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Duchenne muscular dystrophy: recent insights in brain related comorbidities

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Duchenne muscular dystrophy (DMD), the most common childhood muscular dystrophy, arises from *DMD* gene mutations, affecting the production of muscle dystrophin protein. Brain dystrophin-gene products are also transcribed via internal promoters. Their deficiency contributes to comorbidities, including intellectual disability (~22% of patients), autism (~6%) and attention deficit disorders (~18%), representing a major unmet need for patients and families. Thus, improvement of their diagnosis and treatment is needed. Dystrophic mouse models exhibit similar phenotypes, where genetic therapies restoring brain dystrophins improve their behaviour. This suggests that future genetic therapies could address both muscle and brain dysfunction in DMD patients.

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy affecting children. With an incidence between 1:3500-1:5000 live male births[1], the high frequency of *de-novo* mutations in the X-linked *DMD* gene is an obstacle to its eradication.

The DMD neuromuscular and cardiac manifestations are well recognised: affected children are diagnosed in the first few years of life and weakness progresses rapidly, leading to loss of ability to walk by the early teens, and subsequent respiratory and cardiac insufficiency resulting in shortened life span. The course is secondary to the loss of dystrophin, a crucial protein that protects the sarcolemma from contraction-induced damage leading to progressive muscle fibres loss. In the last decade, a few pharmacological and genetic therapies that reduce muscle damage have demonstrated efficacy in clinical trials and are at different stages of approval[2].

However, DMD is much more than a pure neuromuscular disease: already in 1868, the French neurologist Duchenne De Boulogne in his original report of 13 boys with DMD indicated that six of them had a low IQ, two had language problems and another two had epilepsy[3].

These observations have been confirmed in subsequent studies reporting that nearly half of individuals affected by DMD may have a complex neurobehavioural and neurocognitive phenotype. This can variably manifest with specific language disorders, intellectual disability, reading disorder, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), emotional disorders and obsessive-compulsive disorders (OCD)[4–6].

Work performed in the last decade has shed further light on the variable brain involvement: this largely relates to the location of the *DMD* mutation along this large gene. We are now aware that the *DMD* locus produces multiple dystrophin isoforms, which can be differentially affected depending on where the pathogenic variant is located[7].

More recent work has improved the understanding of the role of individual isoforms on the brain phenotypes observed, both in the human and mouse models; and on the biological role of these dystrophins[8].

Ongoing work is exploring the role of genetic therapy administration, not to the muscle but to the brain, in improving the brain comorbidities in animal models of DMD, potentially paving the way to their future root cause correction.

While these basic research efforts continue, improvement in the screening, assessment, and diagnosis of the brain comorbidities in

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patients with DMD need to be implemented, together with a systematic assessment of the role that psychotherapy and psychopharmaca may play in managing some of the neurobehavioural consequences. This is not sufficiently addressed by the current standards of care for DMD[9], and continues to be a major and growing unmet need for this patient population, especially as life expectancy increases.

The DMD locus, brain DMD isoforms and their pattern of expression

The Xp21.1-p21.2 *DMD* gene, the largest gene in the human genome, spans nearly 2.5 Mb. It consists of 79 exons and seven internal promoters, each linked to unique first exons giving rise to at least 7 protein products of different sizes[7]. The full-length isoform (Dp427) is transcribed through 3 different tissue-specific promoters upstream of their first exon sequences, namely Purkinje (P), muscle (M), and cortical (C); they are expressed in different cell types and/or cell compartments in association with different molecular partners, as indicated by transcriptomic studies from Allen Human Brain and BrainSpan atlases (https://atlas.brain-map.org; http://www.brainspan.org) and mouse tissue[8,10]. While Dp427m is mainly expressed in muscles, likely including smooth muscles of brain arterioles, Dp427c is mainly present in the forebrain and cerebellar neurons. The shorter isoforms named according to their molecular weight, Dp260, Dp140, Dp116, Dp71, and Dp40, are produced by independent downstream promoters and exhibit tissue-specific expression patterns as shown in studies on murine and canine embryos and PC12 cell lines[11,12] (Fig. 1). Of note, some of these isoforms also express different alternative splicing that may regulate their subcellular location[12]. While Dp260 and Dp116 are expressed in the retina and peripheral nerve, respectively, transcriptomic analysis from Allen Human Brain and BrainSpan atlases demonstrated that Dp140 and Dp71/Dp40 are expressed in the brain with larger expression in hippocampus and amygdala[8]. Dp71 and Dp140 are also expressed outside the central nervous system (CNS). In particular, Dp71 is expressed in many human adult tissues including liver, lung, kidney, and muscle progenitor cells, and skeletal muscle[13,14], while Dp140 is also transiently expressed during kidney development[15].

The expression of these dystrophin isoforms changes during development. Dp140 is more abundant in the foetal brain; Dp427c and to a less extent Dp427m are more highly expressed in adults compared to foetal brain, while Dp71/Dp40 expression is high both during foetal stages and later in human life[8]. More recently it has been found that Dp427p was absent throughout the development of the brain as shown in transcriptomic analysis from Allen Human Brain and BrainSpan atlases, which is contrast with previous studies[8,16].

Pathogenic *DMD* gene variants, more frequently out-of-frame deletions (65%) or duplication (15%), lead to the absence of dystrophin in muscle resulting in DMD. Allelic variants, often in-frame deletions, can also induce the production of a partially functional dystrophin protein and cause the milder and later onset Becker muscular dystrophy (BMD). The location of the mutation along the *DMD* gene may differentially impact the multiple dystrophin isoforms (Fig. 1). While all mutations affect muscle and brain production of Dp427, the additional involvement of Dp140 and/or Dp71/40 is related to how further downstream in the *DMD* gene the mutations are located (Fig. 1).

