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

Danique M. J. Hellebrekers1,2*, Sandra A. M. van Abeelen1, Coriene E. Catsman3, Sander M. J. van Kuijk4, Annick M. Laridon1, Sylvia Klinkenberg1,2,5, Jos G. M. Hendriksen1,2,6, Johan S. H. Vles2

1 Centre for Neurological Learning Disabilities, Kempenhaeghe, Heeze, The Netherlands, 2 School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands, 3 Department of Neurology, Erasmus Medisch Centrum, Rotterdam, The Netherlands, 4 Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Maastricht, The Netherlands, 5 Department of Neurology, Maastricht University Medical Centre, Maastricht, The Netherlands, 6 Duchenne Centre Netherlands, Nijmegen and Leiden, The Netherlands

* danique.hellebrekers@gmail.com

Abstract

The presence of neurocognitive and behavioral 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 behavioral problems have been found in Neurofibromatosis type 1 (NF1). This study aims to assess disorder specific differences in cognition and behavior between DMD and NF1. Retrospective data of 38 male patients with DMD were aged-matched with data of 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 behavioral 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higher rates of aggressive behavior (13.2%) in DMD, whereas in NF1 higher rates of problems with thinking (15.8%), withdrawn (10.5%) and social behavior (10.5%) were noticed. In the neurogenetic disorders DMD and NF1, on average overlapping cognitive and behavioral problems are noticed, suggesting that these are not only caused by gene mutations resulting in a lack of one specific protein.
netherlands having comorbid disorders and receiving psychological care is limited and thus
data may be easily identified even when sharing a
de-identified data set. The regular clinical care data are
owned by the centre of Neurological Learning
Disabilities of Kempenhaeghe and sharing data is
imposed by the research ethics committee of
Kempenhaeghe. The local Medical Ethical
Committee of Kempenhaeghe imposes the data
sharing. The contact information of the ethics
Committee of Kempenheaghe is: Kempenhaeghe
Dr. M. Trieling-Laan. E-mail: secertariaatMEC@kempenhaeghe.nl Telephone: 0031- 40-2279498.

Funding: Stichting Spieren voor Spieren, SvS15,
Jos G.M. Hendriksen Duchenne Parent Project,
Brain imaging and cognition in Duchenne muscular
dystrophy-2010, Jos G.M. Hendriksen. All
reimbursements were received by Kempenhaeghe,
Heeze, the Netherlands. No personal financial
benefits were received. The funders had no role in
study design, data collection and analysis, decision
to publish, or preparation of the manuscript.

Competing interests: The authors have declared
that no competing interests exist.

Introduction

There is growing evidence that gene mutations can cause abnormal brain development that
lead to cognitive and behavioral 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 muta-
tions 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 fetal life stages,
suggesting that it may influence brain development [11].

Patients with Duchenne frequently exhibit cognitive problems, neurodevelopmental-, and
behavioral 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 behavioral
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%), the numbers vary due to use of various (screening) instruments [14, 19–
22]. Recent studies have tried to assess whether specific gene mutations that affect the produc-
tion of brain isoforms can be related to the cognitive problems, neurodevelopmental-, and
behavioral 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
behavior than patients missing only Dp427,M [19, 21, 23–26].

Neurofibromatosis type 1 (NF1) is caused by germline mutations in the NF1 gene, resulting
in a decreased production of the tumor 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) neurofibro-
mas, café-au-lait spots, skinfold freckling, but also skeletal and muscular problems (e.g. scolio-
sis, pseudo-arthritis, 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. in astrocytes and in neurons of the
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 patients with NF1,
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 behavioral
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 compli-
cated to define a distinct cognitive and behavioral profile [31]. However, recent NF1 studies
have found distinct profiles and showed that patients with microdeletions display more pro-
nounced cognitive impairments and learning disabilities than patients with intragenic muta-
tions [31, 41–43].

For neuropsychological diagnostic work-up and treatment purposes we were interested
whether patients with different neurogenetic disorders such as DMD and NF1 have specific
cognitive and behavioral profiles. In both disorders it has frequently been shown that specific
cognitive and behavioral comorbidities occur [3, 10, 14, 29–33, 35–40]. Current literature on DMD and NF1 shows that the presence of these problems may be correlated to specific genetic mutations i.e. in DMD this concerns mutations affecting multiple brain isoforms [19, 21, 23–26] and in NF1 this concerns having microdeletions [31, 41–43]. We were interested whether the cognitive and behavioral profiles of these two neurogenetic disorder can be distinguished to assume that different genetic mutations affecting different proteins indeed cause specific profiles. Therefore, the current study aimed to assess whether the cognitive and behavioral 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 (1) having a previous genetically confirmed mutation of the dystrophin gene for patients with DMD, or (2) having a clinical diagnosis of Neurofibromatosis type 1 or a previous genetically confirmed mutation of the neurofibromin gene, (3) an age between 6–16 years, (4) an adequate proficiency in Dutch, (5) normal hearing, (6) absence of severe visual impairment and (7) no physical immobility of upper extremities (the reliability of the cognitive tests may be impaired by impairments in hearing, vision and physical immobility of upper extremities). The previously genetic confirmed mutations of DMD and NF1 were established by medical professionals according to the specified criteria [44–46]. Exclusion criteria were: epilepsy, symptomatic optic pathway glioma, brain tumors, hydrocephalus or brain abnormalities (e.g. cortical dysplasia). Males with NF1 with focal abnormal signal intensity were not excluded because no equivocal relation is assumed between the presence of focal abnormal signal intensity and cognitive, developmental impairments and learning disabilities [47, 48]. 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 behavioral questionnaires, standardized for the Dutch population. All patients of CNL give at the beginning of their regular care process verbally consent to use their data for scientific purposes. Since the start of the new European law (5th Mai 2018) concerning using personal data 2, patients had to give written consent. Thereby patients included in current study give their verbal or written consent, which is documented in the patient file. 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 1994.

