects of the covariates age, individual

differences on time between assessment in months, or methylphenidate use on verbal span change score (see Table 3.3).

Table 3.3 *Multiple regression analyses with verbal span change score as outcome.*

					95% CI	
Variables	B	SE_b	β	t-values	Lower	Upper
Age	-0.174	0.190	-0.184	-0.915	-0.565	0.218
Individual differences in time	-0.015	0.029	-0.120	-0.536	-0.074	0.044
Methylphenidate use	-1.248	0.949	-0.289	-1.314	-3.207	0.711

B=unstandardized regression coefficient, SEb=standard error of the coefficient, β=standardized coefficient, 95% CI=95% Confidence Interval, Age=age on baseline in years, Individual differences in time=individual differences in time in months between the first and second neurocognitive assessment. * *p*<.05

Processing speed

The longitudinal raw scores on information processing speed of the 28 males with DMD showed a slight but non-significant increase between the first and second neurocognitive assessment (see Table 3.2). See Figure 3.4 for visualization of raw scores. No significant differences were found on longitudinal scaled scores of information processing speed (see Table 3.2). See Figure 3.5 for visualization of scaled scores.

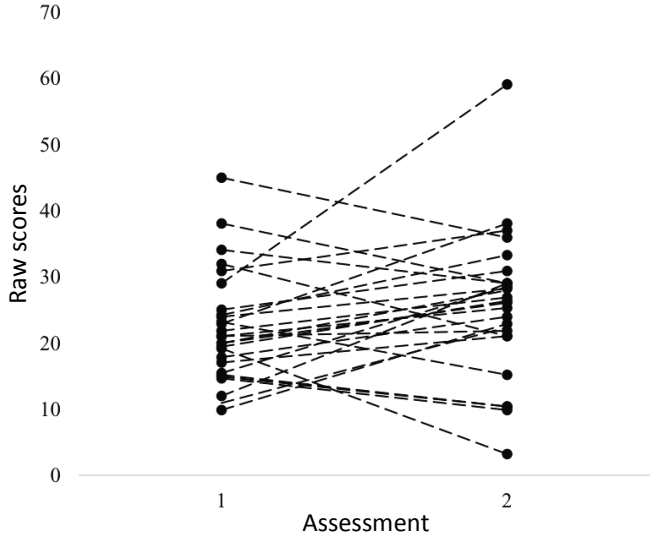

Figure 3.4 *Raw scores of processing speed.*

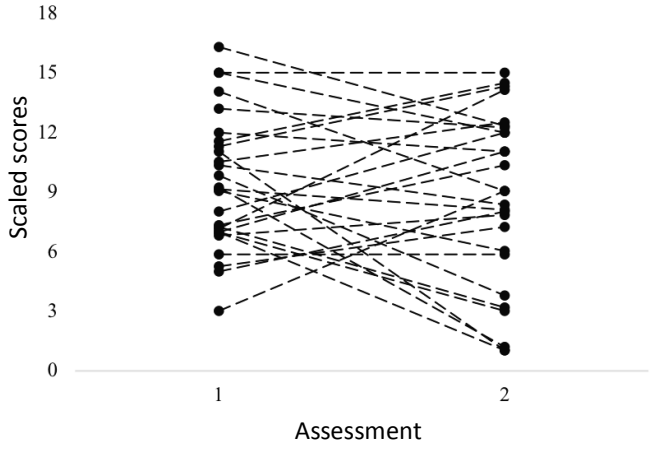

Figure 3.5 *Scaled scored of processing speed.*

No significant clinical differences (≥2 SD) in z-scores were found for 21 (75%) of males between their first and second assessment. Two males (7.1%) showed a clinical relevant improvement at the second neurocognitive assessment. One of these two males had a comorbid diagnosis of ASS and the other male had no comorbid diagnosis. Four males (14.3%) showed a clinical relevant decline at the second neurocognitive assessment. Two of these four males had a comorbid diagnosis of AD(H)D and used methylphenidate medication on the second neurocognitive assessment. In addition, one of these four males had a comorbid diagnosis of ASD and one had no comorbid diagnosis. Regression analyses showed no significant effects of age, individual differences on time between assessment in months, and methylphenidate use on information processing speed change score when these variables were entered as covariates (see Table 3.4).

Table 3.4 *Multiple regression analyses with information processing speed change score as outcome.*

					95% CI	
Variables	B	SE_b	β	t-values	Lower	Upper
Age	-0.737	0.391	-0.379	-1.546	-1.546	0.072
Individual differences in time	0.049	0.060	0.185	0.813	-0.075	0.172
Methylphenidate use	-0.288	2.066	-0.031	-0.139	-4.562	3.986

B=unstandardized regression coefficient, SEb=standard error of the coefficient, β=standardized coefficient, 95% CI=95% Confidence Interval, Age=age on baseline in years, Individual differences in time=individual differences in time in months between the first and second neurocognitive assessment. * p<.05 (two-sided).

Exploring the effect of Dp140 expression on neurocognition

Of the 28 males with DMD, six were identified for group Dp140+ and sixteen were identified for group Dp140-. Six males were excluded from the subgroup analysis, because of the unpredictability of the mutation effect on Dp140 expression. Participant characteristics of the subgroups at the first neurocognitive assessment are presented in Table 3.1. No significant differences were found on demographic and disease related parameters between the Dp140+ subgroup and the Dp140- subgroup (see Table 3.1).
The subgroup comparison on verbal span indicated significantly higher scores for group Dp140+ compared to group Dp140- at the first neurocognitive assessment (p<.05), but not at the second neurocognitive assessment (p>.05; see Table 3.5). The subgroup comparison on information processing speed indicated significantly higher scores for group Dp140+ compared to group Dp140- at both the first neurocognitive assessment (p<.05) and second neurocognitive assessment (p<.05; see Table 3.5).

Table 3.5 *Dp140 isoform expression and neurocognitive outcomes.*

	Dp140- (N=16)	Dp140+ (N=6)	Test statistic value	*p*-value
Verbal span capacity (median, range)				
First assessment	7.0 (4-10)	10.0 (6-12)	-2.194	.028*
Second assessment	5.0 (1-14)	9.5 (4-12)	-1.316	.188
Information processing speed (median)				
First assessment	8.0 (3-15)	12.5 (4-16)	-2.082	.037*
Second assessment	7.5 (1-15)	12.0 (9-14)	-2.157	.031*

Results are median and range. Test statistic values are z-values. DMD_Dp140+=males able to express Dp140, DMD_Dp140-=males unable to express Dp140. * p<.05 (two-sided).

Discussion

The present study consisted of a convenience sample with both research and clinical data. Our results are consistent with the previously described impaired verbal span capacity among males with DMD.[9,14-17] The 28 males with DMD of our sample had lower verbal span capacity on both the first and second neurocognitive assessment compared to norm values. On the contrary, performance on information processing speed was normal for both assessments compared to the norm values. With respect to the longitudinal evaluation, a developmental stagnation on verbal span capacity was found within our study. The developmental stagnation in verbal span was not influenced by factors such as age, individual differences in time between measurements in months, and use of methylphenidate. Despite our finding on the suggested non-progressive

nature of verbal span capacity, it is important to note that a consistently reduced verbal span capacity is expected to severely impair academic development and learning in DMD.[11,14,16-17] Verbal span is an important component of the working memory model proposed by Baddeley and Hitch, assuming that verbal information will be processed, stored and rehearsed by a system, referred as the phonological loop.[25,26] Leaffer et al. (2016) reported that in addition to deficiencies within the phonological loop (i.e. holding verbal information in temporary storage), deficits in executive control cause an overall lower reading performance in DMD.[16,27] Results of Leafer and colleagues (2016) and our results emphasize that cognitive (re-) evaluation with tasks involving the phonological loop as well as the central executive system are important for monitoring neurocognitive development, academic achievement, and learning in DMD. Clinicians should be aware of the possibility of cognitive developmental stagnations in DMD, particularly in domains involving verbal span capacity, academic skills, but also language acquisition. Thereby, it important for clinicians to adhere the clinical recommendations on cognitive re-evaluations that are documented in the updated standards of care for DMD.[28] According to the standards of care, cognitive re-evaluations should be performed every 2-3 years to facilitate early treatment in terms of remedial teaching and tools for teachers and parents when delays arise.[28] For instance, when males exhibit a developmental stagnation in verbal span, tools as speaking simply, use short sentences, repeat verbal information more often, use visual stimuli as contextual cues, or associate pairs of words or digits to existing knowledge should be used at home and school to compensate and improve their ineffectual proficiency in retaining long and complex verbal information.[15,26] A first cognitive evaluation should preferably be performed within the first year of diagnosis of DMD to establish a baseline[28], but also to limit the influence of verbal span impairments on language acquisition. For realizing specific guidelines for DMD care on evaluation of cognition and learning, future research should longitudinally assess the development of working memory using complex dual tasks, crystallized and fluid intelligence as all contribute to academic performance.[29,30]

Exploring the involvement of Dp140 expression on neurocognitive performance

With respect to mutations affecting Dp140 expression, this study further explored the relation between loss of Dp140 and presence of neurocognitive deficits in DMD.[3,4,20] Even though the number of patients for this analysis is small, our subgroup analysis suggests that males with mutations affecting Dp140 expression performed more poorly on verbal span compared to males who can express Dp140. Additionally, processing

speed was lower in males with disrupted Dp140 expression than in males with intact Dp140 expression. In four recent similar-aged population studies of males with DMD, mutations prohibiting Dp140 expression were also associated with neurocognitive deficits, in particular with verbal memory, even though these studies assessed this relation using other neurocognitive tasks or composed scores of cognitive tasks on intelligence, verbal (working) memory, and information processing speed.[4,20,31] It is plausible that the phenotypes of males with DMD at least in part depend on the location of mutation and the additional disturbed expression of specific dystrophin isoforms within brain tissue. Although, further determination of the functions of the different DGC-like components is required to address the underlying mechanisms and to establish their role throughout brain development.

Limitations

Even though our sample size is appropriate for total group analyses, we acknowledge that our sample is too small to properly analyze differences between the subgroups, Dp140+ and Dp140-. However, our explorative results are relevant for clinical and research practices and of interest for future research. Secondly, the majority of our males (53.6%) had a neurodevelopmental or psychiatric comorbidity that may have influenced our results on span development. However, it is previously proven that impairments in working memory and span also occur in males with DMD without neurodevelopmental or psychiatric disorders.[32] Nonetheless, future longitudinal studies should perform subgroup analysis to evaluate the cognitive development of males with DMD without comorbidities, because no longitudinal assessment on their cognitive development exists. Thirdly, we had no control group, whereas other studies on DMD cognitive performance compared males with DMD to siblings or patients with other neuromuscular diseases. This limitation can be addressed in future longitudinal studies investigating DMD cognitive development, as this longitudinal study is the first step for a larger longitudinal follow-up study. Fourthly, some information on cognitive functioning (i.e. estimated verbal intellectual functioning; PPVT-III-NL scores) were not available of all participants due to a limited mental capacity of patients of CNL. Finally, we could not evaluate longitudinal changes of other cognitive domains since there were some differences between the neurocognitive assessment batteries of both institutes. Future research should replicate current longitudinal findings and include other neurocognitive tasks particularly tasks involving more complex working memory functions, intellectual abilities and academic skills (i.e. reading, math, spelling) with varying norm age-related scores, especially with a growing adult DMD population.

Conclusions

We observed a developmental stagnation on verbal span capacity in males with DMD which remains present over time. A relatively stable growth curve has been suggested for information processing speed. Finally, DMD neurocognitive performance in verbal span capacity and information processing speed might be influenced by Dp140 loss, however this relation should be further explored.

Acknowledgement

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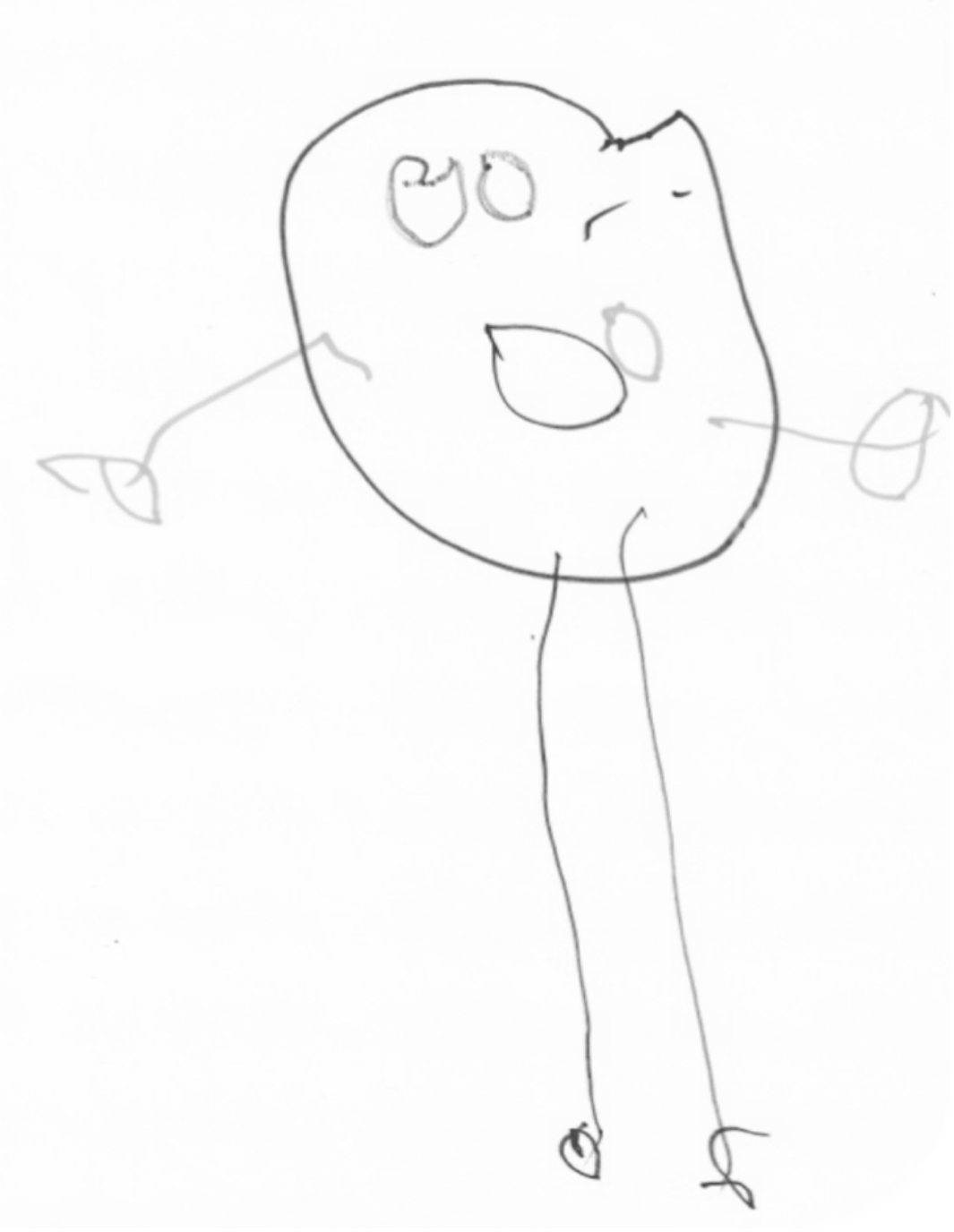
Supplemental data

Table S3.1 *Characteristics of the research and clinical sample.*

	CNL (n=17)	LUMC (n=11)	Test Statistic value
Mean time between measurements[#] (SD)	22.3 (16.5)	37.7 (10.2)	-2.423*
Demographic characteristics			
Mean age in years (SD)	8.1 (1.9)	10.1 (2.0)	-2.917**
Education (%)			
Regular school	10 (58.8)	4 (66.7)	1.000
Adapted education	7 (41.2)	2 (33.3)	
Mean PPVT-III-NL (SD)	107.8 (16.6)	100.3 (10.5)	-1.597
Disease-related characteristics			
Type mutation (%)			
Dp140-	11 (78.6)	5 (62.5)	0.624
Dp140+	3 (21.4)	3 (37.5)	
Wheelchair bound (%)	4 (25.0)	4 (36.4)	0.675
Comorbidity present at assessment (%)	11 (64.7)	5 (45.5)	0.441
Medication use (%)			
Corticosteroids	14 (82.4)	9 (81.8)	1.000
Methylphenidate	6 (35.3)	3 (27.3)	1.000
Neurocognitive outcomes			
Verbal span capacity			
First assessment	7.8 (2.3)	7.4 (3.0)	-0.380
Second assessment	7.4 (3.3)	5.7 (2.6)	-1.792
Information processing speed			
First assessment	9.3 (3.4)	8.8 (3.7)	-0.285
Second assessment	9.1 (4.6)	7.6 (3.7)	-1.086

Results are mean (SD) for continuous variables or frequency (%). Test statistic values are z-values for continuous variables, and X^2 or Fisher exact values for categorical variables, neurocognitive outcomes are scaled scores, DMD_Dp140+=males able to express Dp140, DMD_Dp140-=males unable to express Dp140. [#] mean time in months * p<.05 (two-sided) ** p<.01 (two-sided).



Chapter 4

Minor cognitive impairments in adult males with Becker muscular dystrophy

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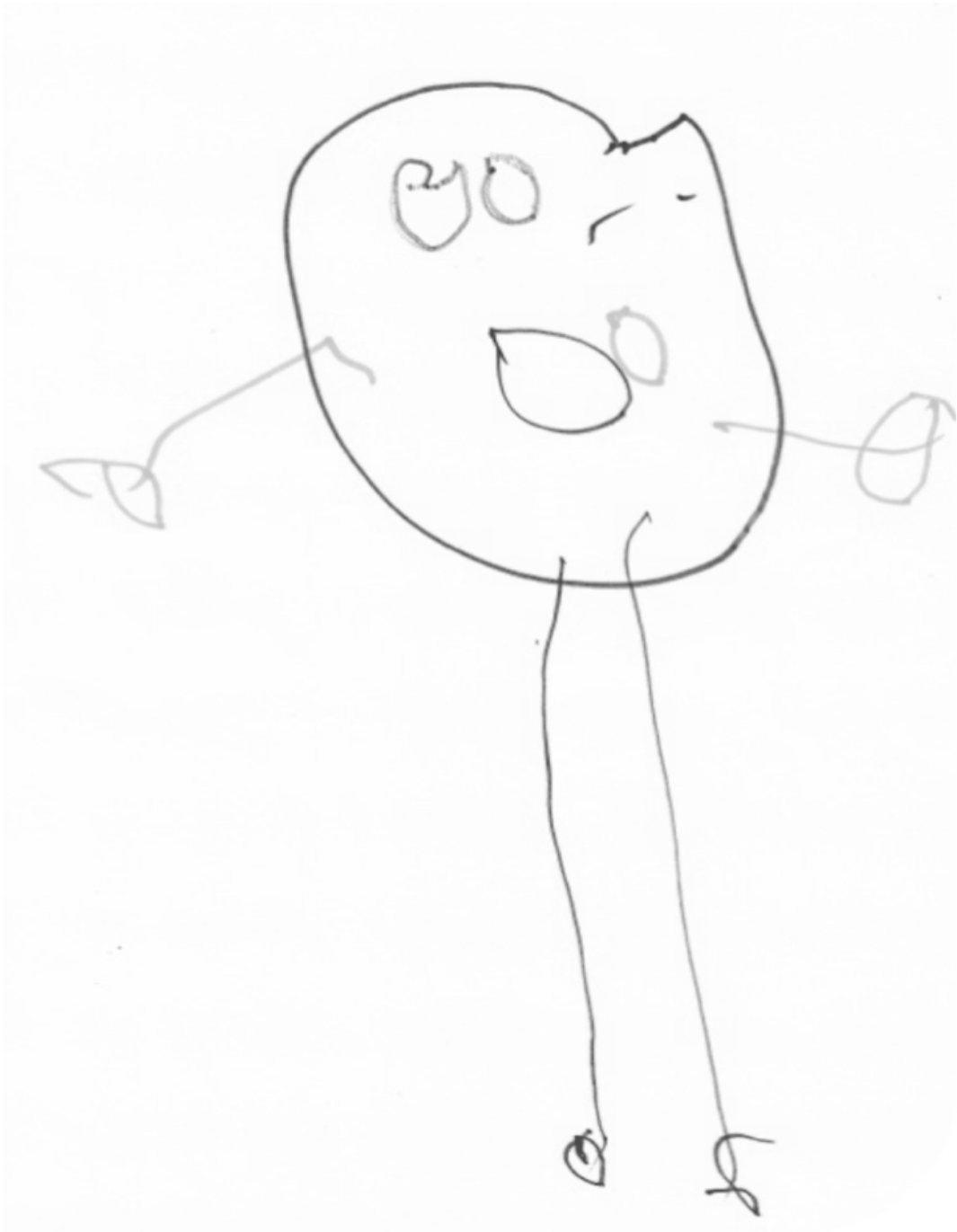

Chapter 5

The neurocognitive and behavioural profiles of three brothers with Becker muscular dystrophy

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Abstract

Becker muscular dystrophy patients generally carry in-frame mutations in the dystrophin gene, allowing the production of partially functional dystrophin protein. The presence of cognitive and behavioural comorbidities and the relation with the location of mutations have been scarcely investigated in Becker. This case report describes the neurocognitive and behavioural profiles of three brothers with Becker carrying an in-frame deletion of exons 45-48. The three cases underwent two consecutive neuropsychological assessments of which one assessment took place when they completed their primary education (age range of the cases: 11.2-12.1 years). Intellectual abilities were normal to high and all cases had difficulties with processing speed and math. The brothers differed in intellectual abilities, executive functions, working memory, attention and reading abilities. Variability in cognitive development was noted as well. This report suggests that cognitive and behavioural functions in Becker vary regardless of gene mutation and exposer to similar environmental factors.

Introduction

Becker muscular dystrophy (BMD) is one of the recessive x-linked dystrophinopathies, caused by mutations in the dystrophin (*DMD*) gene.[1] BMD mutations allow the production of internally deleted, but partially functional full-length dystrophin protein isoforms (Dp427) in various tissues including muscles (M) and the brain (B).[1,2] The (*DMD*) gene produces in addition to the full-length isoform, shorter isoforms, Dp260, Dp140, Dp116 and Dp71/Dp40.[1-3] Dystrophin is a complex scaffold protein that modulates cellular homeostasis and multiple protein interactions.[2] It provides structural stability to muscle fibres during contraction.[2] The clinical severity of patients with BMD varies with some having a near normal functionality, whereas others lose the ability to walk during adolescence or early adulthood.[1] In addition to skeletal muscle and heart pathology, patients with BMD may have neurodevelopmental-, behavioural comorbidities, learning disabilities and epilepsy.[1,4-7] For instance, autism features, inattention/hyperactivity features, language–speech delays and difficulties in reading, spelling and arithmetic are found in BMD.[1,4,6,7] It has been suggested that these comorbidities are related to a disturbed production of brain isoforms (i.e. $Dp427_B$, Dp140 and Dp71).[8-9] However, this relation has been limitedly assessed in BMD. Only Bardoni and colleagues (2000) found intellectual disabilities in patients with BMD carrying mutations affecting $Dp427_B$ and Dp140, but not in patients with only a disturbed expression of $Dp427_B$.[8] A comparable association was assessed by Young et al.(2008), but in their BMD sample the intellectual abilities were not related to the mutation site.[4] Additionally, the neurodevelopmental, behavioural and emotional problems in BMD are suggested to appear regardless of dystrophin gene mutation site.[7] The current case report evaluates the neurocognitive and behavioural profiles of three brothers with BMD having a similar dystrophin mutation, to clarify whether a genotype-phenotype relation may exist in BMD. We expect that the profiles of the brothers are similar

Case report

The reported cases were three brothers with BMD referred to the outpatient clinic of the Centre for Neurological Learning Disabilities (CNL), Kempenhaeghe, Heeze, The Netherlands. The diagnosis of BMD was previously confirmed by genetic testing between December 2011 and February 2012, which revealed an in-frame deletion of exon 45-48 (information on Dp140 promoter was not available). As part of their clinical care, each case received two consecutive neuropsychological assessments between

2012 and 2018. The parents of the boys completed high school education and had no neuro-developmental-, behavioural comorbidities or learning difficulties. Written informed consents of patients and parents were obtained for current report.

Neuropsychological assessment

See Table 5.1 for an overview of tested neurocognitive domains and behavioural questionnaires.

Table 5.1 *Overview of neurocognitive tests and behavioural questionnaires.*

Domains	Tests
Intellectual functioning	WISC-III
general	
verbal intelligence	
performance intelligence	
Cognitive functions	
working memory	KABC-II sequential scale
	Digit span of WISC-III
executive functioning	Mazes of WISC-III
attention	Bourdon Vos (continuous performance task)
speed of information processing	Processing speed index of WISC-III
visuospatial functioning	KABC-II simultaneous scale
visuomotor processing	Beery VMI
Academics	
reading	CB&WL EMB-T50 (word reading)
mathematics	TTA (speeded arithmetic)
Behavioural functioning	CBCL
	TRF

WISC-III=Wechsler Intelligence Scale for Children-third edition, KABC-II=Kaufmann Assessment Battery for Children-second edition, Beery VMI=Beery Visual-Motor Integration, TTA=Tempo Test Automatiseren, CB&WL=Continu Benoemen & Woordlezen, TTL=Tempo test Lezen, CBCL=Child Behaviour Checklist, TRF=Teacher's Report Form.

The Dutch version of the Wechsler Intelligence Scale for Children-Third edition (WISC-III-NL) measured three WISC-III indexes (1) Verbal Comprehension (subtests information, similarities, vocabulary, comprehension, digit span, arithmetic), (2) Perceptual Organization (subtests picture completion, picture arrangement, block design, object assembly and mazes) and (3) Processing Speed (subtests coding and symbol search). Verbal Intelligence Quotient was obtained by adding the scaled scores of Verbal Comprehension index without digit span. Performance Intelligence Quotient (PIQ) was based on Perceptual Organization and Processing Speed indexes. The full-scale intelligence quotient (FSIQ) was obtained by adding scaled scores of all subtests. WISC-III subtest raw scores of the Digit span and Mazes were converted to age-related

norm scores (M=10, SD=3).[10] The Kaufmann Assessment Battery for Children-second edition (KABC-II) evaluated (1) sequential processing based on the subtests Number Recall and Word Order and (2) simultaneous processing using the subtests Rover and Block Counting.[11] Raw scores of the WISC-III (i.e. FSIQ, VIC, PIQ and Processing speed index) and KABC-II were converted to age-related norm scores (M=100, SD=15).[10,11] Sustained attention was assessed using the speed and accuracy outcomes of the Bourdon Vos.[12] Technical reading was evaluated by the Continu Benoemen & Woordlezen (CB&WL) using the EMTB-T50 score subtest. Raw scores reflect total number of words read correctly.[13] Scores of the CB&WL EMTB T50 and of the visuomotor processing task i.e. Beery-VMI were transformed to age-related norm scores (M=10, SD=3).[13,14] The Tempo Test Automatization (TTA) was used to evaluate the degree of automatization of mathematical facts.[15] The TTA consists of four pages with 50 arithmetic problems including separate pages for addition, subtraction, multiplication and division problems.[15] Raw scores are based on number of arithmetic problems answered correctly (range 0-50) and these were converted to age equivalent scores.[15] The calculation of the age equivalent score is derived from a didactic (chronological) age score. This latest represents an expected score based on the number of months of arithmetic education a child has attended. At the end of primary regular education in the Netherlands, the didactic score reach it ceiling score of 60.[15] The age equivalent score of TTA estimates the level of arithmetic functioning according to a patients didactic age. Behavioural functioning was screened using the Child Behaviour Checklist (CBCL) and Teacher Report Form (TRF).[16,17] Both instruments evaluate behaviour based on eight syndrome scales. The syndrome scales can be used to calculate two broadband scale scores (i.e. internalizing and externalizing symptoms) and a total problem score. Raw scores were converted to T-scores (M=50, SD=10). In line with the manual, a cut off-value of T>63 was applied to indicate clinical ranges of the broadband scales and the total problem score.[16,17]

Demographic and disease-related characteristics

The three included brothers had a genetic mutation involving a deletion of exons 45-48 of the *DMD* gene (see Table 5.2 for the age of the cases). None had hearing or vision problems, or used medication (i.e. steroids and stimulants) at time of neuropsychological testing. At first neuropsychological testing (T0), all cases followed regular education, were ambulant and had no formal neurodevelopmental or behavioural disorders. At second neuropsychological testing (T1; see Table 5.2), cases 1 and 2 continued with regular education, both remained ambulant and had no neurodevelopmental or behavioural disorders. Case 3 changed from special primary

education for children with a physical handicap or learning disability to regular high school with a customized education plan. He was non-ambulant for long walking distances. Furthermore, based on the outcomes of his first assessment, case 3 was diagnosed with dyslexia by the neuropsychologist and child neurologist of the clinical team (JH, JV, SK).

Table 5.2 *Neurocognitive and behavioural outcomes of the cases.*

Variables	Case 1		Case 2		Case 3	
	T0	T1	T0	T1	T0	T1
Age at assessment in years	7.7	11.8	11.3	14.5	9.3	12.1
Intellectual functioning						
general	1.3	0.5	1.5	1.5	NA	0.2
verbal index	1.5	1.4	1.5	1.1	NA	0.4
performance index	0.7	-0.6	1.2	1.5	NA	-0.7
Cognitive functions						
working memory						
sequential	0.4	-0.6	-0.2	0.2	0	0.2
digit span	-0.3	0.3	-0.3	1.0	NA	-1.0
executive functioning	0.3	-0.7	2.0	1.0	NA	0.3
attention						
speed	-2.0	-1.0	-1.0	-1.0	0.0	-1.0
accuracy	-1.0	0.0	0.0	1.0	-2.0	0.0
speed of information processing	0.5	-0.7	-0.7	-0.7	0.1	-0.8
visuospatial	1.5	NA	1.8	1.2	0.2	1.1
visuomotor	0.0	NA	0.5	-0.6	0.5	-0.6
Academics						
reading						
EMTB-T50	0.7	0.0	NA	-1.3	-1.7	-2.3
speeded arithmetic ad/sub*	7	31	35	53	13	22
speeded arithmetic ad/sub/mu/di*	-	29	28	45	<15	20
Behavioural functioning						
CBCL						
Internalizing problems	-0.9	NA	1.7	0.4	1.1	0.9
Externalizing problems	-1.7	NA	0.0	-1.0	-0.4	-0.4
Total problems	-0.8	NA	0.4	-0.5	0.5	0.2
TRF						
Internalizing problems	1.8	NA	0.6	NA	0.1	NA
Externalizing problems	0.9	NA	-0.9	NA	-0.9	NA
Total problems	0.6	NA	-0.1	NA	0.0	NA

Results are z-scores (mean=0, SD=1), except the speeded arithmetic scores. * Are didactic age equivalent scores. NA=not available, EMTB-T50 = one minute reading test T50 score, speeded arithmetic ad/sub=speeded arithmetic additions and subtractions total score, speeded ad/sub/mu/di=speeded arithmetic total score based on additions, subtractions, multiplications and division problems, CBCL=Child Behaviour Checklist, TRF=Teacher report Form, T0=first neurocognitive testing, T1=second neurocognitive testing. Higher scores on the cognitive tests reflect better performances. Higher scores on the CBCL and TRF questionnaires reflect more behavioural problems.

Neurocognitive and behavioral assessment at the end of primary education

All cases underwent neuropsychological testing at a similar age (11.3-12.1 years), which was at the end of primary education. Norm scores of the cognitive tests and behavioural questionnaires were transformed to Z-scores (M=0, SD=1). Higher z-scores on the cognitive tests reflect better performances. Higher z-scores on the CBCL and TRF questionnaires reflect more behavioural problems. Results of cognitive testing showed that the three cases exhibited similar difficulties on speed (i.e. visual sustained attention speed and processing speed) and math (see Table 5.2; case 1 at T1, case 2 at T0 and case 3 at T1). The math outcomes of the three cases were lower than expected for their age, case 1 expected didactic score = 57 (at T1), case 2 expected didactic score = 51 (at T0) and the expected didactic score of case 3 (at T1) could not be calculated because the didactic scores are not applicable to special elementary education. We also found differences in cognition. Case 1 performed lower on executive functioning compared to case 2 and 3. Case 3 had dyslexia and attention deficits, and this latest deficit caused high distractibility throughout testing. Additionally, his general and verbal intellectual abilities and working memory scores were lower compared to cases 1 and 2.

Developmental profiles of the cases

Table 5.2 displays the outcomes of the first and second testing of each case. The time between their first and second testing ranged from 2.8 to 4.1 years. Z-scores of +2.0 SD or -2.0 SD were considered as clinical significant changes. At T1, case 1 improved (+1.0 SD) on accuracy and speed of visual sustained attention (see Table 5.2). Furthermore, case 1 had more difficulties on visuospatial abilities (-1.1 SD), executive functioning (-1.4 SD), processing speed (-1.2 SD) and sequential processing (-1.2 SD; see Table 5.2). Other cognitive outcomes of T1 were stable compared to T0. The behavioural outcomes of case 1 could not be evaluated as the Child Behaviour Checklist (CBCL) and Teacher Report Form (TRF) were not completed at T1 (See Table 5.2). Case 2 improved on working memory (+1.0 SD) and accuracy of visual sustained attention (1.0 SD) at T1. Additionally, case 2 performed less on executive functioning (-1.0 SD) and visuomotor processing (-1.0 SD; see Table 5.2). The other outcomes remained comparable to T0, although his math outcomes were not applicable because he followed high school education at T1. With respect to the behavioural outcomes of case 2, we found an elevated score (1.7 SD) on CBCL internalizing subscale (T-score >63) at T0, but no longer at T1 (0.4 SD; see Table 5.2). Finally, case 3, had more difficulties with speed of visual sustained attention (-1.0 SD) and visuomotor processing (-1.1 SD) at T1 compared to T0

(see Table 5.2). Other outcomes remained constant to T0 (see Table 5.2). No behavioural problems were noticed at both assessments of case 3 (see Table 5.2).

Discussion

The current study reports on a possible genotype-phenotype association in patients with BMD. This is the first case study on neurocognitive and behavioural profiles of three brothers with BMD with the same genetic dystrophin mutation, involving an in-frame deletion of exon 45-48. We retrospectively evaluated cognitive and behavioural performances cross-sectionally and longitudinally. Our results showed comparable difficulties in math and processing speed among the cases, but we also noted differences in cognitive abilities. The general intellectual abilities (FSIQ) of case 3 were 1.3 SD lower compared to case 2. A comparable difference in FSIQ has been described by a previous study of Chamova and colleagues, who found a difference of 18 points (1.2 SD) in IQ (83 versus 65) among two brothers with BMD sharing a similar mutation defect of exon 45 to 53.[18] Additionally, in our report, case 3 exhibited severe reading difficulties and attention problems, and this latest problem was expressed by a high internal distractibility throughout testing. A higher incidence of attention problems has previously been described for BMD.[4] The prefrontal cortex which is involved in attentional processes is a region that is rich in dystrophin, which may suggest that abnormal brain dystrophin production contributes to the attention problems of dystrophinopathy patients.[4,19-22] With respect to the development profiles of the cases, we noted non-significant clinical changes and some variability in development. Improvements were noticed for case 1 and 2 on accuracy of visual sustained attention, but both also displayed decreased performances in executive functions and processing speed. Furthermore, case 2 and 3 displayed more difficulties with visuomotor processing, longitudinally.

It was striking that we observed variability in cognitive and behavioural difficulties cross-sectionally and longitudinally, despite the fact that the cases had an identical dystrophin mutation, were tested at a similar age, and grew up in the same environment. We in particular found differences within intellectual abilities, working memory, attention and reading abilities. This may suggests that not only genetic and environmental factors induce interindividual variability in phenotypes. Other factors may modulate brain development as well. There is growing evidence on the fundamental role of maternal health factors on neurodevelopment of new-borns.[23] Factors for instance as maternal stress, malnutrition, or prenatal exposure to toxic

agents may also affect foetal brain development and induce altered brain structures and functions. However, the role of mechanism such as prenatal maternal stress on foetal brain development is not yet fully understood.[23] Our results highlight that further research on cognitive and behavioural comorbidities and it development in the BMD population is necessary.