Role of the different isoforms in the brain

Recent advances in cellular and molecular neuroscience have shed light on the pivotal role of dystrophin isoforms in modulating synaptic transmission and ion channel functioning. The Dp427 isoforms have been implicated in the localisation and functioning of central γ-Aminobutyric acid type A ($GABA_A$) receptors, which has been indirectly confirmed by brain imaging in adults with DMD, although it is not clear if all three full length isoforms contribute to the GABA synaptic functioning[17]. Immunofluorescence studies in the dystrophic *mdx* mice carrying a nonsense mutation in exon 23 have demonstrated that the

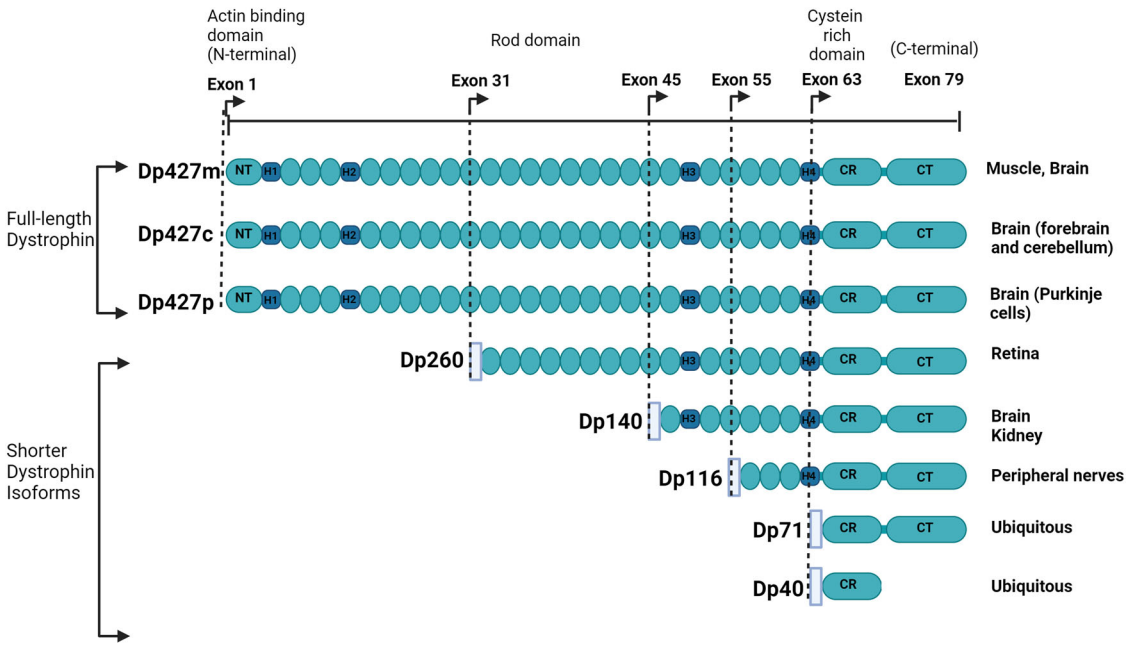

Fig. 1 | DMD gene organization and associated protein products. The full-length dystrophins (Dp427m,c,p) have a modular structure containing the N-terminus (NT) with F-actin binding sites, an extensive central rod domain that consists of β-spectrin-like repeats (oval shape symbols) with binding sites for F-actin, sarcolemma and multiple cellular proteins, and proline-rich hinge regions (H1-H4) predicted to form triple-helical coiled coils, followed by cysteine-rich (CR) and C-terminal (CT) domains. The shorter dystrophin isoforms (Dp260, Dp140, Dp116, Dp71) exhibit at least the cysteine-rich (CR) and C-terminal (CT) domains, except Dp40 that share the Dp71 first exon but misses the CT domain due to an alternative polyadenylation that generates a stop codon. The CR region contains a WW domain, two EF-hands, a β–dystroglycan binding site, and one ZZ domain. The C-terminal region contains two syntrophin binding sites and a coiled-coil domain interacting with dystrobrevins. The light blue rectangular boxes indicate the position of the promoter region of each isoform. The main tissues expressing the distinct dystrophin isoforms are indicated on the right. The figure was Created in BioRender[101].

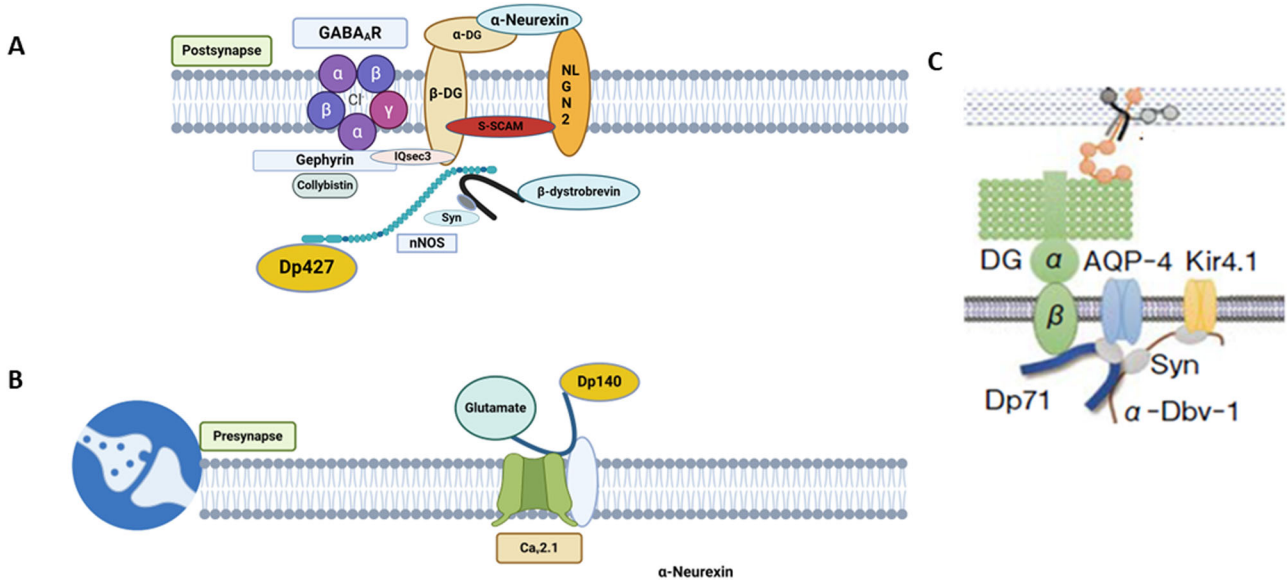

Fig. 2 | Schematic Representations of Dystrophin Interactions in the Nervous System. A Dp427 and Postsynaptic Complexes in Central Inhibitory Synapses. This diagram illustrates the Dp427-associated complex, including α and β dystroglycans, and its role in postsynaptic scaffolding (the black U-shape form represents dystrobrevin). The interaction with key proteins such as Neuroligin-2 (NLGN2), neurexin, S-SCAM, and IQsec3, which are crucial for GABAAR clustering, is depicted. The GABAAR subunits are colour-coded to identify α subunits in light blue, β subunits in purple, and γ2 subunits in red[24]. **B** Dp140 complexes in Synapses. This illustration shows the Dp140 complex associated with $Ca_v2.1$ and glutamate axis. **C** Dp71 and its Association with AQP4 and Kir4.1 Channels in Astrocyte Endfeet. This panel demonstrates the interaction of Dp71 with AQP4 and Kir4.1 channels within the perivascular astrocyte endfeet, indicating its potential role in neurovascular coupling[102]. α-DG α-dystroglycan, β-DG β-dystroglycan, nNOS neuronal nitric oxide synthase, NLGN2 neuroligin 2, IQsec3 gephyrin-associated IQ motif and SEC7 domain-containing protein 3 (also called SynArfGEF), S-SCAM synaptic scaffolding molecule (also called MAGI-2 for membrane-associated guanylate kinase inverted 2); $Ca_V2.1$ calcium channels Kir: potassium channels, AQP-4 aquaporin-4, α-Dbv-1 α-dystrobrevin-1, DG dystroglycan, Syn syntrophin. Created in BioRender[103].

