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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.

1. 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 [8,9]. 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) [10-14].

Abbreviation: AD(H)D, attention-deficit (hyperactivity) disorders; ASD, autism spectrum disorders; DMD, Duchenne muscular dystrophy; Dp140, dystrophin protein 140; FSIQ, Full Scale Intelligence Quotient.

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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 [10,15-18]. 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 [14,17,19]. 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 [12,15,17]. 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 [16,20]. 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.

2. Materials and methods

2.1. 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 cognitive tests, standardised 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.

2.2. 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 the 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+ [21]. 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- [21]. 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 [21]. 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.

2.3. 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) [22] 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 [11,20]. Verbal span capacity was assessed by the forward Number Recall subtest of the Kaufman Assessment Battery for Children - second edition (KABC-II) [23]. 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 [23]. The Symbol Search subtest of the Wechsler Intelligence Scale for Children - third edition (WISC-II) [24] 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 [24]. 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.

2.4. 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 evaluate individual clinical

differences, we transformed the age-related scaled scores to z-scores (mean=0, SD=1).. Z-scores of +2.0 SD or −2.0 SD were considered as clinical significant changes and results were presented as absolute number and proportion [25]. 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 influenced 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).

3. Results

3.1. 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 Fig. 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 1). No significant differences were observed for any of the demographic characteristics such as educational level and estimated IQ scores, or on disease related characteristics such as wheelchair bound, comorbid neuropsychiatric or developmental diagnoses, and use of corticosteroids or methylphenidate medication (see Supplementary Table 1). Patient characteristics of the included participants (n = 28) are displayed in Table 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).

3.2. 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 1) was not significantly different compared to the population mean (100, SD = 15, $p > .05$). On verbal span capacity, a significantly lower mean scaled score was found compared to the expected norm value of 10 on 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 males with DMD was not significantly different with respect to the norm value of 10 on the first (mean = 9.1, SD = 3.4, $p > .05$) or second neurocognitive assessment (mean = 8.6, SD = 4.3, $p > .05$).

3.3. Longitudinal neurocognitive data in DMD

3.3.1. 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 2), even though an increase due to development would have been expected. See Fig. 2 for visualization of individual trajectories of raw scores. In line with this, the longitudinal scaled scores showed a decrease

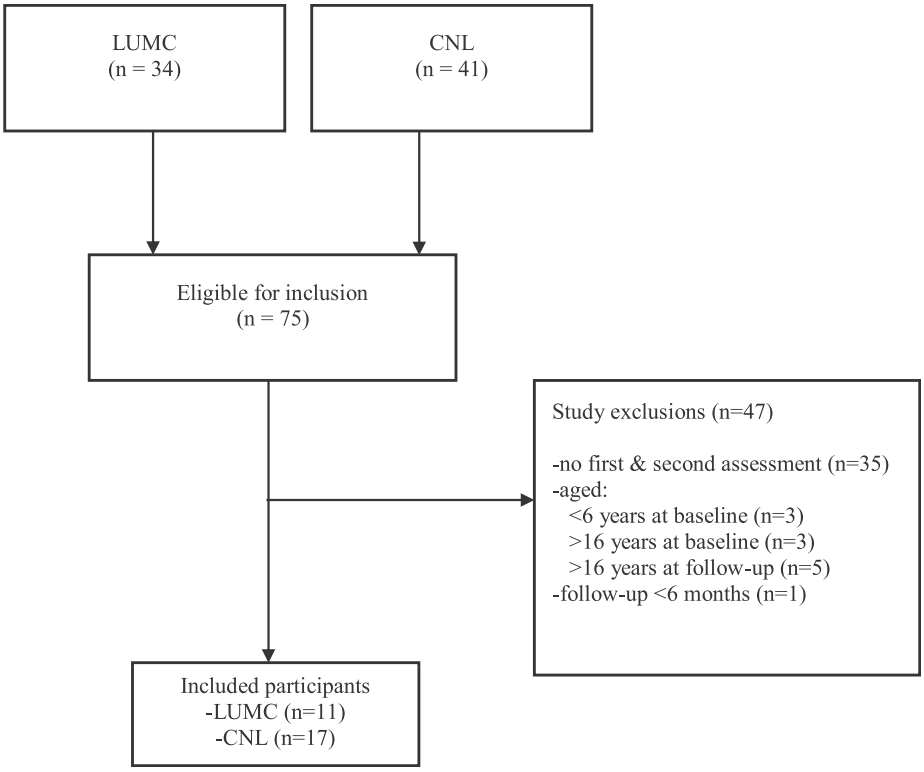

Fig. 1. Flowchart of inclusion.