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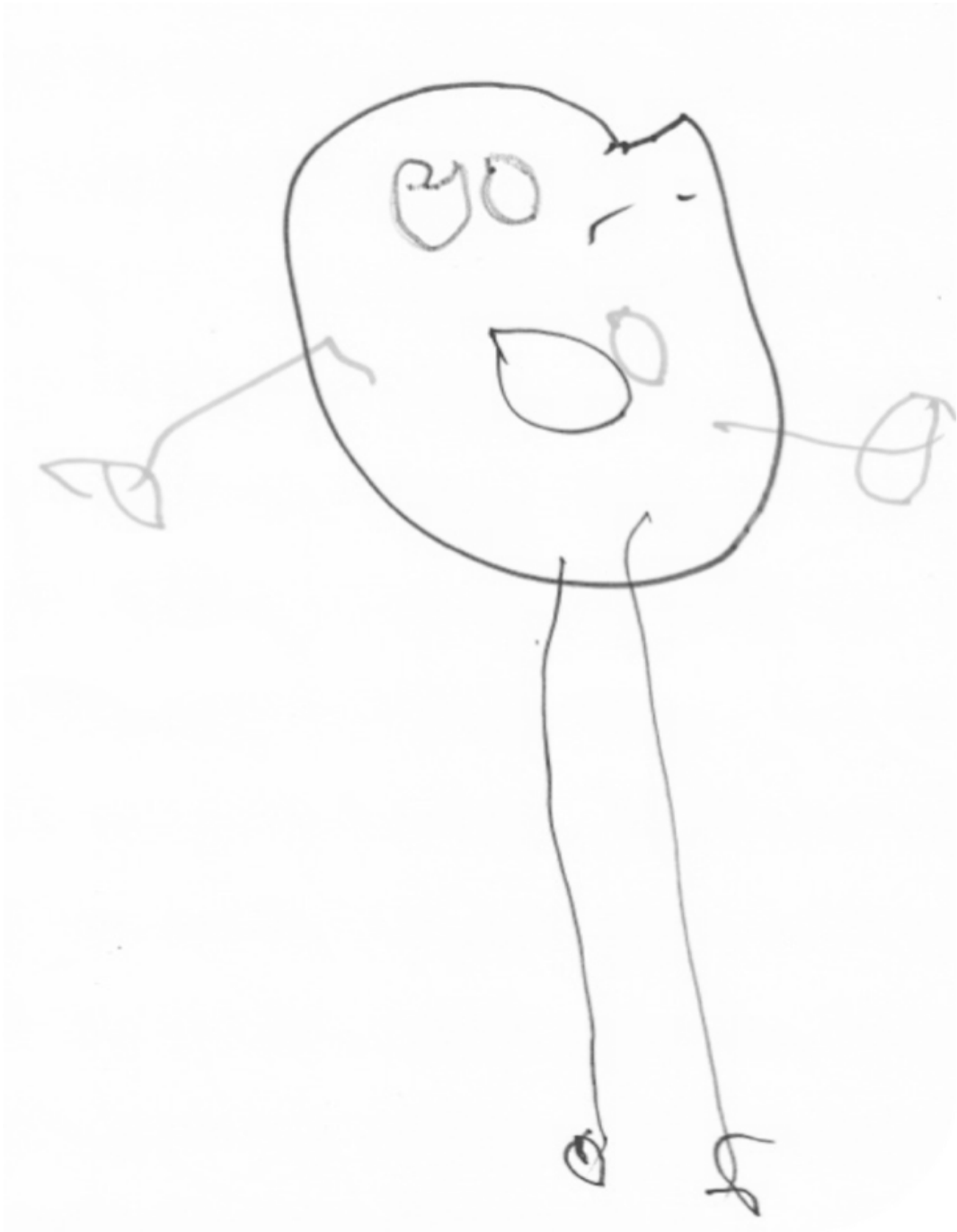

Chapter 6

Instruments for the assessment of behavioral and psychosocial functioning in Duchenne and Becker muscular dystrophy; a systematic review of the literature

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Abstract

This systematic review aims to provide an overview of instruments used to assess behavioural and psychosocial functioning of patients with Duchenne and Becker muscular dystrophy, as well as to review the psychometric properties and applicability of these instruments. Five databases (Embase, Psyc.info, ERIC, Pubmed/Medline, and Cochrane) were searched from inception to June, 2018. Potential articles were rated by two independent reviewers. A predefined PROSPERO form (CRD42017074518) was used to extract data from included articles. Sixty-one instruments were used in 54 studies. The Child Behaviour Checklist is commonly used, but it lacks disease specific psychometric information. Sixteen instruments that contained disease specific psychometric information were included for final evaluation. The results displayed three instruments can be appropriate for screening of psychosocial problems: the Psychosocial Adjustment and Role Skills Scale 3rd edition, the Paediatric Quality of Life Inventory Generic module, and the Life Satisfaction Index for Adolescents with Duchenne muscular dystrophy. Appropriate instruments for screening of behavioural problems may be: the Strengths and Difficulties Questionnaire, the Generalized Anxiety Disorder-7 item questionnaire, and the Patient Health Questionnaire. Further research on psychometric properties of the abovementioned screening instruments is crucial to ascertain a gold standard for clinical and research purposes. Meanwhile, for definite diagnostics purposes we recommend a multi-method, multi-source, multi-setting assessment in this high-risk population.

Introduction

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are allelic disorders covering the spectrum of X-linked dystrophinopathies, and are further mentioned as the dystrophinopathy population. Both disorders are caused by mutations in the *DMD* gene, that encodes multiple dystrophin isoforms in various tissues (i.e. muscles and the brain).[1-3] Depending on mutation location one or more dystrophin protein isoforms are absent in DMD, resulting in progressive muscle wasting.[2,3] By contrast, in BMD, gene mutations cause an open reading frame with a milder and more variable phenotype.[4] In addition to the myopathy, behavioural disorders are common in the dystrophinopathy population.[5-7] High prevalence rates of autism spectrum disorders (ASD; up to 21%), attention-deficit hyperactivity disorders (ADHD; up to 32%), anxiety and depression (up to 27%), oppositional defiant disorders (ODD; 15%), and obsessive compulsive disorders (OCD; up to 5%) have been described in DMD compared to the general.[5,8-12] Additionally, impaired psychosocial functioning has been reported in.[13,14] Three previous BMD studies also investigated the presence of behavioural disorders,[4,7,15] but only one study found increased prevalence rates of attention problems (33%), ASD (8.3%), social problems (33%), and withdrawn behaviour (33%) in BMD compared to the general population.[7] Current evidence suggests that these behavioural disorders are partially caused by neurobiological processes and relates them to impaired or altered expression of brain dystrophin isoforms. A relation between the absence of brain dystrophin isoforms and behavioural comorbidities such as attention-deficit hyperactivity- and autism spectrum disorders has been described in patients with DMD.[1,8,10,11] There is no research available yet on possible relations between partially functional dystrophin production in the brain and behavioural comorbidities in BMD. Research on dystrophin-associated behavioural comorbidities remains limited for both disorders and no clear explanation exists for the different rates in comorbidities between DMD and BMD. It is suggested that the discrepancy might be explained by the difference in expression of brain dystrophin isoforms in DMD versus BMD, but this needs further investigation.

With the increased life expectancy nowadays due to changes in medical care (i.e. improved ventilation assistance), the dystrophinopathy population is confronted with long-lasting or new mental health issues that negatively influence their quality of life.[16.] Recent standards of care for DMD emphasize that adequate and routine behavioural and psychosocial assessment is crucial,[16] though current literature lacks an overview of available and adequate instruments. Nonetheless, the updated standards of care for DMD recommend four instruments: the Strengths and Difficulties Questionnaire (SDQ),

the Patient Health Questionnaire (PHQ-9), the Generalized Anxiety disorder 7-item scale (GAD-7), and the Personal Adjustment and Role Skills Scale-III (PARS-III) for DMD.[16] However, disease-specific psychometric information is unknown for the SDQ, the PHQ-9, and the GAD-7. The suitability of the PARS-III for DMD care has been shown by only one previous study.[17]

Recently, improvements in screening and diagnostics of behavioural and psychosocial problems have received more attention in this high-risk aging population. Several studies have tried to improve the assessment of behavioural and psychosocial problems by using (1) the Diagnostic and Statistical Manual of Mental Disorders criteria, (DSM)[8], (2) more than one instrument, (e.g. informant-ratings in addition to structured clinical interviews),[8,11,18], or (3) instruments with items relevant to dystrophinopathy (e.g. Muscular Dystrophy Child Health Index of Life with Disabilities questionnaire for children with DMD, MDCHILD).[19] However, most studies have used instruments with poor or unevaluated psychometric properties or instruments that contain items unsuited for patients with motor impairments. Therefore, the present systematic review aims to provide an overview of instruments used to assess behavioural and psychosocial functioning, and evaluates their psychometric properties and applicability for the dystrophinopathy population.

Methods

Search strategy and selection criteria

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[20] and predefined PROSPERO protocol (CRD42017074518). Databases (EMBASE, Psyc.info, ERIC, PUBMED/Medline, and Cochrane) were searched from inception to July 2017 and updated to June, 19, 2018. The search strategy is presented in Supplementary Table S6.1. To be eligible for inclusion, studies had to (a) include males with dystrophinopathy (i.e. DMD or BMD), (b) examine the psychometric properties of behavioural and psychosocial instruments, (c) be available in English, Dutch or German, and (4) be longitudinal or cross-sectional design studies. Case report studies (n<10), non-peer reviewed articles, abstracts from scientific meetings, intervention studies or studies using an instrument that consisted of one subscale or one item of a questionnaire were excluded.

Two reviewers (D.H.: psychologist and J.L.: Doctor of Medicine, both having clinical experience with patients with DMD and BMD) independently screened titles and abstracts manually for potential inclusion, using the search terms of Supplementary Table S6.1. Full-texts of articles were retrieved when inclusion could not be based on title and abstract. Cohen's kappa was used to measure the inter-rater reliability between the two independent reviewers (D.H. and J.L.). If no consensus was reached between the two reviewers, a third independent reviewer (J.H. psychologist with clinical experience in DMD and BMD) examined whether the article fulfilled the inclusion criteria. After selection based on title and abstract, one reviewer (D.H.) screened the full-text of the selected articles to assess whether the article could be included for final evaluation (i.e. data extraction). Doubtful articles were examined by a second independent reviewer (J.H.). Furthermore, reference lists of the selected full-text articles were screened to identify whether additional articles had to be included for review.

Data collection and extraction

One reviewer (D.H.) extracted data from included articles for final evaluation using a predefined form (PROSPERO: CRD42017074518). The following data were extracted: (1) authors and year of publication, (2) demographic characteristics (e.g. age), (3) in- and exclusion criteria if specified, (4) study design, (5) instruments used to assess behavioural or psychosocial functioning, (6) results of psychometric properties and applicability of instruments, and (7) study limitations and main conclusion.

Classification of method of assessment

Selected articles were classified according to methods of assessment (Table 6.2): clinical observation ratings, (semi-) structured clinical interviews, informant-ratings, and self-ratings. During clinical observations, a clinician rates the extent of behavioural or psychosocial problems based on clinical judgement. Structured clinical interview instruments are designed to acquire both quantitative as well as qualitative information about the degree of behavioural or psychosocial functioning and are also completed by clinicians. Informant-rating instruments are questionnaires completed by a person who knows the patient well, for instance parents or caregivers. Self-rating instruments are completed by patients themselves.

Evaluation of psychometric properties and applicability

The psychometric properties of the instruments were evaluated by D.H. using seven criteria (see Table 6.1) from previous (systematic review) studies.[21-24] The applicability of the instruments were evaluated based on versions used in previous studies. The following aspects were assessed: availability (an easily obtained instrument), duration of assessment, availability in different languages.

Table 6.1 *Criteria to evaluate psychometric properties*.

	Insufficient	Moderate	Sufficient
1. Internal consistency [a,b,d]			
Cronbach's alpha	<0.70	0.70-0.80	>0.80
2. Test-retest reliability [a,b]			
Spearman / Pearson correlation	<0.70	0.70-0.80	>0.80
3. Interrater reliability [a,b,d]			
Intra-class correlations (ICC), Pearson correlation or Kappa between raters	<0.70	0.70-0.80	>0.80
4. Convergent validity [a,b]			
Spearman / Pearson correlation	<0.30	0.30-0.60	>0.60
5. Construct validity [a,b]			
Principal component analysis	Not confirms structure		Confirms structure
Comparative fit Index (CFI) if available [c]			>0.95
Standardized root mean square residual (SMR) [c]			<0.9
6. Responsiveness [a,b,d]	Non-significant changes: *p*>.05, or effect size <.40		Significant changes: *p*<.05, or effect size >.40
7. Content validity [d]			
Aim of instrument is clarified	No		Yes
Focus on dystrophinopathy	No		Yes
Clarification of concepts of subscales	No		Yes
Important items for population	No		Yes
Interpretability of items (simple, no jargon or two questions at one time)	No		Yes

[a] Visser-Meily et al.[24]; [b] Smeets et al.[22]; [c] Hu & Bentler,[21]; [d] Terwee et al.[23].

Results

The literature search identified 1009 articles based on the inclusion criteria. All articles were accessible. After removing duplicates and excluding articles based on title or abstract, a total of 114 articles remained for full-text screening (see Figure 6.1). Cohen's kappa was calculated to determine the level of agreement between the two independent reviewers (D.H. and J.L.) on title and abstract screening. A moderate agreement was found between the two reviewers, k=0.72. After full-text evaluation of the remaining 114 articles, a total of 53 articles were included for final evaluation.

Reasons for exclusion were (1) conference abstracts, (2) no assessment of behavioural or psychosocial instruments, (3) small sample size <10, (4) study population other than DMD and BMD, or no separate results available for DMD and BMD subpopulation, (5) no cross-sectional or longitudinal study design, and (6) language other than English, Dutch or German. One additional article was extracted from the reference list of the 114 selected articles. This additional article fulfilled the eligibility criteria and was added to the 53 previous included articles, which resulted in a total of 54 included articles (see Figure 6.1).

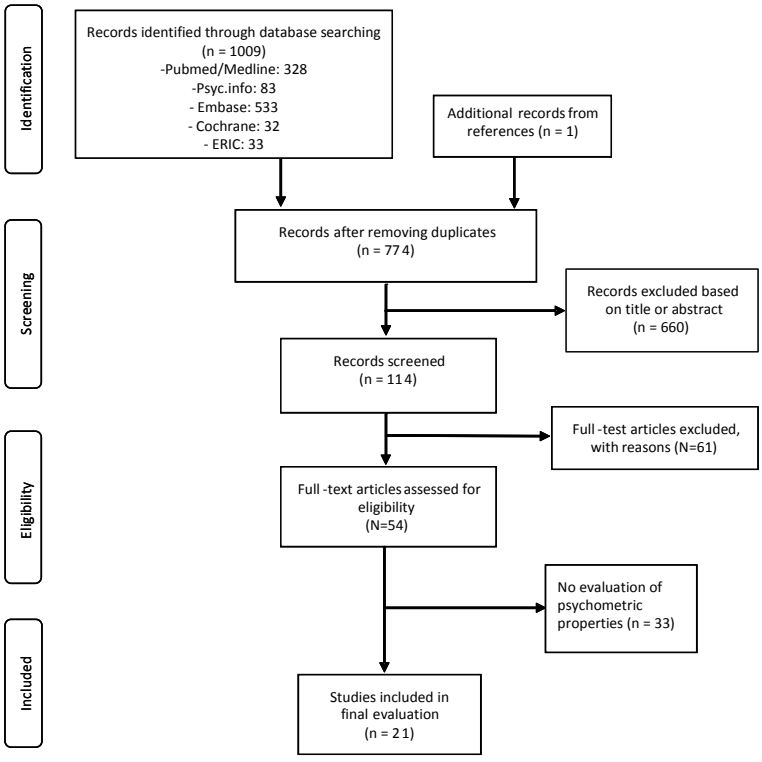

Figure 6.1 *Flowchart of the selected articles.*

Overview of included studies and instruments

Among the 54 included articles (N=51 DMD and N=3 BMD), 61 different instruments (n=1 clinical observation, n=12 semi-structured interviews, n=22 informant-ratings, and n=26 self-ratings) were used to assess behavioural and psychosocial functioning (see Table 6.2).

Table 6.2 *Overview of currently used behavioural and psychosocial instruments in Duchenne and Becker muscular dystrophy.*

Method	Instruments	Recommended age for assessment[#]	Times used	Key feature	Examples of items	N	Key references (authors & year)
Clinical observation	1. ADOS	1 – 23	2	Diagnosing ASD	"Does X ask for help?"	59 47	(Banihani et al. 2015)[8] (Colombo et al. 2017)[18]
(Semi) Structured interviews	2. RG	7 – 12	1	Psychiatric disorders in children	"Is your son anxious?"	23	(Fitzpatrick and Barry 1986)[25]
	3. BSQ	2.5 – 3.5	1	Behavioural problems in young children	"Does X have temper tantrums-shouting?"	33	(Smith et al. 1990)[26]
	4. DAS	18+	1	Social adjustment	"Having difficulties in maintaining a friendship?"	22	(Eggers and Zatz 1998)[27]*
	5. SADS-L	18+	1	Affective disorders and schizophrenia in adults	"Have you felt very good or too cheerful or high - not just your normal self?"	22	(Melo et al. 1995)[15]*
	6. SIDP-R	All ages	1	Psychiatric assessment	NA	22	(Melo et al. 1995)[15]*
	7. Three wishes	6 – 12	1	Material goods, pets/animals, activities, interpersonal/family, future/goal, personal attribute, situational, situation/health-related, altruism	"If you would make three wishes, any three wishes in the world, what would they be?"	74	(Nereo and Hinton 2003)[28]
	8. Open - and structured questions	18 – 42	1	Bodily functions, social participation, quality of life	"Having sexual problems"	65	(Rahbek et al. 2005)[29]
	9. VABS	0 – 90	1	Adaptive behaviour, communication, socialization, daily living, motor skills	"How does the individual interacts with others?"	20	(Cyrulnik et al. 2008)[30]
	10. KSADS	6 – 18	1	Affective disorders and schizophrenia in children and adolescents	"Have you ever felt sad, blue, down, or empty?"	10	(Steele et al. 2008)[12]
	11. Open- and structured	15+	1	Important topics in DMD	"What is it like to live with DMD?"	40	(Abbott and Carpenter 2015)[31]
	12. DAWBA	5 – 17	1	Generating psychiatric diagnosis based on DSM-IV and ICD-10	"In the last for weeks have there been times that X has been very sad, miserable, unhappy or tearful?"	47	(Colombo et al. 2017)[18]

Table 6.2 *(continued)*

Method	Instruments	Recommended age for assessment[#]	Times used	Key feature	Examples of items	N	Key references (authors & year)
	13. 3Di-sv	0 – 18	1	Communication and repetitive/stereotyped behaviour	"Avoids eye-contact"	130	(Ricotti et al. 2016)[11]
Informant ratings	14. RBQ (A)	7 – 13	1	Antisocial, neurotic, somatic behaviour	"Does she/he have eating difficulties?"	57	(Leibowitz and Dubowitz 1981)[32]
	15. RBQ (B)	7 – 13	2	Antisocial, neurotic, somatic behaviour	"Frequently fights with other children?"	57 23	(Leibowitz and Dubowitz 1981)[32] (Fitzpatrick and Barry 1986)[25]
	16. MCBC	9 – 15	1	Internalizing and externalizing behaviour	"Does not try new situations"	34	(Thompson et al. 1992)[13]
	17. RBPC	5 – 18	1	Conduct disorders, socialized aggression, attention problems, anxiety-withdrawal, psychotic behaviour, motor tension	"Seeks attention, shows-off"	44	(Solden et al. 1999)[33]
	18. CBCL	1,5 – 5 6 – 18	11	Anxious/depressed, somatic complaints, attention deficit/ hyperactivity, autism spectrum, oppositional defiant, stress problems	-"Does he argues a lot?" -"Is he inattentive or easily distracted?"	74 26 50 50 10 22 16 159 130 47 24	(Nereo and Hinton 2003)[28] (Hinton et al. 2004)[34] (Hinton et al. 2006)[35] (Hinton et al. 2007)[36] (Steele et al. 2008)[12] (Donders and Taneja 2009)[37] (Donald et al. 2011)[38] (Fee and Hinton 2011)[39] (Ricotti et al. 2016)[11] (Colombo et al. 2017)[18] (Young et al. 2008)[7]*

Table 6.2 *(continued).*

Method	Instruments	Recommended age for assessment[#]	Times used	Key feature	Examples of items	N	Key references (authors & year)
	19. BRIEF	5 – 18	1	Executive behaviour index	"Troubles in remembering things even for a few minutes?"	22	(Donders and Taneja 2009)[37]
	20. PARS-III	5 – 18	1	Psychosocial adjustment	"Is he unable to decide for himself?"	287	(Hendriksen et al. 2009)[17]
	21. SCQ	4 – 23	1	Screens for ASD	"Has he/she ever used odd phrases or said the same thing over and over in almost exactly the same way?"	85	(Hinton et al. 2009)[9]
	22. PedsQL GM	2 – 4 5 – 7 8 – 12 13 – 18 18 – 25 26+	9	Quality of life in children and adolescents	"Problems with feeling afraid or scared?"	35 52 44 203 56 63 99 107 98	(Bray et al. 2010b)[40] (McDonald et al. 2010)[41] (Davis et al. 2010)[42] (Uzark et al. 2012)[14] (Hu et al. 2013)[43] (Lim et al. 2014)[44] (Wei et al. 2015)[45] (Messina et al. 2016)[46] (Wei et al. 2017)[47]
Informant ratings	23. PedsQL NMD	2 – 4 5 – 7 8 – 12 13 – 18	5	Quality of life in children & adolescents with NMD	"Has difficulties in telling the doctors and nurses how he feels"	44 56 99 770 107	(Davis et al. 2010)[42] (Hu et al. 2013)[43] (Wei et al. 2015)[45] (Landfeldt et al. 2016)[48] (Messina et al. 2016)[46]
	24. PODCI	4 – 18	1	Quality of life in children and adolescents	"How happy has your child been with how he looks?"	52	(McDonald et al. 2010)[41]
	25. CHQ-PF50	5 – 18	2	Quality of life in children	"How much of the time do you think your child felt like crying?"	27 34	(Baiardini et al. 2011)[49] (Bray et al. 2011)[50]

Table 6.2 *(continued)*

Method	Instruments	Recommended age for assessment[#]	Times used	Key feature	Examples of items	N	Key references (authors & year)
	26. CTRS-R:L	3 - 17	2	Oppositional, cognitive, social, psychosomatic problems, hyperactivity, anxious-shy, perfectionism	"Does not follow through on instructions and fails to finish schoolwork"	103 59	(Pane et al. 2012)[10] (Banihani et al. 2015)[8]
	27. CPRS-R:L	3 - 17	2	Oppositional, cognitive, social, psychosomatic problems, hyperactivity, anxious-shy, perfectionism	"Cannot remain still"	103 59	(Pane et al. 2012)[10] (Banihani et al. 2015)[8]
	28. PedsQL DMD	5 – 7 8 – 12 13 – 18	2	Quality of life in DMD	"Worries about his muscle problem"	203 99	(Uzark et al. 2012)[14] (Wei et al. 2015)[45]
	29. ABS	0 - 42 months	1	Social-emotional and adaptive behaviour	NA	24	(Connolly et al.2014)[51]
	30. KIDSCREEN-52	8 – 18	2	Quality of life in children and adolescents	"Has your child felt lonely?"	40 85	(Houwen–van Opstal et al. 2014)[52] (Zamani et al. 2016)[53]
	31. HUI	5+	1	Quality of life	"Happy and interested in life"	770	(Landfeldt et al. 2016)[48]
	32. CPRS:S	3 - 17	1	Attention, hyperactivity/impulsivity, learning problems, executive functioning, peer relations, aggression	"Restless or overactive"	130	(Ricotti et al. 2016)[11]
	33. SCDC	3 – 19	1	Social communication disorders	"Not aware of other people's feelings"	130	(Ricotti et al. 2016)[11]
	34. QoML	4 – 18	1	Global quality of life	"Overall his life is …."	98	(Wei et al. 2017)[47]
Informant ratings	35. SDQ	2 – 18	1	Emotional, conduct problems, ADHD, peer relationship, prosocial behaviour	"Does he considers other people's feelings?"	47	(Colombo et al. 2017)[18]

Table 6.2 *(continued)*

Method	Instruments	Recommended age for assessment[#]	Times used	Key feature	Examples of items	N	Key references (authors & year)
Self-ratings	36. MMPI	18 – 80	1	Personality, behavioural difficulties and psychopathology	"I am easily awaked by noises"	44	(Harper 1983)[54]
	37. OSIQ	13 – 19	2	Psychosocial adjustment in adolescents	"I feel so very lonely"	15	(Reid and Renwick 1994)[55]
						32	(Reid and Renwick 2001)[56]
	38. LSIA	12 – 19	2	Life satisfaction in adolescents with DMD	NA	15	(Reid and Renwick 1994)[55]
						95	(Simon et al. 2011)[57]
	39. SWLS	NS	2	Life satisfaction in all ages	"The conditions of my life are excellent"	15	(Reid and Renwick 1994)[55]
						16	(Graham and Rose 2017)[58]
	40. RCMAS	6 – 19.5	1	Anxiety problems in children and adolescents	"I worry a lot of the time"	10	(Steele et al. 2008)[12]
	41. CDI	7 – 18	1	Depression in children	"I hate myself"	10	(Steele et al. 2008)[12]
	42. PEDSQL NMD	5 – 7	7	Quality of life in children & adolescents with NMD	"It is hard for me to tell the doctors and nurses how I feel"	44	(Davis et al. 2010)[42]
		8 – 12				99	(Wei et al. 2015)[45]
		13 – 18				770	(Landfeldt et al. 2016)[48]
						107	(Messina et al. 2016)[46]
						321	(Otto et al. 2017)[59]
						56	(Hu et al. 2013)[43]
						278	(Landfeldt et al. 2018)[60]
	43. PEDSQL GM	5 – 7	9	Quality of life in children & adolescents	"I feel afraid or scared"	44	(Davis et al. 2010)[42]
		8 – 12				203	(Uzark et al. 2012)[14]
		13 – 18				50	(Bendixen et al. 2012)[61]
		18 – 25				56	(Hu et al. 2013)[43]
		26+				63	(Lim et al. 2014)[44]
						99	(Wei et al. 2015)[45]
						107	(Messina et al. 2016)[46]
						321	(Otto et al. 2017)[59]
						85	(Wei et al. 2017)[47]
	44. PEDSQL DMD	8 – 12	2	Quality of life in children & adolescents with DMD	"I worry about my muscle problem"	203	(Uzark et al. 2012)[14]
		13 – 18				99	(Wei et al. 2015)[45]

Table 6.2 *(continued)*

Method	Instruments	Recommended age for assessment[#]	Times used	Key feature	Examples of items	N	Key references (authors & year)
	45.DISABKIDS	4 – 16	1	Quality of life in children with chronic diseases	NA	50	(Elsenbruch et al. 2013)[62]
Self-ratings	46. SF-36	NS	3	Quality of life in adults	"Have you felt calm and peaceful?"	50 79 41	(Elsenbruch et al. 2013)[62] (Pangalila et al. 2015b)[63] (Lue et al. 2017)[64]
	47. DIKJ	8-17	1	Depression in children and adolescents	NA	50	(Elsenbruch et al. 2013)[62]
	48. BDI	13+	1	Depression in adults	"I don't feel like a failure"	50	(Elsenbruch et al. 2013)[62]
	49. KIDSCREEN-52	8 – 18	2	Quality of life in children and adolescents	"Have you felt under pressure?"	40 85	(Houwen-van Opstal et al. 2014)[52] (Zamani et al. 2016)[53]
	50. WHOQOL-BREF	18+	3	Quality of life	"How well are you able to concentrate?"	80 79 41	(Pangalila et al. 2015a)[65] (Pangalila et al. 2015b)[63] (Lue et al. 2017)[64]
	51. HADS	16 – 65	1	Depression and anxiety	"I feel cheerful"	80	(Pangalila et al. 2015a)[65]
	52. KIDSCREEN-10	8 – 18	1	Quality of life in children and adolescents	"Have you felt sad?"	321	(Otto et al. 2017)[59]
	53. YSR	11 – 18	1	Anxious/depressed, somatic complaints, attention deficit/ hyperactivity, autism spectrum, oppositional defiant problems, stress problems	-"I argue a lot" -"I am easily distracted"	47	(Colombo et al. 2017)[18]
	54. GAD-7	16+	1	Anxiety	"Feeling nervous, anxious or on edge"	16	(Graham and Rose 2017)[58]
	55. PHQ-9	12+	1	Depression	"Feeling down, depressed or hopeless"	16	(Graham and Rose 2017)[58]
	56. AAQ	NS	1	Acceptance	"I avoid difficult thoughts and feelings- no matter the cost"	16	(Graham and Rose 2017)[58]
	57. B-IPC	NS	1	Illness perceptions	"DMD causes me distress"	16	(Graham and Rose 2017)[58]

Table 6.2 *(continued)*

Method	Instruments	Recommended age for assessment[#]	Times used	Key feature	Examples of items	N	Key references (authors & year)
	58. CFQ	18+	1	Cognitive diffusion	"My thoughts cause me distress or emotional pain"	16	(Graham and Rose 2017)[58]
Self-ratings	59. QoML	4 – 18	1	Global quality of life	"Overall my life is …."	85	(Wei et al. 2017)[47]
	60. Self-survey	20+	1	Neurodevelopmental, problematic and psychiatric diseases	"Experiencing problematic behaviour like suicide attempts and/or self-mutilation"	125	(Mori-Yoshimura et al. 2018)[4]*
	61. MDCHILD	5 - 18	1	Health-related priorities	"How often were you unhappy or sad?"	19	(Propp et al. 2018)[19]

AAQ = Acceptance and Action Questionnaire; ABS; Adaptive Behavior subtest; ADOS = Autism Diagnostic Observation Schedule; ASD = Autism Spectrum Disorders; BDI = Beck Depression Inventory; B-IPC; Brief Illness perception Questionnaire; BRIEF = Behavior Rating Inventory of Executive functions; BSQ = behavior screening questionnaire; CBCL = Child Behavior Checklist; CDI = Children Depression Inventory; CFQ; Cognitive Fusion Questionnaire; CHQ-PF50 = Children's Health Questionnaire Parent Form 50; CPRS-R:L; Conners Parent Rating Scale-Revised:Long form; CPRS:S = Conners Parent Rating scale Short form; CTRS-R:L; Conners Teachers Rating Scale-Revised:Long form; DAS = Disability Assessment Schedule; DAWBA = Developmental and Well-being Assessment Diagnostic Interview; 3DI-sv = Diagnostic and Dimensional Interview- short version; DIKJ = Depressions Inventar für Kinder und Jugendliche; GAD-7; Generalized Anxiety Disorder Questionnaire 7 items; HADS = Hospital Anxiety and Depression scale; HUI = Health Utilities Index Questionnaire; KIDSCREEN-52 = KIDSCREEN-52 items; KIDSCREEN-10 = KIDSCREEN-10 items; KSADS = The Kiddie Schedule for Affective disorders and Schizophrenia; LSIA = Life satisfaction Index for Adolescents with Duchenne muscular dystrophy; LS = Satisfaction with Life Scale; MCBC = Missouri Children's Behavior Checklist; MDCHILD = Muscular Dystrophy Child Health Index Of Life with Dissabilities; MMPI = Minnesota Multiphasic Personality Inventory; OQIS = Offer Self-Image Questionnaire for Adolescents; PARS-III = Psychosocial Adjustment Rating Scale-III; PEDSQL DMD; Pediatric Quality of Life Inventory Duchenne muscular dystrophy module; PEDSQL GM = Pediatric Quality of Life Inventory generic score module; PEDSQL NMD = Pediatric Quality of Life Inventory Neuromuscular module; PODCI = Pediatric Outcomes Data Collection Instrument; PHQ-9; Patient Health Questionnaire 9 item Scale; QoML = The Quality of My Life questionnaire; RBQ = Rutter Behavior Questionnaire (A) for parents; RBQ B = Rutter Behavior Questionnaire for teachers; RBPC = Revised Behavior Problem Checklist; RG = Rutter and Graham interviews; RCMAS = Revised Children's Manifest Anxiety Scale; SADS-L = Schedule for affective disorders and schizophrenia, Lifetime version; SCDC = Social Communication Disorder Checklist; SCQ = Social Communication Questionnaire; SDQ = Strengths and Difficulties Questionnaire; SF-36 = 36 item Short form Health Survey; SIDP-R = structured interview for DSM-III-R Personality; VABS = Vineland Adaptive Behavior Scales; WHOQOL-BREF = World Health Organization Quality of Life Brief version; YSR = Youth Self-Report. NMD = Neuromuscular disorders; DMD = Duchenne muscular dystrophy; ASD = Autism Spectrum Disorders; ADHD = Attention Deficit Hyperactivity Disorder; NA = Not available; NS = Not specified; N = sample size of study. *BMD studies ; [#] recommended age in years for assessment

The psychometric properties of these instruments were not evaluated in 33 (N=30 DMD and N=3 BMD) of the 54 articles and were excluded for final evaluation of psychometric properties (see Table 6.3 for excluded instruments). Due to the final selection, a total of 21 articles (all DMD) with 16 instruments (n=5 informant-ratings, n=6 self-ratings, and n=5 instruments with informant-ratings and self-ratings) were reviewed. Patients (N=2580) included in these N=21 studies were aged between 0.7 months and 44 years.

Psychometric properties of included instruments

Table 6.4 summarizes the psychometric properties of the 16 reviewed instruments. Values of Table 6.4 are psychometric results of the total scale. Subscale information of the instruments is not included. The different forms (i.e. informant-rating and self-rating) of the KIDSCREEN, the Pediatric Quality of Life inventory general module (PedsQL GM), the PedsQL neuromuscular module (PedsQL NMM), and the PedsQL Duchenne module (PedsQL DMD) were assessed separately. As can been seen in Table 6.4, most psychometric information was available from the PARS-III, the PedsQL GM, and the PedsQL NMM.

The PARS-III had good internal consistency (Cronbach's α=0.91), convergent validity (r=-0.65), and construct validity (factor analysis confirmed structure of instrument; CFI: 0.96, SRMR: 0.06). No information on inter-rater reliability, test-retest reliability, and responsiveness was available.

The PedsQL GM informant-rating form had good internal consistency (Cronbach's α=0.83) and the internal consistency of the PedsQL GM self-rating form was moderate to good (Cronbach's α ranged between 0.73-0.87). The inter-rater reliability of both forms was insufficient (informant-rating and self-rating ICC ranged between 0.20-0.64, and r=0.54). Convergent validity was good for the informant-rating form (r=0.72) but unknown for the self-rating form. Responsiveness was good for both forms (informant-rating: p<.001, self-rating: p=.04). No information was available on test-retest reliability and construct validity of the informant-rating form and self-rating form.