Dp427 deficiency reduces the expression of $GABA_A$ receptors in key brain regions, including the amygdala, hippocampus, cerebral cortex, and cerebellum[18,19]. This disrupts GABAergic inhibitory postsynaptic currents, particularly in the neurons of the basolateral nucleus of the amygdala in response to norepinephrine inputs, which has been associated with abnormal defensive/fear and anxiety behaviours. In hippocampus, altered GABAergic inhibition is posited to enhance NMDA receptor-dependent synaptic plasticity and impacts memory consolidation, as well as synaptic plasticity in cerebellum, with putative impact on both motor and cognitive functions[19–23]. Recent behavioural studies in *mdx* mouse models highlighted that Dp427 deficiency may alter the subunit composition of $GABA_A$ receptor subtypes at both synaptic and extrasynaptic sites, with a differential impact on distinct brain structures[24,25]. Using a different strain of dystrophic mice (DBA/2J *mdx* mouse), and a different stimulation protocol, Bianchi et al could not fully replicate the findings on synaptic plasticity, highlighting the importance of standardising the experimental procedures related to these assessments[26]. As these mouse models are deficient in all three Dp427 isoforms, it is not possible to conclude from these studies which one is relevant for the observed phenotypes, or if they all contribute to this.

Regarding Dp140, gene ontology analysis suggested a role during the early stages of neurodevelopment[8]. The combined absence of both Dp427 and Dp140 in the exon52-deleted *mdx52* mouse model has been associated with abnormal social behaviours and diminished glutamatergic transmission, paralleling the ASD-like symptoms of DMD children lacking this isoform[27,28]. A recent study demonstrated a direct interaction of Dp140 with neuronal voltage-gated Ca2+ channels of the CaV2 subfamily in the mouse brain, using immunoprecipitation and proximity ligation assay techniques, thus providing new avenues for understanding the neurobiology of cognitive dysfunctions in DMD[29].

Dp71, the most abundant isoform in the brain, plays a crucial role in the functioning of astrocytes, as demonstrated in mouse brain and human astrocytes' studies using immunofluorescence and immunocytochemistry techniques[30,31]. Figure 2 provides a schematic representation of the different brain protein complexes involved with the different dystrophin isoforms.

Genotype/phenotype correlations for DMD patients with mutations affecting the different DMD isoforms

Several studies reported the prevalence of brain related comorbidities in DMD, suggesting a role for the site of mutations and their effect on the expression of the different brain dystrophin isoforms. There is a large variability in the reported prevalence of the individual brain related symptoms due to differences in sample sizes, assessment instruments, and data collection methods[4,32,33].

Assessment of neurocognitive and neurobehavioral functioning can be complicated in patients with DMD because of severe motor impairments and consequentially limited social interactions. Normative instruments being used are based on non-motor impaired persons and DMD-specific instruments are not available. However, patients with other severe neuromuscular conditions, such as Spinal Muscular Atrophy[34], glycogen storage disorders, neuropathies and muscular dystrophies due to involvement of dystrophin complex members exclusively expressed in muscle[35] are not associated with the brain comorbidities observed in DMD. Furthermore, the behavioural and neurocognitive defects in the form of autistic spectrum disorder can often manifest before the occurrence of clear muscle weakness in DMD[36].

This, together with clear genotype/phenotype/brain isoforms correlation and the supportive evidence from dystrophic animal models, strongly supports the view that CNS involvement in DMD is a primary consequence of brain dystrophin deficiency, not a secondary phenomenon. Furthermore, in clinical practice and scientific research normative instruments such as the Wechsler intelligence scales prove to be useful[33,37]. An important challenge for future research is to make a DMD specific and sensitive battery of instruments based on currently available instruments.

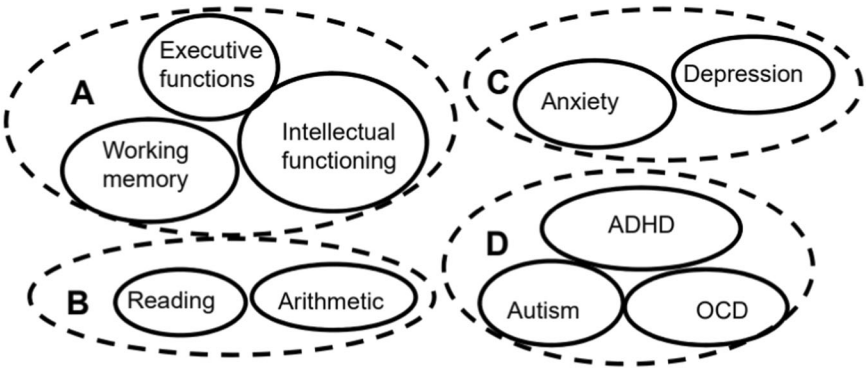

Fig. 3 | Domains and areas of brain function affected in DMD. Systematic overview of brain related comorbidities in DMD (Big ten of Duchenne) representing four domains and ten areas of (dys)functioning: **A** neurocognitive (executive functions, working memory and intellectual functioning); **B** Academics (reading and arithmetic); **C** emotional: (anxiety and depression; **D** neuropsychiatric (autism, Attention-Deficit Hyperactivity Disorder: ADHD, Obsessive Compulsive Disorder: OCD).

Despite these methodological considerations, there is overall consistency in phenotype/genotype correlation concerning specific pathological aspects:

Early development. Developmental milestones in DMD children demonstrate that the milestones requiring more cortical involvement, such as sitting or walking, are typically delayed[38], with a gradient that directly correlates with the number of isoforms affected in the CNS and the associated cognitive function[39,40]. Studies using the Griffiths and the Baileys neurodevelopmental scales suggest that DMD children have a developmental quotient that is on average 1 standard deviation below population mean[41]. The scores in the subscales such as language, personal, social and eye and hand coordination, are lower in patients with involvement of Dp140 and Dp71[41].