Study procedure

All patients with DMD and NF1 received an extensive neuropsychological assessment between October 2008 and August 2019 to evaluate their cognitive and behavioral functioning as part of regular clinical care at CNL. Cognitive assessment evaluated intellectual abilities (FSIQ, 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. Behavioral functioning was screened using questionnaires for parents and teachers. All collected cognitive and behavioral 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
behavioral Diagnostic and Statistical Manual (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. Learning difficulties such as problems with reading, writing, math, automatization or spelling that did not fulfill the criteria for dyslexia and dyscalculia were extracted from the files. The neurodevelopmental and behavioral DSM-IV/DSM-5 that were obtained from the patient files included ADHD, ASD, OCD, developmental coordination disorder, anxiety, depression and tic disorders. All cognitive, behavioral 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 [49] 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) [49].

Neuropsychological assessment

**Cognition.** The Wechsler Intelligence Scale for Children—Third edition (WISC-III) [50] 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) [50]. 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) [51]. 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) [51]. Verbal memory of immediate recall, delayed recall and recognition was tested using the Rey auditory learning task (15-word test) [52]. 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) [52]. Sustained visual attention was measured using the Bourdon Vos [53]. The Test of Everyday Attention for Children, Second Edition (TEA-Ch) [54], subtest Score was used to measure sustained auditory attention. Teach-Ch raw scores were converted to scaled scores (mean = 10, SD = 3) [54]. In our Centre, the outcomes of WISC-III and KABC-II are both evaluated as WISC tasks involving time pressure may negatively influence outcomes of DMD patients due to less functioning of upper extremities.

**Behavior.** Behavioral functioning was screened using two informant rating instruments, the Child Behavior Checklist for Children (CBCL) and the Teacher report Form (TRF) [55]. Both instruments evaluated behavior based on eight syndrome scales (anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior and aggressive behavior). Two broadband scales on internalizing symptoms (made up of withdrawn, somatic complaints and anxious/depressed scales), externalizing symptoms (made up of rule-breaking behavior and aggressive behavior), 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 $T \geq 64$ was applied to indicate the clinical range of internalizing, externalizing symptoms and a total problem score [55].

**Statistical analysis**

Age-matching (restriction within 1 year) was randomly performed by case control matching of SPSS. Demographic and disease-related characteristics of both groups were presented as mean (SD), or absolute number and proportion. Stochastic regression imputation was applied in case of incomplete variables of cognitive and behavioral data [56]. The imputed values were drawn using predictive mean matching [56]. Differences between the DMD and NF1 group on demographic and disease-related parameters as well as cognitive and behavioral outcomes were tested using the independent samples t-test, $X^2$ tests, Fisher exact test, or Mann-Whitney-U tests, as appropriate. Differences within the DMD and NF1 group on the cognitive outcomes of KABC sequential and simultaneous processing were tested using paired samples t-test. Effect sizes (quantified as Cohen’s $d$) were calculated to indicate the strength of differences of the cognitive and behavioral outcomes [57]. Effect sizes were defined as: $0.20–0.50 = \text{small}$, $0.50–0.80 = \text{medium}$ and $\geq 0.80 = \text{large}$ [57]. Multivariate analyses (MANOVA) examined differences between the groups on cognitive and behavioral outcomes corrected for the covariates age, comorbid diagnoses of patients (i.e. ADHD and ASD), use of stimulant medication (MPH), educational status of patients and family history of learning and behavioral problems. Preliminary assumptions associated with all test statistics, such as 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 ($p \geq .001$) [58]. Cognitive outcomes i.e. age-related norm scores were converted to z-scores (Mean = 0, SD = 1). Behavioral outcomes were also evaluated using the clinical cut-off value of T-score $\geq 63$ [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 of 170 patients with NF1 were available (Fig 1 for flowchart of inclusion). A total of 38 patients with DMD were matched on age with males with 38 NF1. Demographic and disease-related characteristics of both groups are displayed in Table 1. 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 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. No information on deletions or duplications was available in the electronic patient files of two males (5.3%). Neurofibromatosis type 1 was clinically diagnosed in $N = 38$ males and of $n = 32$ information on mutation location was available. In $n = 4$ the clinical diagnosis is not genetically confirmed and of $n = 2$ information of mutation location is missing. None of the 32 patients of which mutation information was available had microdeletions (see S1 Table).

Disease-related characteristics are displayed in Table 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 behavioral disorders differed between the DMD and NF1 group (see Table 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 1). The difference in rate of ADHD between the groups is even statistically significant (Table 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 fulfill 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 1).

Cognitive outcomes

**Intellectual abilities.** As shown in Table 2, no discrepancy was found between VIQ and PIQ for the DMD and NF1 group. On all IQ measures no significant differences were found between the DMD and NF1 group.
Table 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 patients (%)      |              |              | .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 behavioral 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            |         |
| 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    |

(Continued)
Table 1. (Continued)

|                        | DMD (N = 38) | NF1 (N = 38) | p     |
|------------------------|--------------|--------------|-------|
| Dyscalculia            | 3 (7.9)      | 0            | .240  |

Note: 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, AD(H) D = Attention-deficit (hyperactivity disorder), ASD = Autism Spectrum Disorder. 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 behavioral problems are based on 1st, 2nd, and 3rd family degree.

* p < .05 (two-sided)
** p < .01 (two-sided)

https://doi.org/10.1371/journal.pone.0275803.t001

WISC distribution of FSIQ of the two groups are displayed in Fig 2. 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 (Fig 2). 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 (Fig 2). 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).

Sequential and simultaneous processing. Results of mean sequential processing and mean simultaneous processing of the two groups are displayed in Table 3. No significant difference was found between the groups on sequential processing and simultaneous processing (see Table 3).

See Fig 3 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).

Verbal memory. On verbal memory i.e. immediate recall, delayed recall and recognition no significant differences were found between the groups (see Table 3). The outcomes on immediate and delayed recall of both groups are visualized in Fig 3. 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. Results on the sustained attention tasks (i.e. visual speed and accuracy as well as auditory attention) showed no significant differences between the DMD and NF1 group (see Table 3). See Fig 3 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. ADHD and ASD), use of stimulant medication (MPH), educational...
status of patients and family history of learning and behavioral 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 4).

### Behavioral reports of parents and teachers.

Outcomes of the behavioral reports of the DMD and NF1 group are displayed in Table 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 behavior was the most frequent observed behavioral problem in DMD (13.2%) according to parents (CBCL) responses. These five DMD males that displayed aggressive behavior 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 behavioral problems reported by parents (CBCL) compared to teachers.