Table 6.3 *Excluded instruments for final evaluation*

Instruments	Clinical observation	(Semi) Structured interviews	Informant-ratings	Self-ratings
1. ADOS	x			
2. RG		x		
3. BSQ		x		
4. DAS		x		
5. SADS-L		x		
6. SIDP-R		x		
7. Three wishes		x		
8. Open- and structured questions On bodily functions, social participation and QOL		x		
9. VABS		x		
10. KSADS		x		
11. Open-and structured questions on important topics for DMD		x		
12. DAWBA		x		
13. 3Di-sv		x		
14. RBQ (A)			x	
15. RBQ (B)			x	
16. MCBC			x	
17. RBPC			x	
18. BRIEF			x	
19. SCQ			x	
20. CTRS-R:L			x	
21. HUI			x	
22. CPRS:S			x	
23. CPRS:L			x	
24. SCDC			x	
25. QoML			x	x
26. MMPI			x	
27. SWLS				x
28. RCMAS				x
29. CDI				x
30. DISABKIDS				x
31. DIKJ				x
32. BDI				x
33. HADS				x
34. AAQ				x
35. B-IPC				x
36. CFQ				x
37. Self-survey				x
38. MDCHILD				x

AAQ = Acceptance and Action Questionnaire; ADOS = Autism Diagnostic Observation Schedule; BDI = Beck Depression Inventory; B-IPC; Brief Illness perception Questionnaire; BRIEF = Behavior Rating Inventory of Executive functions; BSQ = behavior screening questionnaire; CDI = Children Depression Inventory; CFQ ; Cognitive Fusion Questionnaire; CPRS-R:L; Conners Parent Rating Scale-Revised:Long form; CPRS:S = Conners Parent Rating scale Short form; CTRS-R:L; Conners Teachers Rating Scale-Revised:Long form; DAS = Disability Assessment Schedule; DAWBA = Developmental and Well-being Assessment Diagnostic Interview; 3DI-sv =

Diagnostic and Dimensional Interview- short version; DIKJ = Depressions Inventar für Kinder und Jugendliche; HADS = Hospital Anxiety and Depression scale; HUI = Health Utilities Index Questionnaire; KSADS = The Kiddie Schedule for Affective disorders and Schizophrenia; MCBC = Missouri Children's Behavior Checklist; MDCHILD = Muscular Dystrophy Child Health Index Of Life with Dissabilities; MMPI = Minnesota Multiphasic Personality Inventory; QoML = The Quality of My Life questionnaire; RBQ = Rutter Behavior Questionnaire (A) for parents ; RBQ B = Rutter Behavior Questionnaire for teachers; RBPC = Revised Behavior Problem Checklist; RG = Rutter and Graham interviews; RCMAS = Revised Children's Manifest Anxiety Scale; SADS-L = Schedule for affective disorders and schizophrenia, Lifetime version; SCDC = Social Communication Disorder Checklist; SCQ = Social Communication Questionnaire; SIDP-R = structured interview for DSM-III-R Personality; VABS = Vineland Adaptive Behavior Scales.

Table 6.4 *Psychometric properties of included instruments*

Method	Instrument	Internal consistency	Test- retest reliability	Inter-rater reliability	Convergent validity	Construct validity	Responsiveness
Informant-ratings	1. PARS-III	+	?	?	+	+	?
	2. CBCL	?	?	±/-	+/±	?	?
	3. PODCI	?	?	?	+	?	?
	4. CHQ-PF50	±	?	?	?	?	?
	5. ABS	?	?	?	?	?	-
Self-ratings	6. OSIQ	+	?	?	?	?	?
	7. LSIA	+	?	?	+	?	?
	8. YSR	?	?	±/-	?	?	?
	9. SDQ	?	?	?	+/±	?	?
	10. SF-36	?	?	?	±/-	?	?
	11. WHOQOL-BREF	?	?	?	±/-	?	?
Informant & self-ratings	12. PEDSQL GM						
	Informant form	+	?	-	+	?	+
	Self-rating form	+/±	?	-	na	?	+
	13. PEDSQL NMD						
	Informant form	+	+/±	±/-	na	?	+
	Self-rating form	+	±/-	±/-	na	-	-
	14. PEDSQL DMD						
	Informant form	+/±	?	-	na	?	?
	Self-rating form	±	?	-	na	?	?
	15. KIDSCREEN-52						
	Informant form	?	?	±/-	?	?	?
	Self-rating form	?	?	±/-	?	?	?
	16. KIDSCREEN-10						
	Informant form	±	?	?	?	?	?
	Self-rating form	±	?	?	?	?	?

ABS = Adaptive Behavior subtest of Bayley; CBCL = Child Behavior Checklist; CHQ-PF50 = Children's Health Questionnaire Parent Form 50; KIDSCREEN-52 = KIDSCREEN 52 items; KIDSCREEN-10 = KIDSCREEN 10 items; LSIA = Life satisfaction Index for Adolescents with Duchenne muscular dystrophy; OSIQ = Offer Self-Image Questionnaire for Adolescents; PARS-III = Psychosocial Adjustment Rating Scale-III; PEDSQL DMD; Pediatric Quality of Life Inventory Duchenne muscular dystrophy module; PEDSQL GM = Pediatric Quality of Life Inventory generic score module; PEDSQL NMD = Pediatric Quality of Life Inventory Neuromuscular module; PODCI = Pediatric Outcomes Data Collection Instrument; SDQ = Strengths and Difficulties Questionnaire; SF-36 = 36 item Short form Health Survey; WHOQOL-BREF = World Health Organization Quality of Life Brief version; YSR = Youth Self-Report. +: sufficient ; ±: moderate; -: insufficient; ?: unknown/unclear; na: not applicable

The PedsQL NMM informant-rating form and self-rating form had good internal consistency (Cronbach's α informant-rating form: 0.86-0.87 and self-rating form: 0.81-0.92). Test-retest reliability of the informant-rating form was sufficient (r=0.85-0.88) and moderate to insufficient (r=0.66-0.75) for the self-rating form. The inter-rater reliability of both forms ranged from moderate to insufficient (ICC ranged between 0.51-0.78). Convergent validity was good for the informant-rating form (r=0.60-0.71) and the self-rating form (r=0.65-0.67). No information was available on construct validity of the informant-rating form. Construct validity was insufficient for the self-rating form, since the structure of the form was not confirmed by principal component analysis. Responsiveness was good for the informant-rating form (p=.005) but insufficient for the self-rating form (p=.77).

Content validity and applicability of included instruments

Results of content validity and applicability of the 16 reviewed instruments are displayed in Table 6.5. All instruments met criterion 1, signifying that instruments had specific measurement aims. Only two instruments were specifically developed for dystrophinopathy and met criterion 2: the Life Satisfaction Index for Adolescent with Duchenne muscular dystrophy (LSIA) and the PedsQL DMD. All instruments consisted of specified concepts, measured by separate subscales and items (criterion 3), except for the PedsQL NMM self-rating form. Subscales of the PedsQL NMM self-rating form contain non-distinctive items, for instance, "it is hard for me to tell the doctors and nurses how I feel" and "it is hard for me to ask doctors and nurses questions." All instruments met criterion 4 and measured a degree of behavioral or psychosocial functioning relevant for the dystrophinopathy population, though items of two instruments (i.e. Child Behavior Checklist; CBLC Offer Self-Image Questionnaire; OSIQ) are less applicable in dystrophinopathy due to the progressive physical immobility. Less applicable items are for example can't sit still, being restless' (CBCL-ADHD subscale), 'runs away from home' (CBCL-rule breaking behavior subscale), or 'I love the recent changes in my body' (OSIQ). Several instruments did not fulfill criterion 5, since the items contain more than one question at the same time. In addition, items of the PedsQL NMM self-rating form for toddlers and young children (i.e. 'hard to gain or lose weight'; do not have the equipment one needs) are not applicable or too difficult to understand. With regard to the applicability of the instruments, it was found that all instruments were available in English. Most instruments (n=9) were freely available by website, four by author, and three by publisher. Administration time of nine instruments was <10 minutes and of seven instruments the time varied from 10-50 minutes.

Discussion

The purpose of this systematic review was to provide an overview of instruments used to assess behavioural and psychosocial functioning of patients with DMD and BMD, as well as to review the psychometric properties and applicability of these instruments. A total of 61 different instruments have been used in 51 DMD studies and 3 BMD studies. Our review showed that most previous studies provide limited psychometric information. The majority of instruments being used are informant-rating and self-rating instruments. The most common used (N=11 studies) is the CBCL,[66] but only two studies reported psychometric information on convergent validity (ranging from poor to moderate) and inter-rater reliability (ranging from moderate to good.[18,39] Additionally, the content validity of CBCL is less sufficient for patients with motor impairments when questions involve normal motor abilities. This can result in under-identification of behavioural comorbidities due to lower scores in for instance hyperactive or oppositional, aggressive behaviour.[67] Furthermore, the CBCL is developed for screening of various behavioural and emotional symptoms and is not intended to be a diagnostic instrument for establishing definite DSM-5 diagnoses,[68] such as ADHD.[69] To accurately diagnose ADHD clinicians should be able to differentiate symptoms of inattention, hyperactivity, and impulsivity. The symptom items of the CBCL-ADHD subscale have no conceptual link with the diagnostic criteria for ADHD.[69] Other instruments, for instance, the Conners Parent Rating Scale-Revised (CPRS-R) or the SDQ differentiate and ascertain ADHD symptoms more accurately. Since the items of the CPRS-R and SDQ subscales are selected on the basis of nosologically concepts (i.e. DSM criteria and International Statistical Classification of diseases and related Health Problems: ICD-10) as well as on factor analysis.[69-71] This likely explains that Colombo et al.[18] recently found an ADHD comorbidity of 0% in their DMD sample based on CBCL screening, while Banihani et al.[8] found a prevalence rate as high as 32% for ADHD using CPRS-R for ADHD. These data confirm that the prevalence rates of behavioural comorbidities in DMD as previously reported largely depend on the instruments that were used and should, therefore, be considered with caution. The majority of previous studies used instruments with unevaluated or poor psychometric properties, or instruments that are not developed to differentiate behavioural symptoms.

Psychometric properties of included instruments

For the current systematic review disease specific psychometric information was available for 21 DMD studies with 16 instruments being reviewed, including both

informant-ratings and self-ratings. The 33 excluded studies used significantly different instruments including clinical observations and semi-structured interviews, in addition to informant-rating and self-rating instruments. Thereby, this review only describes psychometric properties of informant-rating and self-rating instruments for DMD. With regard to the psychometric properties of the included instruments, more in depth evaluation was found for the PARS-III, the PedsQL GM, and the PedsQL NMM. The PARS-III proves to be an adequate instrument and is therefore recommended in the standards of care for DMD.[16] However, additional validation by replication of reported psychometric results is recommended as well as data on inter-rater reliability, test re-test reliability, and responsiveness. The PedsQL GM informant-rating and self-rating form have relatively good properties, both having only poor inter-rater reliability. Data on PedsQL NMM informant-rating form varies in previous studies and it inter-rater reliability is low. Moderate to poor psychometric results are noted for the PedsQL NMM self-rating form, suggesting that it is no valid instrument for DMD. The inter-rater reliability of both PedsQL modules (GM and NMM) are low, reflecting a discrepancy between patients and their parents/caregivers. This is in line with previous studies showing that parents/caregivers overestimate the magnitude of problems due to their own concerns and perceptions of the illness.[33,40] This could explain the notable difference between behavioural and psychosocial problems reported by patients and caregivers.[42,52,44] Additional validation on psychometric properties of both PedsQL modules and their separate forms is necessary, before using them for clinical or research trials.

With respect to the three (SDQ, GAD-7, and PHQ-9) remaining recommended instruments of the recently published standards of care for DMD,[16] two instruments (GAD-7 and PHQ-9) have no disease specific psychometric information. However, previous studies reported that the GAD-7 is a valid instrument for screening of generalized anxiety disorders as well as for panic, social anxiety, and post-traumatic stress disorders.[72,73] Nevertheless, the GAD-7 provides only a probable diagnosis and further evaluation is necessary to diagnose anxiety. Furthermore, the psychometric properties of the PHQ-9 have been evaluated by multiple clinical studies. This instrument seems favourable in screening for depression in primary and mental health care and is equal or superior to other depression measures.[74] However, previous studies on the GAD-7 and the PHQ-9 evaluated the reliability and validity of these instruments in adult patients and the usefulness for DMD should be assessed accordingly. The third instrument, the SDQ, poses limited psychometric information and Colombo et al.[18] showed that the SDQ has a moderate to good validity in N=47 males with DMD. However, the SDQ has been extensively evaluated in children and

adolescents with or without a chronic illness and it is believed that it is a reliable and valid screener for psychiatric.[75-80] In addition, a higher specificity of the SDQ informant-rating (0.85) has been noted compared to the CBCL (0.72), meaning that the SDQ will result in less overestimation of true behavioural comorbidity. Overall, the SDQ should be considered as a valid and robust instrument for future research and clinical settings, though care should be taken when using the SDQ predictive algorithm to screen for ADHD comorbidity.[71] Further evaluation of the SDQ psychometric properties for the dystrophinopathy population is recommended.

Content validity and applicability of included instruments

The current review systematically evaluated content validity and applicability of the 16 included instruments. Only the LSIA and PedsQL DMD fulfilled the five content validity criteria and may thus be suitable for DMD care. However, our psychometric results revealed sufficient and reliable results for the LSIA, but insufficient results for the PedsQL DMD. Additional research on the reliability of both instruments is recommended. Furthermore, of the 16 included instruments, the majority had items that were (1) limited or not applicable to the dystrophinopathy population, (2) or too difficult to answer for patients or parents/caregivers. In addition, the majority of the included instruments were relatively easily accessible by website and could be filled in quickly (<10 min).

Limitations

This review was designed to capture all behavioural and psychosocial instruments currently used in cross-sectional and longitudinal studies. As a consequence, potentially good instruments used in studies with other designs (e.g. case-report or conference abstracts) have been excluded. For instance, the MDCHILD could not be included in the current review, since no information was available on psychometric properties.[19] Furthermore, we excluded studies with possible adequate instruments when no separate information was available for the dystrophinopathy population. Excluded studies, for instance, used the Autism Diagnostic Interview-Revised,[9] Experience Sampling Method,[81] California Psychological Inventory,[82] Personal Assessment Inventory-Depression,[82] Child Health Questionnaire-Child form-87,[83] Multidimensional Scale of Perceived Social Support (Wilson et al. 2006), Quality of Life Profile Questionnaire,[84,85] and Strips of Life with Emoticons Questionnaire[86] in patients with other neuromuscular disorders (e.g. spinal muscular atrophy, myopathy, and giant axonal neuropathy). An important strength of our study is the use of the psychometric property criteria. However, at the same time this approach limits the finding of

adequate instruments. Previous studies, for instance, used less stringent criteria to assess inter-rater reliability between the informant-rating and self-rating form of the PedsQL GM and PedsQL NMM.[14,42] Despite the less stringent criteria, the outcomes of Davis and colleagues[42] and Uzark and colleagues[14] were in line with the findings of the current review concerning the poor inter-reliability between the informant-rating and self-rating form of both PedsQL modules. Furthermore, for final evaluation, we excluded studies that reported no information on psychometric properties, content validity, and applicability for the dystrophinopathy population. Therefore, all BMD studies were excluded and generalizations of our results regarding the entire dystrophinopathy population should be made with caution. Additionally, the MDCHILD could not be included in the current review, since no information was available on psychometric properties for the dystrophinopathy population.[19]

Clinical recommendations

The current review provides no gold standard for methods of assessment, but based on the findings the PARS-III, LSIA, and PedsQL GM can be valid instruments for screening of psychosocial problems in DMD. Nonetheless, when using the PedsQL GM we recommend to administer both the informant-rating and self-rating form, to limit the error variance caused by disagreements between patients and parents/caregivers perspectives.
Appropriate instruments for screening of behavioural problems in DMD may be the SDQ for paediatric patients, and the GAD-7 and PHQ-9 for adult patients. Additional research on psychometric properties of these instruments for DMD as well for BMD is crucial, and definite outcomes of these screening instruments should be considered with caution.

For definite diagnostics, we recommend to use the gold standard assessment method for behavioural disorders. This is referred to as the multi-method, multi-source, multi-setting assessment and implies using different assessment methods (e.g. behavioural observations, structured clinical interviews, informant-ratings, and self-ratings), different sources (e.g. patients, parents/caregivers, teachers, clinicians), and different settings (e.g. at home, school, the clinic) to get a comprehensive representation of the child's or adolescent's behavioural, emotional, and psychosocial functioning.[87] We believe that this method is particularly important for the ageing high-risk dystrophinopathy population, whereof 20% of patients have more than one comorbid behavioural disorder.[5,8.9,11-14] This multi-method-, source-, setting assessment reduces error variance, resulting in less under-identification of behavioural comorbidities in this

high-risk population. Each neuromuscular team should include a mental health professional (psychologist or psychiatrist) with experience in neurodevelopmental, behavioural, and medical conditions, who routinely screens a patients' behavioural and psychosocial functioning every 2-3 years and applies this multi-method-,source-, setting assessment when necessary for definite diagnostics.[16] Adequate and early detection of behavioural comorbidities can greatly facilitate targeted treatment. We know, for instance, that in the general ADHD population, underdiagnosed ADHD problems put patients at higher risk for educational underachievement, behavioural comorbidities like depression, impairments in social relations, and a reduced quality of life, that can extend throughout adulthood.[88-90] According to our review, only one previous DMD study applied this multi-method-, source-, setting assessment using the DSM-IV criteria together with two screenings instruments, the Conners Parent and Conners Teacher Rating Scales, to diagnose ADHD comorbidity in their DMD sample.[8] Two additional studies administered this method partly and evaluated behavioural problems using structured interviews such as the DAWBA, ADOS, and 3Di-Sv in addition to multiple informant-rating and self-rating instruments.[11,18]

Conclusion

The present review describes a wide variety of instruments used to assess behavioural and psychosocial functioning in the dystrophinopathy population. We argue that the interpretation of behavioural disorders and psychosocial problems as reported in previous studies using these instruments should be taken with caution. Our review shows that for psychosocial screening, the PARS-III, PedsQL GM, and LSIA can be valid. For behavioural screening, the SDQ, GAD-7, and PHQ-9, may be appropriate. Other screening instruments that are valid and appropriate for the dystrophinopathy population may be used as well, but their outcomes should be considered with caution. Additional psychometric data on instruments for screening of behavioural and psychosocial functioning of the dystrophinopathy population is necessary. Since the ageing dystrophinopathy population is confronted with long-lasting or new mental health issues that negatively influence their quality of life. A mental health professional should routinely screen a patient's behavioural and psychosocial functioning, preferably every 2-3 years and particularly during transitioning (e.g. childhood to adolescence and adolescence to adulthood). For definite diagnostics, we believe that a that a multi-method-, source-, setting assessment is the most appropriate method of assessment in this unique population. Given the complexity of behavioural comorbidities, clinicians

and researchers should never diagnose conditions based on the result of one screening instrument.

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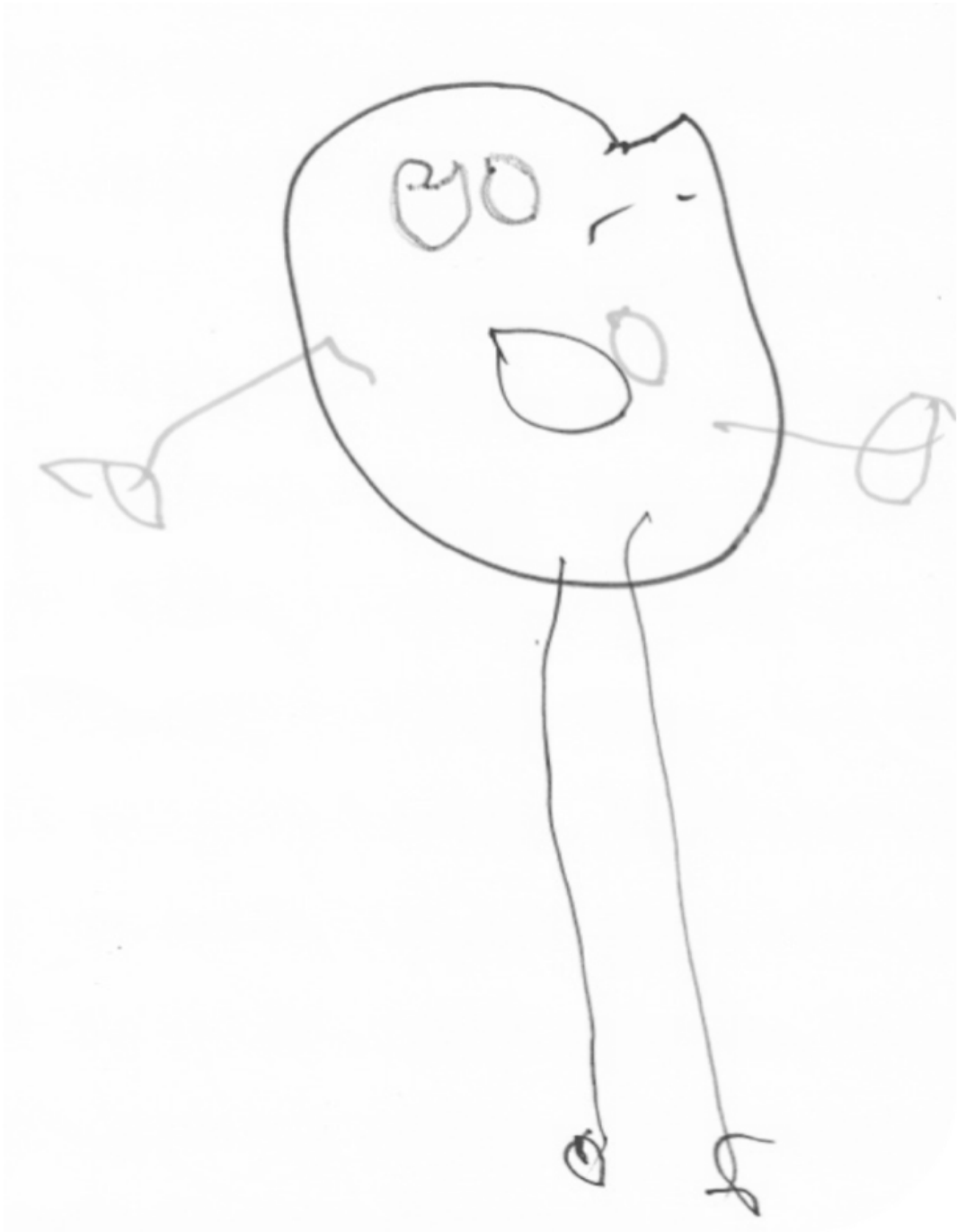

Chapter 7

Computerized working memory training in males with Duchenne muscular dystrophy: a single case experimental design study

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Abstract

Learning disabilities (LDs) and working memory problems (WM) are common brain-related comorbidities in Duchenne muscular dystrophy (DMD). Despite growing evidence on the efficacy of computerized WM training in children with LDs, research in DMD is lacking. This study assessed whether (1) computerized training improves dystrophin-associated verbal WM problems of DMD patients, (2) effects of training are present immediately at post-intervention, at 3 and 8 months follow-up and (3) training improves problems that arise from their LDs. Four DMD patients with LDs and WM problems completed multiple cognitive tests of verbal and visual WM, academics, attention, processing speed and fluid reasoning. Parents and teachers completed executive behavioural questionnaires. Tests and questionnaires were administered at baseline, post-intervention, 3 and 8 months follow-up. A single case experimental design (SCED) additionally evaluated decreases in WM problems of patients based on parent reports. Short and long-term, near-and far transfer effects were found for verbal and visual WM, academics, processing speed and fluid reasoning. Parent and teacher questionnaires showed minimal changes. SCED results showed positive effects on WM. Promising WM training results are shown in DMD that merit further research. SCED is a useful methodology for DMD intervention studies and gives valuable information on cognitive changes.

Introduction

WM is a limited capacity system that temporarily stores, rehearses and processes internally-held information.[1] It is regulated by several (sub)cortical and cerebellar regions.[2-4] WM has an important role in the guidance of everyday behaviour and in performing complex tasks such as learning, comprehension, reasoning and planning.[1,5,6] Traditionally, WM was viewed as a fixed system, but there is increasing evidence that it can be improved by educational support and interventions such as (computerized) WM training.[7-12] Training of WM increases brain activity in (sub)cortical areas e.g. in the basal ganglia and frontoparietal regions and networks.[2-4] The effect of WM training on neuronal bases remains poorly understood. However, changes in white matter structure (increased myelination) and dopamine D1 receptor density have been demonstrated recently.[2,12] Transfer of WM training can be evaluated by assessing near effects (WM related abilities) and far effects (other cognitive abilities, academic skills and behavioural changes). Reliable near and far transfer effects have been described in children with learning disabilities (LDs) or attention-deficit hyperactivity (ADHD) disorders, particularly in the older ones (≥10 year) [9-11,13,14] Short and long-term near and far transfer effects are found for verbal and visuospatial WM, academic skills (reading, arithmetic abilities, spelling, word decoding) and fluid reasoning.[5,7,9-11,13,15,16] Studies using the computerized program Jungle Memory™ displayed the highest effects, especially in visuo-spatial abilities.[9] It is valuable to evaluate whether remediation tools as (computerized) WM training are also beneficial for patients with Duchenne muscular dystrophy (DMD) and a comorbid LD with WM deficiencies.

The recessive X-linked neuromuscular disorder DMD, is caused by mutations in the dystrophin-encoding (*DMD*) gene leading to functional loss of the full-length dystrophin protein (Dp427) in various tissues including muscles and the brain.[17] A lack of dystrophin in muscles causes progressive muscle weakness, which eventually leads to fatal respiratory and cardiac complications.[18,19] In the brain, dystrophin ($Dp427_B$) is localized in the hippocampus, amygdala and the cerebral cortex with a slightly higher expression in the temporal and frontal cortex than in the parietal and occipital cortex.[20-23] In addition to $Dp427_B$, shorter brain isoforms exist i.e. Dp140 and Dp71/Dp40.[20,24,25] Depending on the mutation location in the *DMD*-gene the expression of these shorter isoforms are prohibited. Deficiencies of the brain isoforms result in functional and structural alterations in neurons and glial cells and these have been related to the presence of non-motor comorbidities in patients with DMD including neurocognitive impairments, behavioural disorders and epilepsy.[20,21] For instance in hippocampal neurons dystrophin alters γ-aminobutyric acid type A ($GABA_a$) receptor

functions at inhibitory synapses and glutamergic functions at excitatory synapses.[20,21,26] The malformations and dysfunctions of synapses in crucial neural networks of the hippocampus, likely induce the core impairments in verbal WM or span capacity of patients with DMD.[26] WM deficiencies have been related to the frequently observed LDs in DMD.[27-32] High prevalence rates of verbal LDs such as dyslexia or reading disabilities and non-verbal LDs for instance dyscalculia or arithmetic disabilities have been found.[29,33-36] Reading impairments for example are reported in up to 40% of males with DMD.[27,33-36] Due to the deficient dystrophin effects on neuronal structures and networks involved in cognition (e.g. WM) one might expect that WM training is less effective in DMD patients. Thereby, this study aimed to explore whether (1) computerized training may also improve WM in DMD patients with dystrophin-associated verbal WM problems, (2) effects of the computerized WM training are present immediately at post-intervention and remain at 3 and 8 months follow-up (FU) and (3) WM training improves problems that arise from the comorbid LDs of patients with DMD.

Materials and methods

Participants and procedure

Five male patients with a genetically confirmed diagnosis of DMD attending the outpatient clinic of Kempenhaeghe, Centre for Neurological Learning Disabilities (CNL), Heeze, The Netherlands were asked to participate. Patients had comorbid LDs including reading or arithmetic disabilities, dyslexia, dyscalculia and/or ADHD, which were previously diagnosed by health professionals. Between September 2016 and October 2017, these patients underwent an extensive re-evaluation of cognitive and behavioural functioning on the indication of regular clinical care at CNL. Thereafter, patients were approached by the child neuropsychologist (JH) and child neurologist (SK) for participation in the current study. Inclusion criteria were: (1) age of 10-16 years, (2) intellectual quotient (IQ) score of $\geq$70 to exclude mental retardation, (3) WM problems indicated by z-scores $\geq$-1, (4) intact physical mobility of upper extremities represented by a Brook score $\geq$5, (5) no hearing or vision problems that could interfere with the computerized training or neurocognitive testing, (6) undergoing no other psychological or cognitive interventions, (7) no use of psychostimulants, and (8) having an adequate proficiency in Dutch. Ethical approval was given by Kempenhaeghe Ethics Committee (project number 18.04). Written informed parental and patient consent

were obtained. The study was conducted in accordance with the 18th World Medical Assembly, Helsinki 194.

Study design

The present study consisted of different testing phases (see Figure 7.1). At baseline (T1) patients completed a short battery to estimate IQ, verbal and visual working memory, sustained attention, processing speed and academic skills (reading and arithmetic). In addition, parents and teachers completed questionnaires on executive functioning (Q1). After T1 and Q1, patients and parents jointly received psycho-education on WM and its relation to learning and academic development. Additionally, after T1 a single case experimental design (SCED) i.e. a multiple baseline across patients method was established (see Figure 7.1). The SCED consisted of a baseline period (phase A1), intervention period (phase B1) and follow-up period (phase A2). The baseline period (phase A1) of the SCED, started directly after the baseline cognitive assessment (T1) and the psycho-education. Phase A1, lasted a minimum of three and maximum of nine weeks depending on randomisation outcomes (see Figure 7.1). Simple randomisation (digital dice-throwing) determined whether the patient started with the intervention (Phase B1) in week 4,5,6,7,8 or 9 (see Figure 7.1). Each dice number represented a starting week (e.g. dice number one represented start week 4). The intervention lasted eight weeks in total and took place between week 4 to 17 (see Figure 7.1). After the intervention, the follow-up period started (Phase A2) between week 12 to 20, which lasted three weeks in total (see Figure 7.1). In addition, patients underwent neurocognitive testing (T2) at home and completed the same cognitive battery as at T1, without IQ estimation (see Figure 7.1). At 3 (T3) and 8 months (T4) follow-up, patients completed the same short cognitive battery of T2 at home (see Figure 7.1). Furthermore, at T2, T3 and T4, parents and teachers completed the same questionnaires on executive functioning as at T1 (see Figure 7.1).

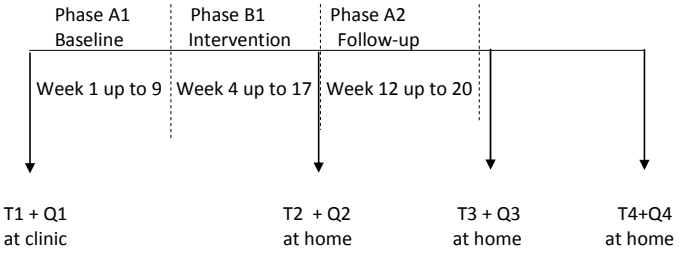

Figure 7.1 *Study design. T=neurocognitive testing, Q=questionnaires for parents and teachers,* Phase A1 = baseline period with a minimum of 3 weeks and maximum of 9 weeks; Phase B1 = intervention period of 8 weeks; Phase A2 = follow-up period of maximum three weeks.

Measures

Demographic and disease-related parameters were extracted from the electronic patient files. Extracted parameters were age, educational level (i.e. regular or special education), handedness, *DMD* gene mutation, comorbid LD diagnose, IQ and memory scores of previous neurocognitive testing between September 2016 to October 2017.

Cognitive and academics testing at T1, T2, T3, and T4

General intellectual functioning was estimated using the Peabody Picture Vocabulary test-III (PPVT-III-NL), which is a commonly used non-motor test in DMD.[28,37] Raw scores were standardized to age-related norm scores (Mean=100, SD=15).[37] Subtests of the Wechsler Intelligence Scale for Children-fifth edition (WISC-V-NL) were used to assess verbal working memory (Digit span and Letter-Number Sequencing), visual working memory (Picture span), fluid reasoning (Matrix Reasoning) and processing speed (Symbol Search).[38] Test-retest reliability of the subtests vary from moderate to high (Digit span =.79, Letter-Number sequencing =.68, Picture span =.60, Matrix Reasoning =.53 and Symbol search =.73).[38] Sustained attention was tested by the subtest Score! of the Test of Everyday Attention for Children, Second Edition (TEA-Ch-II) and its test-retest reliability is moderate (.64).[39,40] Technical reading was evaluated by the Dutch Continu Benoemen & Woorden Lezen (CB&WL) test using the subtests monosyllabic word reading and the EMTB-T50 score. Words of these subtests are not coherent and differ in length and complexity. Based on the EMTB-T50 score a one-minute reading score was calculated as well. Raw scores of the reading tests were based on the total number of words read correctly. Test-retest reliability of the reading subtests are high (range: .90-.91).[41] Raw scores of the WISC-V, TEA-Ch and CB&WL were transformed to standardized scaled scores (Mean=10, SD=3), based on age-adjusted norm data as specified within the test manuals.[38,39,41] The Tempo Test Automatization (TTA) was used to evaluate the degree of memorization of mathematical facts. The TTA consists of four pages of 50 arithmetic problems including one page of addition problems, subtraction problems, multiplication problems and one page of division problems.[42] Scores are based on total number of arithmetic problems answered correctly (range 0-50).[42] The addition and subtraction scores can be computed to calculate a first total score (tta). Scores of all four subtests result in a second total score (TTA). Test-retest reliability of the total TTA scores are high (range: .82-.83).[42]

Behavioural testing at T1, T2, T3, and T4

The Behaviour Rating Inventory for Executive Functions questionnaire for parents (BRIEF-P) and for teachers (BRIEF-T) evaluated executive functioning based on two

indices: Metacognition index (MCI) and Behavioural Regulation Index (BRI).[43] The two indices are assessed by eight subscales: Inhibit, Shift, Emotional control, Initiate, Working Memory, Plan-organize, Organization of Materials and Monitor. A global executive score (GEC) can be computed based on the MCI and BRI outcomes.[43] Parents and teachers rated items using a three-point Likert scale (1= never a problem to 3=often a problem).[43] Higher scores reflected greater difficulties in executive behaviour and abilities. Previous studies described high test-retest reliability for the BRIEF-P for MCI (ICC=.84), BRI (ICC=.95) and GEC (ICC=.86), and for the BRIEF-T for MCI (ICC=.74), BRI (ICC=.76) and GEC (ICC=.77).[43] Raw scores of the BRIEF-P and BRIEF-T were transformed to age-adjusted normative data (T-scores with Mean=50 and SD=10).[43]

SCED: Multiple baseline design measurement

Throughout the baseline period (Phase A1), the intervention period (Phase B1) and the follow-up period (Phase A2) parents digitally completed the WM subscale of the BRIEF-P. The 10-item WM subscale consisted of questions such as “my son has troubles with chores or tasks that have more than one step” or “my son has troubles remembering things, even for a few minutes”.[43] Items were digitally rated on a three-point Likert scale from: 1=never to 3=often, with higher scores representing more difficulties with WM.[43] The minimum total score of this ten-item WM subscale was 10 and the maximum score was 30. It has previously been proven that the internal consistency and test-retest reliability of this subscale is high (Cronbach’s alpha =.90, ICC=.73).[43]

Psychoeducation

Patients and parents jointly received standardised psycho-education on the role of WM problems in daily life during visits at the outpatient clinic of CNL. The information was given by psychologists who were trained Jungle Memory coaches (DH/JW). The following aspects were explained: 1) what is WM? 2) when do you use your WM? 3) what is the importance of good WM? 4) what happens when you have WM problems and (5) what is the goal of the computerized Jungle Memory ™ training and how does this program work? These aspects were written down in a WM sketchbook that was specifically developed for the patients of the current study. This workbook also consisted of pen and paper games on the abovementioned aspects. For example, patients had to read and rehearse information, make puzzles, or perform dual-tasks to learn the functions of WM.

Intervention

Jungle Memory™ (2008) is a web-based WM training program aimed at children aged 7-16 years.[11] This program comprises of three interactive computer games with up to 30 levels of difficulty in each game. Different aspects of WM are trained during each game and children are provided with regular feedback on their progress. Game 1 (Quicksand) involves memory for and later use of word endings, game 2 (Code Breaker) involves mental rotation of letters and game 3 (River Crossing) involves sequential memory of mathematical solutions.[11] The program includes motivational features such as positive verbal feedback, display of patients scores, percentile rankings and the number of monkey's collected as a result of successful completion of training levels.[11] Each game consisted of a maximum of ten trials per training session, leading to a total performance of 30 trials on each day of training. Each training session lasted approximately 15-20 minutes. Patients in the current study used the program four times a week leading to 96 sessions (32 sessions per game) that were completed over an eight-week period of training. Treatment fidelity was monitored by (1) parent supervision, (2) weekly sessions with the Jungle Memory coaches (DH/JW), and (3) log data that was generated from the training program. Each time a patient logged in and completed all 10 trials for the three games, the program recorded their participation in a database log. The Jungle Memory coaches (DH/JW) weekly reviewed the log files to verify compliance of patients.

