Towards harmonization of clinical tools for assessing Brain Involvement in Dystrophinopathies (BIND); report of four expert workshops: Newcastle, Leiden, Rome, Paris

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Abstract:

As part of an international project aimed at improving the characterization of brain involvement in Duchenne and Becker Muscular Dystrophies, a group of clinicians, researchers and family associations held multiple meetings between March 2021 and March 2024 to identify and reach a consensus on the possible tools that could assess the spectrum of neurocognitive and neurobehavioral brain comorbidities in dystrophinopathies. Consensus was achieved on which of these tools should be used across different settings, ranging from screening to clinical practice and scientific research. Screening questionnaires were found to be valuable not only for providing epidemiological data but also for raising awareness among the Duchenne community and professionals. More standardised and detailed online questionnaires, combined with in-depth clinical assessments can help better identify the profile of brain comorbidities and plan appropriate interventions. Additionally, the information gathered from assessing multiple features of brain involvement can be used to explore correlations with other aspects, such as the regional expression of the different dystrophin isoforms, brain imaging, and the animal models deficient in these isoforms.

Introduction

BIND (Brain INvolvement in Dystrophinopathies) is an international, European funded project including 19 partners from Europe and Japan that started in January 2020 for a four-year period. The aim of the project is to improve the characterization of brain involvement in Duchenne and Becker Muscular Dystrophy (DMD and BMD) and to elucidate the role of dystrophin in the brain. Seven neuromuscular centres collaborated in the clinical assessment of DMD and BMD patients: University College London

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As part of this project, a group of European clinicians (psychologists, neurologists and psychiatrists) and researchers with expertise in deep behavioural phenotyping of the Duchenne dystrophic mouse models met in several online meetings between March 2021 and May 2023, and four in-person workshop meetings between May 2023 and March 2024 (Newcastle May 2023, Leiden September 2023, Rome November 2023, Paris March 2024). The aim of these meetings was to identify the tools available for assessing the spectrum of neurocognitive and neurobehavioral brain comorbidities in dystrophinopathies and to reach a consensus on which of these tools could be used in across different settings, from screening to clinical practice and scientific research.

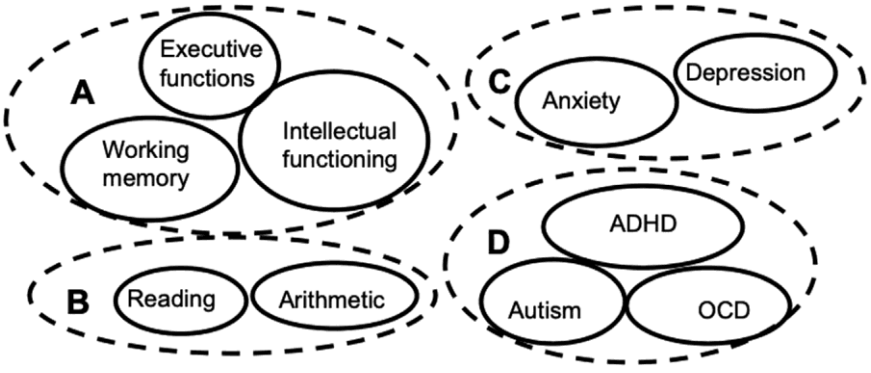

Fig. 1. Big Ten of Duchenne. Systematic overview of brain related comorbidities in DMD representing four domains and ten areas of (dys)functioning: (A) Neurocognitive (executive functions, working memory and intellectual functioning); (B) Academics (reading and arithmetic); (C) Emotional (anxiety and depression); (D) Neuropsychiatric (ASD, ADHD, OCD).

Background

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are caused by mutations in the DMD gene, leading to the absence (DMD) or reduction (BMD) of the protein dystrophin with subsequent progressive muscle weakness, further referred to as dystrophinopathies. Dystrophin is expressed not only in muscles but also in the brain and other organs. In his original description in 13 patients with DMD in 1868, Duchenne de Boulogne already described brain comorbidities: six patients with a low IQ, two with language problems and two with epilepsy [1]. Following Dubowitz's systematic case series report on intelligence in 1965, there has been increasing evidence of intellectual disability and other central nervous system (CNS) co- morbidities such as neurodevelopmental problems and behavioral and psychiatric difficulties [2].