### Table 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             | 86.4 (11.9)                  | 91.5 (15.4)                  | -1.626               | .108  | -0.4        | -11.42  | 1.16    |
| VIQ              | 89.6 (12.0)                  | 93.9 (14.4)                  | -1.387               | .170  | -0.3        | -10.32  | 1.85    |
| PIQ              | 85.3 (12.0)                  | 89.9 (17.0)                  | -1.370               | .175  | -0.3        | -11.38  | 2.11    |
| VC               | 91.5 (9.5)                   | 95.5 (15.0)                  | -1.411               | .163  | -0.3        | -9.81   | 1.69    |
| PO               | 84.9 (8.6)                   | 89.4 (14.5)                  | -1.654               | .103  | -0.4        | -9.98   | 0.95    |
| PS               | 89.5 (16.2)                  | 94.0 (17.3)                  | -1.402               | .165  | -0.3        | -12.17  | 3.15    |

Note: Mean (SD) of scaled scores, 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

https://doi.org/10.1371/journal.pone.0275803.t002

Fig 2. 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. FSIQ mean scores are displayed using frequencies of the group DMD (white) and group NF1 (grey) patients.

https://doi.org/10.1371/journal.pone.0275803.g002
those reported by teachers (TRF), with limited behavioral 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. 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 5).

Table 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           |
| 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              |

Note: 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.

https://doi.org/10.1371/journal.pone.0275803.t003

Fig 3. Mean (SD) outcomes of z-scores 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). The outcomes are frequencies of the mean outcomes. The statistical method used to compare the outcomes of KABC SEQ processing and SIM processing within the DMD or NF1 group was the paired sample t-test. The z-scores represent the mean outcomes and standard deviations on cognitive outcomes of each group.

https://doi.org/10.1371/journal.pone.0275803.g003
A multivariate analysis was run to determine the effect of the covariates, age, comorbid diagnoses of patients (i.e. ADHD and ASD), use of stimulant medication (MPH), educational status of patients, and family history of learning and behavioral problems on the CBCL and TRF broadband internalizing- and externalizing scales and the total problem scores. No differences were found between the groups on the internalizing CBCL scale, internalizing TRF scale score, externalizing CBCL and TRF scale scores and the total problem scores of the CBCL and TRF (see Table 6).

### Discussion

Cognitive- and behavioral 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 behavioral impairments in patients with mutations affecting the full-length and shorter brain isoforms, whereas in NF1 studies revealed more pronounced impairments in cognition, behavior and learning in patients with microdeletions. Since in both neurogenetic disorders, different proteins and regions are involved, we hypothesized that the cognitive and behavioral profiles of patients with DMD differ from patients with NF1. Results of reports of patient characteristics documented within the electronic patient files showed a statistical significant difference in frequencies of having an ADHD diagnose, with a higher prevalence rate for the NF1 group than DMD group. It is likely that the ADHD diagnosis is more difficult to establish in the DMD group.
due to their physical immobility. Though, when exploring possible differences between the ambulant versus non-ambulant DMD group on the presence of an AD(H)D diagnosis we found no significant differences in our study sample.

In addition, 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 behavioral disorders), use of stimulant medication (MPH), use of steroids, educational status of patients and family history of learning and behavioral problems). Results of reported behavioral problems by parents and teachers also displayed no significant differences between the DMD and NF1 group.

### 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]. No discrepancy between verbal IQ and performance IQ was found.

Table 5. Behavioral reports of parents and teachers of the DMD and NF1 group.

| Questionnaires with scales | DMD (n = 38) | NF1 (n = 38) | Definition of clinical range | p | Effect size |
|---------------------------|-------------|-------------|-------------------------------|---|-------------|
|                           | Mean (SD)   | Median     | Min | Max | Clinical range (%) | Mean (SD) | Median | Min | Max | Clinical range (%) |             |             |
| 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       |

Note: Mean scores (SD) are T-scores. 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.

https://doi.org/10.1371/journal.pone.0275803.t005
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 [59]. 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 intellectual disability (FSIQ < 70) have been described previously for DMD (30%) than for NF1 (4–8%), with most patients with NF1 falling in the low-average to normal range [16, 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]. Furthermore, patients with delays in verbal span capacity seem not to grow out their deficit [62], underscoring that early diagnosis and treatment of cognitive and academic problems should be part of regular clinical care of both neurogenetic disorders [65, 66]. 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 [67]. Cognitive training for instance working memory training seems also a beneficial tool for children with short-term

| Questionnaires | DMD (n = 38) | NF1 (n = 38) | p |
|---------------|-------------|-------------|---|
|               | Mean | 95% CI | Mean | 95% CI |     |
|               | Lower | Upper | Lower | Upper |     |
| CBCL int.     | 58.3 | 54.8 | 61.9 | 54.4 | 51.0 | 57.8 | .158 |
| CBCL ext.     | 58.8 | 54.9 | 62.8 | 54.9 | 51.0 | 58.8 | .210 |
| CBCL total    | 60.8 | 57.3 | 64.3 | 58.2 | 54.8 | 61.6 | .347 |
| TRF int.      | 56.8 | 54.2 | 59.5 | 57.1 | 54.5 | 59.7 | .900 |
| TRF ext.      | 57.0 | 54.4 | 59.6 | 55.3 | 52.8 | 57.9 | .416 |
| TRF total     | 57.8 | 55.5 | 60.2 | 57.5 | 55.2 | 59.8 | .864 |

Note: behavioral outcomes are means of t-scores corrected for the covariates age, the presence of comorbidities (ADHD and ASD), use of stimulant medication (MPH), educational status of patients, and family history of learning and behavioral 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)

https://doi.org/10.1371/journal.pone.0275803.t006
memory problems and learning disabilities [67, 68], 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, 69, 70]. 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, in previous NF1 literature the visuospatial disabilities were found in groups that included males and females with NF1. In current study, we compared the cognitive profiles of a male DMD group and a male NF1 group. It is known that 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 [71]. This may explain why we did not found the visuospatial disabilities in our NF1 male group. It would be interesting to address the differences in phenotypes of NF1 male and females in future studies.