Statistical analyses

Demographic, disease-related characteristics and previous neuropsychological testing results on memory of patients were analysed using descriptive statistics. Age-related norm data of the cognitive and behavioural tests were transformed to z-scores (mean=0, SD=1). Reliable change indices (RCI) were calculated to detect clinical significant individual changes on cognitive and behavioural outcomes between 1: baseline (T1) versus post-intervention (T2), 2: baseline (T1) versus three months follow-up (T3), 3: baseline (T1) versus eight months follow-up (T4). An RCI value of z=-1.96 or z=+1.96 was used as criterion for a clinical significant change.[44, 45]

For SCED, the study size was determined on the following formula: p=1/(6*6*6)=0.005, reflecting that effects found attribute to p<.05.[46] This calculation is based on the random assignments of at least n=3 patients who could start with the intervention at six different time-points, namely at week 4,5,6,7,8 and 9. Data of the SCED (multiple baseline measurements) were plotted graphically using R to visually assess a change in WM outcomes during and after the intervention. In addition, Tau-U weighted effect sizes were calculated to determine significant clinical differences between phase A1,

phase B1 and phase A2 for each patient (i.e. phase contrast differences). Tau-U scores ranged from -1 to +1, with positive scores indicating more WM difficulties and negative scores reflecting less WM difficulties. Tau-U effect sizes were defined as: 0-0.62=small, 0.63-0.92=moderate and 0.93-1.00=strong.[47,48] To calculate Tau-U weighted effect sizes an online calculator was used: www.singlecaseresearch.org/calculators/tau-u.[47,48] P-values at the .05 and .01 (two-sided) were considered statistically significant.

Results

Training compliance

Five patients were included of which four completed the entire study. One patient dropped out during the last week of the intervention period, because he was admitted to the hospital for medical problems. The eight-week training period of the four remaining patients was not interrupted by holidays or other activities. The database log for compliance showed that only case 2 trained twice instead of four times at his second week of the intervention, for which we contacted parents to inquire whether they experienced any problems during the training. No problems were reported and parents likely inappropriately closed the training sessions.

The characteristics of the four included patients are displayed in Table 7.1. Three patients (case 2, 3 and 4) visited special education and one (case 1) visited regular education, but received special educational support for his LD. The included patients had reading disabilities, arithmetic disabilities and WM problems (z-scores ranged from -1.3 to -2.3; see Table 7.1). Two patients (case 2-4) were also diagnosed with ADHD. Previous neuropsychological data on long-term memory was available of three patients (case 1,3,4) of which none displayed deficits in this domain.

Table 7.1 *Patient characteristics.*

Case	Age	Genetic mutation	Handedness	Education	IQ	Brooke score	Working memory	Long-term memory
1	12,4	Deletion exon 22-44	R	Regular	84	3	-1.3	-0.5
2	11,2	Deletion exon 51-54	R	Special	95	1	-1.5	-
3	15,7	Deletion exon 45-52	R	Special	94	2	-1.9	+1.3
4	12,1	Deletion exon 52	L	Special	101	3	-2.3	-0.8

Working memory and long-term memory outcomes are z-scores, IQ=intelligence quotient score, R=right, L=left. Brooke scores ranges from 1-6 (1=intact arm/hand function and 6=no useful function of hands).

Evaluation and feedback of patients and parents

The eight-week intervention period was time-consuming and regularly frustrated patients when training levels increased in difficulty. Though their overall experience was positive. Case 1, 3 and 4 experienced improvements in daily life functioning i.e. at home or school during and after the intervention. For instance case 1 and case 4 noticed faster completion of school exercises, whereas case 3 reported less word-finding difficulties during spontaneous conversations.

Cognitive and academic testing outcomes

Table 7.2 displays the outcomes of the multiple cognitive testing measurements. Baseline (T1) results showed that the estimated intelligence indicated by the PPVT-III-NL ranged between 83-108 (see Table 7.2). At post-intervention (T2), results showed reliable improvements on simple verbal working memory task (Digit span; n=1), dual-tasks of verbal working memory (Letter-Digit span; n=2), academic skills of reading (n=4) and arithmetic (n=1), processing speed (n=4) and fluid reasoning (n=1), see Table 7.2. At 3 months follow-up (T3), reliable improvements were still found on dual-task of verbal working memory (n=1), academic skills of reading (n=3) and arithmetic (n=1), processing speed (n=4) and fluid reasoning (n=1), see Table 7.2. In addition, one patient (case 1) showed improved performances on visual working memory when his T3 outcome was compared to his baseline performance, but this improvement was not found at T2. At 8 months follow-up (T4), reliable improvements were yet found on dual-task of verbal working memory (n=1), academic skills of reading (n=2) and arithmetic (n=1), processing speed (n=4) and fluid reasoning (n=1), see Table 7.2. Furthermore, on dual-tasks of verbal working memory two patients (case 1 and 4) performed better at T4 compared to T1, but this effect was not noticed at T2 or T3. Some patients also displayed reliable significant decreased performances instead of improvements on visual working memory (case 2) and arithmetic (case 1 and case 3), see Table 7.2. For case 2, no total math score could be calculated because he was not able to complete divisions due to his LD. On T2, T3, and T4, all cases showed no reliable changes on sustained attention.

Table 7.2 *Cognitive and academic outcomes of testing.*

	Case 1				Case 2				Case 3				Case 4			
Variables	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
Estimated IQ	108				84				83				101			
Verbal WM																
Digit span	-2.0	**0.0**[a]	-1.3	**-0.3**[c]	-2.3	-2.3	-2.0	-2.3	-0.3	-0.3	-0.3	-0.3	-2.0	-2.0	-2.0	-2.3
Letter-Digit	-1.7	-1.3	-1.3	**-0.7**[c]	-2.0	-2.0	-1.7	-2.3	-2.0	**0.0**[a]	**-0.3**[b]	**0.3**[c]	-2.7	**-1.7**[a]	-2.3	**-1.7**[c]
Visual WM	-1.4	-1.0	**-0.7**[b]	-1.3	-1.7	-1.4	**-2.3**[b]	-1.3	-1.0	-1.7	-1.7	-1.3	-1.4	**-2.0**[a]	-1.0	**-1.7**[c]
Reading																
WR	-1.7	**-0.7**[a]	-1.7	-1.7	-2.3	-2.7	-2.3	-2.3	-3.0	-2.7	-2.7	-3.0	-2.0	-1.7	-1.7	-1.3
OMT	66	**70**[a]	**72**[b]	67	27	**32**[a]	**34**[b]	**50**[c]	49	**57**[a]	**55**[b]	47	47	**55**[a]	45	**56**[c]
Arithmetic																
t	65	62	62	68	25	23	28	**42**[c]	49	**36**[a]	55	43	30	39	**43**[b]	**46**[c]
T	109	**96**[a]	**91**[b]	109	NA	NA	NA	NA	78	**57**[a]	81	72	40	**54**[a]	**56**[b]	**62**[c]
Speed	0.0	**1.3**[a]	**1.3**[b]	**1.6**[c]	-2.7	**-1.7**[a]	**-0.7**[b]	**-2.3**[c]	-2.0	-2.3	**-1.0**[b]	**-1.3**[c]	-1.7	**-0.3**[a]	**1.0**[b]	**0.3**[c]
Attention	0.3	-0.3	0.3	-0.3	-1.3	-2.0	-1.7	-0.3	0.0	0.0	0.0	-0.6	-3.0	-3.3	-3.3	-3.0
Fluid Reasoning	0.7	**-0.7**	0.0	-0.3	-2.3	-2.3	-2.0	**-1.7**[c]	-2.0	**1.3**[a]	**1.3**[b]	**-0.3**[c]	-1.0	0.0	-1.0	-0.7

Arithmetic and OMT reading scores are raw scores, higher scores reflect better performances. Other results are z-scores (mean=0, SD=1), with higher scores reflecting better performances. WR=word reading scores of the CB&WL, IQ=intelligence quotient, OMT=One Minute Reading test raw scores, t=total raw score of additions and subtractions of the TTA task, T=total scores of additions, subtractions, multiplications, and divisions of the TTA task. NA=not available, total score could not be calculated for this patient due to an inability to complete the speeded task on divisions, TTA=Tempo Test Automatization. [a] clinical reliable change between baseline (T1) and post-intervention (T2); [b] clinical reliable change between baseline (T1) and 3 months follow-up (T3); [c] clinical reliable change between baseline (T1) and 8 months follow-up (T4); Clinical reliable change was determined by a Z-score=-1.96 or +1.96[32].

Behavioural testing outcomes

Table 7.3 displays the scores of the multiple behavioural testing measurements. Results of the testing showed reliable improvements on the BRIEF subscale MCI and total BRIEF GEC score at post-intervention (T2) based on parent reports in one patient (case 2; see Table 7.3). At 3 months follow-up (T3), reliable changes on the subscales MCI, BRI and total score GEC were documented for case 2 (see Table 7.3). In addition, improvements on BRI and total score GEC were also reported for case 3 (see Table 7.3). At 8 months follow-up (T4), parent reported changes on MCI and total GEC were still noticed for one patient (case 2). No reliable changes were reported by teachers for all patients on the BRIEF subscales MCI, BRI and the BRIEF total scale GEC (see Table 7.3).

Table 7.3 *Behavioral outcomes of parents and teachers.*

	Case 1				Case 2				Case 3				Case 4			
Variables	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
BRIEF-P																
MCI	-0.2	-0.4	**-0.9**[b]	**-1.1**[c]	1.7	**-0.6**[a]	**-1.0**[b]	**-0.3**[c]	-0.9	-0.7	-1.4	-1.1	-0.8	**0.2**[a]	-0.3	-0.4
BRI	-0.4	-0.6	-0.6	-1.0	1.4	0.5	**-0.7**[b]	0.7	1.5	1.3	**0.1**[b]	0.9	0.6	0.6	0.2	0.7
GEC	-0.3	-0.2	**-0.9**[b]	**-1.2**[c]	1.8	**-0.2**[a]	**-1.0**[b]	**0.1**[c]	-0.1	-0.1	**-1.0**[b]	-0.5	-0.3	0.4	-0.1	0
BRIEF-T																
MCI	-0.7	-1.0	-1.0	-0.9	1.1	1.1	1.3	1.7	-1.4	-1.4	-1.4	-0.5	0.9	1.4	1.3	**1.7**[c]
BRI	-0.5	-0.4	-0.4	-0.1	1.8	1.8	1.8	2.1	0.1	0.1	-0.4	0.5	0.3	-0.1	-0.1	1.0
GEC	-0.7	-0.8	-0.8	-0.6	1.5	1.5	1.4	2.0	-0.9	-0.9	-1.1	-0.1	0.7	0.8	0.7	**1.5**[c]

BRIEF outcomes are z-scores with higher (positive) scores reflecting more difficulties. BRIEF-P=Behavior executive functioning questionnaire for parents, BRIEF-T= Behavior executive functioning questionnaire for teachers. MCI=Meta cognition index, BRI=Behavioral regulation index, GEC=Global executive Composite, RCI= Reliable Change Index. [a] clinical reliable change between baseline (T1) and post-intervention (T2); [b] clinical reliable change between baseline (T1) and 3 months follow-up (T3); [c] clinical reliable change between baseline (T1) and 8 months follow-up (T4); Clinical reliable change was determined by a Z-score of -1.96 or +1.96[32].

SCED: Multiple baseline design measurement

The items of the BRIEF-working memory subscale were all administered by mothers of patients. Visual analysis showed that working memory functions of case 1 were approximately the same at baseline (Phase A1), during the intervention (Phase B) and after the intervention (A2) (see Figure 7.2). For case 2, case 3 and case 4 we visually observed a change on WM between Phase A1, Phase B and Phase A2 (see Figure 7.2).

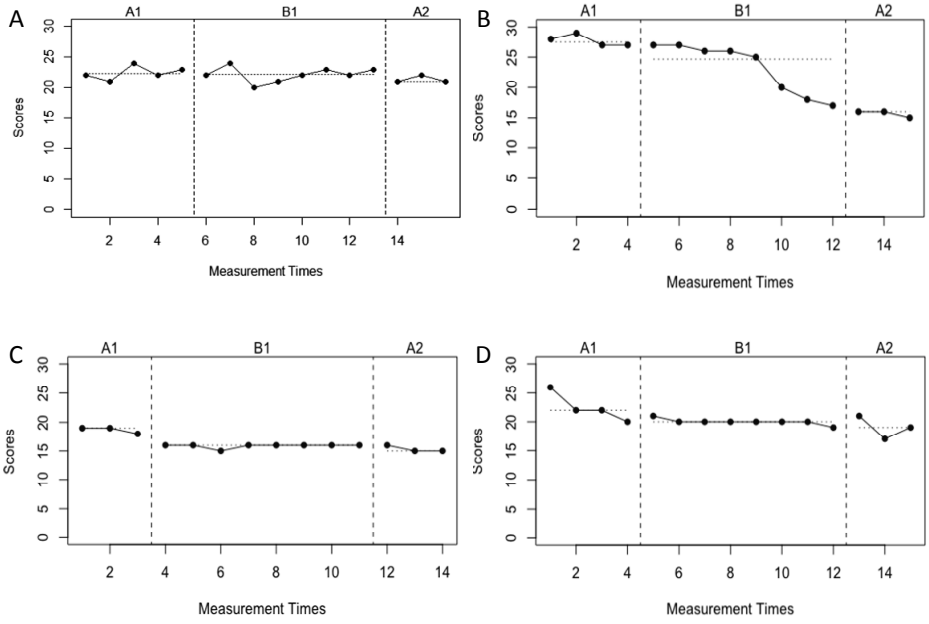

Figure 7.2 A-D *Visual analysis of multiple baseline measurement on WM problems reported by parents of included DMD males (N=4).* A1=baseline period, B1=intervention period, A2=follow-up. Scores are outcomes of BRIEF Working Memory subscale.

In addition to the visual analysis, Tau-U weighted effect sizes determined significant changes in reported WM problems by parents between the different SCED phases: A1, B1 and A2. Tau-U results showed small effects for case 1 and for case 4, moderate for case 3 and strong effects for case 2, see Table 7.4.

Table 7.4 *Multiple baseline design outcomes.*

Case	Tau-U effect size	p-value	CI 95%	
			Lower	Upper
1	-0.26	.323	-0.78	0.26
2	-0.93	.000**	-1	-0.40
3	-0.77	.007**	-1	-0.21
4	-0.55	.044*	-1	-0.14

Results are weighted averages of Tau-U effect sizes, CI 95%=95% confidence intervals. * p<.05 (two-sided); ** p<.01 (two-sided).

Discussion

In the present study, we evaluated whether (1) computerized training improves WM in males with DMD who have dystrophin-associated verbal WM problems, (2) effects of the computerized WM training are present immediately at post-intervention or remain at 3 and 8 months follow-up (FU) and (3) WM training improves problems that arise from the comorbid LD of males with DMD. Despite that the intervention was time-consuming for patients and parents, their overall experience was positive. Neurocognitive testing displayed short and long-term near transfer effects for verbal and visual WM. Short and long-term far transfer effects were found for academic tasks including reading and arithmetic, processing speed and fluid reasoning. Behavioural reports of parents displayed minimal improvements. Outcomes of SCED on WM showed positive small to strong significant effects of the intervention.

Outcomes of cognitive and behavioural testing

Near transfer effects were found immediately after the intervention for verbal WM in simple and dual-tasks. It is important to note that the features of the stimuli in training tasks were different from those of the verbal and visual WM tests, thus gains in WM are unlikely a consequence of improvements in test-taking skills. In addition, we found far transfer effects for academic skills of reading and arithmetic, as well as processing speed and fluid reasoning. Parents reported minimal improvements and teacher reports showed no improvements in executive behaviour. At 3 and 8 months follow-up, near transfer effects were found for verbal and visual WM. Far transfer effects on academic skills of reading and arithmetic, processing speed and fluid reasoning maintained. Parents reported again minimal improvements and teacher reports displayed no improvements in executive behaviour. Our near transfer effects on WM and far transfer effects in academic skills (e.g. reading, arithmetic abilities, spelling),

fluid reasoning (e.g. complex reasoning) are in line with previous studies in school-aged children with LDs or ADHD.[7,10,11,13,15,16] It has been suggested that WM training not solely improves WM related tasks (near effects), but also improves other non-trained domains. For instance, the Jungle Memory™ program includes no fluid reasoning task, but we found a reliable improvement in fluid reasoning in one patient, which is in line with the study findings of Jaeggi and colleagues.[7] WM may thus be a domain-general source and an important component for other cognitive functions.[8,13,49] However, generalizations of improvements to the context of daily life (e.g. at school) should be further investigated, particularly since we found no beneficial improvements reported by teachers. This is similar to the results of Klingberg et al. (2005) and Gray et al. (2012).[13,50] Furthermore, the cognitive outcomes of current study varied between patients and differed between testing measurements. For instance, at 3 and 8 months follow-up we noticed improvements that were not found immediately after the intervention. The delayed improvements may be caused by an 'expectancy' effect of patients on beliefs that training should positively influence WM, academic skills and other cognitive abilities.[8] The delayed follow-up improvements may also be explained by increased self-efficacy or increased motivation.[11,51] Another explanation for the delayed improvements is that in the meantime patients may have developed strategies such as rehearsal or visualization of information that improved their performances at follow-up.[52,53] It has been proven that use of memory skills positively impacts speed, efficiency, accuracy, and leads to more confidence in using WM related functions.[54]

SCED outcomes of reported working memory problems

The SCED visual analysis and Tau-U results of weekly reports on WM problems by parents of patients showed positive small to strong significant effects of the intervention, but parental bias could not be ruled out. Unfortunately, we had no weekly reports of other informants. This could have given valuable information, especially as a discrepancy in ratings between parents of DMD patients and other informants is shown previously.[55] Future studies should also evaluate reports of other informants i.e. patients or teachers and measure effects on academic skills in addition to WM to evaluate whether the training induce generalizations to school performances.

Efficacy of WM training in DMD

Despite that we found positive effects of WM training in a relatively small sample it is not clear whether the intervention will result in altered activity, plasticity and synaptic transmission in the subcortical areas and cortical areas which is shown in other populations.[2-4,56] Since in DMD, dystrophin deficiency alters neuronal excitability and

structural connectivity in hippocampal regions, as well as in the cerebral cortex. Future (fMRI) studies should elucidate whether WM training cause increased activity and alterations in the critical WM networks in patients with DMD. Furthermore, long-lasting effects of training on neuronal excitability and structural connectivity should also be investigated. Since in addition to the loss of neuronal dystrophin, potential contributory factors to DMD-associated cognitive dysfunctions are inflammatory immune mediators (i.e. cytokines such as IL-6, IL-1β, and TNFα).[26] In muscles chronic inflammation is a key symptom and contributory factor to the pathogenesis of DMD patients.[26] Inflammatory immune mediators exert neuronmodulatory effects on the hippocampus and have been linked to altered learning and formation of memories.[26] In this context, one may expect that the effects of WM training on neuronal excitability and structural connectivity are not long-lasting in DMD patients. Yet, there is no evidence that brain levels of neuromodulatory cytokines are altered in DMD.[26] Nonetheless, our explorative results show comparable near and far transfer effects compared to studies evaluating patient populations with LDs or ADHD without DMD.[7,10,11,13,15,16] We might speculate that dystrophin may not be involved in WM regions, networks and functions as previously expected. When this is the case similar effects of WM training are expected in patients with partially functional dystrophin, i.e. Becker muscular dystrophy. Though, another explanation for the comparable findings of our DMD sample may be that compensatory mechanisms create alternative networks when dystrophin is absent to at least partly compensate the shortcomings in WM.

Limitations and future perspectives

This first explorative study assessed whether DMD patients with LD and WM deficiencies benefit from computerized WM training. We determined our sample size based on SCED and for this design a small sample of clinical patients are sufficient to draw conclusions as power is based on the number of repeated measures instead of number of included patients.[57] We solely included patients aged 10-16 years whilst Jungle Memory™ is designed for the age range of 7-16 years and as WM grows over time it would be valuable to compare the benefits of training in different ages. Although it is stated that WM training is more beneficial in children aged 10 years or older, because of their insights in their deficits and needs, their increased attention abilities and semantic knowledge, and the more efficient use of memory strategies.[9,58] Furthermore, our patients were referred to the outpatient clinic CNL on the indication of learning, cognitive or behavioral problems. For this reason, these problems may be more prevalent or severe in our patients than in DMD patients in general, making our results likely less generalizable to the total DMD population. Finally, due to the long

duration of the study, patients may have changed from class or school between the neurocognitive and behavioural testing measurements. For instance, case 4 changed from primary to secondary school after his assessment at 3 months FU, making his teacher ratings at his latest testing (8 months FU) less reliable for comparison with previous outcomes. Additional studies are necessary to confirm and further evaluate near and far transfer effects of computerized WM training and in particular its generalizations to daily life at home and school.

Conclusion

Computerized WM training may be feasible for DMD patients a comorbid LD with WM problems. It appears to improve WM, academic skills and other cognitive domains for a longer period. However, it remains challenging to exclude influencing effects of motivation, increased self-efficacy, use of strategies and expectancy effects of training on performances. Decreases in WM problems reported by parents were solely found using repeated measures (SCED) suggesting that changes in cognition due to interventions such as computerized training cannot be appropriately measured with single measurement points. For a better understanding of generalization of training effects it would be valuable to repeatedly measure effects to academics and development and to evaluate training effects on brain activity and plasticity with fMRI imaging.

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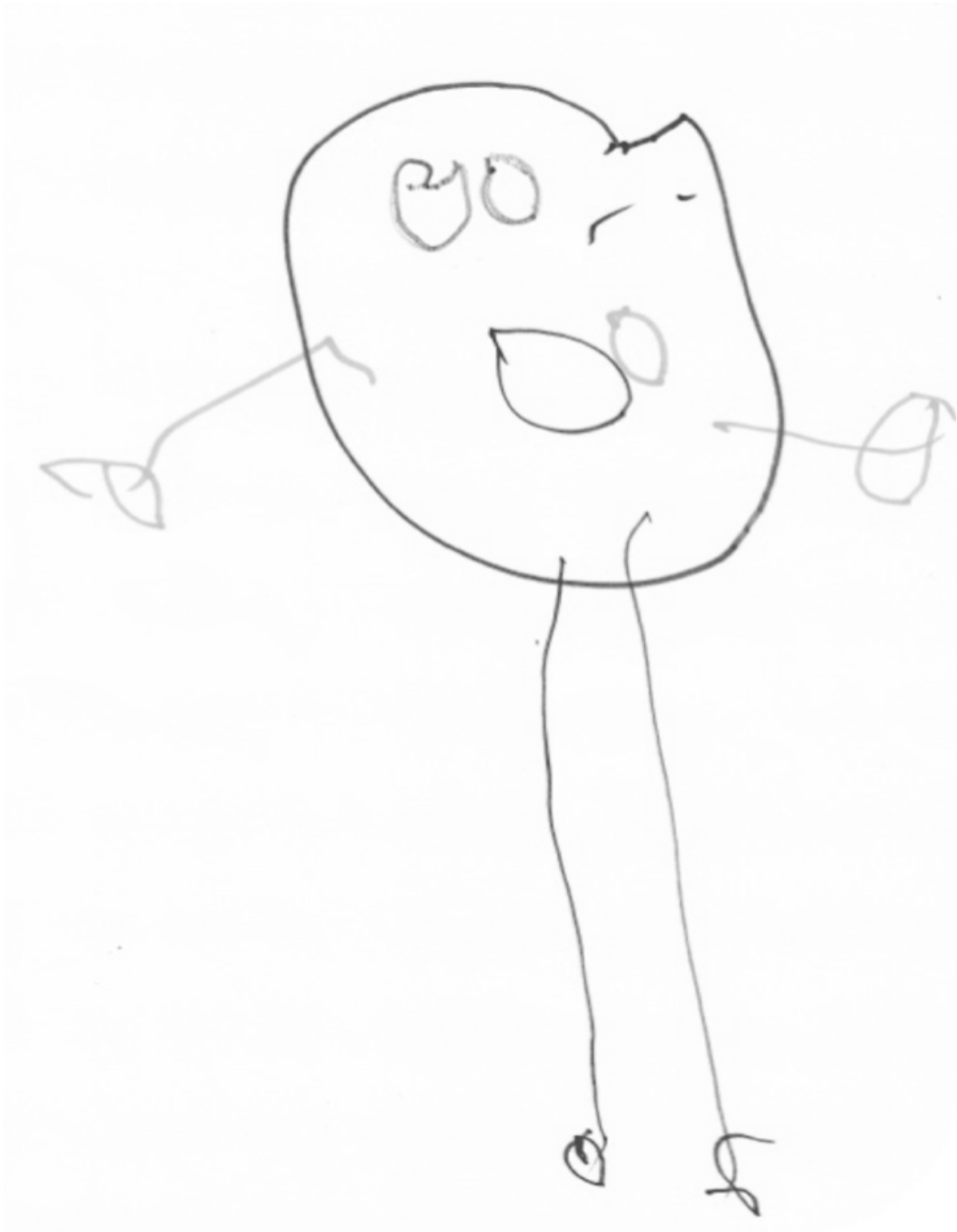

Chapter 8

Methylphenidate use in males with Duchenne muscular dystrophy and a comorbid attention-deficit hyperactivity disorder

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Abstract

Attention-deficit hyperactivity disorder (ADHD) is a common comorbidity in Duchenne muscular dystrophy (DMD). Until now, treatment with methylphenidate (MPH) has never been systematically assessed and described in this population. Our aim was to evaluate the effectiveness and safety of short acting MPH for learning problems in males with DMD and ADHD. Neuropsychological (cognition and behavior) and medical data of a sample of ten males (mean age=8.1 years, range 6.3-9.8) with DMD and an ADHD diagnosis was retrospectively analyzed at baseline (T0; without MPH), short-term follow-up (T1; with MPH; mean interval T0-T1=8.3 months, range 4.3-15.6), and long-term follow-up (T2; mean interval T1-T2=23.1 months, range 2.6–77.7). An initial MPH dose of 5mg/day was given on school mornings, with an increase of 2.5-5 mg/week depending on individual tolerance and treatment response, until a sufficiently effective dose was reached (range 0.2–0.6 mg/kg/day). At T1, results demonstrated an improvement in attention (i.e. concentration, impulsivity, and distractibility) in four patients. Suboptimal effects were reported in four patients, and no effects in two patients. At T2, seven patients showed considerable improvement in attention. No major side effects were reported. Overall, our data show that short acting MPH can be clinically effective for learning problems in males with DMD and ADHD, with regular cardiac follow-up, and close monitoring of side effects, and neuropsychological effects. Furthermore, this underscores the importance of the use of validated cognitive and behavioral measurements tools with adequate sensitivity to objectively evaluate the effect of MPH.

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked neuromuscular disorder with a prevalence of approximately 1 in 5,000 live male births.[1] It is caused by mutations in the *DMD* gene (*Xp21*) that encodes for the dystrophin protein, resulting in the absence of this protein. Absence of dystrophin generally results in characteristic progressive muscle weakness, and eventual fatal cardiac and respiratory complications.[2] In addition to the progressive muscle weakness, learning, neurocognitive, and behavioral disorders are common in DMD.[3-6] Particularly, high prevalence rates of attention-deficit hyperactivity disorder (ADHD; 32% versus 5.3% in the general population) have been described in DMD[5-7], and the milder variant Becker muscular dystrophy,[8] which often results in learning problems. Consequently, appropriate mental health screening (i.e. Strength and Difficulties Questionnaire (SDQ), and Personal Adjustment and Role Skills scale; PARSIII), neuropsychological assessment (cognition and behavior), and pharmacological treatment with stimulants or α-adrenoceptor agonists has been recommended for the diagnosis and treatment of ADHD comorbidity in DMD, as part of the recently updated international standards of care guidelines.[9] However, the optimum ADHD treatment in DMD is not well characterized, and the effectiveness of stimulants has not been systematically assessed and described in this population. Methylphenidate (MPH) has been shown to reduce ADHD symptoms (i.e. hyperactivity, impulsivity, and inattentive behavior), and improve associated behavior, academics, and social functioning in children, adolescents and adults without DMD.[10] In DMD, MPH prescription has been limited because of the presence of comorbidities, such as a cardiomyopathy[2] or epilepsy.[11] With regard to these comorbidities, sympathomimetic agents (i.e. MPH) could potentially provoke complications in these patients. Other potential side effects, such as motor tics, sleep or mood disorders have also been previously reported in neurological disorders.[12] Therefore, the evaluation of MPH is of great importance especially in this population. The present study reports for the first time a systematic medical and neuropsychological evaluation of MPH treatment in ten patients with DMD and ADHD. Our aim was to evaluate the effectiveness and safety of short acting MPH for learning problems in males with DMD and a comorbid ADHD diagnosis.

Materials and methods

Participants

Reported subjects were males with DMD and a comorbid ADHD diagnosis attending the outpatient clinic of the Kempenhaeghe Centre for Neurological Learning Disabilities, Heeze, The Netherlands. Subjects were included if they met the following inclusion criteria: (1) were males, (2) had a proven mutation of the dystrophin gene, (3) had a diagnosis of ADHD according to the DSM-IV criteria[13] (4) had medical and neuropsychological data of baseline and short-term follow-up, (5) received no other psychological interventions, except for psychoeducation, on baseline and follow-up, (6) did not use any psychostimulants on T0, and only MPH on T1, and (7) had an adequate proficiency in Dutch. Exclusion criteria were (1) an age younger than three or older than sixteen years at time of inclusion, and (2) physical immobility of upper extremities (hand and arm function), which may affect the neuropsychological test scores. Ethical approval was granted by Kempenhaeghe Ethics Committee and informed parental consent was obtained. The study was conducted in accordance with the 18th World Medical Assembly, Helsinki 194.

Study design

The diagnosis of ADHD was established by an experienced neuropsychologist (JH) and child neurologist (JV or SK) based on (1) the Diagnostic and Statistical Manual of Mental Disorders-IV criteria for ADHD,[13] (2) teacher and parents observations, and (3) an extensive neuropsychological assessment.[14] All subjects received an extensive medical (performed by treating cardiologist and child neurologist JV or SK), and neuropsychological work-up (performed by JH) as part of regular care at baseline (T0). Medical work-up consisted of standard prescribing practices and guidelines with additional care considerations focusing on the general medical condition of each individual subject (i.e. disease status, cardiac status, medication interactions) based on the international standards of care guidelines for DMD.[9] Cardiac status was evaluated based on standard cardiovascular tract (hetero)anamnesis, blood pressure (BP), heart rate (HR), electrocardiogram (ECG) and non-invasive imaging (e.g. cardiovascular MRI; CMR), which were used to establish cardiac function, rhythm abnormalities, and to screen for underlying anatomical abnormalities that could affect cardiovascular health.[15] Neuropsychological work-up consisted of objective neurocognitive and behavioral assessment, and subjective behavioral observations. Treatment started after parents informed consent, and approval of the treating child cardiologist. All subjects were treated with short acting MPH on the indication of attention problems which

were most prominent during school resulting in learning problems. An initial dose of 5 mg/day was given in the morning before school, with an increase of 2.5-5 mg/week depending on individual tolerance, and treatment response, until a sufficiently effective dose was reached (range 0.2-0.6 mg/kg/day).[16] A second dose for the afternoon school program was given around 12.00 h in addition to the morning dose if needed based on good clinical practice. None of the subjects used MPH at home, on weekends or holidays. Since behavioral problems were not the main problem in this population, we did not prescribe the extended release MPH over time. Treatment effects and potential adverse effects were evaluated at short-term follow-up (T1), and long-term follow-up (T2) as part of regular care.

Assessments

For this study, behavioral assessment consisted of subjective behavioral observations from patients, parents, teachers, and the clinical team, and objective assessment using the Child Behavior Checklist-Attention Problems subscale (CBCL-AP). In line with the CBCL manual, t-scores greater than or equal to 63 were deemed to be in the clinical range.[17] A change in clinical range is defined as a clinically relevant effect. Neurocognitive assessment consisted of the Symbol Search subtest to measure processing speed. Raw scores were converted to standardized age-related scores (SS; with a range of 1-19, mean 10 and standard deviation (SD) of 3 in healthy controls).[18] In line with the Wechsler manual, a change in SS of 3 is defined as a clinically relevant effect. Full intelligence quotient (FIQ) was assessed by the Wechsler Intelligence Scale for Children-III.[18] Neuropsychological assessment was focussed on each individual request for help based on good clinical practice, and at least consisted of abovementioned assessment tools.

Statistical analysis

Descriptive statistics displayed frequencies and means (SD) of demographic and disease-related characteristics. Wilcoxon rank sum tests were used to assess difference between baseline and short-term follow-up of CBCL-AP and processing speed. Underlying assumptions were checked before carrying out actual analyses. Normality distributions of residuals were checked by visual inspection of histograms. All statistical analyses were carried out using SPSS version 24 for MAC OS X. Results were considered statistically significant if $p<.05$.

Results

Participants

Reported subjects were males with DMD and a comorbid ADHD diagnosis (mean age=8.1, SD=1.3, range 6.3-9.8 years). Intelligence quotient (IQ) as assessed by the Wechsler Intelligence Scale for Children-III[18] ranged between 66-118 (mean IQ=91.8, SD=17.6). Subject characteristics are summarized in Table 8.1. Within our clinical sample, subject 7 was previously diagnosed with absence epilepsy; he was seizure free with sodium valproate. Subject 9 had an oppositional defiant disorder, which was treated with dipiperon. Dyslexia was diagnosed in subject 10. Subjects 7-9 had problems with sleeping throughout the night at T0.

Table 8.1 *Subject characteristics and MPH effects (N=10).*

Subject	Age (years)	DNA mutation	MPH dose T1 (mg/kg/day)	MPH adverse effect	T0-T1 MPH effect	T1- T2 MPH effect
1	7	Deletion exon 8-13	0,5	Delayed sleep onset	+	+
2	9	Deletion exon 51-54	0,2	Delayed sleep onset	+/-	-
3	9	Deletion exon 49-50	0,3	NAE	+	+
4	9	Deletion exon 51	0,3	NAE	+	+
5	9	Deletion exon 52	0,3	NAE	+	+
6	6	Deletion exon 45 - 50	0,2	Delayed sleep onset	+/-	+
7	8	Out of frame exon 45-52	0,2	NAE	+/-	+
8	7	Deletion exon 58	0,2	NAE	+/-	+
9	7	Deletion exon 46-52	0,4	Delayed sleep onset	-	-
10	6	Deletion exon 48-54	0,3	Loss of appetite	-	-

mg=milligram, MPH=methylphenidate, NAE=no adverse effects, T0=neuropsychological baseline measurement, T1=neuropsychological short-term follow-up measurement, T2=long-term regular follow-up, +=subjective reported positive effect of MPH, +/-=subjective reported suboptimal effect MPH, -=subjective reported no effect MPH.

MPH effect at short-term follow-up

Mean time between T0 and T1 was 8.3 months (SD=3.4, range 4.3-15.6).

Medical effects

Medical monitoring data concerning BP, HR, height and weight (Body Mass Index) remained within the normal range for the evaluated age category. Regular cardiac follow-up showed no cardiovascular side effects. Additionally, no seizures were noted. Reported side effects consisted of a loss of appetite in subject 10, and delayed sleep onset (subjects 1-2, subject 6, subject 9), whereupon melatonin was prescribed in

subject 1 with success. Of the four patients who reported delayed sleep onset, one patient (subject 1) used a relatively high MPH dosage (0.5 mg/kg/day; maximum daily dose of 15 mg in two doses with latest administration time of 12.00 h).[19] One patient (subject 8) with problems sleeping throughout the night at baseline developed delayed sleep onset when using MPH. Two patients discontinued treatment due to a lack of effect (subjects 9-10).

Neuropsychological effects

At T1, patients, parents, teachers, and the clinical team observed an improvement in attention (i.e. concentration, impulsivity, and distractibility) in four patients (subject 1, subjects 3-5). Suboptimal effects - which were defined as starting, yet insufficient effects on attention - were observed in four patients (subject 2, subjects 6-8). No effects were noted in subjects 9 and 10. Behavioral assessments (n=5) showed a trend towards significance (Mdn T0=63, Mdn T1=57), z=-1.841, *p*=.066, and a clinically relevant effect (cut off value <63) in two patients. Neurocognitive assessment (n=8) showed no statistically significant effect (Mdn T0=11, Mdn T1=12), z=-0.736, *p*=.462 and in one patient a clinically relevant effect (SD>1) was found.

MPH effect at long-term follow-up

Mean time between T1 and T2 was 23.1 months (SD=26.7, range 2.6-77.7). At T2, Medical monitoring data (i.e. BP and Body Mass Index) were within the normal range and no cardiovascular side effects were described. One patient discontinued treatment due to mood problems (subject 2). Behavioral observations of patients, parents, teachers and the clinical team showed an improvement in attention in seven patients (subject 1, subjects 3-8). In subjects 6-8 with suboptimal effects at T1 an improvement in attention was observed at T2.