The area of interest of this workshop (brain related comorbidities) has previously been described in an ENMC meeting (Hendriksen et al. 2020) [3]. Four domains of brain involvement are to be considered encompassing ten different and potential areas of problematic functioning (referred to as the 'Big Ten of Duchenne': see Fig. 1): intelligence, attention and executive function in the cognitive domain, reading and arithmetic in the learning domain, Attention Deficit Hyperactivity disorder (ADHD), Autism Spectrum Disorder (ASD), Obsessive Compulsive Disorder (OCD) in the psychiatric domain, and anxiety and depression in the emotional domain.

Several studies have reported a significant association between cognitive abilities and the concomitant involvement of multiple brain dystrophin isoforms whose expression is differentially affected by the site of the DMD mutations [4–7]. Patients with mutations upstream exon 44 have involvement of Dp427 only; mutations after exon 51 affect both Dp427 and Dp140, and mutations after exon 63 involve Dp427, Dp140 and Dp71. Mutations between 44 and 51 have recently been considered separately as the extent of the involvement of Dp140 in these patients cannot always be unequivocally predicted. While the association between brain dystrophin isoforms and cognitive abilities has been systematically established, there is less consensus on their association with behavioural and psychiatric disorders, as reported prevalence is very variable in current literature [8]. The variability observed in several studies may partly be caused by small cohorts, different inclusion criteria, and different tools being used [9]. Most of the studies focused on individual aspects of brain related involvement; a systematic assessment of the full range of brain related comorbidities, including both cognitive, academic and behavioral aspects, and their interrelation has not been reported. Furthermore, despite the international care recommendations strongly suggesting to combine cognitive assessments and questionnaires such as the Personal Adjustment and Role Skill scale (PARS III) [14] for the assessment of psychosocial adjustment, this is often not implemented in clinical practice. Even in research settings, the studies typically focus on specific aspects of cognitive or behavioural difficulties without making a systematic effort to identify a comprehensive battery of tests that cover all the relevant aspects of brain involvement in DMD.

Topics discussed

Eugenio Mercuri (Catholic University and Centro Clinico Nemo, Rome, Italy), Ruben Miranda (Universidad Complutense de Madrid, Spain), and Jos Hendriksen (Kempenhaeghe Centre for Neurological Learning Disabilities, Heeze, the Netherlands) introduced the topics of the workshops, that were structured in five sections focused on different aspects of assessment.

The first section was dedicated to a review of the literature on existing assessment tools and to the identification of different clinical domains of brain involvement reporting the results of a survey investigating the tools currently used in the participating centres.

The second section focused on the identification of questionnaires that could be used in large cohorts to capture an overview of possible comorbidities.

The third section was dedicated to the identification of a battery of tests to be used in a clinical setting to assess in

depth cognitive and academic performances, paying particular attention to the aspects related to specific brain areas or networks that are known to be more commonly involved in dystrophinopathies.
The fourth section aimed at identifying a short screening tool to explore possible co-morbidities in a wider group of dystrophinopathy families with the support of advocacy groups.
A final section was conducted to provide an overview of the application of these tools as part of an international project and to evaluate the suitability of the selected tools.

Review of the literature and initial survey among participating countries
Pien Weerkamp (Kempenhaeghe Centre for Neurological Learning ~~Disabilities, Heeze, the Netherlands)~~ and Daniela Chieffo (Catholic University, Rome, Italy) provided an overview of the literature, focusing on the tools used in the different studies and the prevalence of cognitive and behavioural disorders in dystrophinopathies. A critical analysis of the published results highlighted how some of the tools used in previous studies were not always appropriate for individuals affected by DMD, as some of the activities may be strongly influenced by motor function. Further analysis was performed to identify the studies reporting comorbidities and the association between individual or multiple aspects of brain-related comorbidities and brain dystrophin isoforms.

The session also included the results of a survey performed across the seven clinical centres participating in BIND to define number of patients, available instruments and formats used in clinical routine to assess patients with a dystrophinopathy [10]. A structured questionnaire was completed by all seven sites to make an inventory of all instruments being used across the three domains of functioning (cognition, behaviour and academics) in different age groups (3–5 years, 6–18 years and adulthood 18+ years).

The results of the survey showed that in the participating centres there was consensus for the intelligence testing, using the Wechsler scales, but all other functions such as memory, attention, behavioural problems and academics were tested with a wide variety of instruments in the participating centres. As part of the survey, we also analysed if the tests that were thought to be relevant were available across the participating countries.