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, 72], whereas two other studies used a processing speed task or verbal memory task [69, 70]. 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 [73].

**Behavioral 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 behavioral problems. More detailed analyses on abnormal ranges of the groups showed that parents and teachers of males with DMD more often reported aggressive behavioral 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 behavioral problems i.e. aggressive behavior than boys taking no steroids. This may explain the higher rates of aggressive behavior in our DMD group. However, results on the relation steroid use and higher incidences of externalizing behavioral problems are equivocal [58, 74, 75]. Furthermore, patients with DMD deal with physical milestones during the disease course, which may induce aggressive behavior 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 behavioral 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 [76, 77]. Our findings emphasize that screening of behavioral problems should be done by evaluating different perspectives (i.e. parents, teachers, patients and clinicians) on patients functioning [78]. This is particularly important in neurogenetic disorders due to the presence of more than one cognitive or behavioral comorbidity and their overlap in symptoms. Furthermore, the CBCL may be no suitable instrument for screening behavioral problems, which we previously described in our systematic review [78]. 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 behavioral disorders [79]. In addition, insufficient psychometric properties have been found recently for the CBCL especially for patients with DMD [78]. 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. Many years the CBCL was used as gold standard in our Centre. However, the diagnostic work-up of patients with DMD is currently adapted due to our recent sensitivity findings of the CBCL [78].

**Neurophysiology in relation to cognition and behavior 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, 80–82]. 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, 80, 81, 83]. 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 (Dp427B) links to inhibitory γ-aminobutyric acid type A (GABA<sub>A</sub>) receptors at the postsynaptic neural membrane [7, 84]. A lack of dystrophin results in a decreased density of GABA<sub>A</sub> receptor clustering of receptor sub-units at inhibitory synapses [83, 84]. Aberrant anchoring of GABA<sub>A</sub> receptors causes an increased extrasynaptic expression of GABA<sub>A</sub> receptors, which triggers a disruption of calcium homeostasis and makes cells vulnerable to necrosis [85, 86]. 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 signaling molecule, leading to increased GABAergic inhibition in the hippocampus due to impaired long-term potentiation [30, 81]. Furthermore, neurofibromin is localized at excitatory synapses postsynaptically where it interacts with the NMDA receptor [30, 81]. Overall, in both disorders neuronal alterations in GABA<sub>A</sub> and glutamate functions are
found and these have been linked to the presence of neurocognitive deficits [7, 10, 30, 80–82]. 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 affects the presence and severity of cognitive deficits. Another possible etiology 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 [87]. 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 [87].

Limitations and future perspectives

This study has some limitations. At first, 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. The available data of the cognitive test used were adequate for the purpose of current study. Since these measures evaluate whether the frequent observed cognitive problems (i.e. deficits in intellectual abilities, verbal (working) memory and attention) that are found in both neurogenetic disorders are also shown in current study. The data of behavioral outcomes of the CBCL which is the gold standard for evaluating the presence of frequent observed comorbidities such as ADHD and ASD may lack some sensitivity in our groups. This is further described within the sixth limitation below.

Secondly, 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. Thirdly, all participants of the present study were referred to the outpatient clinic CNL, and these patients frequently have more (severe) learning, cognitive or behavioral 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 previous literature on cognition in patients with DMD and NF1. Furthermore, the group with DMD having these comorbid cognitive and behavioral diagnosis are limited. This makes it difficult to have a required minimum sample size based on power analysis for finding statistical significant differences between the DMD group and any other neurogenetic or dystrophy disorders. However, the additional power analysis displayed a power of 20% based on the sample size of current study. Fourthly, we solely included participants aged 6–16 years to allow for the administration of the cognitive test and behavioral questionnaires, standardized for the Dutch population which also limited our study sample group. However, cognitive and behavioral 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. Fifthly, current study used both the WISC-III and KABC-II. Additional correlations showed only small correlations between the subtests of the batteries indicating that in this study the subtests measured different domains of cognition. In DMD time restricted WISC tasks may negatively influence the outcomes due to less upper extremity functioning, therefore we choose to administer both batteries. Sixthly, a disadvantage of using retrospective data was that the reported comorbid
diagnosis differed from data collected by measurements completed by parents and teachers. For instance 23% of DMD patients had a diagnosis of ASD but the parent and teacher rating did not identified significant social and behavioral concerns. Additionally, when comparing the reports on ADHD diagnoses we found a significant difference between NF1 and DMD, with a higher prevalence rate for the NF1 group. It is likely that due to the lack of sensitivity of the CBCL measure we did not objectively found a significant difference between the groups on ASD and ADHD. Future prospective studies should include more sensitive measures such as a clinical structured interview, the Autism Diagnostic Observation Scale [22]. Nevertheless, our findings emphasize that comorbidities in cognition, behavior and learning difficulties may arise in both neurogenetic disorders. Early cognitive and behavioral (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 future grow in or out of their cognitive, behavioral and learning comorbidities. A nice addition to the NF1 literature would be to evaluate genotypes-phenotypes in severity and impact of cognitive, behavioral and learning comorbidities. These analyses could not be carried out in current study, since none of the NF1 patients of which mutation information was available (n = 32) had microdeletions.

It can be speculated that we found no differences in cognitive profiles since not only genetic mutations are responsible for the neurocognitive outcomes, or it is likely that the cognitive and behavioral tests used lack sensitivity for these specific neurogenetic disorders. Although, when the profiles are associated with mutations we would aspect to find differences during diagnostics or during interventions. Recently for instance, positive effects have been observed when using a general cognitive intervention i.e. computerized working memory training in patients with DMD and a comorbid learning disability and these effects seem similar to those found in patients with learning disabilities without DMD [88]. This suggests that also general interventions are applicable for patients with neurogenetic disorders despite that the comorbidities may be associated to the genetic mutations. It can be wondered which other factors than mutations are responsible for the cognitive and behavioral profiles of patients with neurogenetic disorders. There is growing evidence that epigenetic factors (e.g. maternal stress) may modulate brain development as well [73].

**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. However, 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. Furthermore, the parental reported ADHD prevalence rate was higher within the NF1 group compared to the DMD group. With regard to other behavioral features, aggressive behavior 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 behavior. 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 behavioral functioning is required in both neurogenetic disorders. Possible cognitive or behavioral 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.