Motor function in relation to CNS involvement. Several studies using the North Star Ambulatory Assessment (NSAA) motor function scale that also includes timed items, have demonstrated significantly lower peak achievement in children lacking Dp140 and even lower in those also lacking Dp71[39,40,42–44]. Importantly similar differences in motor function can also be observed in the different mdx mouse models lacking different dystrophin isoforms[39].

Intellectual functioning, cognitive and academic abilities. A recent meta-analysis of 32 studies using the Wechsler intelligence scale (preschool, child and adult studies) in 1234 DMD individuals found that the mean full-scale IQ is approximately 1 standard deviation below average norm, i.e full-scale IQ of 84.76[33]. A review of the global prevalence of intellectual developmental disorder, operationalized as a full-scale IQ of less than 70 (2 standard deviations below the mean of 100), was found in 22% of DMD patients with lower prevalence (12%) in patients with exclusive involvement of Dp427, and 2.5 and 6 fold higher prevalence when Dp140 and Dp71 were also involved[45]. Neurocognitive functions such as working memory and executive functions (inhibition, switching, problem solving and planning) are often impaired even in boys with a normal full-scale IQ[46,47]. Other studies have specifically assessed academic abilities, demonstrating a higher prevalence of reading disabilities[46,48–50] and reduced arithmetic skills[51]. Academic performances were also lower for mutations affecting both Dp140 and Dp71[46]. Longitudinal studies have shown that using the Wechsler scales the full-scale IQ is consistent over time[37]. However, DMD boys with attention and behavioural disorders often had less consistent results with larger full-scale IQ changes over consecutive assessments.

Neuropsychiatric comorbidities. Prevalence rates of these disorders are significantly higher than in the general population. There is, however, a large degree of heterogeneity in reported prevalence rates over different studies[32] with prevalence of 0.00 indicating a 0% prevalence and prevalence of 1.00 indicating a 100% prevalence: ASD (13 studies; 0.01 to 0.21 with a mean of 0.06 and 0,0076 in general population), ADHD (10 studies; 0.03 to 0.50 with a mean of 0.18 and 0,034 in general population) and OCD (6 studies; 0.05 to 0.33 with a mean 0.12 and 0,012 in general population). Interestingly, data on the milder BMD variant describes comparable prevalence rates: ASD 0.06, ADHD 0.28 and OCD 0.07[32].

While intellectual function is clearly linked to the integrity of the two shorter Dp140 and Dp71 isoforms, the correlation for the behavioural comorbidities is less consistently linked to these isoforms. Indeed, neuropsychiatric aspects such as ASD and to a certain extent also ADHD, can be found across the spectrum of mutations, pointing towards a role for Dp427[4,32,52,53]. A recent metanalysis has nevertheless suggested that ADHD might be more often associated with boys lacking all the isoforms, i.e. Dp427, Dp140 and Dp71[32].

Other studies have more specifically addressed anxiety and fear-based disorders (such as social and separation anxiety, panic disorder and specific phobias) that are reported in 24% to 33% of people with DMD[54], hence more common than in the general population[5,55,56]. Obtaining objective measures of anxiety using behavioural startle responses, children with DMD presented increased unconditioned startle responses to threats. This pathological response is a feature of all DMD children hence likely related to lack of the Dp427 isoforms; in addition, there was evidence that the additional involvement of the Dp140 isoform further increased the abnormal startle response and the risk of anxiety[56]. Figure 3 gives a schematic representation of ten areas of brain related comorbidities (big ten of Duchenne). It is important to recognise that in clinical practice there may be a complex overlap of these areas. This complexity may hinder adequate screening and assessment[57].

Brain Imaging. Brain magnetic resonance imaging (MRI) reveals no structural abnormalities; however total brain and grey matter volumes are reduced compared to healthy controls[58]. Measurements of the white matter show lower fractional anisotropy, and higher diffusivity in DMD children than in healthy controls. Genotype/phenotype correlation revealed that children lacking both Dp427 and Dp140 had more obvious grey matter volume differences and reduced cerebral blood flow compared to those with involvement of Dp427 only[58]. The connectomic disturbances have been confirmed by tractography and functional MRI studies using a resting state and suggest an over-activation of the default mode network and executive control network, with suppression of primary sensorimotor cortex and cerebellum-visual circuit[58,59]. The combination of functional and structural MRI together with neuropsychological tests has also allowed one to collect information on the relationship between function and structures and the involvement of neural networks including the cerebellar-thalamo-cortical loop. The pathological white matter connectivity and fibre organization in

cerebellar tracts may both contribute to neurocognitive dysfunctions observed in children with DMD[59–62].

Brain comorbidities in DMD female carriers. As DMD is an X-linked disorder, female carriers are typically asymptomatic. However, a recent report found that carrier mothers had poorer cognition performance in attention, working memory, verbal memory, visuospatial skills, and executive functions[63]. This suggests that there may be a degree of brain involvement in carrier mothers of children with DMD, an aspect that requires further investigation.

Management of neurobehavioural comorbidities in DMD

Management and treatment of the neurobehavioural and neurocognitive comorbidities is of great interest for clinical practice, especially as life expectancy of people affected by DMD increases. It first requires establishing a firm diagnosis, as in clinical practice there is an enormous overlap of neurobehavioral and cognitive symptoms[57]. Scientific evidence on how to manage these problems or which psychological interventions are recommended is scarce. The international guidelines on diagnosis and management of DMD[9] recommend regular screening, psychotherapy and pharmacological treatment, but there is a lack of concrete evidence-based guidelines or standard operating procedures.

The first step in management is psycho-education of affected individuals and families on understanding symptoms, their implications for daily functioning and treatment options. Additionally, educating teachers, physicians and allied professionals on the typical profile of neurocognitive and behavioural problems will result in early detection, prevention and intervention.

Non-pharmacological treatment for DMD have not yet been described. Various psychotherapy approaches such as cognitive behaviour therapy and problem-solving therapy could be effective in influencing the emotional and neuropsychiatric domain of the big ten (domains C and D in Fig. 3). Acceptance and Commitment Therapy (ACT) has successfully been used in adult individuals with various muscle diseases such as myotonic dystrophy and proven effective in improving Quality of Life[64]. Given the brain-related comorbidities in DMD one might speculate on the effectiveness of nutritional interventions as in nutritional psychiatry[65], and potentially medical hypnosis contributing to functional changes in brain activities[66]. Training of neurocognitive disabilities, another domain of the big ten (A in Fig. 3), has proven to be effective in DMD children by using a computerised working memory training[67].