The final discussion underscored the need for the development of Standard Operating Procedures to be used in this multi-centre project and in particular the need for technical manuals on administration, scoring and interpretation of the results. It also empahasized the need for translation of materials, standardization of patient inclusion and follow-up of patients' dropout, and uniform patient feedback forms for cognitive and behavioural data as part of the study. The technical manual that was written for this purpose is available upon request.

D**evelopment of an online battery of questionnaires for assessing comorbidities (Part 1)**

While in the original BIND proposal an in-depth assessment of brain related comorbidities was scheduled to be conducted by clinical examiners in the first part of the study, the COVID 19 pandemic and the resulting limited access to clinic and patient contacts forced us to change the order of the assessments and to anticipate the development of the online questionnaires originally scheduled for the second part of the project. Therefore, the online questionnaire-based testing was identified as Part 1 and the in- person neuropsychological assessment as Part 2.
Jos Hendriksen reported on the development of the online questionnaire battery on the basis of a recent review of instruments being used in DMD. The aim was to develop a multi-method, multi-informant assessment [9]. Neurobehavioural assessment should compose (1) proxy report by parents and teachers, (2) self-report questionnaires in boys older than 15 years of age and (3) clinical oriented data using DSM-5 criteria [11].
This started with the identification of two tools recommended by the recent standard of care instructions [12]: (1) the 25- item Strength and Difficulties Questionnaire (SDQ) for assessing mental health [13] and (2) the 28-item Personal Adjustment and Role Skill scale (PARS-III) [14]. For the adult participants with dystrophinopathy the 22-item Personal Adjustment and Role Skill scale-Adult version (PARS-A) was used to assess coping and adjustment strategies with Duchenne normative data are available [15,16]. Two other tools as recommended by the standards of care (9-item Patient Health questionnaire (PHQ-9) [17] for depression screening, and the 7-item General Anxiety Disorder (GAD-7) [18] were not selected as they are only used in adult populations.

The Kempenhaeghe History Taking Questionnaire (KHTQ) is a 47-item instrument designed to assess the neurodevelopmental history of patients with dystrophinopathies. It can be used either as a self-report measure or by proxy to describe neurodevelopmental, behavioural, and emotional symptoms, as well as psychiatric diagnosis common in dystrophinopathies and any treatments received for this (e.g., speech therapy, psychotherapy, psychopharmacological use). The items are adapted from a recently published article of Darmahlasih et al. (2020) in boys with a dystrophinopathy [4,19]. In this questionnaire we also aimed to assesses the family history of neurodevelopmental disorders as well as educational level of the parents, as these are important factors to control for in the project. The educational level of the parents/guardians and young patients are based on the international standard classification of education (ISCED) categories of 2011 [20].

To screen for learning and cognition problems, a Learning Questionnaire (KLQ) questionnaire was developed comprising four a-priori subscales based on relevant domains: reading, mathematics, working memory and executive functioning and covering four domains of the "Big Ten" [3]. Items of the first two subscales (reading; 6 items, and math; 4 items) are based on the Colorado Learning Difficulties Questionnaire (CDLQ) [21].) Two of the five items (item 2 and 3) of the reading subscale where rephrased to make them easier to understand for non- professionals. Psychometric qualities of the original subscales are good. Furthermore, three existing questionnaires -with good psychometric properties - were used to formulate items on working memory (5 items) and executive functioning (5 items): five to fifteen-R (5–15R) [22], Behaviour Rating Inventory of Executive function (BRIEF) [23]), and Questionnaire of Memory (Q- MEM) [24].