Discussion

This is the first study reporting on the clinical effectiveness and safety of short acting MPH treatment for learning problems in ten males with DMD and a comorbid ADHD diagnosis using an extensive medical and neuropsychological work-up at baseline, and short-term follow-up. Results demonstrate that MPH treatment considerably improves attention in seven subjects according to the subjective reports of patients, parents, teachers and the clinical team at long-term follow-up. No major side effects were reported.

Neuropsychological outcomes

Literature on neuropsychological evaluation of MPH is scarce in neurological disorders. A recent study evaluated the effect of MPH in Neurofibromatosis type 1, a neurogenic disorder in which ADHD comorbidity is common as well. Full-scale IQ scores improved significantly in Neurofibromatosis type 1 patients with ADHD who received MPH.[20] These improvements in full-scale IQ scores were also correlated with an improvement in reaction time variability based on the Test of Variables of Attention.[20] Furthermore, MPH use has been shown to significantly reduce behavioral and social dysfunction, and causing lower CBCL scores in Neurofibromatosis type 1 patients with ADHD.[21] Both the CBCL-AP and the Conners Rating Scale Revised are the most commonly used measurements to support the diagnosis of ADHD in children and adolescents, and previous research on the diagnostic accuracy of these scales yielded moderate sensitivity and specificity in supporting the diagnosis of ADHD.[22] Unfortunately, in our study only five patients completed the CBCL-AP at baseline and short-term follow-up, thus our results are rather explorative.

Side effects

Reported side effects in our subjects were having difficulty falling asleep, which is in line with previous finings in patients with ADHD without comorbidity.[12] Stimulants may exacerbate delayed sleep-onset, but may also be related to a rebound effect - increase over baseline values in ADHD symptoms when MPH wears off - rather than to the medication itself.[23] Notably, difficulty falling asleep often occurs during titration, and may improve over time.[24] Management of sleep problems in our subjects consisted of sleep problems and health education, and melatonin prescription with positive results, which is in line with previous research.[25, 26] Neurological side effects, such as motor tics or seizures, were not found in our subjects, even though one patient had epilepsy. MPH has also a potential impact on cardiac functioning which may have clinical consequences, especially in DMD patients. It is a sympathomimetic agent that increases noradrenergic and dopaminergic transmission, which affects heart HR and BP.[27] A recent systematic review on cardiovascular effects of MPH in children and adolescents with ADHD found a significant effect on systolic BP. Since this is considered a risk factor for cardiovascular morbidity and mortality during adult life, it was recommended that BP and HR should be monitored closely and regularly.[28] As cardiac management is already part of regular care of DMD patients, all subjects were regularly seen and monitored by their child cardiologist, and BP and HR remained stable from baseline to follow-up.

Limitations

Due to our small sample, there might be a lack of power to observe effects on the objective neuropsychological outcome variables. Additionally, the time between the baseline and short-term follow-up was not equal for each subject, and may have been too short to measure clinical effects on cognition. The ten subjects which are described in this study, where all seen for regular outpatient clinical care. Information of certain cognitive variables (working memory and attention measures) and behavioral variables (CBCL-AP) were limited or not available. Thereby the change between baseline and short-term follow-up on these measures could not be analyzed accurately.

Future perspectives

Further prospective research should include a follow-up time of at least six months and one year, and needs to include an age-matched control group of DMD males with a comorbid ADHD, without MPH or receiving other treatment to determine whether the effects are caused by MPH treatment. To further evaluate the different dose effects of MPH in this population, a second long-term follow-up neuropsychological work-up should be included. This neuropsychological work-up should be performed using a standard protocol of validated ADHD specific tools, such as the CBCL-AP or Conners Parent Rating Scale[22]/IOWA Conners Rating Scale[29], as well as the SDQ and PARSIII as recommended in the international standards of care guidelines for DMD.[9] Importantly, since these measurement tools are developed for the general population, certain items involving physical mobility may not be applicable for patients with impaired motor function, and should be interpreted with caution. Whether these ADHD specific tools are sensitive for ADHD comorbidity in DMD patients should be further investigated. Eventually, the effect of MPH should be evaluated in a larger sample preferably using a randomized control trial design.

Conclusion

Current data shows clinically effective use of short acting MPH for learning problems in males with DMD and a comorbid ADHD diagnosis, with regular cardiac follow-up, and close monitoring of side effects and neuropsychological effects. Overall, our results underscore the importance of the use of validated behavioral – psychosocial measurements tools, and use of psychopharmacological interventions in DMD as recommended by the international standards of care guidelines for DMD.

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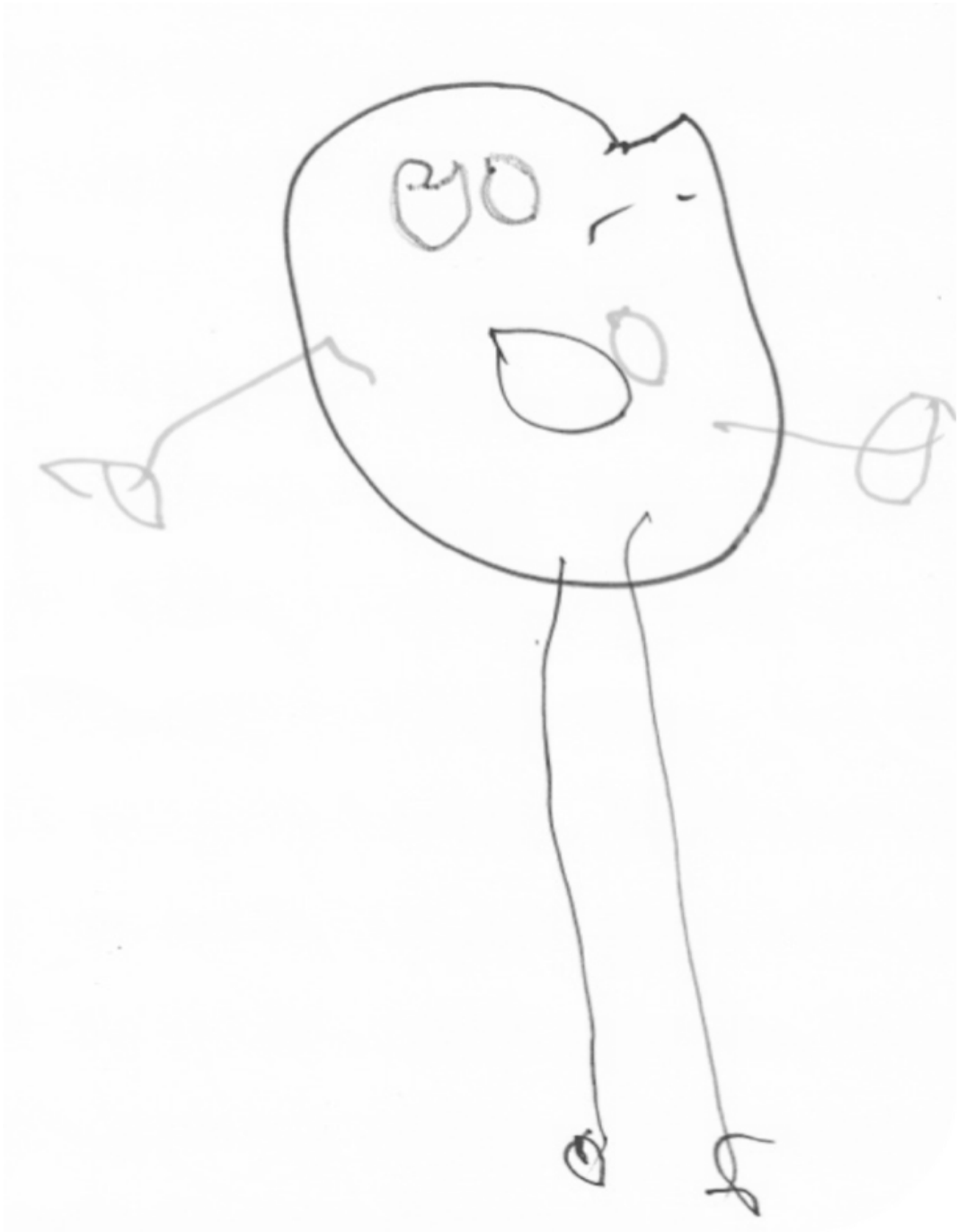

Chapter 9

General discussion

The main aim of this thesis was to provide new insights on neurocognition and behaviour, diagnostic work up and interventions in Duchenne (DMD) and Becker muscular dystrophy (BMD). In this chapter the main findings of the studies are reported and implications of the results for clinical practice and scientific research are discussed.

A summary of main findings

- Gene mutations affecting the production of dystrophin protein isoforms may not only predict the neurocognitive and behavioural features in paediatric DMD (Chapter 2) and BMD patients (Chapter 5).
- In DMD, a developmental stagnation in verbal span capacity may exist and appears to be more pronounced in patients missing Dp140 isoform (Chapter 3).
- Neurocognitive and behavioural features are less prominent in adult BMD patients and no relevant correlations are found with disease severity (Chapter 4).
- In DMD, a wide variety of assessment instruments for behavioural and psychosocial functioning have been used. Analyses of psychometric properties and applicability of instruments revealed that three instruments are potentially valid for psychosocial screening: the Psychosocial Adjustment and Role Skills Scale 3rd edition (PARS-III), the Life Satisfaction Inventory for Adolescents with DMD and the Paediatric Quality of Life Inventory Generic Module (PedsQL GM) (Chapter 6).
- Promising short and long-term results of computerized WM training are shown in a small sample of patients with DMD (N=4) and a comorbid learning disability with working memory deficiencies using Single Case Experimental Design (SCED; Chapter 7).
- Preliminary results showed that short acting stimulant medication (methylphenidate) may be clinically effective in patients with DMD and an attention-deficit hyperactivity disorder (N=10). No side effects were reported (Chapter 8).

Discussion of the results

Duchenne and Becker muscular dystrophy are neuromuscular disorders in which brain-related comorbidities in neurocognition and behaviour are described.[1-9] The origin of these comorbidities have been linked to the role of dystrophin deficiencies in the brain and it interaction with other proteins of the dystrophin glycoprotein complexes (e.g. syntrophin).[3,10-16] It is questionable whether brain dystrophin determines the presence

as well as the severity of these brain-related comorbidities when considering the main findings of present thesis. In **chapter 2** we compared DMD males to age matched males with another multifactorial, neurogenetic disorder, Neurofibromatosis type 1. We found no significant differences between these two groups on cognitive phenotypes i.e. in full-scale intellectual functioning (FSIQ), verbal short-term memory/span capacity, sustained and visual attention, processing speed and visuospatial abilities. Additionally, behavioural reports of parents and teachers of the two groups showed no significant differences. In **chapter 5**, we evaluated the cognitive phenotypes of three brothers with BMD who had a similar dystrophin gene mutation (involving exon 45-48), were tested at a similar age and grow-up in a similar environment. The cognitive phenotypes of these brothers differed in several cognitive domains i.e. in FSIQ, verbal short-term memory/span capacity, attention and reading. Their cognitive development differed as well. The brothers had only similar difficulties in processing speed and math. In **chapter 4** we also noticed no obvious neurocognitive or behavioural dystrophinopathy profile in adult males with BMD. Despite the fact that the adult BMD males exhibited low-average intellectual properties with minor deficits in executive functions, there outcomes fell within normal range. Though it is important to keep in mind that in both BMD studies (**chapter 4 and 5**) no information was available on whether specific brain dystrophin isoform expression (i.e. Dp140) is disturbed. This makes it difficult to predict whether a loss of Dp140 in addition to the full-length dystrophin isoform ($Dp427_B$) may have resulted in more specific or severe cognitive and behavioural problems in both studies. For instance in our DMD sample in **chapter 3** we found that the additional loss of Dp140 was linked to more problems in verbal short-term memory/span capacity compared to DMD patients with intact Dp140 expression. Nevertheless, the proposed mechanisms involved in neurocognitive and behavioural functioning remain versatile[16] and questions may arise on the role of (specific) brain dystrophin expression in relation to the phenotypes of DMD and BMD patients. In **chapter 7** and **chapter 8** we for instance found that interventions such as computerized working memory training (**chapter 7**) and methylphenidate treatment (**chapter 8**) in DMD patients with comorbidities in cognition, behaviour or learning are feasible, safe and have a similar (positive) effect in our DMD patient samples compared to other patient populations. It was expected that these treatments had no comparable positive effect due to the absence of dystrophin in brain areas and networks responsible for these neurocognitive and behavioural functions. Nevertheless, the findings of present thesis acknowledge that in DMD and BMD, problems may arise in neurocognition and behaviour. Our results are in line with previous studies and reveal that FSIQ is approximately one standard deviation lower (mean IQ 85) in DMD and approximately normal in BMD (mean estimated IQ 91) compared to norm population (**chapter 2, 4 and 5**).[5-7,17,18]

Additionally, we found processing speed difficulties in both our DMD and BMD samples (**chapter 3, 4 and 5**) despite the exclusion of patients with impaired functions of upper extremities. We further confirmed the consistent cognitive feature i.e. limited verbal short-term memory/verbal span capacity in DMD (**chapter 2, 3 and 7**).[4,14,19-23] It appears that BMD patients may exhibit some problems in this function as well (**chapter 4**). Verbal short-term memory and span capacity are important and powerful predictors for academic skills such as reading, writing and math.[19, 22-25] Therefore, it is important that possible deficits are indicated at an early age, in particular because these verbal memory / span deficits may remain present longitudinally (**chapter 3**). This reflects that the suggested (re) evaluation of cognition, behaviour and learning and it development is of great importance, especially during transitioning phases from for instance childhood to adolescence.[26] Previous studies used various methods to evaluate the brain-related comorbidities making it difficult to characterize specific profiles and to compare outcomes of studies. For instance in **chapter 6** we found that 61 behavioural and psychosocial instruments (e.g. questionnaires and interviews) were used in 51 previous DMD and 3 BMD studies. An essential step for clinicians and researchers is to determine whether it is necessary to develop DMD and BMD specific testing batteries for the evaluation of cognitive and behavioural functioning. It seems that the deficits in FSIQ and verbal short-term memory/span capacity and learning disabilities in reading are found regardless of instruments used in DMD.[4,14,17,19-22,24,27-29] Though, results on attention, planning, speed and visuospatial deficits differ between previous studies.[4,14,21,30,31] This may depend on the different cognitive tasks used by previous studies. However, it also likely that these deficits are not consistent in DMD. With regard to behaviour, it was noticed that the prevalence rates of disorders vary between DMD studies. Some display high rates of for instance ADHD symptoms (32%) whereas others found no symptoms (0%).[32,33] In our thesis, **chapter 2**, we also found that some DMD patients had a diagnosis of ADHD, but not all scored in the clinical range for attention problems using the Child Behaviour Checklist (CBCL). This finding in addition to our results of **chapter 6** emphasize that certain behavioural (screening) instruments may have underidentified behavioural symptoms or disorders in previous studies. Due to the overlap in symptoms clinicians and researchers should never diagnose conditions based on the results of one screening instruments. For definite diagnostics a multimethod-, source- setting is the most appropriate approach for assessment.

Overall, it remains difficult to attribute the brain-related comorbidities i.e. the neurocognitive impairments and behavioural disorders of DMD and BMD patients solely to the aberrant expression of (specific) brain dystrophin isoforms. So far no single mechanism can be identified for the brain-related comorbidities. Previous DMD

neuroimaging studies also found no single brain (structure) abnormality in patients,. They rather found individual variability in brain structures, networks, perfusion and metabolism.[12] Future DMD and BMD studies should determine which mechanisms play a role in the presence and the differentiation of minor to severe problems in neurocognition and behaviour. This would provide better diagnostic work-up and would facilitate the use of targeted therapeutic interventions.

What does this thesis contribute?

Implications for clinical practice

- (Re) evaluation of neurocognition and behaviour is recommended in DMD and BMD because one or more impairments and disorders may occur.
- Implementing a diagnostic battery for (re) evaluation of neurocognitive impairments to characterize the incidence and severity of deficits in both patient populations.
- Implementing a gold-standard protocol for screening and diagnosing behavioural, emotional and psychosocial problems in both patient populations.
- Training of cognition in particular working memory may be an effective intervention in patients with DMD and a comorbid learning disability.
- Stimulant medication may be a safe and effective treatment for ADHD symptoms in patients with DMD, but close and regular evaluation of side effects is important.

Implications for future research

- Connecting neurocognitive and behavioural outcomes to genetics, neurophysiological alterations and neuroimaging to better determine the factors involved in the presence and severity of the DMD and BMD cognitive and behavioural phenotypes.
- Longitudinal follow up of neurocognitive, behavioural and academic assessment to investigate whether DMD or BMD patients further grow in or out their comorbidities.
- Additional evaluation of psychometrics of psychosocial screening questionnaires; PARS-III, the LSIA, the PedsQL GM, and the behavioural screening questionnaires; the SDQ, GAD-7 and PHQ-9 for DMD and BMD.
- Developing a gold-standard protocol for screening and diagnosing behavioural and psychosocial problems in DMD and BMD.

- Evaluating possible (long-lasting) neuronal effects of cognitive interventions in DMD and BMD using fMRI imaging.
- Using SCED methodology to evaluate intervention effects in a small DMD or BMD patient samples.
- Evaluating the effectivity and safety of psychopharmacological medication (e.g. MPH for ADHD comorbidity) in larger sample sizes preferably using a randomized control trial design or SCED and with additional neurocognitive and behavioural outcomes

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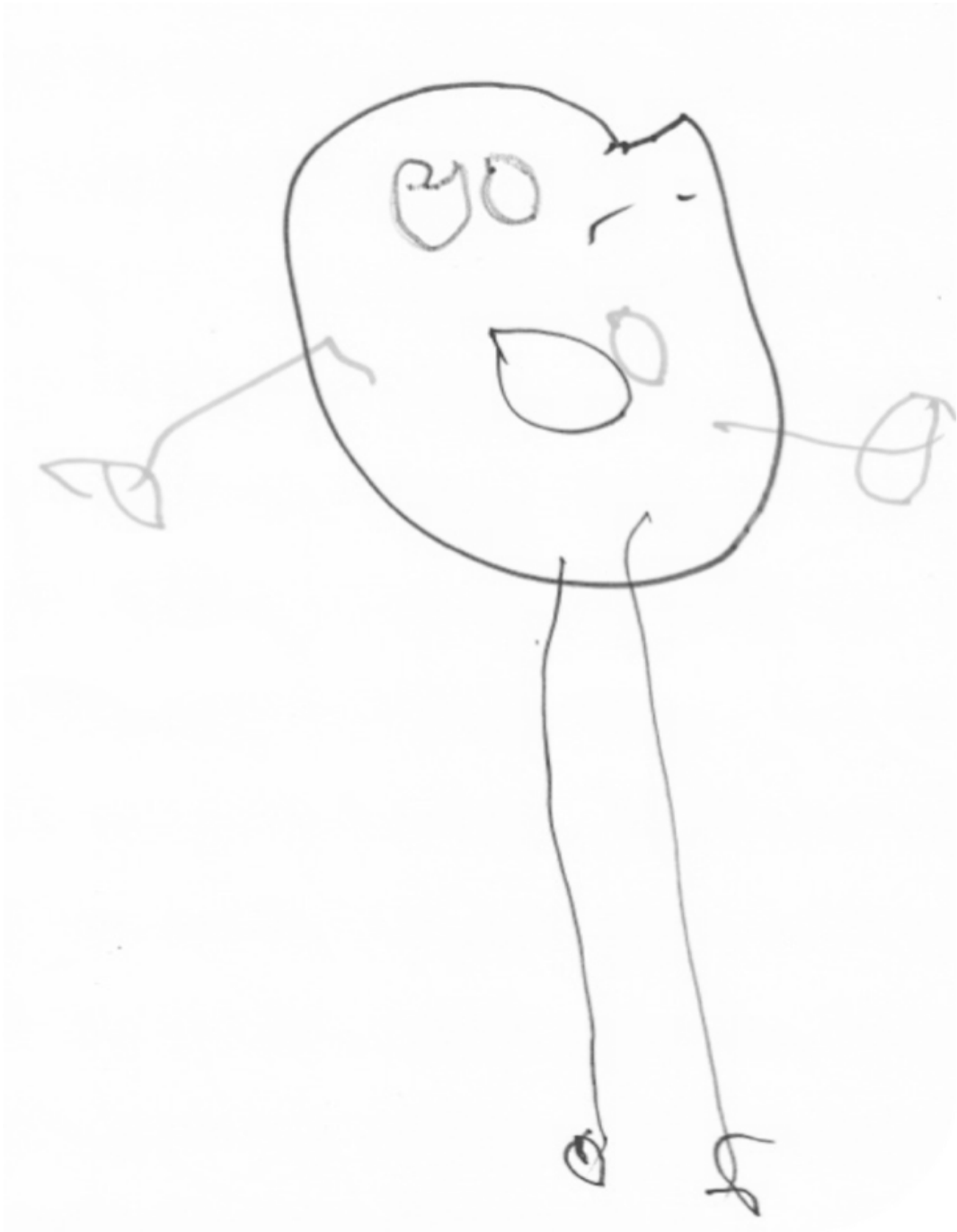

Addendum

Summary

In **Chapter 1**, we introduced the subject and the aims of this thesis.
Duchenne (DMD) and Becker (BMD) muscular dystrophy are heritable progressive neuromuscular disorders that are caused by mutations in the dystrophin (*DMD*) gene. Both disorders predominantly occur in boys. Mutations in the *DMD* gene result in an absence of the dystrophin protein in DMD and a partial production of dystrophin in the less severe variant BMD.

The *DMD* gene is responsible for encoding multiple dystrophin isoforms in various tissues (i.e. muscles, kidneys, retina and the brain). Previous research has focused on the relation between disturbed brain dystrophin expression and the presence and severity of brain-related comorbidities such as neurocognitive and behavioural problems. For both disorders, additional information on the existence of dystrophin-associated neurocognitive and behavioural problems is recommended. Furthermore, with regard to the diagnostic work-up, various measurements have been used to evaluate the presence of behavioural and psychosocial problems in DMD and BMD, but an overview of adequate measurements is lacking. Finally, interventions that may limit the influence of the brain-related comorbidities have not been evaluated scientifically previously. In this thesis, we aimed to examine the (1) presence of dystrophin-associated neurocognitive and behavioural problems in DMD and BMD, (2) diagnostic work-up for the assessment of behavioural and psychosocial problems in DMD and BMD and (3) treatment effects i.e. a psychological intervention (i.e. cognitive working memory training) and a psychopharmaceutic (methylphenidate) treatment in DMD.

In **Chapter 2**, we compared the presence of disorder specific differences in neurocognition and behaviour of male patients with DMD to male patients with Neurofibromatosis type 1 (NF1). NF1 is caused by mutations in the NF1 gene which is responsible for the production of the neurofibromin protein. This protein is localized in various tissues such as in neurons and glial cells in the brain. Previous NF1 literature has focused on a relation between the disturb production of neurofibromin in brain tissue and the presence of cognitive and learning problems. In current study, patients of the DMD and NF1 groups underwent neurocognitive assessment for regular clinical care. Results displayed that males with DMD not significantly differ in intellectual abilities, verbal (working) memory, visuospatial abilities and sustained attention compared to males with NF1. Results of behavioural questionnaires completed by parents and teachers displayed no significant differences between the DMD and NF1 group. On average, overlapping neurocognitive and behavioural problems were found for the

neurogenetic disorders, DMD and NF1, suggesting that these problems are not solely caused by gene mutations resulting in a lack of expression of one specific protein.

In **Chapter 3**, we longitudinally assessed neurocognitive data on verbal span capacity and information processing speed of males with DMD. Additionally, we explored the presence of a genotype-phenotype relation. The outcomes of span capacity and processing speed of the total sample were compared at two time points. The cohort was further dived in subgroups to explore associations between the dystrophin brain isoform (Dp140) and performances on verbal span and processing speed. For the total group we found lower verbal span capacity at the first and second assessment, whereas processing speed was normal at both assessments. Subgroup analyses suggested lower scores on verbal span and processing speed for males missing the brain dystrophin isoform, Dp140, compared to males with intact Dp140 expression. In DMD, a developmental stagnation in verbal span capacity, irrespective of processing speed, is detected through longitudinal follow-up. This stagnation appears to be more pronounced in males missing the brain dystrophin isoform, Dp140.

In **Chapter 4**, outcomes of neurocognitive testing and self-report behavioural questionnaires were used to described the neurocognitive and behavioural features of adult BMD patients. Results of the BMD group were compared to norm data and were additionally correlated with disease severity measures (i.e. motor function tests such as ten meter run/walk test and the Performance Upper limb test 1.2). Results showed that the (estimated) intellectual abilities, verbal memory, processing speed and executive functions were below average compared to the norm population, though outcomes still fell within normal clinical ranges. Results of self-report questionnaires were on average normal. Our findings reveal that adult BMD patients may exhibit minor neurocognitive impairments and no significant behavioural problems.

In **Chapter 5**, we described the neurocognitive and behavioural profiles of three brothers with BMD carrying a similar in-frame deletion of exons 45-48. The intellectual abilities of the brothers ranged from normal to high. All had difficulties with processing speed and math. Outcomes of executive functioning, working memory, attention and reading differed between the brothers. In addition, a variability in cognitive development between the brothers was noted as well. Our findings suggest that the cognitive and behavioural features of paediatric BMD patients may vary regardless of gene mutations and exposer to similar environmental factors.

In **Chapter 6**, we described a systematic review on instruments used to assess behavioural and psychosocial functioning of patients with DMD and BMD. Additionally, we reviewed the psychometric properties and applicability of the instruments used. Sixty-one instruments were used in 54 studies (51 DMD and 3 BMD) of which the CBCL is the most commonly used instrument, despite that it lacks disease specific psychometric information. Based on our psychometric results, three instruments can be appropriate for screening of psychosocial problems: the Psychosocial Adjustment and Role Skills Scale 3rd edition, the Paediatric Quality of Life Inventory Generic module, and the Life Satisfaction Index for Adolescents with Duchenne muscular dystrophy. Psychometric properties of screening instruments for behavioural and emotional problems should be further evaluated, though appropriate instruments may be: the Strengths and Difficulties Questionnaire, the Generalized Anxiety Disorder-7 item questionnaire, and the Patient Health Questionnaire. To ascertain a gold standard for screening of behavioural, emotional and psychosocial functioning of DMD and BMD patients further research should evaluate the abovementioned instruments. For definite diagnostics of behavioural disorders, it is recommended to administer the gold standard multi-method, multi-source and multi-setting assessment, because of the high risk for overlapping comorbidities in DMD and BMD.

In **Chapter 7**, we studied whether (1) computerized training improves dystrophin-associated verbal working memory problems of DMD patients, (2) effects of training are present immediately at post-intervention, at 3 and 8 months follow-up and (3) training improves problems that arise from the learning disabilities of the patients. We found short and long-term, near and far transfer effects for verbal and visual working memory, academics (reading and math), processing speed and fluid reasoning. Parent questionnaires showed minimal changes in executive behaviour, whereas teachers reported no changes at all time-points. Though, the repeated measures of parent reports on working memory functioning displayed positive effects of training. These effects were evaluated using single case experimental design analyses. Our findings show promising results of computerized working memory training in DMD patients with a comorbid learning disability and working memory problems. Our explorative near and far transfer effects are comparable to outcomes of previous studies evaluating patient populations with learning disabilities or ADHD without DMD. We might speculate that dystrophin is not involved in working memory networks as previously expected.

In **Chapter 8**, we evaluated the effectiveness and safety of methylphenidate (MPH) treatment for learning problems in males with DMD and comorbid attention-deficit hyperactivity disorder (ADHD). At short-term follow-up an improvement in attention

(i.e. concentration, impulsivity and distractibility) was noticed in four of ten patients. Suboptimal effects were reported in another four patients and no effects were found for two patients. At long-term follow-up, seven patients considerably improved in attention. No major medical side effects were reported. Our data showed that MPH can be clinically effective for learning problems in DMD with comorbid ADHD. Regular cardiac follow-up and close monitoring of it side effects and neuropsychological effects is recommended.

Overall, the studies in this thesis provide new information on brain-related comorbidities in cognition and behaviour in DMD and BMD. Evaluation of cognition and behavioural functions and their development is of great importance for both neuromuscular disorders. No consensus is shown on diagnostic work-up of behavioural and psychosocial problems in DMD and BMD. Additionally, we presented first positive effects of psychological (i.e. cognitive) interventions and psychopharmacological treatment to reduce brain-related comorbidities in DMD. Future studies should elucidate the mechanisms (e.g. genetics, neurophysiological alterations and brain structure abnormalities) that may underlie the brain-related comorbidities and how these influence the severity of the comorbidities. This would improve the diagnostic work-up and would facilitate the use of appropriate and targeted interventions.

Samenvatting

In **hoofdstuk 1** introduceren we het onderwerp en het doel van dit proefschrift.
Duchenne (DMD) en Becker (BMD) Spierdystrofie, zijn erfelijke, progressieve spierziekten die veroorzaakt worden door veranderingen oftewel mutaties in het Duchenne Muscular Dystrophy (*DMD*) gen. Dit gen is onderdeel van het erfelijk materiaal, het DNA. Deze spierziekten komen vrijwel uitsluitend voor bij jongens.

De mutaties in het DMD-gen zorgen ervoor dat het eiwit dystrofine niet - bij Duchenne Spierdystrofie - of minder wordt aangemaakt - bij de mildere variant Becker Spierdystrofie. Het dystrofine gen is verantwoordelijk voor de productie van meerdere dystrofine isoformen die voorkomen in verschillende lichaamsweefsels, namelijk in de spieren, de nieren, het oog en het brein. Het wetenschappelijk onderzoek heeft de laatste jaren zich beziggehouden met het onderzoeken van het verband tussen de verstoorde productie van dystrofine in het brein en het vaker voorkomen van neurocognitieve (d.w.z. leer- en denkproblemen) en gedragsproblemen. De exacte rol van dystrofine in cognitie en gedrag blijft onduidelijk. Het doel van dit proefschrift was om de relatie tussen dystrofine in het brein en de veelvoorkomende gedrags- en neurocognitieve problemen verder te beschrijven. Tevens hebben we middels een literatuurstudie de in de wetenschappelijke literatuur gebruikte psychologische meetinstrumenten in kaart gebracht.
Tot slot, er is nog weinig onderzoek verricht naar behandelingen om de gevolgen van de gedrags- en neurocognitieve problemen te verminderen. In dit proefschrift onderzoeken we twee behandelingen bij jongens met DMD, namelijk een psychologische interventie (cognitieve werkgeheugentraining) en een medicamenteuze behandeling ter verbetering van de aandacht (methylfenidaat).

In **hoofdstuk 2** vergelijken we het neurocognitief en gedragsmatig functioneren van jongens met DMD met dat van jongens die een andere genetische aandoening hebben, namelijk het neurofibromatose type 1 (NF1). NF1 wordt veroorzaakt door een mutatie in het NF1 gen dat verantwoordelijk is voor de productie van het eiwit neurofibromin. Dit eiwit komt voor in verschillende lichaamsweefsels, onder andere in neuronen en glia cellen in het brein. De huidige NF1 literatuur heeft zich de laatste jaren beziggehouden met het verband tussen de verstoorde productie van het eiwit neurofibromin in het brein en het voorkomen van cognitieve- en leerproblemen.
Uit de resultaten van ons onderzoek blijkt dat de jongens met DMD niet verschillen van jongens met NF1 voor wat betreft intelligentie en specifieke neurocognitieve functies zoals intellectuele vaardigheden, werkgeheugen, visueel-ruimtelijke vaardigheden en

volgehouden aandacht. Op basis van gedragsvragenlijsten die zijn ingevuld door ouders en leerkrachten, kunnen geen significante verschillen in het voorkomen van gedragsproblemen vastgesteld worden tussen de DMD- en de NF1-groep. Concluderend, er zijn overeenkomstige neuropsychologische profielen bij de DMD- en NF1 groep. Dit wekt de suggestie dat gedrags- en neurocognitieve problemen bij deze genetische aandoeningen niet alleen veroorzaakt worden door een genetische mutatie, voortvloeiend uit de afwezigheid van één specifiek eiwit.

In **hoofdstuk 3** beschrijven we in een longitudinaal retrospectief onderzoek de neurocognitieve gegevens van verbale geheugenspanne en informatieverwerkings-snelheid van jongens met DMD. Bovendien hebben we de mogelijke aanwezigheid van een genotype-fenotype relatie onderzocht. Hiermee wordt bedoeld een verband tussen de erfelijke (DNA) eigenschappen en de uiterlijke kernmerken van een individu.
De resultaten van twee meetmomenten naar verbalegeheugenspanne en verwerkingssnelheid voor de totale groep jongens met DMD werden vergeleken. Vervolgens werd de totale groep opgedeeld in subgroepen, om het verband tussen het dystrofine isoform in het brein (Dp140) en de neurocognitieve gegevens te onderzoeken. Op beide meetmomenten presteerde de totale groep laag op de verbalegeheugenspannetaak, terwijl de verwerkingssnelheid normaal was. Gegevens van de subgroepen laten na analyse zien dat jongens waarbij het dystrofine isoform in het brein (Dp140) ontbreekt, een lagere prestatie leveren in verbalegeheugenspanne en verwerkingssnelheid dan jongens waarbij dit eiwit intact is.
Concluderend zien we bij jongens met DMD een stagnatie in de ontwikkeling van verbalegeheugenspanne, die onafhankelijk blijkt te zijn van problemen in verwerkingssnelheid. Deze stagnatie lijkt nadrukkelijker aanwezig te zijn bij jongens, waarbij het dystrofine isoform (Dp140) in het brein mist.

In **hoofdstuk 4** beschrijven we de resultaten van neurocognitieve testen en gedragsvragenlijsten op basis van zelf-rapportage van volwassen patiënten met BMD.
De resultaten van de BMD-groep werden vergeleken met normdata. Daarnaast werden correlaties onderzocht tussen de uitkomsten van de neurocognitieve testen en gedragsvragenlijsten en de meetscores die de ernst van ziekte weergeven (in het bijzonder door gestandaardiseerde testen die informatie geven over spierkracht en bewegen zoals de 10-meter-ren-/looptest en de Performance Upper Limb Test 1.2.).
De resultaten lieten zien dat de (geschatte) intellectuele vaardigheiden, het verbale geheugen, de verwerkingssnelheid en de executieve functies van de BMD groep laaggemiddeld zijn ten opzichte van de normdata. Echter, klinisch gezien vallen de uitkomsten binnen de normale waardes. De gedragsvragenlijsten toonden geen

afwijkende scores voor de BMD groep. Voorts werd voor geen enkele persoon een neuro-ontwikkelingsdiagnose gemeld zoals een autisme-spectrumstoornis (ASD) of een obsessief-compulsieve stoornis (OCD). Slechts één patiënt was gediagnosticeerd met een aandachts-deficiëntie/hyperactiviteitsstoornis (ADHD). De scores voor de ernst van de ziekte en de resultaten van de neurocognitieve testen en de vragenlijsten correleerden niet significant.
Onze bevindingen tonen aan dat bij volwassen met BMD geringe cognitieve problemen kunnen voorkomen, onafhankelijk van de ernst van de ziekte. Voor de klinische zorg is het van belang dat clinici op de hoogte zijn van de mogelijke aanwezigheid van deze geringe cognitieve problemen.

In **hoofdstuk 5** beschrijven we de gedrags- en neurocognitieve profielen van drie jonge broers met BMD. Deze broers hebben precies dezelfde mutatie in het DMD-gen (van exon 45-48).
De intellectuele vaardigheden van deze broers variëren van normaal tot hoog. Alle drie de jongens presteren moeizaam in verwerkingssnelheid en rekenvaardigheid. De resultaten van de broers in executief functioneren, werkgeheugen, aandacht en lezen zijn verschillend. Daarnaast worden er verschillen in de cognitieve ontwikkeling gevonden.
Uit deze casuïstische beschrijving kan afgeleid worden dat de gedrags- en neurocognitieve kenmerken van jonge patiënten met BMD ondanks een gelijke mutatie in het DMD-gen en ondanks gelijke omgevingsfactoren, verschillend kunnen zijn.