An interventional step aimed at domains C and D (Fig. 3) is psychopharmacology. Interestingly and in contrast to the experience of this therapeutic strategy for other similar comorbidities[68], this treatment option has not been well documented in the DMD literature[69]. Brusa, Gadaleta et al. (2022) reviewed all studies between 2000 and 2021 on psychopharmacological treatments for mental disorders in neuromuscular diseases[69]. They found five studies in DMD: two case reports, two case series (one of them not reporting on symptom improvement) and one observational study without a control group. The observational study on methylphenidate[70] in 10 boys with DMD (mean age 8 years) and comorbid ADHD reported a 70% clinical improvement and no significant side effects. The case series of 15 individuals with DMD and OCD[71] found a significant effect of selective serotonin reuptake inhibitors (SSRIs) in 67%; however, side effects were not reported in this study. A recent observational retrospective study[72] describes real-world data of 52 males with DMD (mean age 11 years) from two neuromuscular centres treated with psychopharmacology for ADHD, OCD, ASD and anxiety. The clinical condition improved in 54.2% treated with methylphenidate, in 38.9% of the individuals treated with fluoxetine, and in 22.2% treated with risperidone. Anxiolytics were prescribed in two adults (mean age 21) with severe anxiety, with good clinical response. In another more recent study on 19 adult individuals with DMD (mean age 34 years), 42% of them experienced psychiatric symptoms requiring psychoactive drug treatment[73]. However, this intervention is not readily available to the majority of individuals with DMD, due to lack of evidence-based management recommendations and clear risk/ benefit analyses in patients with additional cardiorespiratory comorbidities. This is becoming increasingly acute as recent evidence suggests that DMD adults with neurodevelopmental comorbidities have poorer survival than those without[74]. Indeed, the mean age of death in a cohort of 37 young adults with DMD and comorbid neurodevelopmental disorders was 22.5 years, at least 7 years less than the general DMD population, likely related to less compliance with standards of care surveillance and intervention for the myopathy[74].

In view of the common cardiac involvement in DMD, there have been concerns for cardiac complications due to stimulant medication which may have important implications in DMD, especially ventricular arrhythmia and sudden cardiac death and SSRIs which may decrease heart rate and systolic blood pressure. No systematic data in DMD has been reported on these issues. In an expert meeting on psychiatric prescribing in DMD[75] reassuring data from general populations were described.

Finally, it is worth noting that a combination of psychopharmacological treatment and psychotherapy has been shown to be superior in improving quality of life in depression[76,77], but there is no experience of this combinatorial approach as yet in DMD.

Deep phenotyping of DMD mouse models with mutations affecting differently the different isoforms

A variety of dystrophic animal models has provided invaluable insights into the aetiology and neurobiology of DMD[78]. DMD mouse models carry a variety of spontaneous, chemically- and transgenically-induced mutations along the *DMD* gene, leading to differential loss of one, several or all brain dystrophins, thus offering relevant tools to decipher the specific behavioural profile of animals missing different isoforms (Fig. 4A).

Behavioural studies involve controlled conditions, comparisons to wild-type littermate mice and standardised experimental tests designed to tackle specific cognitive and behavioural processes, and previously validated by the neuroscience community using brain lesions, pharmacology, optogenetics and mouse models of other neurodevelopmental diseases (Fig. 4B). The Dp427-deficient *mdx* mouse model, the most widely studied model, exhibits delays in some learning tasks and selective long-term memory deficits implicating memory consolidation, and behavioural alterations[79,80]. *Mdx* mice have deficits in tests involving hippocampal or amygdala-dependent recognition, spatial and fear memories, and exhibit behavioural disturbances including changes in emotional, depression-related and social behaviour. Their most robust phenotype is a dramatically enhanced stress reactivity, characterized by abnormal defensive behaviour referred to as an unconditioned fear in response to mild stressors such as scruff restraint. This was attributed to amygdala dysfunction and GABAergic disinhibition[19,25,81]. The abnormal fear response is conserved in mammalian dystrophic models (pigs, in which dystrophin deficiency causes a severe porcine stress syndrome, rats)[82,83] and occurs in boys with DMD[5,56]. While moderate stress in the *mdx* mice manifests itself with the temporary immobility (unconditioned fear response), more severe stressors are associated with lethality in these dystrophic mice, likely related to their exaggerated neuroendocrine sensitivity to stressors[84].

Recent studies compared behavioural performance of *mdx* mice lacking Dp427 alone to that of *mdx52* or *mdx4cv* mice lacking both Dp427 and Dp140, and to *mdx3cv* and *Dmd-null* mice lacking all dystrophins (Table 1). All dystrophic mouse models display enhanced anxiety, in line with the enhanced anxiety also reported in children with DMD regardless of their genotype, supporting a role for the Dp427 isoforms in emotional disturbances[52]. However, *mdx52* mice