Supporting information

S1 Table. Mutations of the NF1 patients.

(DOCX)

Acknowledgments

The authors would like to thank the following people: prof. dr. E. Legius for his personal comments on genetic information on NF1, dr. M. Sinnema for the genetic information on microdeletions of the included patients with NF1, the patients of the Centre for Neurological Learning Disabilities that give consent to use their clinical data for scientific research purposes, and Erasmus Medical Centre for the collaboration in Neurofibromatosis 1 clinical care and scientific purposes.

Author Contributions

Conceptualization: Sandra A. M. van Abeelen, Johan S. H. Vles.

Data curation: Danique M. J. Hellebrekers, Sandra A. M. van Abeelen, Coriene E. Catsman, Annick M. Laridon, Sylvia Klinkenberg, Jos G. M. Hendriksen, Johan S. H. Vles.

Formal analysis: Danique M. J. Hellebrekers, Sander M. J. van Kuijk.

Funding acquisition: Jos G. M. Hendriksen, Johan S. H. Vles.

Investigation: Danique M. J. Hellebrekers, Johan S. H. Vles.

Methodology: Danique M. J. Hellebrekers, Sander M. J. van Kuijk, Johan S. H. Vles.

Project administration: Danique M. J. Hellebrekers, Sandra A. M. van Abeelen, Jos G. M. Hendriksen, Johan S. H. Vles.

Resources: Sandra A. M. van Abeelen, Coriene E. Catsman, Annick M. Laridon, Sylvia Klinkenberg, Jos G. M. Hendriksen.

Software: Sander M. J. van Kuijk.

Supervision: Sandra A. M. van Abeelen, Jos G. M. Hendriksen, Johan S. H. Vles.

Validation: Danique M. J. Hellebrekers, Sandra A. M. van Abeelen, Coriene E. Catsman, Sander M. J. van Kuijk, Johan S. H. Vles.

Visualization: Danique M. J. Hellebrekers, Sandra A. M. van Abeelen, Sander M. J. van Kuijk.

Writing – original draft: Danique M. J. Hellebrekers.

Writing – review & editing: Sandra A. M. van Abeelen, Coriene E. Catsman, Sander M. J. van Kuijk, Annick M. Laridon, Sylvia Klinkenberg, Jos G. M. Hendriksen, Johan S. H. Vles.

References

1. Bishop D. Genes, cognition, and communication: insights from neurodevelopmental disorders. Annals of the New York Academy of Sciences 2009; 1156:1–18. https://doi.org/10.1111/j.1749-6632.2009.04419.x PMID: 19338500

2. Simon TJ. Clues to the foundations of numerical cognitive impairments: evidence from genetic disorders. Developmental neuropsychology 2011; 36:788–805. https://doi.org/10.1080/87565641.2010.549879 PMID: 21761998
3. Snow WM, Anderson JE, Jakobsson LS. Neuropsychological and neurobehavioral functioning in Duchenne muscular dystrophy: a review. Neuroscience & Biobehavioral Reviews 2013; 37:743–752. https://doi.org/10.1016/j.neubiorev.2013.03.016 PMID: 23545331

4. Hyman SL, Shores A, North KN. The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. Neurology 2005; 65:1037–1044. https://doi.org/10.1212/01.wnl.0000179303.72345.cce PMID: 16217056

5. Morel A, Demily C. Social cognition in children with neurogenetic syndromes: A literature review. Archives de pediatrie: organe officiel de la Societe francaise de pediatrie 2017; 24:757–765.

6. Walter E, Mazaika P, Reiss A. Insights into brain development from neurogenetic syndromes: evidence from fragile X syndrome, Williams syndrome, Turner syndrome and velocardiofacial syndrome. Neuroscience 2009; 164:257–271. https://doi.org/10.1016/j.neuroscience.2009.04.033 PMID: 19376197

7. Waite A, Brown SC, Blake DJ. The dystrophin–glycoprotein complex in brain development and disease. Trends in Neurosciences 2012; 35:487–496. https://doi.org/10.1016/j.tins.2012.04.004 PMID: 22626542

8. Hoffman EP, Brown RH Jr, Kunkel LM. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. Cell 1987; 51:919–928. https://doi.org/10.1016/0092-8674(87)90579-4 PMID: 3319190

9. Ehmsen J, Poon E, Davies K. The dystrophin-associated protein complex. Journal of cell science 2002; 115:2801–2803. https://doi.org/10.1242/jcs.115.14.2801 PMID: 12082140

10. Hendriksen RG, Hoogland G, Schipper S, Hendriksen JG, Vles JS, Aalbers MW. A possible role of dystrophin in neuronal excitability: a review of the current literature. Neuroscience & Biobehavioral Reviews 2015; 51:255–262. https://doi.org/10.1016/j.neubiorev.2015.01.023 PMID: 25677308

11. Doorenweerd N, Mahfouz A, van Putten M, et al. Timing and localization of human dystrophin isoform expression provide insights into the cognitive phenotype of Duchenne muscular dystrophy. Science Report 2017; 7:1–12. https://doi.org/10.1038/s41598-017-12981-5 PMID: 28974727

12. Lidov H, Byers T, Kunkel L. The distribution of dystrophin in the murine central nervous system: an immunocytochemical study. Neuroscience 1993; 54:167–187. https://doi.org/10.1016/0306-4522(93)90392-s PMID: 8515841

13. Chamberlain JS, Pearlman JA, Muzny DM, et al. Expression of the murine Duchenne muscular dystrophy gene in muscle and brain. Science 1988; 239:1416–1418. https://doi.org/10.1126/science.3347839 PMID: 3347839

14. Banihani R, Smile S, Yoon G, et al. Cognitive and Neurobehavioral Profile in Boys With Duchenne Muscular Dystrophy. Journal of Child Neurology 2015; 30:1472–1482. https://doi.org/10.1177/0883073815570154 PMID: 25660133

15. Cyrlunik SE, Fee RJ, Batchelder A, Kiefel J, Goldstein E, Hinton VJ. Cognitive and adaptive deficits in young children with Duchenne muscular dystrophy (DMD). Journal of the International Neuropsychological Society 2008; 14:853–861. https://doi.org/10.1017/S135561770808106X PMID: 18764980

16. Cotton S, Vouldouris NJ, Greenwood KM. Intelligence and Duchenne muscular dystrophy: Full-Scale, Verbal, and Performance intelligence quotients. Developmental Medicine & Child Neurology 2001; 43:497–501.