David Skuse (UCL, London, UK) introduced the DAWBA (DEVELOPMENT AND WELL BEING ASSESSMENT) [25], a validated package of online interviews, questionnaires and rating techniques designed to generate ICD-10 and DSM-IV [26,27] or DSM-5 psychiatric diagnoses [11], with population norms available for 2–17-year-olds and available in 25 languages. Firstly, the SDQ [13] is administered using the self-report, parent report or teacher report version (25 items each version). This is a commonly used screening questionnaire to determine if there are issues with emotional or behavioural problems and the impact on family life and daily functioning. The DAWBA itself, is a long-format structured by-proxy rated questionnaire that covers the common emotional, behavioural and hyperactivity disorders, including more severe disorders later classified according to either DSM-IV/5 or ICD-10. The clinical interpretation of the DAWBA responses can be made by a trained clinical psychologist or psychiatrist. For the purposes of the present study based on previous literature of reported problems in dystrophinopathies, clinical ratings for the following 11 diagnostic categories were pre-agreed by the group at the meeting in Leiden in September 2023: ASD, ADHD, Tics, Separation Anxiety, Social Phobia, Specific Phobia, Generalized Anxiety, Major Depression, Oppositional Defiant Disorder (ODD), Conduct Disorder and OCD. For a direct comparison with KHQ data from Part 1 of the testing battery, the 4 anxiety-type diagnoses (i.e., Separation Anxiety, Social Phobia, Specific Phobia, Generalized Anxiety) were combined into a single Anxiety-Related Disorders category, and Conduct Disorder was removed as a diagnostic category resulting in a final set of six neuropsychiatric disorders (as agreed in a Paris meeting, March 2024).

Table 1
Summary of tests used in the in-person cognitive assessment.

Cognitive Assessment: Intelligence, cognitive functions, academics	Duration (min.)
Intelligence	
WPPSI-III preschool intelligence (2002) WPPSI-IV preschool intelligence (2012)	50,
WISC-IV children (2003) WISC-V children (2014)	65,

WAIS-IV adults (2008)	60, −90,
RAVEN 2 nonverbal concept formation	30,
Cognitive functions	
Auditory memory: RAVLT	15,
Language: NEPSY-II comprehension of instruction	20,
Language: NEPSY-II speeded naming	
Language: NEPSY-II phonological processing	
Social cognition: NEPSY-II theory of mind	
Attention: FePsy Simple reaction times	10,
Executive functions: BADS(-C) key search	5,
Academics	
Speeded reading	10,
Speeded arithmetic	10,

Note. WPPSI: Wechsler Preschool and Primary Scale of Intelligence; WISC: Wechsler Intelligence Scale for Children; WAIS: Wechsler Adult Intelligence Scale; RAVLT: Rey Auditory Verbal Learning task; NEPSY: A developmental NEuroPSYchological Assessment; BADS: Behavioural Assessment of Dysexecutive Syndrome.

The interpretation of the assessment responses and allocation of a research diagnosis were based on DSM-5 criteria by clinicians. Additional training on the administration and interpretation of the DAWBA assessment results was provided to all BIND testing sites through a two-day course led by David
Skuse at UCL, London, UK in September 2022. Reliability testing of diagnostic accuracy were carried out by David Skuse and Anna Kolesnik at UCL (2023–2024).

Neuropsychological testing and Academics (Part 2).

Furthermore, patients underwent an in-depth face-to-face cognitive phenotyping and academics assessment in a clinical setting by a trained psychologist. A test battery was developed using standardized, reliable, validated instruments that have adequate and sufficient normative data for each language to evaluate (1) intelligence, (2) a number of neurocognitive functions and (3) academics (see table 1). It was requested, due to the heterogeneous nature of the patients being included and inclusion of patients with an intellectual disability and patients with neuropsychiatric comorbidities, that testing should be done by a trained and qualified psychologist with adequate experience in testing patients with a dystrophinopathy. Several online training meetings for psychologists, led by Jos Hendriksen, were organised to ensure consistency in assessment and scoring procedures.
The tests selected were: (1) easy to administer, (2) suitable for making clinically sound diagnoses, (3) available in the language of participating countries and (4) realizable in the overall research protocol with multiple assessments for each participating centre. A multi-centre study on psychological test usage was performed as a starting point for this process [10].

Intelligence.

The Wechsler Scales (WPPSI-III/IV preschool; WISC -IV/V child version; WAIS IV for patients older than 16 years) [28–32] were used to assess intelligence in all participating countries. Results of a recent review using this test were considered [10]. The Wechsler scales provide the opportunity to test patients from early childhood till adulthood with different age-related scales that assess similar intelligence constructs, so that a comparison over the whole age range can be done. The WISC-V version was not available in Italian, so that it was decided to use the latest version available, the WISC-IV version in the Italian site. Besides the Full Scale IQ (FSIQ), the following subscale scores can be computed in all sites: (1) verbal comprehension, (2) visuo-spatial functioning, (3) working memory and (4) speed of information processing. It was also agreed to include the RAVEN-2 test [33], as this is a non-language test of nonverbal concept formation that has been recently normed for different EU languages and is available in a digital electronic short (20 item) version.