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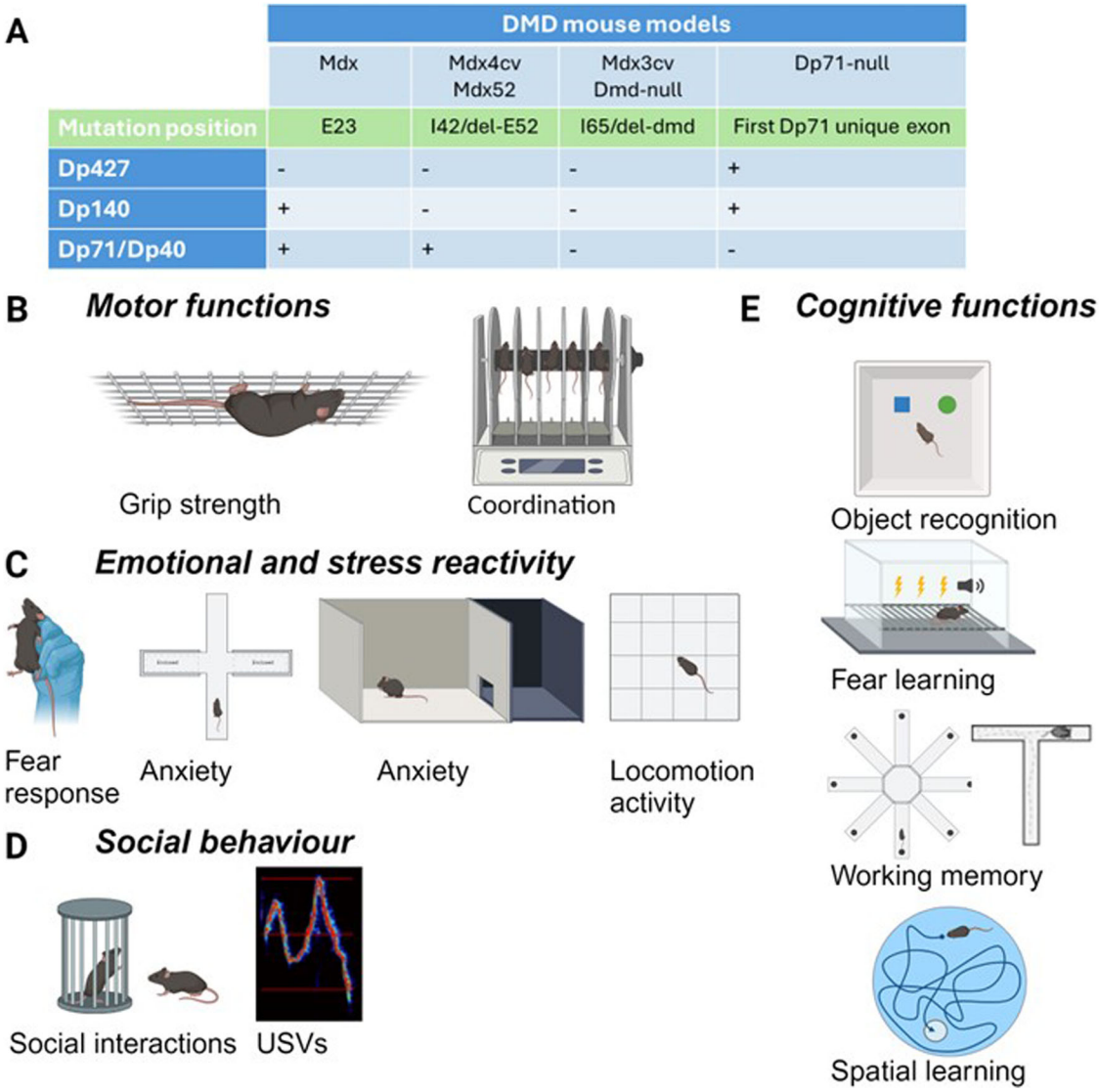

Fig. 4 | Behavioural phenotyping of DMD mouse models. A Expression pattern of brain dystrophins in dystrophin-deficient mouse lines. Mutation position and differential expression of the three brain dystrophins are shown for mouse lines carrying spontaneous mutations (*mdx*), chemically-induced mutations (*mdx4cv*, *mdx3cv*), transgenic deletion of a specific exon (*mdx52*) or whole *dmd* gene (*dmd-null*), and transgenic insertion (*Dp71-null*). E: exon; I: intron; del-: deletion; (+) protein expressed; (-) protein absent. **B**–**E** Illustrative images of the main behavioural tests that revealed key phenotypes in DMD mouse models. The tests tackled distinct brain-related functions including: **B** motor functions using the inverted grid (left) and rotarod (right) tests; **C** emtional and stress reactivity following scruff restraint (left drawing) or using elevated plus maze, light-dark choice and open-field anxiety tests (three last drawings, respectively); **D** social behaviour during social approach test (left) and socially-induced ultrasonic vocalisations (right); **E** cognitive functions using, respectively from top to bottom drawings, an object recognition test, fear conditioning, spatial working memory tasks in radial or T mazes, and spatial learning tasks in water maze. Created in BioRender[104].

exhibit higher anxiety and more impaired fear learning and memory compared to *mdx* mice, suggesting that Dp140 loss aggravates emotional disturbances[85]. In *mdx* mice and another model lacking Dp427 and Dp140 (*mdx4cv*), mild changes in short-term memory, discrimination learning, and movement patterns have also been reported, suggesting a role for Dp427 in these functions[86]. A study highlighted the ASD-like behaviours present in *mdx52* mice lacking Dp140, with reduced glutamatergic transmission in basolateral amygdala (BLA) pyramidal neurons compared to wild-type and *mdx* mice, suggesting a role for Dp140 in ASD-related behaviour[28]. Along similar lines to what is described in humans, the dystrophic mice lacking both Dp427 and Dp140 (*mdx52*) or all dystrophins (*Dmd-null*) have more severe motor dysfunction compared to Dp427-deficient *mdx* mice, suggesting a role for Dp140 in contributing to coordination and motor performance[39]. The studies in *Dmd-null* mice are scarce and inconclusive regarding the functional impact of Dp71 deficiency[39,87,88]. However, mice with a selective loss of Dp71 (*Dp71-null*) display alterations in working memory, cognitive flexibility and social behaviour[89,90], in line with what is observed in children with distal mutations.

Mouse studies thus provide critical and translational insights into the genotype-phenotype relationships, the nature of altered cognitive processes and the brain circuits underlying brain-related comorbidities in DMD (Table 1). Moreover, preclinical rescue studies confirmed the central origin of several phenotypes of DMD mouse models and validated their use as biomarkers for preclinical evaluations of therapies (Fig. 5).

Dp427-deficient DE50-MD dogs have been deeply phenotyped with the demonstration of subtle structural abnormalities in the grey matter[91] as detected by brain MRI associated with a neurocognitive phenotype including reduced attention, problem solving and exploration of novel objects[92]. Likewise, an exon52-deleted pig model was shown to display some impairments in cognitive abilities[93]. The

Table 1 | . Main phenotypes of DMD mouse models

DMD MOUSE MODELS → Brain dystrophin(s) deficiency →	*mdx* Dp427	*Mdx52*, mdx4cv#* Dp427, Dp140	*Dp71-null* Dp71	*Mdx3cv*, dmd-null#* Dp427, Dp140, Dp71
Motor functions				
Grip strength	Slightly reduced(1)	Reduced*(1)	Unaffected(2)	Reduced#(1)
Motor coordination (rotarod)	Reduced(1)	Reduced*(1)	Unaffected(2)	Reduced#(1)
EMOTIONAL AND STRESS REACTIVITY				
Fear response	Abnormally strong(3,4,5)	Abnormally strong* (1,4)	Unaffected(6)	Abnormally strong*(6)
Anxiety	Mild increase(3,4,5)	Increased*(4)	Mild increase(6)	Increased*(7)
Exploration (open field)	Reduced(3)	Reduced(4)	Unaffected(2)	(-)
Social behaviour				
Sociability/social motivation	Unaffected(8)	Increased* (1)	Unaffected(6)	(-)
Social novelty preference	Unaffected(8)	(-)	Impaired(6)	(-)
Social interactions	Slightly altered(8)	(-)	Unaffected(6)	(-)
Socially-induced vocalisations	Reduced in specific contexts(8)	(-)	Increased(6)	(-)
Cognitive functions				
Object recognition	Impaired long-term memory(9)	(-)	Unaffected(9)	(-)
Fear Learning	Impaired(3)	Impaired*(4)	Unaffected(6)	(-)
Working memory	Slightly impaired(10)	Slightly impaired#(10)	Impaired(11)	*Impaired*(12)*
Spatial learning	Impaired long-term memory, unaffected flexibility(13,14)	Unaffected learning and flexibility#(10)	Impaired learning and flexibility(11)	(-)