17. Wicksell RK, Kihlgren M, Melin L, Eeg-Olofsson O. Specific cognitive deficits are common in children with Duchenne muscular dystrophy. Developmental Medicine & Child Neurology 2004; 46:154–159. PMID: 14995084

18. Wingeier K, Giger E, Strozzi S, et al. Neuropsychological impairments and the impact of dystrophin mutations on general cognitive functioning of patients with Duchenne muscular dystrophy. Journal of Clinical Neuroscience 2011; 18:90–95. https://doi.org/10.1016/j.jocn.2010.07.118 PMID: 21109441

19. Pane M, Lombardo ME, Alfieri P, et al. Attention deficit hyperactivity disorder and cognitive function in Duchenne muscular dystrophy: phenotype-genotype correlation. Journal of Pediatrics 2012; 161:705–709. https://doi.org/10.1016/j.jpeds.2012.03.020 PMID: 22560791

20. Hendriksen JG, Vles JS. Neuropsychiatric Disorders in Males With Duchenne Muscular Dystrophy: Frequency Rate of Attention-Deficit Hyperactivity Disorders (ADHD), Autism Spectrum Disorder, and Obsessive–Compulsive Disorder. Journal of Child Neurology 2008; 23:477–481.

21. Ricotti V, Mandy WP, Scoto M, et al. Neurodevelopmental, emotional, and behavioural problems in Duchenne muscular dystrophy in relation to underlying dystrophin gene mutations. Developmental Medicine and Child Neurology 2016; 58:77–84. https://doi.org/10.1111/dmcn.12922 PMID: 26365034

22. Colombo P, Nobile M, Tesei A, et al. Assessing mental health in boys with Duchenne muscular dystrophy: Emotional, behavioural and neurodevelopmental profile in an Italian clinical sample. European Journal of Paediatric Neurology 2017; 21:639–647 https://doi.org/10.1016/j.ejpn.2017.02.007 PMID: 28392227
23. Chamova T, Guergueltcheva V, Raycheva M, et al. Association between loss of dp140 and cognitive impairment in duchenne and becker dystrophies. Balkan Journal of Medical Genetics 2013; 16:21–29. https://doi.org/10.2478/bjmg-2013-0014 PMID: 24265581

24. Doorenweerd N, Straathof CS, Dumas EM, et al. Reduced cerebral gray matter and altered white matter in boys with Duchenne muscular dystrophy. Annals of Neurology 2014; 76:403–411. https://doi.org/10.1002/ana.24222 PMID: 25043804

25. Thangarajh M, Hendriksen J, McDermott M, Martens W, Hart K, Griggs R. Relationships between DMD mutations and neurodevelopment in dystrophinopathy. Neurology 2019; 93:1597–1604 https://doi.org/10.1212/WNL.0000000000008363 PMID: 31594858

26. Bardoni A, Felisari G, Sironi M, et al. Loss of Dp140 regulatory sequences is associated with cognitive impairment in dystrophinopathies. Neuromuscular Disorders 2000; 10:194–199. https://doi.org/10.1016/s0960-8966(99)00108-x PMID: 10734267

27. Savar A, Cestari DM. Neurofibromatosis type I: genetics and clinical manifestations. Seminars in ophthalmology; 2008: 45–51. https://doi.org/10.1080/08830738021745223 PMID: 18214791

28. Rietman AB, Oostenbrink R, Bongers S, et al. Motor problems in children with neurofibromatosis type 1. Journal of neurodevelopmental disorders 2017; 9:19. https://doi.org/10.1186/s11689-017-9198-5 PMID: 28529667

29. Gutmann DH. Neurofibromin in the brain. Journal of child neurology 2002; 17:592–601. https://doi.org/10.1177/08830738020170089 PMID: 12403558

30. Acosta MT, Bearden CE, Castellanos XF, et al. The Learning Disabilities Network (LeaDN): using neurofibromatosis type 1 (NF1) as a paradigm for translational research. American Journal of Medical Genetics Part A 2012; 158:2225–2232. https://doi.org/10.1002/ajmg.a.35355 PMID: 22821737

31. Torres Nupan MM, Velez Van Meerbeke A, Lopez Cabra CA, Herrera Gomez PM. Cognitive and behavioral problems in children with neurofibromatosis type 1. Developmental Medicine and Child Neurology 2005; 47:237–242. https://doi.org/10.1177/08830738020170089 PMID: 12403558

32. Schwetye KE, Gutmann DH. Cognitive and behavioral problems in children with neurofibromatosis type 1: challenges and future directions. Expert review of neurotherapeutics 2014; 14:1139–1152. https://doi.org/10.1586/14737175.2014.953931 PMID: 25161109

33. Hachon C, Iannuzzi S, Chaix Y. Behavioural and cognitive phenotypes in children with neurofibromatosis type 1 (NF1): the link with the neurobiological level. Brain and Development 2011; 33:52–61. https://doi.org/10.1016/j.braindev.2009.12.008 PMID: 20106617

34. North K, Hyman SL, Arthur E, North KN. Learning disabilities in children with neurofibromatosis type 1: subtypes, cognitive profile, and attention-deficit-hyperactivity disorder. Developmental Medicine & Child Neurology 2006; 48:973–977.

35. Hyman SL, Arthur E, North KN. Learning disabilities in children with neurofibromatosis type 1: subtypes, cognitive profile, and attention-deficit-hyperactivity disorder. Developmental Medicine & Child Neurology 2006; 48:973–977.

36. Johnson H, Wiggs L, Stores G, Huson SM. Psychological disturbance and sleep disorders in children with neurofibromatosis type 1. Developmental Medicine and Child Neurology 2005; 47:237–242.