In **hoofdstuk 6** beschrijven we een systematisch literatuuronderzoek naar meetinstrumenten voor het psychosociale en gedragsmatig functioneren van DMD- en BMD-patiënten. Daarnaast beoordelen we de psychometrische kwaliteiten en toepasbaarheid van deze meetinstrumenten.
In 54 wetenschappelijke onderzoeken (51 voor DMD, 3 voor BMD) zijn er in totaal 61 meetinstrumenten gebruikt. Daarvan wordt de Child Behavior Checklist het frequentst gehanteerd, ondanks het ontbreken van ziekte-gerelateerde psychometrische informatie. Op basis van de psychometrische bevindingen achten we drie meet-instrumenten geschikt voor het screenen van psychosociale problemen: de Psychosocial Adjustment and Role Skills Scale 3rd edition, de Pediatric Quality of Life Inventory Generic Module en de Life Satisfaction Index for Adolescents with Duchenne Muscular Dystrophy.
De psychometrische kwaliteiten van meetinstrumenten die gebruikt kunnen worden voor het screenen van gedrags- en emotionele problemen, zouden verder geëvalueerd moeten worden, hoewel de Strengths and Difficulties Questionnaire, de Generalized

Anxiety Disorder-7 item questionnaire en de Patient Health Questionnaire mogelijk bruikbare meetinstrumenten zijn.
Om tot de gouden standaard te komen voor het screenen van gedragsmatig, emotioneel en psychosociaal functioneren van DMD- en BMD-patiënten is verdere evaluatie van de zes bovengenoemde meetinstrumenten geboden. Voor het diagnosticeren van gedragsstoornissen adviseren wij de huidige gouden standaard toe te passen. Dit houdt in dat behandelaars de multi-method, multi-source en multi-setting methode in het assessment gebruiken. Voor de DMD- en BMD-populatie is deze werkwijze aan te bevelen, gelet op het hogere risico van comorbiditeiten (oftewel bijkomende aandoeningen).

In **hoofdstuk 7** beschrijven we of (1) door computertraining van het cognitieve werkgeheugen dystrofine-geassocieerde problemen van het verbale werkgeheugen van jongens met DMD verminderen, of (2) de effecten van training onmiddellijk na interventie, na 3 en 8 maanden follow-up, waarneembaar zijn, en of (3) training leerproblemen kan verminderen.
We vonden korte-en-lange-termijneffecten op het verbale en visuele werkgeheugen, op schoolse vaardigheden als lezen en rekenvaardigheid, verwerkingssnelheid en logisch redeneren. Bij alle meetmomenten hebben ouders op vragenlijsten minimale veranderingen in executieve functiegedragingen gemeld en leerkrachten rapporteerden geen veranderingen. Daarentegen constateerden we aan de hand van terugkerende ouderrapportages positieve effecten op het werkgeheugen als gevolg van training. We gebruikt daarvoor single case experimental design analyses.
Onze bevindingen tonen positieve effecten van gecomputeriseerde training van het werkgeheugen, zowel op de korte als de lange termijn. Deze effecten zijn ook eerder vastgesteld in onderzoeken bij patiënten met leerproblemen of een ADHD-diagnose, zonder DMD. Dit wekt mogelijk de suggestie dat dystrofine een beperktere rol speelt in de specifieke hersennetwerken van het werkgeheugen dan men verwacht. Echter, een andere verklaring zou kunnen zijn dat compenserende mechanismen alternatieve hersennetwerken voor het werkgeheugen gecreëerd hebben om aldus tekortkomingen op te lossen.

In **hoofdstuk 8** beschrijven we met het oog op leerproblematiek de effectiviteit en veiligheid van een medicamenteuze behandeling -bestaande uit een preparaat van methylfenidaat – bij patiënten met DMD en comorbide ADHD.
Op korte termijn werd er bij vier patiënten een vooruitgang in aandacht (concentratie, impulsiviteit en afleidbaarheid) geconstateerd. Bij vier andere patiënten zagen we suboptimale effecten en bij twee patiënten konden we geen effecten rapporteren.

Op lange termijn zagen we een verbetering in aandacht bij zeven van de tien patiënten. Er werden geen bijwerkingen van de medicijnen gemeld.
Uit de gegevens blijkt dat het preparaat methylfenidaat effectief is voor de behandeling van leerproblemen bij patiënten met DMD en comorbide ADHD. Het verdient aanbeveling bij deze populatie regelmatig een cardiale controle uit te voeren en te monitoren op bijwerkingen (zoals geadviseerd in de landelijke richtlijnen) en neuropsychologische effecten.

Concluderend kunnen we zeggen dat de onderzoeken in deze dissertatie hebben bijgedragen aan nieuwe kennis over de DMD en BMD hersengerelateerde comorbiditeiten. Het (herhaald) evalueren van gedrags- en kennisfuncties en de ontwikkeling van deze comorbiditeiten is van groot belang voor beide spierziekten. Daarnaast zien we nog weinig consensus in het gebruik van psychologische instrumenten bij DMD en BMD. Tevens hebben we in deze dissertatie een eerste aanzet gedaan tot het onderzoeken van interventies gericht op de hersengerelateerde comorbiditeiten bij DMD. Deze resultaten tonen aan dat een psychologische (dwz cognitieve) interventie en medicamenteuze behandeling bestaande uit methylfenidaat de gedrags- en neurocognitieve problemen kunnen verminderen. De rol van diverse mechanismen (o.a. de genetica, neurofysiologische afwijkingen en anatomische afwijkingen van de hersenen) in het voorkomen van en de diversiteit van gedrags- en neurocognitieve problematiek behoeft verder onderzoek. Dit zal het stellen van diagnoses en het opzetten van interventies door zorgprofessionals optimaliseren.

Impact paragraph

Introduction

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are hereditary neuromuscular disorders covering the spectrum of X-linked dystrophinopathies. Both disorders are caused by mutations in the *DMD* gene, that encodes multiple dystrophin isoforms in various tissues (e.g. skeletal striated and smooth muscles, kidney, retina, urinary and the brain). Depending on mutation location the production of one or more dystrophin protein isoforms are disturbed. The absence of the full-length dystrophin is responsible for the progressive muscle pathology in DMD. By contrast, in BMD, gene mutations cause variable levels of partially functional dystrophin, resulting in a milder and more variable phenotype ranging from adult onset muscle cramps to severe muscle weakness. An aberrant expression of dystrophin isoforms in the brain has recently been related to the frequently observed comorbid neurocognitive impairments, neurodevelopmental- (e.g. attention-deficit hyperactivity disorder or autism spectrum disorders) and behavioural disorders (e.g. depression or obsessive-compulsive disorder) in DMD and BMD. However, these features differ between patients. Furthermore, since the muscle pathology is progressive, questions arise concerning the neurocognitive features: are these progressively deteriorating as well or do they remain stable over time reflecting a developmental stagnation?
Treatment of muscle functioning currently consists of corticosteroid treatment and physiotherapy for maintaining and strengthening muscles. This is also described in the DMD standards of care. There are some recommendations in the 2018 updated DMD standards of care on treatment of the features i.e. neurocognitive impairments and neurodevelopmental-, and behavioural disorders, but scientific research is lacking. It would be valuable to evaluate neurocognitive or behavioural treatment options, especially when the cognitive impairments develop progressively over time or are caused by a developmental delay and when the behavioural problems negatively affect development and/or quality of life of patients. This paragraph describes the aims and results of this thesis and it relevance for science and practical applications.

Aim, results and conclusions

Current thesis has focused on the neurocognitive impairments and neurodevelopmental and behavioural disorders in both dystrophinopathies (**chapter 2-5**). Furthermore, we evaluated and systematically reviewed assessment tools used to establish behavioural and psychosocial problems in males with DMD (**chapter 6**). Finally, we explored whether nonmotor treatment options i.e. cognitive training and

pharmacological treatment used in other (chronic) patient populations may be effective and safe for males with DMD (**chapter 7-8**).
The findings of present thesis acknowledge that in DMD and BMD, problems may arise in neurocognition, particularly in intellectual functioning, processing speed and verbal short-term memory/ verbal span capacity. This latest problem is suggested to remain present over time in DMD patients (**chapter 3**). However, no typical neurocognitive or behavioural dystrophinopathy profile was found within our paediatric DMD and BMD males and adult BMD males when they were compared to normative data or patients with other neurogenetic disorders (**chapters 2-4-5**). With regard to treatment options, results of this thesis display positive effects of cognitive interventions such as working memory training (**chapter 7**) and pharmacological treatment such as stimulant medication (**chapter 8**) in paediatric DMD patients with comorbid working memory problems or ADHD. Furthermore, we found that behavioural and psychosocial assessment in DMD and BMD has been performed increasingly in the last two decades. However, the reported prevalence rates of behavioural disorders or psychosocial problems vary extensively. This may depend on (1) the different instruments used by previous studies and (2) a lack of good psychometric properties of the instruments used (**chapter 6**).

This thesis confirms that both dystrophinopathy disorders are not only characterized by (progressive) myopathy. For now, the name Duchenne muscular dystrophy should be adapted and appointed as Dystrophin Multi-organ Disease. Neurocognitive impairments may be important features as well. It remains unclear whether these impairments progressively deteriorate or whether they are caused by a developmental stagnation due to alterations in maturation. Based on a first longitudinal analyses of findings of DMD patients, we found indications for a developmental stagnation with respect to working memory. Future longitudinal studies are required to further explore this developmental profile. Concerning treatment of the neurocognitive and behavioural features we recommend using evidence-based interventions i.e. cognitive training or psychopharmacological treatment as these may stimulate (academic) development and increase quality of life.

Relevance

The research described in this thesis can be considered innovative in several ways.
Results acknowledge that patients with dystrophinopathies (DMD and BMD) may exhibit neurocognitive impairments and behavioural disorders. In particular impairments in intellectual abilities, processing speed and verbal short-term memory/

verbal span capacity (**chapter 2-5**). These may even remain present over time, suggesting that the cognitive impairments may be caused by a developmental delay. This emphasizes that (re) evaluation of cognitive functioning is important, since these impairments may (eventually) impact academic skills development (i.e. reading and math) and successes.

Results of present thesis displays the effect of training i.e. computerized working memory training on verbal short-term memory impairments in paediatric DMD patients. Improvements were shown in academic skills as well as on parent reports using a SCED design (**chapter 7**). For treatment of these impairments, health-care professionals may implement this training in standard care when working memory problems are stagnating development. However, generalizations to daily life situations i.e. academic skills and development at school should be further investigated. Previous studies in other populations using computerized cognitive training, show that generalizations to daily life situations can be achieved by using strategies such as explicit strategy instruction. This promotes using strategies on computerized training tasks and it additionally ensures that patients relate new acquired strategies to relevant daily life areas. Future research, should evaluate the combination of training and explicit strategy instruction when treating cognitive impairments.

Furthermore, results of present thesis have shown that stimulant medication may be effective and safe for paediatric DMD males with attention problems. Recent updated standards recommend the use of this pharmacological treatment in patients with attention problems. However, since these patients are more at risk for cardiovascular problems, it is important that treatment efficacy and safety is evaluated beforehand. Our study (**chapter 8**) describes scientific data showing that simulant medication i.e. methylphenidate considerably improves attention in DMD patients, without major medical side effects (in cardiac status). Though, future studies should evaluate the efficacy and safety of stimulant medication in this population, using a randomized controlled trial or single case design with additional and more complete neuropsychological outcomes.

Finally, results of the review study in the present thesis show that neurodevelopmental- , behavioural disorders as well as psychosocial problems of DMD and BMD patients have been evaluated frequently by previous studies using various instruments. Our systematic review (**chapter 6**) gives an overview of all instruments being used and results showed that three instruments: the Psychosocial adjustment and Role Skills Scale 3rd edition (PARS-III), the Paediatric Quality of Life Inventory

Generic Module (PedsQL GM) and the Life Satisfaction Index for Adolescents with DMD (LSIA) have good psychometric properties and should be implemented in standard psychosocial screening of DMD care. However, unknown psychometric information (e.g. construct validity or test-retest reliability) of these psychosocial instruments should be further evaluated. Concerning behavioural screenings instruments, we encourage researchers to further evaluate the psychometrics and applicability of instruments to determine which should be implemented during standard screening. In case of diagnosing behavioural disorders, our review suggests that researchers and clinicians should not use one instrument for establishing a definite diagnosis, but should apply the multi-method, multi-source, multi-setting approach. Approximately 20-30% of DMD patients display more than one neurodevelopmental or behavioural disorder and the overlapping symptoms may result in under or overdiagnosis when disorders are diagnosed based on one screening instrument.

Target population

The findings presented in this thesis are of interest for several target groups. To patients (and their parents/caregivers) with Duchenne or Becker muscular dystrophy and educational professionals, it provides additional information on the presence and variable severity of neurocognitive impairments, neurodevelopmental-, and behavioural problems in both dystrophinopathies. Awareness for cognitive and behavioural disfunctions may lead to increased referrals to health professionals.

All health care professionals (paediatric neurologists, paediatricians, (neuro)psychologists, psychiatrists, rehabilitation physicians, general practitioners, paramedics such as physiotherapist) treating patients with DMD or BMD are important stakeholders as well. They are the ones who should be aware of the risk for developing neurocognitive impairments, neurodevelopmental- and behavioural disorders during different life stages and should inform patients and caregivers appropriately. Early screening and diagnosis of these problems may contribute to better academic achievements and an increased health-related quality of life of DMD and BMD patients. Additionally, psychologist and other professionals may take the results of our review in account when applying behavioural screening and assessment. Results of this thesis also informs health care professionals about psychological or pharmacological interventions and their possible (side) effects, when paediatric DMD patients display verbal working memory or attention problems.

The findings from this thesis are also relevant for researchers in the DMD and BMD field, as they may shed more light on the variable severity and development of neurocognitive- and behavioural problems in DMD and BMD. Our data may encourage researchers to further assess the role of abnormal brain functioning (i.e. aberrant brain dystrophin expression or brain structure abnormalities) on neuro- cognition, development and behaviour. Additionally, researchers may be encouraged to further evaluate (1) psychometrics of behavioural and psychosocial instruments for the DMD and BMD population and (2) treatment effects of other known evidence-based interventions. For instance the effectiveness of pharmacological treatment i.e. selective serotonin-reuptake inhibitors in DMD or BMD patients with comorbid anxiety, depression or obsessive-compulsive disorders. Furthermore, it is valuable to know that research designs such as single case experimental design studies may be useful tools to analyse treatment effects in relatively small groups of patients with dystrophinopathies. It is often difficult to include large DMD or BMD sample sizes and follow them longitudinally. Patients are also frequently contacted by several researchers, which may overburden them. SCED designs may diminish these problems.

Implementation and future work

The knowledge derived from the studies presented in this thesis will be used for continuation of research on one hand and implemented in health care on the other hand. Researchers should connect (longitudinal) neurocognitive and behavioural data to neurophysiological and neuroimaging alterations, to assess the relation of the underlying aetiology and neuro- cognitive, developmental and behavioural disfunctions in both dystrophinopathies. With respect to diagnostic work-up, additional evaluation of psychometrics of psychosocial screening instruments (i.e. the PARS-III, PedsQL GM and LSIA) and behavioural screening instruments should be performed to determine a gold standard protocol. With respect to interventions researchers can further focus on the efficacy and safety of known evidence-based psychological or pharmacological interventions for DMD and BMD patients.

In clinical practice the results of this thesis can by implemented by health care professionals during diagnostic work-up of cognitive and behavioural functioning. Furthermore, the review of instruments being used as described in this thesis may encourage health care professionals (1) to adequately use screening instruments and (2) to implement the multi-method, source, setting approach in case of definite diagnostics. The intervention i.e. computerized working memory training can be implemented during DMD care by educational and health care professionals when

DMD patients exhibit problems in this domain. Furthermore, prescribing health care professionals may implement the use of stimulant medication such as methylphenidate in DMD patients with comorbid attention problems, with awareness for both the neuropsychological and medical (side) effects, in particular to cardiovascular adverse events.

Activities and products

The findings of this thesis have been presented at national and international conferences. These conferences were attended by health care professionals and researchers. Moreover, results have been discussed at (clinical) symposia and expert meetings in clinical settings. Some results have for instance been presented to a network of health care professionals (psychologists ad educationalists) working with males with DMD in special education schools, rehabilitation centres and university hospitals in the Netherlands and Belgium. New insights were communicated to health care professionals, researchers as well as to patients and their caregivers at (1) the Dutch parent platform, (2) the annual organised symposia (Duchenne Parent Project) and (3) working conferences of the Duchene Center Netherlands (which is a collaboration of the Leiden University Hospital, Radboud University Hospital, Maastricht University Hospital and Kempenhaeghe Center of Neurological Learning Disabilities. Results of this thesis are also available at the website of the Duchenne Center Netherlands.

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Tot slot, leefste (papa) Stef. Wat höbbe veer in bekans 6 jaor tied vääl dinger metgemaak. Veer zien gaon samenwoene, höbbe vääl gereis, same 'n hoes gekoch en verbouwd, same hiel vääl gelache mer ouch same mote jenke en dierbare mote aofgeve. Noe höbbe veer same eus wönder Sepp. Iech wil diech bedaanke veur de ruimte die stiech miech gaofs veur mien ontwikkeling, dien adviezen en dien support es iech weer eins in paniek raakte op die (zwarte) pieste…. Het is fien um te wete dat stiech 'r altied veur miech bis! Iech loer oet nao euze touwkoms met euze Sepp!!

Curriculum Vitae

Danique Mariëtte Josephine Hellebrekers was born on October 7, 1991 in Maastricht, the Netherlands. After graduating from high school (Porta Mosana College, Maastricht) in 2009, she started with her bachelor of Nursing at Hogeschool Zuyd and finished her propaedeutic year in 2010. In 2010 she started to study Health Medicine & Life Sciences, track mental health at Maastricht University and she graduated in 2013. In 2013 Danique started with the Master Neuropsychology at Maastricht University and graduated in 2015. She performed a research internship on the CASPER study at the Department of Psychiatry and Neuropsychology of Maastricht University. Additionally, she performed a clinical internship at the Memory Clinic of Maastricht University and acquired her psychodiagnostic registration (BAPD). In 2015 she graduated and started working as a psychologist at Elkerliek Ziekenhuis, Helmond. Thereafter she worked as a research assistant at the Department of Psychiatry and Neuropsychology and additionally started in 2016 as a psychologist at Zuyderland Zorgcentra. In 2016, Danique started working as a PhD candidate on the Duchenne and Becker project at the Department of Neurology of Maastricht University and the Centre of Neurological Learning Disabilities of Kempenhaeghe under supervision of prof. dr. J.S.H. Vles, dr. J.G.M. Hendriksen and dr. S. Klinkenberg. Currently, Danique is working as a psychologist at Adelante in Maastricht University Medical Centre+ (MUMC+).

Danique Mariëtte Josephine Hellebrekers is geboren op 7 oktober 1991 te Maastricht, Nederland. In 2009 behaalde ze haar HAVO diploma aan het Porta Mosana College te Maastricht. Hierna begon Danique aan de studie HBO-verpleegkunde en behaalde haar propedeuse in 2010. Vervolgens startte Danique met de bachelor Gezondheidswetenschappen aan de Universiteit Maastricht. In het tweede studiejaar koos zij voor de richting Geestelijke Gezondheidszorg. De bachelor werd afgerond in 2013. In hetzelfde jaar begon Danique met de Master Neuropsychology aan de Universiteit van Maastricht. Een combinatiestage in onderzoek en kliniek was onderdeel van deze master. Het onderzoek was gericht op de CASPER studie bij de afdeling Psychiatrie en Neuropsychologie van de Universiteit Maastricht. De klinische stage vond plaats bij de geheugepoli in MUMC+. Ten tijde van de klinische stage

behaalde Danique tevens de registratie psychodiagnostiek (BAPD). Begin 2015 studeerde Danique af en startte als psycholoog in het Elkerliek ziekenhuis te Helmond. Vervolgens is Danique gaan werken bij de afdeling Psychiatrie en Neuropsychologie van de Universiteit Maastricht als onderzoeksassistente. Tevens startte Danique als psycholoog bij Zuyderland Zorgcentra in 2016. In het najaar van 2016 is Danique begonnen als promovenda op het Duchenne en Becker project bij de afdeling Neurologie van de Universiteit Maastricht en het centrum voor Neurologische Leer en Ontwikkelingsstoornissen van Kempenhaeghe onder supervisie van prof. dr. J.S.H. Vles, dr. J.G.M. Hendriksen en dr. S. Klinkenberg. Momenteel is Danique werkzaam als psycholoog bij Adelante, locatie MUMC+.

List of publications and presentations

International journals

Hellebrekers, D.M.J, Doorenweerd, N., Sweere, D.J.J., van Kuijk, S.M.J., Aartsma-Rus, A. M., Klinkenberg, S., Vles, J.S.H., & Hendriksen, J.G.M. (2020). Longitudinal follow-up of verbal span and processing speed in Duchenne muscular dystrophy. European Journal of Paediatric Neurology, 28, 120-126.

Hellebrekers, D. M.J., Lionarons, J.M., Faber, C.G., Klinkenberg, S., Vles, J.S.H., & Hendriksen, J.G.M. (2019). Instruments for the Assessment of Behavioral and Psychosocial Functioning in Duchenne and Becker Muscular Dystrophy; a Systematic Review of the Literature. Journal of Pediatric Psychology, 44(10), 1205-1223.

Hellebrekers, D.M.J., Vles, J.S.H., Klinkenberg, S., Hendriksen, J.G.M. (2020). The neurocognitive and behavioral profiles of three brothers with Becker muscular dystrophy. Child Neurology Open,

Lionarons, J.M.[*], **Hellebrekers, D.M.J**.[*], Klinkenberg, S., Faber, C.G., Vles, J.S.H., & Hendriksen, J.G.M. (2019). Methylphenidate use in males with Duchenne muscular dystrophy and a comorbid attention-deficit hyperactivity disorder. European Journal of Paediatric Neurology, 23(1), 152-157.

Submitted to international journals

Hellebrekers, D.M.J., van Abeelen, S.A.M., van Kuijk, S.M.J., Laridon, A.M., Klinkenberg, S., Hendriksen, J.G.M., Vles, J.S.H. Cognitive and behavioural functioning in two neurogenetic disorders; how different are these aspects in Duchenne muscular dystrophy and Neurofibromatosis type 1?

Hellebrekers, D.M.J., Wirken, J.M.A., Lionarons, J.M., van Kuijk, S.M.J., Klinkenberg, S., Vles, J.S.H., Hendriksen, J.G.M. Computerized working memory training in males with Duchenne muscular dystrophy: a single case experimental design study.

Drafts

Koeks, Z.[*], **Hellebrekers, D.M.J**.[*], van de Velde, N.M., Alleman, I., Spitali, P., van Duyvenvoorde, H.A., Verschuuren, J.J.G.M., Hendriksen, J.G.M.[*], Niks E.H.[*] Minor cognitive impairments in adult males with Becker muscular dystrophy

Other publications

Douven, E., Staals, J., Freeze, W. M., Schievink, S. H., **Hellebrekers, D.M.J**., Wolz, R., ... & Köhler, S. (2020). Imaging markers associated with the development of post-stroke depression and apathy: Results of the Cognition and Affect after Stroke–a Prospective Evaluation of Risks study. European Stroke Journal, 5(1), 78-84.

Hellebrekers, D., Winkens, I., Kruiper, S., & Van Heugten, C. (2017). Psychometric properties of the awareness questionnaire, patient competency rating scale and Dysexecutive Questionnaire in patients with acquired brain injury. Brain Iinjury, 31(11), 1469-1478.

Lionarons, J. M., Hoogland, G., Hendriksen, R. G., Faber, C. G., **Hellebrekers,D.M.J**., Van Koeveringe, G. A., ... & Vles, J.S.H. (2019). Dystrophin is expressed in smooth muscle and afferent nerve fibers in the rat urinary bladder. Muscle & Nerve, 60(2), 202-210.

Van Heugten, C., Meuleman, S., **Hellebrekers, D**., Kruitwagen-van Reenen, E., & Visser-Meily, J. (2018). Participation and the role of neuropsychological functioning in myotonic dystrophy type 1. Journal of Neuromuscular Diseases, 5(2), 205-214.

Published abstracts of conference presentations

World Muscle Society:

Hellebrekers, D.M.J., Doorenweerd, N., Sweere, D., Kuijk, S., Aartsma-Rus, A.M., Klinkenberg, S., Vles, J.S.H., Hendriksen, J.G,M. (2018). Poster 23. Longitudinal follow-up of verbal working memory and processing speed in males with Duchenne muscular dystrophy. Neuromuscular Disorders, 28, S38.

Hellebrekers, D.M.J.[*], Lionarons, J.M.[*], Klinkenberg, S., Faber, C.G., Hendriksen, J.G.M., Vles, J.S.H. (2018). Poster 22. Evaluation of methylphenidate in males with Duchenne muscular dystrophy and a comorbid attention deficit hyperactivity disorder: a preliminary study. Neuromuscular Disorders, 28, S38.

Hellebrekers, D.M.J., Lionarons, J.M., Wirken, J.M.A., Klinkenberg, S., Vles, J.S.H., Hendriksen, J.G.M. (2019). E-Poster 85. Exploring the trainability of working memory and learning in Duchenne muscular dystrophy using computerized memory training. Neuromuscular Disorders, 29, S177.

MH&NS

Thesis defenses from MHeNs - School for Mental Health and Neuroscience

2013

Rob Havermans: Bipolar disorder in daily life; Mood and cortisol responses to naturallyoccurring events. Supervisor: prof.dr. M. de Vries; Co-Supervisor: dr. N. Nicolson.

Véronique Moers-Hornikx: Deep brain stimulation and the cerebellum. Supervisors: prof.dr. J. Vles / prof.dr. Y. Temel; Co-Supervisor: dr. G. Hoogland.

Nicole Veldhorst-Janssen: Intranasal delivery of rapid acting drugs. Supervisors: prof.dr. M. Marcus / prof.dr. C. Neef; Co-Supervisor: dr. P.H. van der Kuy.

Stéphanie Knippenberg: Vitamin D and Multiple Sclerosis: immunological and clinical outcome. Supervisor: prof.dr. J. Cohen-Tervaert; Co-Supervisors: dr. J. Damoiseaux / dr. Y. Bols.

Erik D. Gommer: Dynamic Cerebral Autoregulation: from methodology towards clinical application. Supervisors: prof.dr. W.H. Mess / prof.dr. R.B. Panerai, UK; Co-Supervisor: dr.ir. J.P.H. Reulen.

Olga A.H. Reneerkens: Can PDE inhibition improve cognition ? Translational insights. Supervisor: prof.dr. H.W.M. Steinbusch; Co-Supervisor: dr. J. Prickaerts;.

Lyzel S. Elias-Sonnenschein: Clinical and biomarker correlates of genetic risk factors for Alzheimer's disease. Supervisor: prof.dr. F.R.J. Verhey; Co-Supervisor: dr. P.J. Visser.

Diego F. Mastroeni: Epigenetic Dysregulation and the Pathophysiology of of Alzheimer's Disease. Supervisors: prof.dr. H.W.M. Steinbusch / prof.dr. P.D. Coleman, Sun City, Arizona; Co-Supervisors: dr. B.P.F. Rutten / dr. D.L.A. van den Hove.

Leonidas Chouliaras: Epigenetic Regulation in Aging and Alzheimer's disease: A translational perspective. Supervisor: prof.dr. H.W.M. Steinbusch; Co-Supervisors:dr. B.P.F. Rutten / dr. D.L.A. van den Hove.

Liesbeth Knaepen: Perinatal events and altered pain sensitivity in later life. Supervisors: prof.dr. E.A.J. Joosten / prof.dr. D. Tibboel, EUR; Co-Supervisor: dr. J. Patijn.

Marisela Martinez-Claros: Hippocampal plasticity and corticosterone: From dendrites to behaviour. Supervisor: prof.dr. H.W.M. Steinbusch; Co-Supervisors: dr. J.L. Pawluski / dr. J. Prickaerts.

Marcus D. Lancé: A circle of improvement in bleeding management: from laboratory to clinic and back. Supervisors: prof.dr. M.A.E. Marcu / prof.dr. J.W.M. Heemskerk; Co-Supervisor: dr. Y.M.C. Henskens.

Hilde Braakman: Imaging the brain; neuronal correlates of cognitive impairment in children with frontal lobe epilepsy. Supervisors: prof.dr. A.P. Aldenkamp / prof.dr. J.S.H. Vles; Co-Supervisors: dr.ir. W.H. Backes / dr. P.A.M. Hofman.

Willem H. van Zwam: Aneurysmal subarachnoid hemorrhage: imaging strategies and cost-effectiveness aspects in diagnostic work-up and post-therapeutic follow-up. Supervisors: prof.dr. J.T. Wilmink / prof.dr. J.E. Wildberger; Co-Supervisor: dr. P.A.M. Hofman.

Klara De Cort: The Pathogenesis of Panic Disorder. Supervisors: prof.dr. I. Myin-Germeys / prof.dr. E.J.L. Griez; Co-Supervisors: dr. K.R.J. Schruers / dr. I. Van Diest, Leuven.

Kim van Wijck: Mind the Gap; experimental studies on splanchnic hyperfusion and gastrointestinal integrity loss in man. Supervisors: prof.dr. W.A. Buurman / prof.dr. C.H.C. Dejong; Co-Supervisor: dr. K. Lenaerts.

Yvette Roke: Antipsychotic-induced hyperprolactinemia in children and adolescents with mainly autism spectrum disorders. Prevalence, symptoms, clinical consequences and genetic risk factors. Supervisors: prof.dr. P.N. van Harten / prof.dr. J.K. Buitelaar (RUN); Co-Supervisor: dr. A. Boot (UMCG).

Fleur Goezinne: Retinal detachment surgery: pre and postoperative prognostic factors. Supervisors: prof.dr. F. Hendrikse / prof.dr. C.A.B. Webers; Co-Supervisor: dr. E.C. La Heij (Amsterdam).
Ralph L.J.G. Maassen: The Merits of Videolaryngoscopy during Glottic Visualisation for Endotracheal Intubation. Supervisors: prof.dr. M. Marcus / prof.dr. A. van Zundert (University of Queensland).

Maria J. de Sousa Guerreiro: The role of sensory modality in age-related distraction. Supervisor: prof.dr. C.M. van Heugten; Co-Supervisor: dr. P.W.M. van Gerven.

Ine Rayen: Effects of developmental fluoxetine exposure on neurobehavioral outcomes. Supervisor: prof.dr. H.W.M. Steinbusch; Co-Supervisors: dr. J.L. Pawluski / dr. T.D. Charlier (Ohio University, USA).

Nynke M.G. Bodde: Psychogenic non-epileptic seizures; a separate disorder or part of a continuum? Supervisors: prof.dr. R. van Oostenbrugge / prof.dr. K. Vonck (UZ Gent); Co-Supervisors: dr. R. Lazeron / dr. A. de Louw (Epilepsiecentrum Kempenhaeghe, Heeze).

Alejandro M. Gomez: Novel strategies for making myasthenia less gravis: targeting plasma cells and the neuromuscular junction. Supervisor: prof.dr. M.H. De Baets; Co-Supervisors: dr. M. Losen / dr. P. Martinez-Martinez.

Mohammad S. Rahnama'i: Prostaglandins and Phosphodiesterases in the Urinary Bladder Wall. Supervisors: prof.dr. Ph. Van Kerrebroeck / prof.dr. S. de Wachter (Universiteit Antwerpen); Co-Supervisor: dr. G. van Koeveringe.

Mariken B. de Koning: Studying biomarkers in populations at genetic and clinical high risk for psychosis. Supervisors: prof.dr. T. Amelsvoort / prof.dr. J. Booij (AMC).

Fabien Boulle: Epigenetic regulation of BDNF/TrkB signaling in the pathophysiology and treatment of mood disorders. Supervisors: prof.dr. H.W.M. Steinbusch / prof.dr. L. Lanfumey (Universiteit Parijs); Co-Supervisors: dr. D. van den Hove /dr. G. Kenis.

2014

Iris Nowak-Maes: Tinnitus; assessment of quality of life & cost-effectiveness. Supervisors: prof.dr. M. Peters / prof.dr. B. Kremer; Co-Supervisors: dr. M. Joore / dr. L. Anteunis.

Marjolein Huijts: Cognitive function in patients with cerebral small vessel disease.Supervisor: prof.dr. R.J. van Oostenbrugge; Co-Supervisors: dr. A.A. Duits / dr. J. Staals.

Markus Gantert: Fetal inflammatory injury as origin of long term disease: Lessons from animal models. Supervisors: prof.dr. B. Kramer / prof.dr. L. Zimmermann; Co-Supervisor: dr. A. Gavilanes.

Elke Kuypers: Fetal development after antenatal exposures: Chorioamnionitis and maternal glucocorticoids. Supervisors: prof.dr. B.W. Kramer / prof.dr. H.W. Steinbusch / prof.dr. Suhas G. Kallapur (University of Cincinnati, Ohio, USA).

Pieter Kubben: Ultra low-field strength intraoperative MRI for Glioblastoma Surgery. Supervisor: prof.dr. J.J. van Overbeeke; Co-Supervisor: dr. H. van Santbrink.

Laura Baijens: Surface electrical stimulation of the neck for oropharyngeal dysphagia in Parkinson's disease: therapeutic aspects and reliability of measurement. Supervisor: prof.dr. B. Kremer; Co-Supervisor: dr. R. Speyer, Townsville.

Janneke Hoeijmakers: Small fiber neuropathy and sodium channels; a paradigm shift. Supervisor: prof.dr. R.J. van Oostenbrugge; Co-Supervisors: dr. C.G. Faber / dr. I.S.J. Merkies.

Stephanie Vos: The Role of biomarkers in preclinical and prodromal Alzheimer's disease. Supervisor: prof.dr. F.R. Verhey; Co-Supervisor: dr. P.J. Visser.

Muriël Doors: The Value of Optical Coherence Tomography in Anterior Segment Surgery. Supervisors: prof.dr. R.M. Nuijts / prof.dr. C.A. Webers; Co-Supervisor: dr. T.T.J.M. Berendschot.

Anneke Maas: Sleep problems in individuals with genetic disorders associated with intellectual disability. Supervisors: prof.dr. I. Curfs / prof.dr. R. Didden.

Sebastiaan van Gorp: Translational research on spinal cord injury and cell-based therapies; a focus on pain and sensorimotor disturbances. Supervisors: prof.dr. B. Joosten / prof.dr. M. van Kleef; Co-Supervisors: dr. J. Patijn / dr. R. Deumens, KU Leuven.

Andrea Sannia: High risk newborns and brain biochemical monitoring. Supervisor: prof.dr. J.S.H. Vles; Co-Supervisors: dr. D. Gazzolo, Alessandria, Italy / dr. A.W.D. Gavilanes.

Julie A.D.A. Dela Cruz: Dopamine mechanisms in learning and memory: Evidence from rodent studies. Supervisors: prof.dr. H.W.M. Steinbusch / prof.dr. R.J. Bodnar, New York; Co-Supervisor: dr. B.P.F. Rutten.

René Besseling: Brain wiring and neuronal dynamics; advances in MR imaging of focal epilepsy. Supervisors: prof.dr. A.P. Aldenkamp / prof.dr.ir. W.H. Backes; Co-Supervisor: dr. J.F.A. Jansen.

Maria Quint-Fens: Long-term care after stroke; development and evaluation of a long- term intervention in primary care. Supervisors: prof.dr. J.F.M. Metsemakers / prof.dr. C.M. van Heugten / prof.dr. M. Limburg, Almere; Co-Supervisor:dr. G.H.M.I. Beusmans.

Veronique Moulaert: Life after survival of a cardiac arrest; the heart of the matter. Supervisors: prof.dr. J.A. Verbunt / prof.dr. C.M. van Heugten / prof.dr. D.T. Wade, Oxford,UK.

Feikje Smeets: The hallucinatory-delusional state: a crucial connection in the psychosis symptom network. Supervisor: prof.dr. J. van Os; Co-Supervisor: dr. T. Lataster.

Lies Clerx: Alzheimer's disease through the MR-eye; novel diagnostic markers and the road to clinical implementation". Supervisor: prof.dr. F. Verhey; Co-Supervisors: dr. P.J. Visser / P. Aalten.

Sonny Tan: The subthalamic nucleus in Parkinson's disease. Supervisors: prof.dr. Y. Temel / prof.dr. H.W.M. Steinbusch / prof.dr. T. Sharp, Oxford, UK / prof.dr. V. Visser-Vandewalle, Koln.

Koen van Boxem: The use of pulsed radiofrequency in the management of chronic lumbosacral radicular pain. Supervisors: prof.dr. M. van Kleef / prof.dr. E.A.J. Joosten; Co-Supervisor: Assoc. prof.dr. J. van Zundert.