The table describes the phenotypes identified using the tests listed in Fig. 4 B-E. * and # specify the specific mouse model used in the study. (-) Not tested. Main references indicated by numbers as follows: (1)[28]; (2)[97]; (3)[25]; (4)[85]; (5)[19]; (6)[90]; (7)[88]; (8)[98]; (9)[99]; (10)[86]; (11)[89]; (12)[87]; (13)[79]; (14)[100].

presence of brain anomalies, abnormal stress reactivity and cognitive deficits in large animal models supports part of the data reported in mouse models and have translational significance. However, the variety of mutations expressed in large animal models remains limited, and the generation of new dog or pig models holding distinct mutations would help address genotype-phenotype relationships and efficacy of therapeutic interventions, as in the studies of mouse models. The functional data on animal models should be interpreted with caution, perhaps particularly mouse data since DMD mouse models fail to reproduce major DMD skeletal muscle and heart manifestations. This, however, is advantageous to carry out behavioural studies with limited influence of motor functions on cognitive performance. The current mouse data suggest Dp427-dependent emotional disturbances, which are conserved in various animal models and present but still underrated in patient studies. The loss of Dp140 appears to worsen some phenotypes, such as emotional disturbances and motor performance, which seems relevant to the global increase in the severity of central alterations in patients. In contrast, extending mouse data to genotype/phenotype correlations in patients for social behaviour disturbances and cognitive/executive performance is still premature and may require additional studies. Despite the limitations of the mouse models, it would undoubtedly be beneficial to continue phenotyping of patients and animal models in parallel, and to encourage cross-fertilisation between these two fields of research.

Genetic therapies for restoring brain dystrophin production in the different mouse models

Therapeutic approaches based on RNA therapies (i.e. antisense oligonucleotides [ASO] to induce exon-skipping and restoration of the reading frame in individuals with DMD with deletions) or adeno-associated viral gene therapies have made tremendous progress for the treatment of DMD in the past few years and reached market approval in the US and Japan. However, none of these therapies addresses the brain comorbidities associated with DMD, mostly due to their inability to cross the blood brain barrier (BBB). Until recently the therapeutic development has focused on addressing the DMD muscle pathology. However, several studies have recently demonstrated encouraging neurobehavioural improvements following genetic treatments in mouse models of DMD. Work in the *mdx* mouse model lacking only the Dp427 isoform showed that direct intracerebroventricular (ICV) infusion of an ASO made of phosphorodiamidate morpholino oligomer (PMO) lead to a partial restoration of brain Dp427 and an improvement of the characteristic fear-motivated defensive behaviour in these mice[19]. This was further confirmed using a different type of ASO made of tricyclo-DNA, administered intravenously and capable of normalising the unconditioned fear response thanks to its ability to cross the BBB albeit at very low levels[94]. Other studies in *mdx* mice reported recovery of $GABA_A$-receptor clustering and normalisation of hippocampal synaptic plasticity, following partial rescue of hippocampal dystrophin induced by intra-hippocampal administration of adeno-associated virus vectors encoding a specific U7snRNA that induced continuous production of the exon skipping ASO[95]. These earlier studies focused on the exaggerated fear response but not on the memory deficits that also characterise this model. In 2022, however, ICV administration of tricyclo-DNA-ASO not only rescued expression brain Dp427 isoforms expression but also significantly restored long-term memory retention of *mdx* mice in an object recognition task. These novel findings suggest for the first time that postnatal re-expression of brain dystrophin could reverse or at least alleviate some cognitive deficits associated with DMD[24]. These studies also highlighted a dose-dependent restoration of Dp427 following administration of various doses of ASO, associated with a dose-dependent decrease of the abnormal unconditioned fear responses.

Given that the combined loss of both Dp427 and Dp140 in *mdx52* mice may be associated with higher emotional disturbances as compared to Dp427-only deficient *mdx* mice[85], and because this also induces abnormal social behaviour[28], further experiments were recently performed in the *mdx52* mouse model. The evaluation of therapeutic approaches in this model is particularly relevant, as it holds a deletion of exon 52, a region frequently found mutated in individuals with DMD. Moreover, this particular exon deletion is amenable to two possible exon-skipping strategies for which exon