Additional tests were selected for assessment of specific neurocognitive functions included in the Big Ten and described in the literature:

Memory:

The Rey Auditory Verbal Learning Task (RAVLT) [34] evaluates memory through immediate recall over five consecutive trials, delayed recall after 20 min, and recognition of a 15-word list.
Language Processing: two NEPSY-II [35] subtests were used:

Comprehension of Instruction

Measuring language abilities including to receive, process, and execute oral instructions of increasing syntactic complexity, and (2) Speeded Naming to measure verbal fluency i.e. production of names of colours, shapes, sizes, letters or numbers.

Phonological Processing:

Another NEPSY-II subtest [35], assesses phonological processing at the level of word segments (syllables) and of letter sounds (phonemes)

Social Cognition:

Theory of Mind is evaluated using NEPSY-II, assessing the ability to understand mental functions, thoughts, and emotions of others in given various social contexts using pictures.

Attention:

Auditory and visual simple reaction times, two subtests of the FePsy (http://www.fepsy.com) a computerized neuropsychological test battery, measure reaction time to visual and auditory stimuli, reflecting alertness and speed of information processing.

Executive Function:

Behavioural Assessment of Dysexecutive Syndrome (BADS) [36,37] was used. The Key Search task evaluates executive functioning, particularly planning and implementing efficient plans of action, by having children and adults search for a lost key on a field.

Reading:

Speeded Reading Tests assess reading speed, with variations such as the one minute reading test (Een Minuut Test) [38] in the Netherlands, PREDISCAL [39] in Spain, Lecture de mots et Comprehension (LMC-R) [40] in France, MT-avazantte di Lettura [41] in Italy, and the Wechsler Individual Achievement Test [42] (WIAT-III UK) in the UK.

Mathematics:

Speeded Arithmetic Tests measure arithmetic speed, with assessments like the Speeded automatization test (Tempo Test Automatiseren) [43] in the Netherlands, PREDISCAL in Spain [39], AC-MT (per la valutazione dei disturbi di calcolo) [44] in Italy, and WIAT-III UK's Maths Fluency [42].

BIND Screener

Given the complexity and heterogeneity of brain related comorbidities, there is need for a screening tool to quickly detect them in regular clinical practice. Based on the outcome of the screener, clinicians should be able to decide to refer patients for a further in-depth assessment. Therefore, as part of the BIND project we aimed to explore possible comorbidities in a larger group of patients through a BIND Screener. This questionnaire was constructed and eventually distributed with the support of the World Duchenne Organization (WDO). For the sake of clarity, quick tick box questions were used based on existing questionnaires with proven validity based on the areas of the Big Ten (Fig. 1). The questionnaire should be easy to administer, with strict answer alternatives that should enable conclusive interpretation of the answers. For that reason, N/A (not applicable) was not used as an answer alternative. The screener is divided in three parts:

18 items on behavioural and cognitive concerns with 2 items per domain: ASD, ADHD, OCD, anxiety, depression, working memory, executive functions, reading and arithmetic. The domain of intelligence of the Big Ten is not included in these items as this is mainly based on IQ testing.

Table 2
Number of patients recruited as a function of diagnosis and age group.

	N Total	Mean age∗
DMD (5–17)	323	10,3 (3,3)
BMD (5–17)	36	10,1 (3,3)
BMD (18–50)	74	35,9 (9,3)

Note. ∗Age expressed in years as 'Mean (SD)'.

Table 3
Number of patients recruited across the different study parts as a function of diagnosis and age.

	DMD (5–17)	BMD (5–17)	BMD (18–50)	N Total
Part 1	280 (74 %)	34 (9 %)	63 (17 %)	377
DAWBA	239 (75 %)	33 (10 %)	46 (14 %)	318
Part 2	254 (75 %)	27 (8 %)	58 (17 %)	339

Note. Part 1: Online questionnaires (KHQ, Kempenhaeghe History Taking Questionnaire; KLQ, Kempenhaeghe Learning Questionnaire; PARS, Personal Adjustment and Role Skill scale). DAWBA: Development and Well-Being Assessment. Part 2: Face-to-face neuropsychological assessment. ∗Age expressed in years as 'Mean (SD)'.