Jérôme Waterval: Hyperostosis cranialis interna. Supervisors: prof.dr. J.J. Manni / prof.dr. R.J. Stokroos.

Sylvie Kolfschoten-van der Kruijs: Psychogenic non-epileptic seizures; the identification of neurophysiological correlates. Supervisors: prof.dr. A.P. Aldenkamp / prof.dr. K.E.J. Vonck, Universiteit Gent; Co-Supervisors: dr. J.F.A. Jansen /dr. R.H.C. Lazeron, Kempenhaeghe.

Wouter Pluijms: Spinal cord stimulation and pain relief in painful diabetic: polyneuropathy, a translational approach. Supervisors: prof.dr. M. van Kleef /prof.dr. E.A. Joosten; Co-supervisor: dr. C.G. Faber.

Ron Handels: Health technology assessment of diagnostic strategies for Alzheimer's disease. Supervisors: prof.dr. F.R.J. Verhey / prof.dr. J.L. Severens (EUR); Co-Supervisor:dr. M.A. Joore / dr. C.A.G. Wolfs.

Evelyn Peelen: Regulatory T cells in the pathogenesis of Multiple Sclerosis: potential targets for vitamin D therapy. Supervisors: prof.dr. R.M.M. Hupperts / prof.dr. J.W. Cohen Tervaert; Co-Supervisor: dr. J.G.M.C. Damoiseaux / dr. M.M.G.L.Thewissen, Diepenbeek.

Reint Jellema: Cell-based therapy for hypoxic-ischemic injury in the preterm brain. Supervisors: prof.dr. B.W.W. Kramer / prof.dr. H.W.M. Steinbusch; Co-Supervisor: dr. W.T.V. Germeraad / dr. P. Andriessen, Veldhoven.

Maria Wertli: Prognosis of Chronic Clinical Pain Conditions: The Example of ComplexRegional Pain Syndrome 1 and Low Back Pain. Supervisors: prof.dr. M. van Kleef; Co-Supervisor: dr. F. Brunner, Zürich / dr. R. Perez, VUmc.

Dagmar Zeef: An experimental model of Huntington's disease: Validation & Stimulation. Supervisors: prof.dr. Y. Temel / prof.dr. H.W.M. Steinbusch; Co-supervisor: Dr. A. Jahanshahi.

Jeroen Decoster: Breaking Down Schizophrenia into phenes, genes and environment. Supervisors: prof.dr. I. Myin-Germeys / prof.dr. M. De Hert, KU Leuven; Co-Supervisor:dr. R. van Winkel.

Eaja Anindya Sekhar Mukherjee: Fetal Alcohol Spectrum Disorders: exploring prevention and management. Supervisor: prof.dr. L.M.G. Curfs; Co-Supervisor: prof. S. Hollins, St. George's University of London, UK.

Catherine van Zelst: Inside out; On stereotype awareness, childhood trauma and stigma in psychosis. Supervisors: prof.dr. Ph. Delespaul / prof.dr. J. van Os.

Ibrahim Tolga Binbay: Extended Psychosis Phenotype in the Wider Social Environment. Supervisor: prof.dr. J. van Os; Co-Supervisor: dr. M. Drukker.

Frank Van Dael: OCD matters in psychosis. Supervisors: prof.dr. J. van Os / prof.dr. I. Myin-Germeys.

Pamela Kleikers: NOXious oxidative stress: from head toe too and back. Supervisors: prof.dr. H.H.H.W. Schmidt / prof.dr. H.W.M. Steinbusch; Co-Supervisor: dr. B. Janssen.

José Luis Gerardo Nava: In vitro assay systems in the development of therapeutic interventions strategies for neuroprotection and repair. Supervisors: prof.dr.med. J. Weis / prof.dr. H.W.M. Steinbusch; Co-Supervisor: dr. G.A. Brook, RWTH Aachen.

Eva Bollen: Cyclic nucleotide signaling and plasticity. Supervisors: prof.dr. H.W.M. Steinbusch / prof.dr. R. D'Hooge, KU Leuven; Co-Supervisor: dr. J. Prickaerts.

2015

Jessica A. Hartmann: A good laugh and a long sleep; Insights from prospective and ambulatory assessments about the importance of positive affect and sleep in mental health. Supervisor: prof.dr. J. van Os; Co-Supervisors: C.J.P. Simons / dr. M. Wichers.

Bart Ament: Frailty in old age; conceptualization and care innovations. Supervisors: prof.dr. G.I.J.M. Kempen / prof.dr. F.R.J. Verhey; Co-Supervisor: dr. M.E. de Vugt.

Mayke Janssens: Exploring course and outcome across the psychosis-continuum. Supervisor: prof.dr. I. Myin-Germeys; Co-Supervisor: dr. T. Lataster.

Dennis M.J. Hernau: Dopayours is not dopamine: genetic, environmental and pathological variations in dopaminergic stress processing. Supervisor: prof.dr. I. Myin- Germeys; Co-Supervisors: prof.dr. F.M. Mottaghy / dr. D. Collip.

Ingrid M.H. Brands: The adaptation process after acquired brain injury Pieces of the puzzle. Supervisors: prof.dr. C.M. van Heugten / prof.dr. D.T. Wade, Oxford UK; Co-Supervisors: dr. S.Z. Stapert / dr. S. Köhler.

Francesco Risso: Urinary and salivary S100B monitoring in high risk infants. Supervisor: prof.dr. J.S.H. Vles; Co-Supervisors: dr. D. Gazzolo, Genoa,Italy / dr. A.W.D. Gavilanes.

Alessandro Borghesi: Stem and Progenitor Cells in Preterm Infants: Role in the Pathogenesis and Potential for Therapy. Supervisor: prof.dr. L. Zimmermann; prof.dr. B. Kramer; Co-Supervisors: dr. D. Gazzolo, Genoa,Italy / dr. A.W.D. Gavilanes.

Claudia Menne-Lothmann: Affect dynamics; A focus on genes, stress, and an opportunity for change. Supervisor: prof.dr. J. van Os; Co-Supervisors: dr. M. Wichers / dr. N. Jacobs.

Martine van Nierop: Surviving childhood new perspectives on the link between childhoodtrauma and psychosis. Supervisors: prof.dr. I. Myin-Germeys / prof.dr. J. van Os; Co-Supervisor: dr. R. van Winkel.

Sylvia Klinkenberg: VNS in children; more than just seizure reduction. Supervisors:prof.dr. J. Vles / prof.dr. A. Aldenkamp; Co-Supervisor: dr. H. Majoie.

Anouk Linssen: Considerations in designing an adult hearing screening programme. Supervisor: prof.dr. B. Kremer; Co-Supervisors: dr. L. Anteunis / dr. M. Joore.

Janny Hof: Hearing loss in young children; challenges in assessment and intervention. Supervisors: prof.dr. B. Kremer / prof.dr. R. Stokroos / prof.dr. P. van Dijk, RUG; Co-Supervisor: dr. L. Antheunis.

Kimberly Cox-Limpens: Mechanisms of endogenous brain protection; Clues from the transcriptome. Supervisors: prof.dr. J. Vles / prof.dr. L. Zimmermann; Co-Supervisor: dr. A. Gavilanes.

Els Vanhoutte: Peripheral Neuropathy outcome measures; Standardisation (PeriNomS)study part 2: Getting consensus. Supervisors: prof.dr. C. Faber / prof.dr. P. van Doorn; Co-Supervisor: dr. I. Merkies, Spaarne ziekenhuis Hoofddorp.

Mayienne Bakkers: Small fibers, big troubles; diagnosis and implications of small fiberneuropathy. Supervisors: prof.dr. C. Faber / prof.dr. M. de Baets; Co-Supervisor: dr. I. Merkies, Spaarne ziekenhuis Hoofddorp.

Ingrid Kramer: Zooming into the micro-level of experience: An approach for understanding and treating psychopathology. Supervisor: prof.dr. J. van Os; Co-Supervisors: dr. M. Wichers, UMC Groningen / dr. C. Simons.

Esther Bouman: Risks and Benefits of Regional Anesthesia in the Perioperative Setting. Supervisors: prof.dr. M. van Kleef / prof.dr. M. Marcus, HMC, Qatar / prof.dr. E. Joosten; Co-Supervisor: dr. H. Gramke.

Mark Janssen: Selective stimulation of the subthalamic nucleus in Parkinson's disease; dream or near future. Supervisors: prof.dr. Y. Temel / prof.dr. V. Visser-Vandewalle, Keulen / prof.dr. A. Benazzouz, Bordeax, France.

Reina de Kinderen: Health Technology Assessment in Epilepsy; economic evaluations and preference studies. Supervisors: prof.dr. S. Evers / prof.dr. A. Aldenkamp; Co-Supervisor: dr. H. Majoie / dr. D. Postulart, GGZ O-Brabant.

Saskia Ebus: Interictal epileptiform activity as a marker for clinical outcome. Supervisors: prof.dr. A. Aldenkamp / prof.dr. J. Arends, TUE / prof.dr. P. Boon, UniversiteitGent, België.

Inge Knuts: Experimental and clinical studies into determinants of panic severity. Supervisor: prof.dr. I. Myin-Germeys; Co-Supervisor: dr. K. Schruers; Influencing panic.

Nienke Tielemans: Proactive coping post stroke: The Restored4Stroke Self-Management study. Supervisors: prof.dr. C. van Heugten / prof.dr. J. Visser-Meily, UMC Utrecht; Co-Supervisor: dr. V. Schepers, UMC Utrecht.

Tom van Zundert: Improvements Towards Safer Extraglottic Airway Devices. Supervisors: prof.dr. A.E.M. Marcus / prof.dr. W. Buhre / prof.dr. J.R. Brimacombe,Queensland, Australia / prof.dr. C.A. Hagberg.

Tijmen van Assen: Anterior Cutaneous Nerve Entrapment Syndrome Epidemiology and surgical management. Supervisors: prof.dr. G.L. Beets / prof.dr. M. van Kleef / dr. R.M.H. Roumen / dr. M.R.M. Scheltinga, MMC Veldhoven.

Rohit Shetty: Understanding the Clinical, Immunological and Genetic Molecular Mechanisms of Keratoconus. Supervisors: prof.dr. R.M.M.A. Nuijts / prof.dr. C.A.B.Webers.

Christine van der Leeuw: Blood, bones and brains; peripheral biological endophenotypesand their structural cerebral correlates in psychotic disorder. Supervisor: prof.dr. J. van Os; Co-supervisor: dr. M. Marcelis.

Sanne Peeters: The Idle Mind Never Rests; functional brain connectivity across the psychosis continuum. Supervisor: prof.dr. J. van Os; Co-supervisor: dr. M. Marcelis.

Nick van Goethem: α7 nicotinic acetylcholine receptors and memory processes: mechanistic and behavioral studies. Supervisor: prof.dr. H.W.M. Steinbusch; Co-supervisor: dr. J. Prickaerts.

Nicole Leibold: A Breath of fear; a translational approach into the mechanisms of panic. Supervisor: prof.dr. H.W.M. Steinbusch; Co-supervisors: dr. K.R.J. Schruers / dr. D.L.A. van den Hove.

Renske Hamel: The course of mild cognitive impairment and the role of comorbidity. Supervisor: prof.dr. F.R.J. Verhey; Co-supervisors: dr. I.H.G.B. Ramakers / dr. P.J. Visser.

Lucia Speth: Effects of botulinum toxin A injections and bimanual task-oriented therapyon hand functions and bimanual activities in unilateral Cerebral Palsy. Supervisors: prof.dr. J. Vles; prof.dr. R. Smeets; Co-supervisor: dr. Y. Janssen-Potten, Adelante Hoensbroek.

Yuan Tian: The effects of Lutein on the inflammatory pathways in age-related macular degeneration (AMD). Supervisors: prof.dr. C. Webers; prof.dr. A. Kijlstra, WUR; Co- supervisor: dr. M. Spreeuwenberg; dr. H. Tange.

Peggy Spauwen: Cognition and Type 2 diabetes; the interplay of risk factors. Supervisors: prof.dr. F. Verhey; prof.dr. C. Stehouwer; Co-supervisor: dr. M. van Boxtel

Marc Hilhorst: Crescentic glomerulonephritis in ANCA associated vasculitis. Supervisors: prof.dr. J. Cohen-Tervaert; Co-supervisor: dr. P. van Paassen

Martin Gevonden: The odd one out: exploring the nature of the association between minority status and psychosis. Supervisors: prof.dr. J-P. Selten; prof.dr. J. Booij, Uva; prof.dr. I. Myin-Germeys

Bart Biallosterski: Structural and functional aspects of sensory-motor Interaction in the urinary bladder. Supervisors: prof.dr. Ph. Van Kerrebroeck; prof.dr. S. De Wachter, UvAntwerpen; Co-supervisors: dr. G. van Koeveringe; dr. M. Rahnama'i.

Alexandra König: The use of information and communication technologies (ICT) for the assessment of patients with Alzheimer's Disease and related disorders. Supervisors: prof.dr. F. Verhey; prof.dr. Ph. Robert, Nice, Fr; Co-supervisors: dr. P. Aalten; dr. R. David,Nice. Fr.

Michelene Chenault: Assessing Readiness for Hearing Rehabilitation. Supervisors: prof.dr. M.P.F. Berger; prof.dr. B. Kremer; Co-supervisor: dr. L.J.C. Anteunis.

Anand Vinekar: Retinopathy of Prematurity. Recent advances in tele-medicine screening, risk factors and spectral domain optical coherence tomography imaging. Supervisor: prof.dr. C.A.B. Webers; Co-supervisor: dr. N.J. Bauer

Fleur van Dooren: Diabetes and Depression: exploring the Interface between Pathophysiological and Psychological factors. Supervisors: prof.dr. F.R.J. Verhey; prof.dr. J.K.L. Denollet, UvT; prof.dr. F. Pouwer, UvT; Co-supervisor: dr. M.T. Schram.

Gabriëlla Pons van Dijk: Taekwondo and physical fitness components in middle-aged healthy volunteers; the Sekwondo study. Supervisors: prof.dr. J. Lodder;prof.dr. H. Kingma; Co-supervisor: dr. A.F. Lenssen.

Yara Pujol López: Development and psychoneuroimmunological mechanisms in depression. Supervisor: prof.dr. H.W.M. Steinbusch; Co-supervisors: Dr. G. Kenis; Dr. D.van den Hove; Dr. Aye Mu Myint, München.

Romina Gentier: UBB^{+1}; an important switch in the onset of Alzheimer's disease. Supervisors: Prof. H. Steinbusch; Prof. D. Hopkins; Co-supervisor: Dr. F. van Leeuwen.

Sanne Smeets: Insights into insight: studies on awareness of deficits after acquired brain injury. Supervisor: Prof. C. van Heugten; Prof. R. Ponds; Co-supervisor: Dr. I. Winkens

Kim Beerhorst: Bone disease in chronic epilepsy: fit for a fracture. Supervisor: Prof. A.Aldenkamp; Prof. R. van Oostenbrugge; Co-supervisor: Dr. P. Verschuure.

Alex Zwanenburg: Cerebral and cardiac signal monitoring in fetal sheep with hypoxic-ischemic encephalopathy. Supervisor: Prof. T. Delhaas; Prof. B. Kramer; Co-supervisors:Dr. T. Wolfs; Dr. P. Andriessen, MMC.

Ismail Sinan Guloksuz: Biological mechanisms of environmental stressors in psychiatry. Supervisor: Prof. J. van Os; Co-supervisors: Dr. B. Rutten; Dr. M. Drukker.

Seyed Ehsan Pishva MD: Environmental Epigenetics in mental health and illness. Supervisor: Prof.dr. J. van Os; Co-supervisors: Dr. B.P.F. Rutten; Dr. G. Kenis.

Ankie Hamaekers: Rescue ventilation using expiratory ventilation assistance; innovating while clutching at straws. Supervisors: Prof.dr. W.F. Buhre; Prof.dr. M. van Kleef.

Rens Evers. 22q11.2 deletion syndrome: intelligence, psychopathology and neurochemistry at adult age. Supervisors: Prof.dr. L.M.G. Curfs; Prof.dr. T. v. Amelsvoort.

Sarah-Anna Hescham. Novel insights towards memory restoration. Supervisor: Prof.dr. Y. Temel; Co-supervisor: Dr. A. Blokland; Dr. A. Jahanshahi.

João P. da Costa Alvares Viegas Nunes. Insulin receptor sensitization improves affectivepathology in various mouse models. Supervisor: Prof.dr. H.W.M. Steinbusch; Co- supervisors: Dr. K-P. Lesch; Dr. T. Strekalova; Dr.B.H. Cline, Oxford.

Yanny Ying-Yee Cheng. Clinical Outcomes After Innovative Lamellar Corneal Transplantation Surgery. Supervisor: Prof.dr. R.M.M.A. Nuijts; Co-supervisor: Dr. J.S.A.G. Schouten.

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Oliver Gerlach. Parkinson's disease, deterioration during hospitalization. Supervisor: Prof.dr. R. van Oostenbrugge; Co-supervisor: Dr. W. Weber.

Remo Arts. Intracochlear electrical stimulation to suppress tinnitus. Supervisor: Prof.dr. R.J. Stokroos; Co-supervisor: Dr. E.L.J. Georg.

Mitchel van Eeden. The €- Restore4stroke study: Economic evaluation of stroke care in the Netherlands. Supervisors: Prof.dr.mr. S.M.A.A. Evers; Prof.dr. C.M. v. Heugten; Co-supervisor: dr. G.A.P. van Mastrigt.

Pim Klarenbeek. Blood pressure and cerebral small vessel disease. Supervisor: Prof.dr. R.J. van Oostenbrugge; Co-supervisor: Dr. J. Staals.

Ramona Hohnen. Peripheral pharmacological targets to modify bladder contractility. Supervisor: Prof.dr. Ph.E.V. van Kerrebroeck; Co-supervisors: Dr. G.A. van Koeveringe; Dr. M.A. Sahnama'i; Dr. C. Meriaux.

Ersoy Kocabicak. Deep brain stimulation of the subthalamic nucleus: Clinical andscientific aspects. Supervisors: Prof.dr. Y. Temel; Prof.dr. K. van Overbeeke; Co-supervisor: Dr. A. Jahanshahi.

Sven Akkerman. Temporal aspects of cyclic messenger signaling in object recognition memory; a pharmalogical approach. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisors: dr. J. Prickaerts; dr. A. Blokland.

Anja Moonen. Emotion and Cognition in Parkinson's disease; etiology and neurobiological mechanisms. Supervisor: Prof.dr. F.R.J. Verhey; Co-supervisor: dr. A.F.G.Leentjens.

Anna Schüth. Three-dimensional bladder tissue morphology. Supervisors: Prof.dr. G.A. van Koeveringe; Prof.dr. M. v. Zandvoort, Aachen; Prof.dr. Ph. V. Kerrebroeck.
Elisabeth van der Ven. Ethnic minority position as risk indicator for autism- Spectrum and psychotic disorders. Supervisors: Prof.dr. J.P. Selten; Prof.dr. J. van Os.

Zuzana Kasanova. Environmental reactivity for better or worse; The impact of stress and reward on neurochemistry, affect and behavior across the psychosis continuum. Supervisor: Prof.dr. I. Myin-Germeys, KU Leuven/UM; Co-supervisor: dr. D. Collip.

Danielle Lambrechts. Ketogenic diet therapies; treatment for children and adults with refractory epilepsy. Supervisors: Prof.dr. H.J.M. Majoie; Prof.dr. J.S.H. Vles; Prof.dr. A.P. Aldenkamp; Co-supervisor: dr. A.J.A. de Louw, Kempenhaghe, Heeze.

Frank van Bussel. Advanced MRI in diabetes; cerebral biomarkers of cognitive decrements. Supervisors: Prof.dr.ir. W.H. Backes; Prof.dr. P.A.M. Hofman; Co-supervisor: dr. J.F.A. Jansen.

Lisa Schönfeldt. Neurostimulation to treat brain injury? Supervisors: Prof.dr. Y. Temel; Prof.dr. S. Hendrikx, Hasselt; Co-supervisor: dr. A. Jahanshahi.

Rianne Geerlings. Transition in patients with childhood-onset epilepsy; a long way to adulthood. Supervisor: Prof.dr. A.P. Aldenkamp; Co-supervisors:dr. A.J.A. de Louw, dr. L.M.C. Gottmer, Kempenhaeghe.

Nele Claes. B cells as multifactorial players in multiple sclerosis pathogenesis: insights from therapeutics. Supervisors: Prof.dr. V. Somers, Hasselt; Prof.dr. R. Hupperts; Co-supervisors: Prof.dr. P. Stinissen, dr. J. Fraussen, Hasselt.

Olaf Schijns. Epilepsy surgery and biomarkers from history to molecular imaging. Supervisors: Prof.dr. J.J. van Overbeeke; Prof.dr. H. Clustermann, Aachen; Co-supervisors:dr. G. Hoogland; dr. M.J.P. v. Kroonenburgh.

Lizzy Boots. Balanced and Prepared; development and evaluation of a supportive e- health intervention for caregivers of people with early-stage dementia. Supervisors: Prof.dr. F.R.J. Verhey; Prof.dr. G.I.J.M. Kempen; Co-supervisor: dr. M.E. de Vugt.

Wouter Donders. Towards patient-specific (cerebro-) vascular model applications. Supervisors: Prof.dr. T. Delhaas; Prof.dr.ir. F.N. van de Vosse, TUE; Co-supervisor: dr.ir. W. Huberts.

Sizzle Vanterpool. The implications of intrauterine invasion by microbes for placental Pathology and the occurrence of adverse pregnancy outcomes. Supervisor: Prof.dr. B.W. Kramer. Co-supervisors: dr. J.V. Been, Erasmus MC Rotterdam, dr. U von Rango.

Manuela Heins. The Relationship between Social Adversity, Psychosis, and Depression across an Individual's Life Span. Supervisor: Prof.dr. I. Myin-Germeys.

Christianus van Ganzewinkel. NEONATAL PAIN; Out of Sight, Out of Mind? Supervisor: Prof.dr. B.W.W. Kramer; Co-supervisor: dr. P. Andriessen, MMC Veldhoven.

Anne-Hilde Muris. Hype or hope? Vitamin D in multiple sclerosis; A clinical and immunological perspective. Supervisor: Prof.dr. R.M.M. Hupperts; Co-supervisor: dr. J.G.M.C. Damoiseaux.

Gerard Bode. The link between ceramide transporters, innate Immunity and Alzheimer's disease. Supervisor: Prof.dr. M.H.V. de Baets; Co-supervisors: dr. P. Martinez, dr. M. Losen.

Jo Stevens. Advanced diagnostics and therapeutics for Alzheimer's disease. Supervisor:Prof.dr. M. de Baets; Co-supervisors: dr. M. Losen, dr. P. Martinez-Martinez.

Rosan Luijcks. Stress and pain in muscles and brain; developing psychophysiological paradigms to examine stress and pain interactions. Supervisors: Prof.dr. J.J. van Os; Prof.dr.ir. H.J. Hermens, UT; Co-supervisor: dr. R. Lousberg.

M.C. Haanschoten. Towards efficient cardiac surgery – the integrating role of anesthesiology and intensive care. Supervisors: Prof. dr. W. Buhre; Prof. dr. A. van Zundert (Queensland); Co-supervisors: Dr. M.A. Soliman Hamad; Dr. A. van Straten (Catharina zkhs.)

Harmen Jan van de Haar. Microvascular and blood-brain barrier dysfunction in Alzheimer's disease. Supervisor: Prof.dr.ir. W. Backes; Prof.dr. F. Verhey; Co-supervisor:Dr. J. Jansen; Dr.ir. M. v. Osch, LUMC.

Coenraad Itz. Chronic low back pain, considerations about: Natural Course, Diagnosis, Interventional Treatment and Costs. Supervisor: Prof.dr. M. van Kleef; Prof.dr. F. Huygen, EUR; Co- supervisor: Dr. B. Ramaekers.

Willemijn Jansen. The Path of Alzheimer's disease: from neuropathology to clinic. Supervisor: Prof.dr. F. Verhey; Co-supervisors: Dr. P.J. Visser; Dr. I. Ramakers.

Ligia dos Santos Mendes Lemes Soares. Phosphodiesterase inhibitors: a potential therapeutic approach for ischemic cerebral injury. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisors: Dr. R.M. Weffort de Oliveira, Brazil; Dr. J. Prickaerts

Martijn Broen. Anxiety and depression in Parkinson's disease. Supervisor: Prof.dr. R.J. van Oostenbrugge; Co-supervisors: Dr. A.F.G. Leentjens; Dr. M.L. Kuijf.

Sandra Schipper. Extrasynaptic receptors as a treatment target in epilepsy. Supervisor: Prof.dr. J.H.S. Vles; Co-supervisors: Dr. G. Hoogland; Dr. S. Klinkenberg; Dr. M.W. Aalbers, RUG.

João Casaca Carreira. Making sense of Antisense Oligonucleotides Therapy in Experimental Huntington's disease. Supervisor: Prof.dr. Y. Temel; Co-supervisors: Dr. A. Jahanshahi; Dr. W. van Roon-Mom, LUMC.

Dominique IJff. Trick or Treat? Cognitive side-effects of antiepileptic treatment. Supervisors: Prof.dr. A.P. Aldenkamp; Prof.dr. M. Majoie; Co-supervisors: Dr. J. Jansen; Dr. R. Lazeron, Kempenhaeghe.

Alfredo Ramirez. Neurogenetic approach in neurodegenerative disorders. Supervisors: Prof.dr. B.P.F. Rutten; Prof.dr. H.W.M. Steinbusch; Prof.dr. M.M. Nöthen, University of Bonn.

Nienke Visser. Toric Intraocular lenses in cataract surgery. Supervisor: Prof.dr. R.M.M.A. Nuijts; Co-supervisor: Dr. N.J.C. Bauer.

Jakob Burgstaller. Prognostic indicators for patients with degenerative lumbar spinal stenosis. Supervisor: Prof.dr. M. van Kleef; Co-supervisors: Dr. M.M. Wertli, University of Zurich; Dr. H.F. Gramke.

Mark van den Hurk. Neuronal Identity and Maturation: Insights from the Single-Cell Transcriptome. Supervisors: Prof.dr. H.W.M. Steinbusch; Prof.dr. B.P.F. Rutten; Co- supervisors: Dr. G. Kenis; Dr. C. Bardy, Adelaide.

Maria Nikiforou. Prenatal stress and the fetal gut. Potential interventions to prevent adverse outcomes. Supervisors: Prof.dr. B.W. Kramer; Prof.dr. H.W. Steinbusch; Co- supervisor: Dr. T.G. Wolfs.

Janneke Peijnenborgh. Assessment of cognition, time perception, and motivation in children. Supervisors: Prof.dr. J.S.H. Vles; Prof.dr. A.P. Aldenkamp; Co-supervisors: Dr. J. Hendriksen; Dr. P. Hurks.

Joany Millenaar. Young onset dementia; towards a better understanding of care needs and experiences. Supervisors: Prof.dr. F. Verhey; Prof.dr. R. Koopmans, RUN; Co- supervisors: Dr. M. de Vugt; Dr. C. Bakker, RUN.

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Adriana Smits. Perinatal factors and hearing outcome. Supervisors: Prof.dr. R.J. Stokroos; Prof.dr. B.W. Kramer; Prof.dr. B. Kremer.

Angela Bouwmans. Transcranial sonography in parkinsonian disorders: clear window or blurred vision. Supervisor: Prof.dr. W.H. Mess; Co-promotores: Dr. W.E.J. Weber; Dr. A.F.G. Leentjens.

Björn K. Stessel. Patient centred care after day surgery: scope for improvement. Supervisors: Prof.dr. W. Buhre; Prof.dr. B. Joosten. Co-supervisor: Dr. A.H. Gramke.

Jan Guy Bogaarts. Quantitative EEG and machine learning methods for the detection of epileptic seizures and cerebral asymmetry. Supervisor: Prof.dr. W.M. Mess; Co-supervisor: Dr.ir. J.P.H. Reulen; Dr.ir. E.D. Gommer.

Martin M. Müller. Pregnancy derived products for treatment of perinatal brain injuries. Supervisors: Prof.dr. B.W.W. Kramer; Prof.dr. D. Surbek, Bern; Co-supervisors: Dr. T. Wolfs; Dr. G. Gavilanes.

Daan Ophelders. Novel treatment strategies for the protection of the preterm brain; Re-balancing inflammation and regeneration. Supervisor: Prof.dr. B. Kramer; Co-supervisor: Dr. T. Wolfs; Dr. R. Jellema.

Rosalie van Knippenberg. Experience sampling in dementia care; an innovative intervention to support caregivers in daily life. Supervisors: Prof.dr. F. Verhey; Prof.dr. R. Ponds; Prof.dr. I. Myin-Germeys, KU Leuven; Co-supervisor: Dr. M. de Vugt.

Claudia Vingerhoets. Investigating neurobiological mechanisms underlying comorbid cognitive symptoms in psychosis and substance use. Supervisors: Prof.dr. T. van Amelsvoort; Prof.dr. J. Booij, UvA; Co-supervisor: Dr. O. Bloemen

Dennis Oerlemans. Evolution of Neuromodulation for Lower Urinary Tract Dysfunction; Past, Present and Future. Supervisors: Prof.dr. Ph. van Kerrebroeck; Prof.dr. G. van Koeveringe. Co-supervisors: Dr. E. Weil; Dr. T. Marcelissen.

Marion Levy. Evaluation of BDNF/TrkB signaling as a common target in the treatment of major depression and Alzheimer's disease. Supervisors: Prof.dr. H. Steinbusch; Prof. L. Lanfumey, Université Paris Descartes, France. Co-supervisors: Dr. G. Kenis; Dr. D. van den Hove.

Patrick Domen. Stay connected: a family-based diffusion imaging study in psychotic disorder. Supervisor: Prof.dr. J. van Os. Co-supervisor: Dr. M. Marcelis

Geor Bakker. Innovative Approaches to Understanding the Neurobiology of Psychosis. Supervisors: Prof.dr. T. van Amelsfoort; Prof.dr. J. Booij, UvA. Co-supervisor: dr. M. Caan,UvA; dr. O. Bloemen.

Wilma Boevink. HEE! Over Herstel, Empowerment en Ervaringsdeskundigheid in de psychiatrie. Supervisors: Prof.dr. J. van Os; Prof.dr. Ph. Delespaul. Co-supervisor: dr. H. Kroon.

Nataliia Markova . Modified swim test as a mouse depression paradigm of enhanced Cognitive processing: the role of GSK3β. Supervisor: Prof.dr. H. Steinbusch; Prof.dr. K-P.Lesch, University of Wuerzburg. Co-supervisor: Dr. T. Strekalova.

Merijn van de Laar. Individual differences in insomnia; implications of Psychological factors for diagnosis and treatment. Supervisor: Prof.dr. A. Aldenkamp; Prof.dr. D. Pevernagie, Universiteit Gent. Co-supervisor: Dr. S. Overeem, TUE.

Willem Buskermolen. If only I could tell …; Measuring predictors for challenging behaviour in people with both intellectual disability and hearing impairment. Supervisor: Prof.dr. A. Aldenkamp. Co-supervisor: Dr. J. Hoekman, UL.

Kay Deckers. The role of lifestyle factors in primary prevention of dementia; an epidemiological perspective. Supervisor: Prof.dr. F. Verhey. Co-supervisor: Dr. M. vanBoxtel; Dr. S. Köhler.

Brechje Dandachi-FitzGerald. Symptom validity in clinical assessments. Supervisors: Prof.dr. R. Ponds; Prof.dr. F. Verhey.

Maurice Theunissen. Understanding factors affecting postoperative Quality of Life. Supervisors: Prof.dr. M. Peters, Prof.dr. M. Marcus. Co-supervisor: Dr. H. Gramke.
Anna Cleutjens. COgnitive-Pulmonary Disease? Neuropsychological functioning in patients with COPD. Supervisors: Prof.dr. E. Wouters, Prof.dr. R. Ponds. Co-supervisors:Dr. D. Janssen, Horn, Dr. J. Dijkstra.

Laura Serpero. Next Generaton Biomarkers in Perinatal Medicine: S100B Protein. Supervisors: Prof.dr. D. Gazzalo, Alessandria, Italy; Prof.dr. B..W.W. Kramer. Co-supervisor: Dr. A.W.D. Gavilanes.

Alessandro Varrica. S100B Protein and Congential Heart Diseases: Brain Aspects. Supervisors: Prof.dr. D. Gazzalo, Alessandria, Italy; Prof.dr. J.S.H. Vles; Prof.dr. L.J.I. Zimmermann. Co-supervisor: Dr. A.W.D. Gavilanes.

Pim R.A. Heckman. Targeting phosphodiesterase type 4 for improving cognitive fronto- striatal function: a translational approach. Supervisor: Prof.dr. J.G. Ramaekers. Co- supervisors: Dr. J.H.H.J.. Prickaerts; Dr. A. Blokland.

Sven van Poucke. Platelets, form sample to big data; exploring granularity in platelet research. Supervisors: Prof.dr. M.A.E. Marcus; Prof.dr. W. Buhre. Co-supervisor: Dr. M.Lancé.

Désirée M.J. Vrijens. Dysfunctions of the Lower Urinary Tract and Affective Symptoms. Supervisors: Prof.dr. Ph.E.V. van Kerrebroeck; Prof.dr. G.A. van Koeveringe. Co- supervisors: Dr. C. Leue.

Tamar van Veenendaal. Neurotransmitters & Networks. An MR view on epilepsy andantiepileptic drugs. Supervisors: Prof.dr.ir. W.H. Backes; Prof.dr. A.P. Aldenkamp. Co- supervisor: Dr. J.F.A. Jansen.

Evelien M. Barendse. Autism Spectrum Disorders in High functioning Adolescents; Diagnostic considerations (AHA). Supervisors: Prof.dr. A.P. Aldenkamp; Prof.dr. R.P.C. Kessels, Radboud University.

Roy Lardenoije. A venture into the epigenetics of aging and Alzheimer's Disease. Supervisors: Prof.dr. B.P.F. Rutten; Prof.dr. H.W.M. Steinbusch. Co-supervisors: Dr. D. van den Hove; Dr. C.A. Lemere, USA.

Charlotte L. Mentzel. The course recognition and treatment of movement disorders in severe mental illness. Supervisors: Prof.dr. P.N. van Harten; Prof.dr. M.A.J. de Koning- Tijssen, UMCG. Co-supervisor: Dr. P.R. Bakker.
Tim Batink. Third Wave Behaviour Therapy: Process Measures and Contextual Interventions. Supervisors: Prof.dr. F.P.M.L. Peeters; Prof.dr. J.J. van Os; Prof.dr. M.C.Wichers, UMC Groningen.

Kevin L.J. Rademakers. Detrusor Underactivity: From Theory To Clinical Assessment. Supervisors: Prof.dr. G.A. van Koeveringe; Prof.dr. Ph.E.V. van Kerrebroeck. Co-supervisor:Dr. M. Oelke.

Iris M.J. Lange. Should I stay or should I go ? Brain mechanisms underlying fear and safety learning, and explosure therapy outcome. Supervisors: Prof.dr. K.R.J. Schruers; Prof.dr. T.A.M.J. van Amelsfoort. Co-supervisor: Dr. L. Goossens.

Ruben G.F. Hendriksen. Evidence for a dystrophin-associated encephalopathy in Duchenne Muscular Dystrophy. Supervisor: Prof.dr. J.S.H. Vles. Co-supervisors: Dr. G. Hoogland; Dr. M.W. Aalbers, UMC Groningen.

Michael Gofeld. Strengths and limitations of the lumbar spine ultrasound-guided interventions. Supervisor: Prof.dr. M. van Kleef. Co-supervisor: Dr. M. Sommer.

Willem A.R. Zwaans. Strategies for chronic inguinal pain. Supervisor: Prof.dr. M. van Kleef. Co-supervisors: Dr. R.H.M. Roumen; Dr. M.R.M. Scheltinga, MMC Veldhoven.

Linda M. Rolf. Mapping the effects of vitamin D in multiple sclerosis A 3D Perspective. Supervisor: Prof.dr. R.M.M. Hupperts. Co-supervisors: Dr. J.G.M.C. Damoiseaux; Dr. J.J.F.M. Smolders, CWZ Nijmegen.