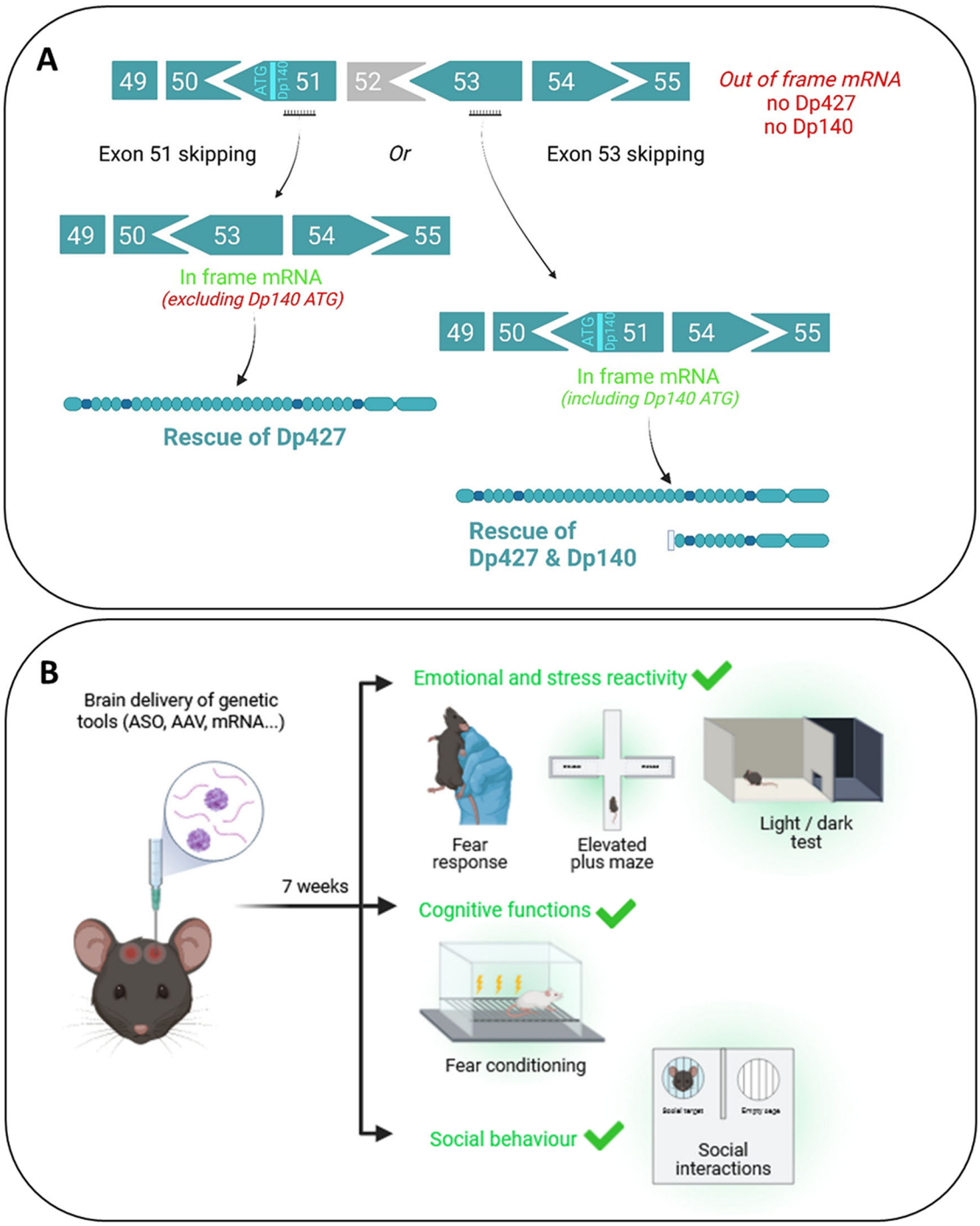

Fig. 5 | Impact of genetic therapies on mouse neurobehavioural phenotypes. **A** Possible exon skipping strategies to restore the open reading frame in DMD mouse model carrying a deletion of exon 52. Exon 52 deleted *dmd* mRNA is out of frame and no functional Dp427 and Dp140 are thus produced. Skipping of exon 51 can restore Dp427 expression but not Dp140 expression because exon 51 contains Dp140 start codon. In contrast, exon 53 skipping offers the opportunity to restore both Dp427 and Dp140. **B** The brain delivery of genetic tools allowing dystrophin isoforms restoration improves key neurobehavioural phenotypes in DMD mouse models including emotional and stress reactivity (e.g. using fear response, elevated plus maze, light-dark choice tests), cognitive functions using a fear conditioning test and social behaviour during social approach test. This figure was created using Biorender.com, panel **A** and[105] **B** (Created in BioRender[106]).

skipping drugs are already approved (for systemic treatment). Skipping of exon 51 will restore solely Dp427 expression, leaving the Dp140 isoform absent due to its reliance on exon 51 for the start codon. In contrast, exon 53 skipping offers the opportunity to restore both Dp427 and Dp140 isoforms (Fig. 5A). Recent studies exhibited that ICV administration of tricycloDNA-ASO targeting the *Dmd* exon 51 resulted in partial Dp427 restoration in the brain of *mdx52* mice and significantly reduced anxiety and unconditioned fear[96]. Additionally, this partial rescue of Dp427 fully normalised the acquisition of fear conditioning, while fear memory tested 24 h later was only partially improved. Another study on the same mouse model, demonstrated that either injecting a PMO-ASO targeting *Dmd* exon 53 directly into the basolateral amygdala (BLA) or administering directly in the same region Dp140 mRNA-loaded polyplex nanomicelles restored Dp140 expression. This intervention also ameliorated the deficits in glutamatergic transmission and

improved the abnormal social behaviour in 8-week-old *mdx52* mice, corresponding to late adolescent / young adult stages in humans[28]. Altogether, these studies provide encouraging data and reveal that postnatal partial restoration of the two most commonly affected dystrophin isoforms, Dp427 and Dp140, can improve the neurocognitive and neurobehavioral and emotional deficits associated with their absence in the brain of DMD mouse models. Although this offers promising avenues for future treatment of brain comorbidities in individuals with DMD, the translational gap between mouse and human remains a significant challenge, as illustrated by the incomplete functional benefit induced by these genetic therapies in muscles.

Conclusion and future directions

In the last decade, there has been very considerable progress in addressing the molecular basis for the brain involvement which characterises people affected by DMD. A clear role for the different dystrophin isoforms in regulating GABAergic and glutamergic synaptic transmission and ion channel activity, and maintaining a physiological neural balance, has emerged. Deep phenotyping of different dystrophic models is allowing us to dissect the contribution of the individual dystrophin isoforms on discrete neurobehavioural aspects of the condition, and genetic therapies provide clear evidence for postnatal improvement of at least some of the comorbidities. This suggests that the brain phenotype induced by dystrophin deficiency is not exclusively developmental in origin, providing hope for future development of these brain targeted approaches.

The considerable neurobiological advances on the role of dystrophins in the brain are largely related to the studies on the dystrophic mouse models. Linking mouse model data to human neurobehavioral functioning is an important challenge. The human neurobehavioral data are more complex and while some traits found in the mouse can be clearly recognised in the affected boys, there is variability of their severity and prevalence. Nevertheless, several symptoms are now well recognised and both screening and diagnostic assessment of ASD, ADHD, OCD, anxiety, depression, reading and arithmetic disorders and neurocognitive disorders such as working memory and executive function problems should be systematically performed in affected children. It is possible that in the future genetic therapies focused on brain dystrophin deficiency could provide an exciting resource to address the root cause of these comorbidities, although their modality of administration, efficacy and biodistribution in larger animal models requires further work. In the meantime, the current psychopharmaceutic should be more systematically used, to address the current unmet needs for these individuals. Furthermore, the characterisation of the links between DMD and other conditions, i.e. OCD, ADHD, intellectual disability may result in further insight on the role that specific neurotransmission pathways play in these comorbidities.

Search strategy

We searched PubMed for articles published in English from 1st January 2019, to January 1st, 2024, with the search terms "Duchenne", "dystrophinopathy" "mdx" or the causative gene, "*DMD*", and "brain". This resulted in 133 publications in Pubmed in the last 5 years.

We generated the final reference list based on topics that fit the scope of this review and included landmark papers as well.

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Author contributions

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Competing interests

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