37. Rietman AB, van der Vaart T, Plasschaert E, et al. Motor problems in children with neurofibromatosis type 1. Journal of attention disorders 2013; 17:489–496. https://doi.org/10.1177/108705471143342 PMID: 22354384

38. Hyman SL, Arthur E, North KN. Learning disabilities in children with neurofibromatosis type 1: subtypes, cognitive profile, and attention-deficit-hyperactivity disorder. Developmental Medicine & Child Neurology 2006; 48:973–977.

39. Johnson H, Wiggs L, Stores G, Huson SM. Psychological disturbance and sleep disorders in children with neurofibromatosis type 1. Developmental Medicine and Child Neurology 2005; 47:237–242.

40. Johnson NS, Saal HM, Lovell AM, Schorry EK. Social and emotional problems in children with neurofibromatosis type 1: evidence and proposed interventions. The Journal of Pediatrics 1999; 134:767–772. https://doi.org/10.1016/s0022-3476(99)00296-9 PMID: 10356149

41. Croxen MH, van der Est MN, Breuning MH, et al. Deletions spanning the neurofibromatosis type 1 gene: implications for genotype-phenotype correlations in neurofibromatosis type 1? Human mutation 1997; 9:458–464.

42. Leppig KA, Kaplan P, Viskochil D, Weaver M, Ortenberg J, Stephens K. Familial neurofibromatosis 1 microdeletions: cosegregation with distinct facial phenotype and early onset of cutaneous neurofibroma. American Journal of Medical Genetics 1997; 73:197–204.

43. Boyd KP, Korf BR, Theos A. Neurofibromatosis type 1. Journal of the American Academy of Dermatology 2009; 61:1–14. https://doi.org/10.1016/j.jaad.2008.12.051 PMID: 19539839

44. Kern R. E., Huson S., & Evans D. G. R. (2011). Neurofibromatoses in clinical practice. Springer Science & Business Media.
45. National Institutes of Health Consensus Development Conference Statement: neurofibromatosis. Bethesda, Md., USA, July 13–15, 1987 Neurofibromatosis, 1 (3) (1988), pp. 172–178

46. Emery A. E. (1997). Diagnostic criteria for neuromuscular disorders. London: Royal society of medicine press.

47. Saiman MS, Hossain S, Alqublan L, Bunge M, Rozovsky K. Cerebellar radiological abnormalities in children with neurofibromatosis type 1: part 1-clinical and neuroimaging findings. Cerebellum & ataxias 2018; 5:14. https://doi.org/10.1186/s40673-018-0093-y PMID: 30410779

48. Roy A, Barbatos S, Charbonnier V, et al. Examining the frontal subcortical brain vulnerability hypothesis in children with neurofibromatosis type 1: are T2-weighted hyperintensities related to executive dysfunction? Neuropsychology 2015; 29:473. https://doi.org/10.1037/neu0000151 PMID: 25365565

49. Verhage F. Intelligence and age: research among the Dutch between 7 and 77 years of age. Assen: Van Gorcum 1964.

50. Wechsler D. Manual for the Wechsler intelligence scale for children-(WISC-III). San Antonio, TX: Psychological Corporation 1991.

51. Kaufman A. Manual for the Kaufman Assessment Battery for Children (K-ABC-II). Circle Pines (MN): American Guidance Service 2004.

52. Kalverboer A, Deelman B. De 15-woorden tests A en B:(een voorlopige handleiding)(15WT/VWT). Groningen: Academisch Ziekenhuis Groningen, afd Neuropsychiologie 1988.

53. Vos P. Handleiding Bourdon-Vos test, 3e herziene uitgave. Lisse, Netherlands: Swets Test Publishers, 1998.

54. Manly T, Anderson V, Crawford J, George, M, Underbjerg M, Robertson I. TEA-Ch: The test of everyday attention for children manual, Second Edition. 2016.

55. Achenbach T, Edelbrock C. Manual for the child behavior checklist (4–18) and 1991 Profile. Burlington: VT: University of Vermont, Department of Psychiatry, 1991.

56. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Bmj 2009; 338. https://doi.org/10.1136/bmj.b2393 PMID: 19564179

57. Cohen J. A power primer. Psychological Bulletin 1992; 112:155. https://doi.org/10.1037//0033-2909.112.1.155 PMID: 19565683

58. Field A. Discovering statistics using IBM SPSS statistics: Sage, 2013.

59. D’Angelo MG, Lorusso ML, Civati F, et al. Neurocognitive profiles in Duchenne muscular dystrophy and gene mutation site. Pediatric Neurology 2011; 45:292–299. https://doi.org/10.1016/j.pediatrneurol.2011.08.003 PMID: 22003008

60. Hinton V, Fee R, Goldstein E, De Vivo D. Verbal and memory skills in males with Duchenne muscular dystrophy. Developmental Medicine & Child Neurology 2007; 49:123–128. https://doi.org/10.1111/j.1469-8749.2007.0123.x PMID: 17254000

61. Leafher EB, Fee RJ, Hinton VJ. Digit span performance in children with dystrophinopathy: a verbal span or working memory contribution? Journal of the International Neuropsychological Society 2016; 22:777–784. https://doi.org/10.1017/S1355617716000461 PMID: 27268852

62. Hellebrekers DM, Doorenweerd N, Sweere DJ, et al. Longitudinal follow-up of verbal span and processing speed in Duchenne muscular dystrophy. European Journal of Paediatric Neurology 2020. 25.120–126 https://doi.org/10.1016/j.ejpn.2020.01.002 PMID: 31964551

63. Billard C, Gillet P, Barthez MA, Hommet C, Bertrand P. Reading ability and processing in Duchenne muscular dystrophy and spinal muscular atrophy. Developmental Medicine & Child Neurology 1998; 40:12–20. https://doi.org/10.1111/j.1469-8749.1998.tb15351.x PMID: 9459212

64. Alloway TP, Alloway RG. Investigating the predictive roles of working memory and IQ in academic attainment. Journal of Experimental Child Psychology 2010; 106:20–29. https://doi.org/10.1016/j.jecp.2009.11.003 PMID: 20018296

65. Birnkran DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the life-span. The Lancet Neurology 2018; 17:445–455. https://doi.org/10.1016/S1474-4422(18)30026-7 PMID: 29398641

66. Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. Journal of Medical Genetics 2007; 44:81–88. https://doi.org/10.1136/jmg.2006.045906 PMID: 17105749

67. Alloway T. Can interactive working memory training improving learning? Journal of Interactive Learning Research 2012; 23:197–207. 72

68. Alloway TP, Bibile V, Lau G. Computerized working memory training: Can it lead to gains in cognitive skills in students? Computers in Human Behavior 2013; 29:632–638.
69. Hinton VJ, De Vivo DC, Nereo NE, Goldstein E, Stern Y. Selective deficits in verbal working memory associated with a known genetic etiology: the neuropsychological profile of Duchenne muscular dystrophy. Journal of the International Neuropsychological Society 2001; 7:45–54. https://doi.org/10.1017/s1355617701711058 PMID: 11253841

70. Cotton S, Crowe SF, Voudouris N. Neuropsychological profile of Duchenne muscular dystrophy. Child neuropsychology: a journal on normal and abnormal development in childhood and adolescence 1998; 4:110–117.

71. Diggs-Andrews KA, Gutmann DH. Modeling cognitive dysfunction in neurofibromatosis-1. Trends in neurosciences 2013; 36:237–247. https://doi.org/10.1016/j.tins.2012.12.002 PMID: 23312374

72. Billard C, Gillet P, Signoret J, et al. Cognitive functions in Duchenne muscular dystrophy: a reappraisal and comparison with spinal muscular atrophy. Journal of Neuromuscular Disorders 1992; 2:371–378. https://doi.org/10.1016/s0960-8966(06)80008-8 PMID: 1300185

73. Faas G, Manchia M, Pintus R, Gerosa C, Marcialis MA, Fanos V. Fetal programming of neuropsychiatric disorders. Birth Defects Research Part C: Embryo Today: Reviews 2016; 108:207–223.

74. Sienko S, Buckon C, Fowler E, et al. Prednisone and Deflazacort in Duchenne Muscular Dystrophy: Do They Play a Different Role in Child Behavior and Perceived Quality of Life? PLoS Currents 2016; 8. https://doi.org/10.1371/currents.md.7628d9c014bfa298f821a5cd19723bbaa PMID: 27525172

75. Hinton VJ, Nereo NE, Fee RJ, Cyrulnik SE. Social behavior problems in boys with Duchenne muscular dystrophy. Journal of Developmental and Behavioral Pediatrics 2006; 27:470–476. https://doi.org/10.1097/00004703-200612000-00003 PMID: 17164619

76. Bray P, Bundy AC, Ryan MM, North KN, Everett A. Health-related quality of life in boys with Duchenne muscular dystrophy: Agreement between parents and their sons. Journal of Child Neurology 2010; 25:1188–1194. https://doi.org/10.1177/0883073809357624 PMID: 2179004

77. Nereo NE, Fee RJ, Hinton VJ. Parental Stress in Mothers of Boys with Duchenne Muscular Dystrophy. Journal of Pediatric Psychology 2003; 28:473–484. https://doi.org/10.1093/jpepsy/jsg038 PMID: 12968039

78. Helblebrekers DMJ, Lionarons JM, Faber CG, Klinkenberg S, Vles JSH, Hendriksen JGM. 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 2019; 44:1205–1223. https://doi.org/10.1093/jpepsy/jsz062 PMID: 31429914

79. Goodman R, Scott S. Comparing the Strengths and Difficulties Questionnaire and the Child Behavior Checklist: is small beautiful? Journal of Abnormal Child Psychology 1999; 27:17–24. https://doi.org/10.1023/a:102658229914 PMID: 10197403

80. Shilyansky C, Karlsgodt KH, Cummings DM, et al. Neurofibromin regulates corticostriatal inhibitory networks working memory performance. Proceedings of the National Academy of Sciences 2010; 107:13141–13146. https://doi.org/10.1073/pnas.1004829107 PMID: 20624961

81. Costa RM, Silva AJ. Molecular and cellular mechanisms underlying the cognitive deficits associated with neurofibromatosis 1. Journal of Child Neurology 2002; 17:622–626. https://doi.org/10.1177/088307380201700813 PMID: 12403561

82. Patrakitkomjorn S, Kobayashi D, Morikawa T, et al. Neurofibromatosis type 1 (NF1) tumor suppressor, neurofibromin, regulates the neuronal differentiation of PC12 cells via its associating protein, CRMP-2. Journal of Biological Chemistry 2008; 283:9399–9413. https://doi.org/10.1074/jbc.M708206200 PMID: 18218617

83. Anderson J, Morley J, Head S. Duchenne muscular dystrophy and brain function: INTECH Open Access Publisher, 2012.

84. Vaillend C, Perronnet C, Ros C, et al. Rescue of a dystrophin-like protein by exon skipping in vivo restores GABAA-receptor clustering in the hippocampus of the mdx mouse. Molecular Therapy 2010; 18:1683–1688. https://doi.org/10.1038/mt.2010.134 PMID: 20588257

85. Kueh SL, Dempster J, Head SJ, Morley JW. Reduced postsynaptic GABAA receptor number and enhanced gaboxadolin induced change in holding currents in Purkinje cells of the dystrophin-deficient mdx mouse. Neurobiology of disease 2011; 43:558–564. https://doi.org/10.1016/j.nbd.2011.05.002 PMID: 21601636

86. Culligan K, Glover L, Dowling P, Ohlendieck K. Brain dystrophin-glycoprotein complex: persistent expression of β-dystroglycan, impaired oligomerization of Dp71 and up-regulation of utrophins in animal models of muscular dystrophy. BMC cell biology 2001; 2:2.

87. Doorenweerd N. Combining genetics, neuropsychology and neuroimaging to improve understanding of brain involvement in Duchenne muscular dystrophy—a narrative review. Neuromuscular Disorders 2020; 30:437–442. https://doi.org/10.1016/j.nmd.2020.05.001 PMID: 32522501
88. Hellebrekers D, Wirken J, Lionarons J, Kuijk van S, Klinkenberg S, Vles J, et al. Computerized working memory training in males with Duchenne muscular dystrophy: a single case experimental design study. Neuropsychological Rehabilitation. Forthcoming. https://doi.org/10.1080/09602011.2022.2096080
PMID: 35876193