Maarten van Beek. Spinal Cord Stimulation in Clinical and Experimental Painful Diabetic Polyneuropathy. Supervisors: Prof.dr. E.A. Joosten; Prof.dr. M. van Kleef. Co-supervisor: Dr. S.M.J. van Kuijk.

Melina Barkhuizen. Genetic and perinatal risk factors for movement disorders. Supervisors: prof.dr. B.W.W. Kramer, prof.dr. H.W.M. Steinbusch, Prof.dr. A.F. Grobler. Co- supervisor: dr. A.W.D.Gavilanes-Jimenez.

Renske Uiterwijk. Cognitive function and cerebral small vessel disease in hypertension. Supervisor: prof.dr. R.J. van Oostenbrugge. Co-supervisor: Dr. J.E.A. Staals.

Elles Douven. Depression and apathy after stroke. Supervisor: prof.dr. F.R.J. Verhey. Co-supervisors: Dr. P. Aalten, dr. J. Staals.

Mauro Pessia. Brain K+ Channels: from molecular and physiological features to autism spectrum disorder and intellectual disability. Supervisors: prof.dr. H.W.M. Steinbusch, prof.dr. M.B. Donati, It.

Carsten Leue. Hyperarousal in the Hospital and what to do about it: the MED-PSYCH- NET - a transitional network approach fostering personalized care in psychosomatic medicine. Supervisors: Prof.dr. J. van Os, Prof.dr. A. Masclee. Co-supervisors: Dr. J. Strik, Dr. J. Kruimel

Andrea S. Herrera Soto. Aminochrome, an endotoxin for inducing a new rat model of Parkinson's Disease. Supervisor: prof.dr. H.W.M. Steinbusch. Co-supervisors: Prof.dr. Juan Segura-Aquilar; prof. G. Diaz-Veliz, Santiago of Chile

Eline E.B. de Clerck. Ocular neurodegenerative changes and macular cysts in prediabetes and type 2 diabetes. Supervisors: Prof.dr. C.A.B. Webers, Prof.dr. C.D.A.Stehouwer. Co-supervisor: Dr. J.S.A.G. Schouten

Steven T.H. Honings. Exploring psychosis and multidirectional violence: a prospectivestudy in the general population. Supervisor: Prof.dr. J. van Os. Co-supervisor: Dr. M. Drukker

2018

Sau May Wong. Advances in Microvasculair MRI Techniques: Breaking the Pathophysiological Barriers in Cerebral Small Vessel Disease. Supervisor: Prof.drir. W.H. Backes, Porf.dr. R.J. van Oostenbrugge. Co-supervisor: Dr. J.F.A. Jansen

Mark B.N. van Winkel. Lonely at heart and stressed in company of Others; the influenceof daily life social experiences and emotions on depression. Supervisors: prof.dr. F. Peeters; prof.dr. I. Myin-Germeys, KU Leuven/UM; prof.dr. M. Wichers, UMC Groningen

Harsha Birur Laxmana Rao. Revisiting the vascular theory of glaucoma using optical coherence tomography angiography. Supervisors: prof.dr. C.A.B. Webers; prof.dr. R.N.Weinreb, University of California, San Diego

Babette L.R. Reijs. Cognitive correlates of cerebrospinal fluid biomarkers for Alzheimer's disease. Supervisor: prof.dr. F.R.J. Verhey. Co-supervisors: dr. P.J. Visser;dr. I.H.G.B. Ramakers

Rachel Slangen. Spinal cord stimulation in painful diabetic peripheral Neuropathy. Clinical- and cost-effectiveness. Supervisors: prof.dr. M. van Kleef; Prof.dr. C. Dirksen;prof.dr. C. Faber

Ganne Chaitanya. Epilepsy: A network disorder. Supervisors: prof.dr. A.P. Aldenkamp; prof. P. Satishchandra, NIMHANS, Bangalore, India. Co-supervisors: Dr. J.F.A. Jansen; Dr. S. Zinger, TUE

Sumitha Rajendrarao. New Insight into the Multifaceted Pathogenic Mechanisms of Sporadic Amyotrophic Lateral Sclerosis. Supervisors: prof.dr. B.W. Kamer; prof.dr. H.W. Steinbusch. Co-supervisor: prof. T.R. Raju, NIMHANS, Bangalore, India

Suzanne Roggeveen. Interference of mobile phone with electrophysiology and emotions; results from short-term experimental studies. Supervisor: prof.dr. J. van Os. Co-supervisor: dr. R. Lousberg.

Matthias Walter. Multi-methodological approaches to investigate lower urinary tractfunction in health and disease. Supervisors: prof.dr. Ph.E.V.A. van Kerrebroek; prof.dr. G.A. van Koeveringe; prof.dr. A. Curt, Zürich, CH.

Lalit Gupta. Inhomogeneities in spontaneous brain fluctuations. Supervisors: prof.dr.ir. WH. Backes; prof.dr. P.A.M. Hofman. Co-supervisor: dr. J.F.A. Jansen.

Chaitra Jayadev. Impact of imaging the pediatric retina. Supervisor: prof.dr. C.A.B. Webers. Co-supervisor: dr. N.J.C. Bauer; dr. A. Vinekar.

Annelie Klippel. Navigating through complexity; processes and mechanisms underlying the development of psychosis. Supervisors: prof.dr. I. Myin-Germeys, KU-Leuven; prof.dr. M.C. Wichers, UMC Groningen. Co-supervisor: dr. U. Reininghaus.

Kürşat Altinbaş. Reconstructing The Diagnostic Framework of Bipolarity. Supervisor:Prof.dr. J. van Os. Co-supervisor: Dr. I.S. Gülöksüz.

Andrea J.R. Balthasar. Eyes of the needle; Spectral tissue sensing, an innovative technology for detecting various tissue types during percutaneous needle-based procedures in locoregional anesthesia and pain medicine. Supervisor: prof.dr. M. van Kleef. Co-supervisor: dr. G-J. van Geffen, Radboud UMC Nijmegen.

Walmari Pilz. Shedding light on oropharyngeal dysphagia in myotonic dystrophy type 1. Supervisor: prof.dr. B. Kremer. Co-supervisors: dr. L.W.J. Baijens; dr. V. Lima Passos.

Nynke J. van den Hoogen. Repetitive painful procedures in the neonate: Treatment andadult pain sensitivity. Supervisors: prof.dr. E.A.J. Joosten, prof.dr. D. Tibboel, Erasmus MC-Sophia, Rotterdam. Co-supervisor: dr. J. Patijn.

Carlota Mestres Gonzalvo. Medication optimisation; Methodological aspects and new strategies. Supervisors: prof.dr. F.R.J. Verhey, prof.dr. P.H.M. van der Kuy, Erasmus MC Rotterdam. Co-supervisors: dr. R. Janknegt, Zuyderland MC.

Carolin Hoffmann. The Brain under Attack: Autoantibodies in Psychotic Disorders. Supervisors: prof.dr. P. Martinez, prof.dr. B. Rutten, prof.dr. J. van Os, UU/UM.

Jindra M. Bakker. On the bumpy road of happiness: Mechanisms of daily life reward processing and how it can be changed. Supervisors: prof.dr. M. Wichers, UMC Groningen, prof.dr. I. Myin-Germeys, KU Leuven/UM. Co-supervisor: dr. L. Goossens.

Marasha-Fiona de Jong. Between mood and matter; studies on the interface between mood disorders and physical conditions. Supervisor: prof.dr. F.P.M.L. Peeters. Co- supervisors: prof.dr. Mischoulon.

Anouk Smeets. New insights in deep brain stimulation for Tourette syndrome. Supervisor: prof.dr. Y. Temel. Co-supervisors: dr. L. Ackermans, dr. A.A. Duits, de. A.F.G.Leentjens.

Margaretha Skowron. Cisplatin resistance in urothelial carcinoma; Understanding and targeting inherent and acquired mechanisms. Supervisors: prof.dr. G.A. van Koeveringe, prof.dr. P. Albers, Heinrich-Heine Univ. Düsseldorf. Co-supervisors: dr. J.G.H. van Roermund, dr. A. Romano.

Thierry Mentzel. Capturing the cacophony of movement. Supervisors: prof.dr. P.N. van Harten, prof.dr. H.A.M. Daanen, VUA. Co-supervisor: dr.mr. O.J.N. Bloemen, GGZ Hilversum/UM.

Petronella de Meij. Quality indicators for the assessment of pain clinic care: A step forward? Quality from professionals and pain patients' perspective (QiPPP). Supervisors: prof.dr. G.D.E.M. van der Weijden, prof.dr. M. v. Kleef. Co-supervisor: dr. A.J.A. Köke.

Thomas Vaessen. Stress sensitivity in psychosis: assessment, mechanism & intervention. Supervisor: prof.dr. I. Myin-Germeys, KU Leuven/UM.

Yori van der Steen. Dissecting the psychosis continuum; risk factors along the pathway from experiences to disorder. Supervisor: prof.dr. I. Myin-Germeys, KU Leuven/UM, prof.dr. R. van Winkel, KU Leuven.

Aryo Zare. Unveiling the sensory connections between the bladder and the brain thatinvolve the periaqueductal gray matter. Supervisor: prof.dr. G.A. van Koeveringe; Co- supervisor: dr. A. Jahanshahi.

Magdalena Weidner. Brain serotonin throughout development – for better and for worse. Supervisors: prof.dr. H.W.M. Steinbusch, prof.dr. K.P. Lesch, JM.Univ. Würzburg. Co- supervisor: dr. D.L.A. van den Hove.

Catherine Vossen. Cortical processing of pain; the role of habituation. Supervisors: prof.dr. E.A. Joosten, prof.dr. J. van Os, UU/UM. Co-supervisor: dr. R. Lousberg.

Whitney Freeze. Microvascular contributions to dementia; Exploring the role of blood- brain barrier leakage in cerebral small vessel disease and Alzheimer disease. Supervisors: prof.dr. F.R.J. Verhey, prof.dr.ir. W.H. Backes. Co-supervisor: dr. H.I.L. Jacobs.

Simone Schüller. Characterization of Stem and Immune Cell Ontogeny to Inform Prevention and Treatment of Infections in Preterm Newborns. Supervisors: prof.dr. B.W.W. Kramer, prof.dr.med. A. Berger, Wien. Co-supervisor: dr. E. Villamor.

Michael J. Kemna. Predicting relapses in ANCA associated vasculitis. Supervisor: prof.dr. J.W. Cohen Tervaert. Co-supervisors: dr. J. Damoiseaux, dr. P. van Paassen.

Artemis Iatrou. Epigenetics in mental and neurodegenerative disorders. Supervisor: prof.dr. B.P.F. Rutten. Co-supervisors: dr. D.L.A. van den Hove, dr. G. Kenis.

Laura Wielders. Prevention & Treatment of Cystoid Macular Edema after Cataract Surgery. Supervisor: prof.dr. R.M.M. Nuijts. Co-supervisors: dr. J.S.A.G. Schouten, CWZ Nijmegen, dr. B. Winkens.

Daisy Hoofwijk. The way to understanding Chronic Postsurgical Pain; From clinical and psychological predictors to incorporating genetics. Supervisor: prof.dr. W.F.F.A. Buhre; prof.dr. E.A.J. Joosten; Co-Supervisor: dr. H.-F. Gramke; dr. A.A.A. Fiddelers.

Loes Leenen. Self-management in Epilepsy; The Goal is: “Live with a Z(s)mile. Supervisors: prof.dr. H.J.M. Majoie; prof.dr.mr. S.M.A.A. Evers; prof.dr. C.M. van Heugten.

Chiara Peila. ‘Effects of Pasteurization and Refrigerated Storage on Human MilkNeurobiomarkers Concentrations. Supervisors: prof.dr. D. Gazzallo, Alessandria, It./MUMC+; prof.dr. G. Visser, UU; prof.dr. E. Bertino, Alessandria, It.

Raymond van de Berg. The Vestibular Implant: Feasibility in humans. Supervisor: prof.dr. H. Kingma; Co-supervisor: dr. J.-P. Guyot, Université de Genève, CH.

Nils Guinand. The Vestibular Implant: a more stable horizon for patients with a bilateralvestibular deficit? Supervisors: prof.dr. H. Kingma; rof.dr. J.-P. Guyot, Université de Genève, CH.

Jasper Smit. Exploring deep brain stimulation as a treatment for tinnitus. Supervisors: prof.dr. R.J. Stokroos; prof.dr. Y. Temel; Co-supervisor: dr. Jahanshahianvar.

Bindu Paravil Sankaran. Brain MRI in Mitochondrial Disorders: Correlating the Phenotype with Genotype. Supervisor: prof.dr. H. Smeets; prof.dr. A. Taly, NIMHANS,Bangalore, India.

Syenna Schievink. Vascular cognitive impairment; at the heart of the matter. Supervisor: prof.dr. F.R.J. Verhey; prof.dr. R.J. van Oostenbrugge; Co-supervisor: dr. S.Köhler.

Isabelle Bos. Biomarkers of Alzheimer’s disease; relations with vascular factors and cognition in the pre-dementia stages. Supervisor: dr. P.J. Visser; prof.dr. F.R.J. Verhey;Co-supervisor: dr. S.J.B. Vos.

Stijn Michielse. Road work ahead; cerebral pathways mediating Psychological mechanisms underlying the psychosis spectrum. Supervisor: prof.dr. J.J. van Os; Co- supervisor: dr. M.C. Marcelis.

Georgios Schoretsanitis. Risperidone-based therapeutic regimens; Drug interactions and adverse drug reactions. Supervisor: prof.dr. K.R.J. Schruers; Co-supervisor: dr. M. Bak .

Alieske Dam. INLIFE; An innovative online social support intervention for caregivers of persons with dementia. Supervisor: prof.dr. M.E. de Vugt; prof.dr. F.R.J. Verhey; Co- supervisor: dr. M.P.J. van Boxtel.

Roel Haeren. Vascular ventures; Analysis of vascular structures and function in epilepsy. Supervisor: prof.dr. Y Temel; Co-supervisor: dr. K. Rijkers; dr. G. Hoogland.

Chiara Fabbri. Pharmacogenomics of antidepressant drugs: perspectives for thepersonalization of treatment in depression. Supervisors: prof.dr. K. Schruers; prof.dr. A. Serretti, Bologna.

Esther van Duin. Dancing in the (B)rain'; neurobiology of reward, stress & Information processing in 22q11.2 deletion syndrome. Supervisors: prof.dr. T. van Amelsvoort; prof.dr. J. Booij, UvA. Co-supervisor: dr. D. Hernaus.

Rob Verdonschot. Oropharyngeal dysphagia and its psychiatric Comorbidities; The prevalence of affective symptoms and the unmet clinical need for integrated care in medically unexplained symptoms. Supervisor: prof.dr. B. Kremer; Co-supervisors; dr. L.Baijens; dr. S. Vanbelle.

Lisanne Breuer. Accelerated Cognitive Ageing in Epilepsy' Does it Exists? Supervisors: prof.dr. A. Aldenkamp; prof.dr. P. Boon, UZ Gent; Co-supervisors: dr. A. de Louw, Kempenhaeghe, Heeze; dr.ir. S. Zinger, TUE.

Liselot Kerpershoek. Access to formal dementia care; A European perspective. Supervisors: prof.dr. F. Verhey; prof.dr. M. de Vugt; prof. B. Woods, Bangor University, UKCo-supervisor: dr. C. Wolfs.

Henrietta Steinhart. Same Same but Different; Psychological Interventions and how to Mind the Knowledge Practice Gap. Supervisor: prof.dr. I. Myin-Germeys. Co-supervisor: dr. U. Reininghaus.

Ulrich Mehnert. The management of urine storage dysfunction in the neurological patient. Supervisors: prof.dr. G. van Koeveringe; prof.dr. Ph.van Kerrebroeck; prof.dr. S. Wachter, Antwerpen; prof.dr E. Chartier-Kastler, Sorbonne, Paris.

Giovanne B. Diniz. Weaning-induced alterations on neuropeptidergic populations of the rat hypothalamus. Supervisors: prof.dr. H. Steinbusch; prof.dr. J. Bittencourt, ICB/USP, Brasil.

Rajani Ravindra Battu. Inherited Retinal Diseases: New Imaging and Molecular Genetics. Supervisor: prof.dr. C.A.B. Webers. Co-supervisors:dr. J.S.A.G. Schouten, CWZ; dr. T.T.J.M. Berendschot.

2019

Jans van Ool. Diagnostic and neuropsychiatric considerations in epilepsy and intellectualdisability; Psychological perspectives. Supervisor: prof.dr. A. Aldenkamp. Co-supervisors: dr. J. Hendriksen; dr. H. Schelhaas, Kempenhaeghe.

Eveline Janssen. Depression in the elderly: focus on high risk groups. Supervisors: prof.dr. F. Verhey; prof.dr. M. de Vugt. Co-supervisor: pr. M. Schram.

Cécile Kicken. Extreme blood coagulation; investigating the influence of physiologicalextremes on thrombin generation and platelet activation. Supervisor: prof.dr. W. Buhre Co-supervisors; dr. B. de Laat; dr. M. Lancé, Qatar.

Martinus van Eerd. Diagnosis and Interventional Pain Treatment of Cervical Facet Joint Pain. Supervisor: prof.dr. M. van Kleef. Co-supervisor; dr. J. Patijn, Eindhoven; dr. M. Sommer.

Chenxing E. Zhang. Novel insights in the pathophysiology of cerebralsmall vessel disease –a study using advanced imaging techniques. Supervisors: prof.dr. R.J. van Oostenbrugge; prof.dr.ir. W.H. Backes; Co-supervisor: dr. J. Staals.

Ivo Eijkenboom. A zebrafish model of small-fiber neuropathy. Supervisors: prof.dr. H.J.M.Smeets; prof.dr. C.G. Faber; Co-supervisor: dr. J. Vanoevelen.

Bianca de Greef. Small fiber neuropathy: from underlying conditions to treatment. Supervisor: prof.dr. C.A. Faber; Co-supervisor: dr. I.S.J. Merkies; dr. J.G.J. Hoeijmakers.

Lotte Berk. MINDFULNESS AND AGING: Exploring Mechanisms and Interventions. Supervisors: prof.dr. J. van Os; prof.dr. M.W. de Vugt; Co-supervisor: dr. M.P.J. van Boxtel.

Mor Dickman. Practice patterns and outcomes of corneal transplantation. Supervisor: prof.dr. R.M.M.A. Nuijts; Co-supervisors: dr. T.J.M. Berendschot; dr. F.J.H.M. van den Biggelaar.

Thyagi Ponnamperuma. Mental Health Problems in Sri Lankan Adolescents Exposed to the Tsunami and Other Traumatic Events. Supervisor: prof.dr. M.W. De Vries; Co-supervisor: dr. N.A. Nicolson.

Robbert C. Maatman. Anterior cutaneous nerve entrapment syndrome (acnes): an analysis of various subtypes and alternative treatment modalities. Supervisor: prof.dr. M. van Kleef; Co-supervisors: dr. R.M.H. Roumen, dr. M.R.M. Scheltinga.

Mari Elshout. Neovascular Age-Related Macular Degeneration in the Era of Value-Based Health Care. Supervisor: prof.dr. C.A.B. Webers; Co-supervisor: dr. J.S.A.G. Schouten.

Jeroen Deenik. Thinking inside the box; Changing lifestyle to improve the health status of inpatients with severe mental illness. Supervisor: prof.dr. P.N. Harten; Co-supervisors: dr. D.E. Tenback; dr. I.J.M. Hendriksen.

Thomas Draak. Peripheral Neuropathy outcome measures Standardisation (PeriNomS) studypart 3: Capturing the Patient's Voice. Supervisor: prof.dr. C.G. Faber; Co-supervisor: dr. I.S.J. Merkies.

Ana Luisa Gil Martínez. Neuroprotection in neurodegenerative processes associated with Parkinsonism and aging. Correlation between dopaminergic neuronal death and glial activation. Supervisor: prof.dr. H.W.M. Steinbusch, prof.dr. Maria-Trinidad Herrero Ezquerro, University of Murcia.

Bernice J.A. Gulpers. Anxiety in older adults; Correlates, comorbidities and prognosis with lifespan perspectives. Supervisor: prof.dr. F.R.J. Verhey, prof.dr. R.C. Oude Voshaar; Co-supervisor: dr. S. Köhler.

Elke Devocht. Combining a cochlear implant and a hearing aid in opposite ears: The best of both worlds. Supervisor: prof.dr. H. Kingma; co- supervisor: dr. E.I.J. George.

Gillian Townend. Rett Syndrome: Recognising the Communication Challenges, Needs and Potential of Individuals Living with a Rare Disease. Supervisor: prof.dr. L.M.G. Curfs; co-supervisor: dr. P.B. Marschik, Med. University of Graz, Austria.

Takashi Koizumi. Genetic and neuroinflammatory components of familial and sporadic cerebral Small Vessel Disease. Supervisor: prof.dr. H. Steinbusch, prof.dr. T. Mizuno,Japan; co-supervisor: dr. S. Foulquier.

Muhammad Ali. Integrative network-based approaches for modelling Human disease.Supervisor: prof.dr. J. Kleinjans; co-supervisor: dr. D. van den Hove; dr. E. Pishva.

Guillaume Durand. The adaptive side of psychopathy. Investigating adaptive characteristics associated with the psychopathic personality. Supervisor: prof.dr. B. Rutten; co-supervisor: dr J. Lobbestael.

Darius C. Henatsch. Honey: A Novel Treatment in Chronic Ear Infections. Supervisor: prof.dr. R.J. Stokroos; UMC Utrecht/UM; co-supervisor: dr. J.J. Briedé.

Reinhilde J. Melles. Vaginal penetration: pain or pleasure? The role of fear and sexual arousal. Supervisor: prof.dr. M.L. Peters; co-supervisor: dr. M. ter Kuile, LUMC, dr. M. Dewitte.

Raul Felipe Abella Antón. Cardiac Surgery Biochemical Monitoring in Congenital Heart Diseases Infants. Supervisors: prof. dr. D. Gazzolo, prof. dr. L.J.I. Zimmermann, prof. dr. J.S.H. Vles, co-supervisor; dr. A.W.D. Gavilanes.

Francesca M. Snoeijen-Schouwenaars. Diagnostic, neuropsychiatric and therapeutic considerations in epilepsy and intellectual disability – medical perspectives –. Supervisor: prof.dr. A.P. Aldenkamp, co-supervisors: dr. H.J. Schelhaas, SEIN Zwolle; dr. J.G.M. Hendriksen, Kempenhaeghe, Heeze.

Mariëlle H.J. Pruppers. Peripheral Neuropathies: Standardizing Functional Assessment. Supervisors: prof.dr. C.G. Faber; prof.dr. N.C. Notermans, UU; dr. I.S.J. Merkies, ius promovendi.

Shenghua Zong. Autoantibodies in disorders of the brain: expanding the spectrum. Supervisor: prof.dr. P. Marinez; co-supervisor: dr. M. Losen; dr. R. Rouhl.

Jan-Willem Kallewaard. Diagnosis and minimally invasive treatment of chronic discogenic low back pain. Supervisor: prof.dr. M. van Kleef; co-supervisors: prof.dr. H. van Santbrink; dr. P. Willems.

Simone M. Crivelli. Sphingolipid metabolism in the pathophysiology and treatment of Alzheimer's disease. Supervisors: prof.dr. P. Martinez-Martinez; prof.dr. E. deVries, VUmc. Co-supervisors: dr. M. Losen; dr. M. Mulder, Rotterdam.

Natasha Pahuja. Etiopathogenesis, advanced imaging and treatment outcomes in Asian Indians with keratoconus. Supervisor: prof.dr. R. Nuijts, co-supervisor: dr. R.Shetty, Bengaluru.

Pooja Khamar Mayur Raksha. Clinical, Molecular and Biomechanical outcomes of SMILE (small incision lenticule extraction) and other refractive surgery techniques. Supervisor: prof.dr. R. Nuijts, co-supervisor: dr. R. Shetty, Bengaluru.

Niels Janssen. Patterns and pathways. Indicators for potential improvements of dementia care. Supervisors: prof.dr. F. Verhey; prof.dr.mr. S. Evers; Co-supervisor: dr. R.Handels.

Giovanni Mansueto. Childhood adversities and Psychosis: investigation of the potential aetio-pathogenetic mechanisms. Supervisor: prof.dr. K. Schruers; co-supervisors: prof.dr. F. Cosci, University of Florence, It; prof.dr. R. van Winkel, KU Leuven.

Joke Debruyne. Cochlear implantation in adults with early-onset deafness. Supervisors:prof.dr. B. Kremer; prof.dr.ir. T. Francart, KU Leuven; Co-supervisor: dr.ir. J. Brokx.

Koenraad Meuwissen, Burst Spinal Cord Stimulation in a Rat Model of Chronic Neuropathic Pain: Spinal and Supraspinal Mechanisms. Supervisors: prof. dr. E.A.J.Joosten; prof. dr. M. van Kleef.

Lisa Schmiedek, Episodic memory in ageing and AD: a possible target for electrical stimulation ? Supervisors: prof. dr. F.R.J. Verhey; prof. dr. A.T. Sack; co-supervisor: dr. H.I.L. Jacobs

Paolo Maino, Implantable Intrathecal Drug Delivery in Treatment of Chronic Intractable Pain and Spasticity: Improvement of Safety and the Use of ImagingTechniques. Supervisors: prof. dr. E.A. Joosten; prof. dr. M. van Kleef.

José Geurts, Chronic Pain; Impact of Chronic Pain on a Societal, Personal, and Treatment Level. Supervisors: prof. dr. C.D. Dirksen; prof.dr. M. van Kleef; co-supervisor:dr. P.C. Willems.

Brigitte Brouwer, Painful Small Fiber Neuropathy; Symptoms, assessments and interventions. Supervisor: prof. dr. C.F. Faber; co-supervisors: dr. I.S.J. Merkies, Willemstad, Curaçao; dr. J.G.J. Hoeijmakers.

Ruth Gussenhoven, Antenatal inflammatory insults and preterm brain injury: Pathophysiology and therapeutic strategies. Supervisors: prof. dr. B.W. Kramer; prof. dr. L.J.I. Zimmermann; dr. T.G.A.M. Wolffs.

Adriana (Janine) Collet, Specific Care on the Interface of Mental health and Nursing home “SpeCIMeN”. Supervisors: prof. dr. M.E. de Vugt; prof. dr. J.M.G.A. Schols; prof. dr. F.R.J. Verhey.

Fares Nigim, Glioblastoma and Meningioma Biology, Targeted Therapy and Oncolytic Virus Therapy. Supervisors: prof. dr. Y. Temel; prof. dr. S.D. Rabkin, Harvard; co- supervisors: dr. H. Wakimoto, Harvard; dr. L. Ackermans.

Leonie Banning, Neuropsychiatric symptoms in Alzheimer’s disease; Associations withbiomarkers. Supervisor: prof. dr. F.R.J. Verhey; co-supervisors: dr. P. Aalten; dr. I.H.G.B.Ramakers.

Johan Haumann, Prevalence and pharmacological treatment of pain in patients with cancer; The role of opioids with and without NMDA receptor affinity. Supervisor: prof.dr. E.A. Joosten; co-supervisors: prof.dr. M.H.J. van den Beuken-van Everdingen; dr. S.M.J. Van Kuijk.

Joost Riphagen, Vascular matters in aging and dementia. Supervisor: prof.dr. F.R.J. Verhey; co-supervisor: dr. H.I.L. Jacobs.

Nikos Priovoulos, Structural and functional imaging of the locus coeruleus at 7T: from methodological to clinical application. Supervisor: prof.dr. F.R.J. Verhey; co-supervisors: dr. H.I.L. Jacobs; dr. B.A. Poser.

Simone Verhagen, The power of individual landscapes; A clinical exploration of personal experience sampling and new horizons. Supervisors: prof.dr. P.A.E.G. Delespaul; prof.dr. J.J. van Os, UM/UU; co-supervisor: dr. C.J.P. Simons.

Nagy Youssef, Epigenetics, resilience and brain stimulation: advances in the mechanistic and therapeutic utility in patients with affective (PTSD and mood) disorders. Supervisor: prof.dr. B.P.F. Rutten; co-supervisor: prof. dr. P. Sienaert, KU Leuven.

Abhishek Appaji, Retinal vascular features as a biomarker for psychiatric disorders. Supervisor: prof. dr. C.A.B. Webers; co-supervisor: dr. T.T.J.M. Berendschot, dr. Naren P.Rao.

Koos Hovinga, Angiogenesis Inhibition in Glioblastoma. Supervisor: prof. dr. Y. Temel; co-supervisor: Prof. V. Tabar, New York, USA.

Gerhard Drenthen, Myelin and networks, Magnetic Resonance Imaging in Epilepsy. Supervisors: prof.dr.ir. W.H. Backes; prof.dr. A.P. Aldenkamp; co-supervisor: dr. J.F.A.Jansen.

Anna Gorlova, Understanding the Molecular Mechanisms of Aggression in BALB/C and TPH2-Deficient Mice. Supervisor: prof.dr. K. Lesch, Universitätsklinikum Würzburg, co- supervisors: dr. T. Strekalova; prof.dr. L. Bettendorff, University of Liège.

Ekaterina Veniaminova, The impact of the 'Western Diet' on Emotional, Social and Cognitive Behaviours as revealed by a study on conventional and serotonin Transporter-Deficient Mice. Supervisor: prof.dr. K. Lesch, Universitätsklinikum Würzburg, co-supervisors: dr. T. Strekalova; prof. D.C. Anthony, Oxford.

Dmitrii Pavlov, The contribution of CNS inflammation and Glycogen Synthase Kinase-3 (GSK-3)-cascades on adverse memory learning on mouse models of emotional stress. Supervisor: prof.dr. K. Lesch, Universitätsklinikum Würzburg, co-supervisors: dr. T.Strekalova; prof.dr. L. Bettendorff, University of Liège.

Eric Fonseca Wald, Absence Epilepsy and Panayiotopoulos Synrome: Neurocognition and Brain Development. Supervisor: prof.dr. R.J. Vermeulen; co-supervisors: dr. S. Klinkenberg; dr. M.J.A. Debeij-van Hall; dr. J.G.M. Hendriksen, Epilepsiecentrum Kempenhaeghe.

Kimberley S. Noij, Cervical vestibular evoked myogenic potentials; Toward optimizing clinical use. Supervisors: prof.dr. H. Kingma; prof. S.D. Rauch, MD, Massachusetts Eye and Ear, Harvard; co-supervisor: dr. R. van de Berg.

Mark J. van Tilburg, Advancement in cVEMP's. Supervisors: prof.dr. H. Kingma; prof.dr. S. Rauch, Harvard; co-supervisors: dr. R. van de Berg; dr. B. Herrmann, Boston.

Nalini Atcharayam, Duchenne Muscular Dystrophy: The NIMHANS Experience. Supervisors: prof.dr. T. Delhaas; prof.dr. B.W. Kramer.

Murat L Atagün, Cognitive neurophsysiology and neurochemistry in bipolar disorder. Supervisor: prof. dr. Therese van Amelsvoort; co-supervisors: dr. Sinan Guloksuz; dr. Marian Drukker.

Majed Aldehri, Deep brain stimulation, memory functions and mechanisms. Supervisor: prof. dr. Y. Temel; co-supervisors: dr. S. Hescham; dr. A. Jahanshahianvar.

Printha Kentheeswaran-Wijesinghe, Age-related cytoskeletal pathologies: A study on elderly brains to investigate the extent of neuropathological and cerebrovascular changes at death ad their risk factors. Supervisor: prof. dr. H. Steinbusch, prof. dr. R. De Silva - (University of Sri Jayewardenepura), prof. dr. D. Shankar - (NIMHANS Bangalore).

Mahmoud Elbatrik, Network pharmacology for mechanistically redefined comorbidities. Supervisor: prof. dr. H.H.H.W. Schmidt; co-supervisors: dr. A.I. Casas Guijarro.

Alexander Grønning, Big Data Analytics in Bioinformatics. Supervisors: prof. dr. J. Baumbach - (University of Southern, Denmark), prof. dr. H.H.H.W. Schmidt; co-supervisor:dr. R. Röttger.

Britta Nijsse, Cognition after stroke; various perspectives. Supervisors: prof. dr. C.M. vanHeugten, prof. dr. J.M.A. Visser/Meily, prof. dr. J.M. Spikman; co-supervisor: dr. P.L.M. deKort.

Eva Koetsier. Dorsal Root Ganglion Stimulation for Pain Relief in Painful Polyneuropathy: Efficacy and Mechanism of Action. Supervisors: prof. dr. E.A.J Joosten ,prof. dr. J.A.M. van Zundert; co-supervisor: dr. S.M.J. van Kuijk.

Youssef Yakkioui, Molecular biomarkers in skull base chordoma. Supervisors: prof. dr. Y. Temel, prof. dr. M. van Engeland.

Sascha Meyer, Visual Associative Learning in Alzheimer's Disease and Performance Validity. Supervisor: prof. dr. R.W.H.M. Ponds; co-supervisor: dr. J.F.M. de Jonghe.

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Sara Bartels, Monitoring Everyday Life in Aging & Dementia - Perspectives from Experience Sampling and Technology Use. Supervisors: prof. dr. F.R.J. Verhey, prof. dr. M.E. de Vugt; co-supervisors: dr. R.J.M. van Knippenberg, dr. C. Malinowsky -(Karolinska Institutet, Sweden).

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Anne Mulders, Monitoring and Modulating Neuropsychiatric Symptoms in Parkinson's disease and obsessive-compulsive disorder. Supervisors: prof.dr. A.F.G. Leentjens, prof.dr. Y. Temel.

Mayke Oosterloo, Controversies and pitfalls in diagnosing Huntington's Disease. Supervisors: prof. dr. R.A.C. Roos (LUMC, Leiden), prof. dr. C.E.M. de Die-Smulders; co- supervisor: dr. E.K. Bijlsma (LUMC, Leiden).

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Glenn Franken, Neuromodulation of the Dorsal Root Ganglion in Experimental Chronic Neuropathic Pain: Efficacy and Mechanisms of Action. Supervisors: prof. dr. E.A.J. Joosten, prof. dr. J.H.M. van Zundert; co-supervisors: dr. A.L. Liem, MC Jan van Goyen, Amsterdam.

Raghu Raghu, Automated seizure detection for remote monitoring. Supervisors: prof. dr. Y. Temel, prof. dr. N. Sriraam, Karnataka, India; co-supervisors: dr. P.L. Kubben, dr. E.D.Gommer.

Jonas Weijers, Mentalization and psychosis Trying to understand the “un- understandable”. Supervisors: prof. dr. J.P.C.J. Selten, prof. dr. E.H.M. Eurelings-Bontekoe, Universiteit Leiden; co-supervisor: dr. W. Viechtbauer.

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Lotta-Katrin Pries, The interplay between the genome and the exposome in psychosis spectrum. Supervisors: prof. dr. B.P.F. Rutten, prof. dr. J. van Os; co-supervisor: dr. S. Guloksuz.

Suat Kucukgoncu, Metabolic Disturbances in Mental Illness. Supervisor: prof. dr. B.P.F.Rutten; co-supervisor: dr. S. Gölöksüz.

Raffael Pazinatto Aguiar, Synthesis and biological evaluation of new tyrosol-salicylate derivatives as potential antiinflammatory agents. Supervisor: prof dr. J. Prickaerts; co- supervisor: dr Rúbia Maria Weffort de Oliveira, State University of Maringá Maringá, Paraná, Brazil.

Marina Damas, Autoantibodies in the nervous system: pathophysiology and new therapeutic strategies. Supervisor: prof. dr. P. Martinez; co-supervisors: dr. M. Losen, dr. R.P.W. Rouhl.

Angélique Gruters, Neuropsychological Assessment at the Memory Clinic: Innovations in communicating neuropsychological test results in the diagnostics of dementia. Supervisor: prof. dr. V.C.G. Tjan-Heijnen; co-supervisors: dr. LE.M. Duijm, CanisiusNijmegen, dr. A.C. Voogd.

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Raoul Stevens, Unboxing the Brain; Development of Technologies for Non- Invasive Assessment of Cerebral Pathologies. Supervisor: prof. dr. T. Delhaas, prof.dr. W.H. Mess; co-supervisors: dr.ir. W. Huberts.

Talakad Narasappa Sathyaprabha, Cardiovascular autonomic regulation in health and neurological disorders. Supervisors: prof.dr. B.W.W. Kramer, prof.dr. H.W.M. Steinbusch; co-supervisors: dr. T.R. Raju, Bangalore.