10 items informing whether the patient/respondent has ever received a diagnosis according to the diagnoses distinguished in the Big Ten by a doctor or health professional. 6 items informing on the burden of care.

The BIND Screener was piloted and found to be easy to understand and to be completed by families and patients.

Final considerations

A finalization meeting was organized in Paris (March 2024) and provided the opportunity to highlight both the challenges and the achievements after using the tools selected in the first 30 months of the BIND project. Elizabeth Vroom (World Duchenne Organization) provided an overview of the patient organization input in the project, from the development of the protocols to the dissemination. She also highlighted the importance of sharing information with the families who have participated to the project and, in general, of providing feedback to the dystrophinopathy community.

Ruben Miranda (Department of Psychobiology, Universidad Complutense de Madrid, Spain) provided an overview of the cohorts enrolled in the project. The total number of patients assessed by the protocol was as follows: 323 patients with DMD aged 5–17 years old; 36 BMD patients aged 5–17 years and 74 adult patients with BMD (age 18–50). Details are shown in Tables 2 and 3.

The online questionnaires from Part 1 were completed from 377 patients. Of these, 318 patients participated in the DAWBA interview, and in-depth cognitive phenotyping through face-to-face neuropsychological assessment was obtained in 339 patients (see Table 3). Typically, these assessments were completed over two sessions. The analyses of these assessments are currently underway and will be reported separately in the future.

As mentioned in section I, all families of participants with a dystrophinopathy received feedback on their cognitive and behavioural data in a standardized form. A template of the feedback form is available upon request. Of all participants, one family chose to withdraw from participation after receiving of the feedback form.
Anna Kolesnik (UCL, London, UK), Pien Weerkamp, Chloe Geagan, and Jos Hendriksen provided an overview of how to classify the available data. A discussion involving all the participants brought to a consensus on how the results of the different tests could be used to achieve a final diagnosis of the individual aspects assessed: ASD, ADHD, OCD, Anxiety disorder (also including separation anxiety, specific phobia, social phobia, separation anxiety), Major Depression, dyslexia and dyscalculia.

Francesco Muntoni (UCL, London, UK) as the coordinator/principal investigator of the entire BIND project highlighted how the batteries piloted in our project were found to be suitable and could contribute in multiple ways:
The screener questionnaire could provide valuable epidemiological data while simultaneously raising awareness withing the DMD community about the frequency and severity of brain-related comorbidities.
In a clinical setting, a detailed assessment of the comorbidities, as defined by this working group can identify the profile of difficulties and inform appropriate interventions. The meetings highlighted that behavioural and psychosocial difficulties are often under-recognised and, even when diagnosed, are frequently not treated with therapies (e.g. psychopharmaca). The data to be collected using this consensus battery can contribute to the development of a dystrophinopathy- specific and sensitive assessment battery, which is greatly needed in clinical practice.

In a research setting, the information provided by assessments of multiple aspects of brain involvement can be correlated with other aspects, such as the regional expression of the different dystrophin isoforms, brain imaging results, and findings from animal models deficient in these isoforms.

Additional data mining on the effectiveness of the different assessment scales, their correlation with the location of the DMD mutations, and the occurrence of multiple comorbidities within the same individual is essential.
It is concluded that the harmonisation processes described in this report, involving seven EU neuromuscular centres, which is unique in this field of interest, have contributed to (1) addresssing issues related to the assessment of brain comorbidities in dystrophinopathies (e.g. heterogeneity of comorbidities assessed by different instruments lacking specific normative data), and (2) providing recommendations to the scientific and clinical community interested in this field on tools that can be used.

Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

CRediT authorship contribution statement

Jos Hendriksen: Writing – review & editing, Writing – original draft, Conceptualization. Pien Weerkamp: Writing – original draft, Conceptualization. Ruben Miranda: Writing – original draft, Data curation. Anna Kolesnik: Writing –

review & editing, Conceptualization. Daniela Chieffo: Writing – review & editing, Data curation, Conceptualization. David Skuse: Writing – review & editing, Conceptualization. Elizabeth Vroom: Writing – review & editing, Conceptualization. Chloe Geagan: Writing – review & editing. Francesco Muntoni: Writing – review & editing, Funding acquisition, Data curation, Conceptualization. Eugenio Mercuri: Writing – review & editing, Writing – original draft, Data curation, Conceptualization.

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