Table 1
Patient characteristics of the total DMD sample and of subgroups.

	Total cohort	Subgroups			
	(n = 28)	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)	−.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)	−.654	.513
Disease-related characteristics					
Wheelchair dependency (%)	8 (29.6)	2 (33.3)	4 (26.7)	.093	1.000
Comorbidity present at assessment (%)	15 (53.6)	4 (66.7)	8 (50)	.489	.646
Medication use (%)					
Corticosteroids	23 (82.1)	6 (100)	14 (87.5)	.825	1.000
Methylphenidate	9 (32.1)	2 (33.3)	5 (31.3)	.009	1.000

NOTE: 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.

Table 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)	−.895	.379	−2.44	.961

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

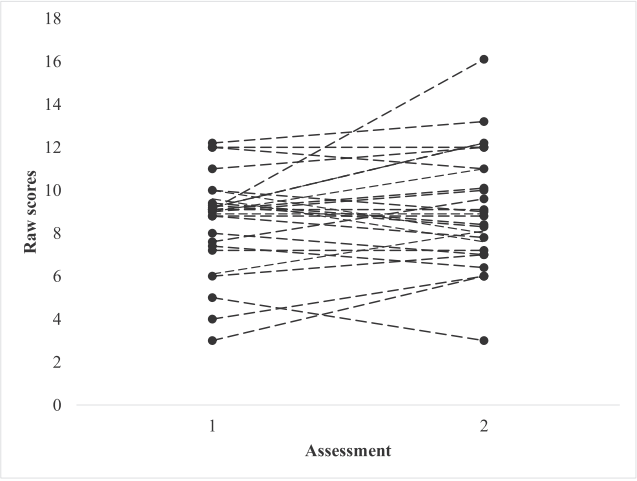

Fig. 2. Raw scores of verbal span capacity of the total DMD sample (N=28).

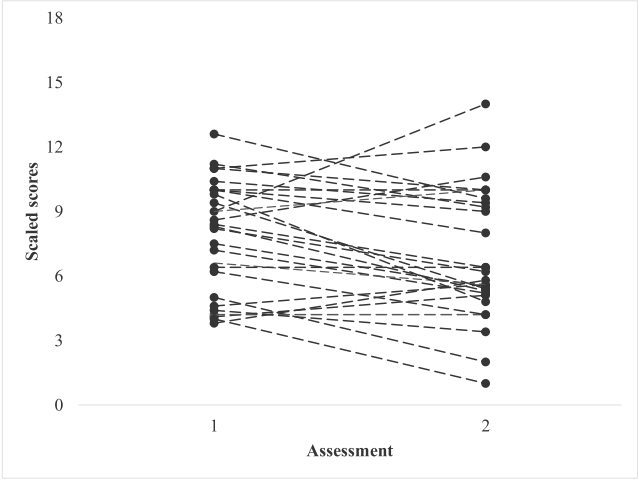

Fig. 3. Scaled scores of verbal span capacity of the total DMD sample (N=28).

over time on verbal span capacity, with a significant lower mean scaled score at the second neurocognitive assessment compared to the first neurocognitive assessment (see Table 2). Fig. 3 depicts the visualization of the decreased scaled scores.

When assessing relevant clinical differences, results showed that the scores at the second assessment did not changed (>2 SD or <2 SD) compared to the first assessment, indicating that none grown further into 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).

3.3.2. *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 2). See Fig. 4 for visualization of raw scores. No significant differences were found on longitudinal scaled scores of information processing speed (see Table 2). See Fig. 5 for visualization of scaled scores.

No relevant clinical differences (≥2 SD) in z-scores were found for 21 males (75%) between their first and second assessment. Two males (7.1%), of which one had a comorbid diagnosis of ASD,

Table 3
Multiple regression analyses with verbal span change score as outcome.

Variables	B	SE_b	β	t-values	95% CI Lower	Upper
Age	−.174	.190	−.184	−.915	−.565	.218
Individual differences in time	−.015	.029	−.120	−.536	−.074	.044
Methylphenidate use	−1.248	.949	−.289	−1.314	−3.207	.711

NOTE: 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. N=28 males with Duchenne muscular dystrophy
*p < .05.

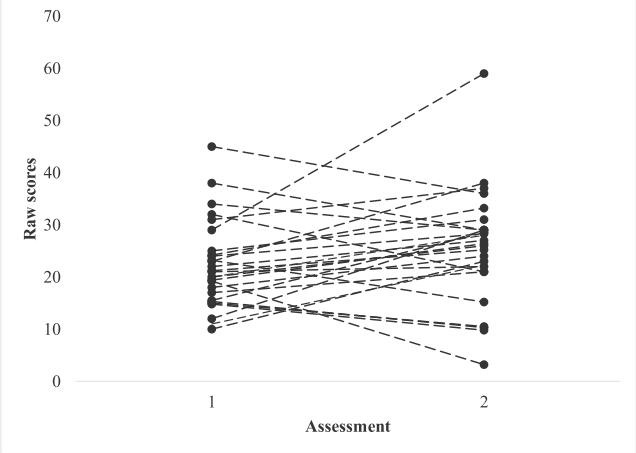

Fig. 4. Raw scores of processing speed of the total DMD sample (N=28).

showed a clinical relevant improvement at the second assessment. Four males (14.3%), of which two had a comorbid diagnosis of AD(H)D and used methylphenidate, showed a clinical relevant decline at the second assessment. In addition, one of the 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 4).

3.4. 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 analyses, 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 1. No significant differences were found on demographic and disease related parameters between the Dp140 + subgroup and the Dp140-subgroup (see Table 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 5). The subgroup comparison on information processing speed indicated significantly higher scores for group Dp140 + compared to group Dp140- at the first neurocognitive assessment ($p < .05$) and second neurocognitive assessment ($p < .05$; see Table 5).

4. 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 [10,15-18]. The 28 males with DMD of our sample had lower verbal span capacity on both the first and second neurocognitive assessment compared to the 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 [12,15,17,18]. Verbal span

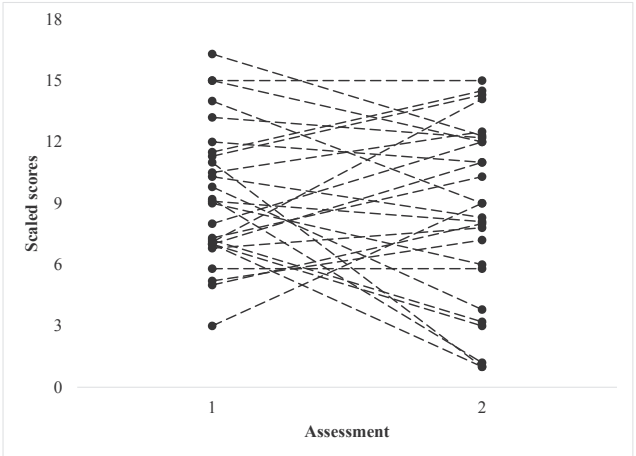

Fig. 5. Scaled scored of processing speed of the total DMD sample (N=28).

Table 4
Multiple regression analyses with information processing speed change score as outcome.

					95% CI	
Variables	B	SE_b	β	t-values	Lower	Upper
Age	−.737	.391	−.379	−1.546	−1.546	.072
Individual differences in time	.049	.060	.185	.813	−.075	.172
Methylphenidate use	−.288	2.066	−.031	−.139	−4.562	3.986

NOTE: 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. N=28 males with Duchenne muscular dystrophy.
*p < .05 (two-sided).

Table 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*

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

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 [26,27]. 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 [17,28]. 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 [29]. 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 [29]. For instance, when males exhibit a developmental stagnation in verbal span, certain tools should be used such as speaking simple, using short sentences, repeating verbal information more often, using visual stimuli as contextual cues, or associating pairs of words or digits to existing knowledge. These tools can be applied at home and school to compensate and improve for their ineffectual proficiency in retaining long and complex verbal information [16,27]. A first cognitive evaluation should preferably be performed within the first year of diagnosis of DMD to establish a baseline [29], 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, but also crystallized and fluid intelligence because all are important for academic performance [30,31].

4.1. 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 [3,4,21]. Even though the number of patients for this analysis is small, our subgroup analyses 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 [4,21,32]. 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.

4.2. Limitations

Even though our sample size is appropriate for total group analyses, we acknowledge that our sample is too small to properly analyse 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 [33]. Nonetheless, future longitudinal studies should perform subgroup analyses 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 burden 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 the 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 age-related norm scores, especially with a growing adult DMD population.

5. 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.

Declarations of competing interest

None of the authors has any conflict of interest to disclose. All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be a potential conflict of interest. A selection of this data was presented at the World Muscle Society Congress (Mendoza, Argentina, October 2-6, 2018).

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2020.01.002.

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