CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	Cognitive dysfunction in Duchenne muscular dystrophy: a possible role for neuromodulatory immune molecules
Authors	Rae, Mark G.;O'Malley, Dervla
Publication date	2016-09-01
Original Citation	Rae, M.G. and O'Malley, D. (2016) 'Cognitive dysfunction in Duchenne muscular dystrophy: a possible role for neuromodulatory immune molecules', Journal of Neurophysiology, 116(3), pp.1304-1315. doi: 10.1152/jn.00248.2016
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1152/jn.00248.2016
Rights	© 2016, The American Physiological Society.
Download date	2026-10-13 12:54:30
Item downloaded from	https://hdl.handle.net/10468/3189

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Cognitive dysfunction in Duchenne Muscular Dystrophy: a possible role for neuromodulatory immune molecules.

Mark G. Rae[1] and Dervla O'Malley[1,2].

1. Department of Physiology, University College Cork, Western Road, Cork, Ireland.
2. APC Microbiome Institute, University College Cork, Western Road, Cork, Ireland.

Correspondence to:

Dr. Dervla O'Malley,

Department of Physiology,

Western Gateway Building,

University College Cork,

Cork, Ireland.

d.omalley@ucc.ie

Telephone: +353-21-4205483 **Fax:** +353 (0)21 4205370

For submission to: Journal of Neurophysiology – a multidisciplinary neuroscience journal.

Running title: Cytokines in DMD-associated cognitive dysfunction.

Acknowledgements: We wish to acknowledge funding support from Muscular Dystrophy Ireland.

Disclosures: No conflict of interest, financial or otherwise.

Abstract

Duchenne Muscular Dystrophy (DMD) is an X chromosome-linked disease characterized by progressive physical disability, immobility and premature death in affected boys. Underlying the devastating symptoms of DMD is the loss of dystrophin, a structural protein which connects the extracellular matrix to the cell cytoskeleton and provides protection against contraction-induced damage in muscle cells, leading to chronic peripheral inflammation. However, dystrophin is also expressed in neurons within specific brain regions, including the hippocampus, a structure associated with learning and memory formation. Linked to this, a subset of boys with DMD exhibit non-progressing cognitive dysfunction, with deficits in verbal, short-term and working memory. Furthermore, in the genetically comparable dystrophin-deficient *mdx* mouse model of DMD, some, but not all, types of learning and memory are deficient and specific deficits in synaptogenesis and channel clustering at synapses has been noted. Little consideration has been devoted to the cognitive deficits associated with DMD in comparison to the research conducted into the peripheral effects of dystrophin deficiency. Therefore, this review will focus upon what is known about the role of full length dystrophin (Dp427) in hippocampal neurons. The importance of dystrophin in learning and memory will be assessed and the potential importance that inflammatory mediators, which are chronically elevated in dystrophinopathies, may have on hippocampal function will also be evaluated.

Key Words (5 max): Duchenne Muscular Dystrophy, dystrophin, hippocampus, learning, memory.

Introduction

The fatal, X chromosome-linked disease, Duchenne muscular dystrophy (DMD) is caused by the loss of the structural protein, dystrophin (Bulfield et al. 1984). Interactions between dystrophin and the dystrophin associated protein complex (DAPC), which includes the membrane spanning β dystroglycan component, serves to link the sub-sarcolemmal cytoskeletal actin to the extracellular matrix in skeletal muscle. In such contracting cells dystrophin, through interactions with the DAPC, protects the sarcolemma against the mechanical stresses of repeated contractions. Thus, loss of functional dystrophin, which comprises 0.1% of the total human genome (Barbujani et al. 1990; Koenig et al. 1987), causes muscle fibres to become more susceptible to contraction-induced damage. This, in turn, results in muscle inflammation and myophagocytosis (Anderson et al. 1987) leading to progressive physical disability, eventual immobility and, finally, premature death in affected boys. There is currently no cure for DMD, with patients experiencing an average life expectancy of just over 20 years (Yiu & Kornberg 2008), and most eventually succumbing to death *via* cardio-respiratory failure.

Chronic inflammation is a key symptom and contributory factor in the pathogenesis of DMD, due in part to the secretion of pro-inflammatory immune mediators from damaged dystrophin-deficient muscle fibers (De Paepe and De Bleecker 2013; Porter et al. 2002). Pro-inflammatory cytokines, including Tumor necrosis factor (TNF)α (Kuru et al. 2003; Porreca et al. 1999), interleukin (IL)-1β (Evans et al. 2009), IL-6 (Messina et al. 2011; Rufo et al. 2011) and the promotor of ongoing inflammation, IL-17 (De Pasquale et al. 2012) are elevated in muscle biopsies from DMD patients.

Although dystrophinopathies have principally been studied in the context of skeletal muscle dysfunction, DMD itself is actually a multi-system disorder due to the fact that dystrophin is also expressed in cardiac and smooth muscle, endocrine glands and neurons. In healthy individuals, neurons in the central nervous system (CNS) express full length dystrophin (Dp427). Specifically, it is expressed in the hippocampus, cerebellum, cerebral cortex and amygdala (Bies et al. 1992; Knuesel et al. 2000; Lidov et al. 1993; Lidov et al. 1990; Sekiguchi et al. 2009). Consistent with the functional importance of dystrophin in the CNS, boys with DMD often exhibit varying degrees of non-progressing cognitive impairment (Anderson et al. 2002; Bresolin et al. 1994), with their intelligence quotients (IQ) shifted downward one standard deviation below the normal range (Felisari et al. 2000; Nardes et al. 2012). Moreover, boys with DMD have difficulty communicating. They exhibit social behavior problems and have poor facial affect recognition (Hinton et al. 2007; Hinton et al. 2006). Interestingly, expression of Dp71, a protein product produced through a mutation in the dystrophin gene and only expressed in the CNS, has been linked to intellectual disability without an attendant muscular dystrophy phenotype (de Brouwer et al. 2014). In the context of the frontal cortex and hippocampus, both of which facilitate learning and memory processes, DMD patients exhibit deficits in verbal, short-term and working memory (Hinton et al. 2000; 2001; Snow et al. 2013). As it is now recognized that activation of the immune system in the periphery greatly influences the normal function of the central nervous system (Marin and Kipnis 2013), this review will assess the possible role of inflammatory mediators in DMD-associated cognitive dysfunction focusing on the hippocampus.

The potential role of inflammatory molecules in DMD-associated cognitive dysfunction.

Chronic inflammation is a key aspect of DMD pathophysiology. Indeed, corticosteroids with potent anti-inflammatory effects are the most effective treatment for delaying the onset and

progression of the disease (Gloss et al. 2016). Skeletal muscle biopsies exhibit necrotic and degenerating fibers surrounded by macrophages and CD4+ lymphocytes in the early stages of the disease, when new myocytes are still being produced, however, the capacity to regenerate new myofibres becomes exhausted and muscle fibers are eventually replaced by connective and adipose tissue. There is also evidence of immune cell infiltration into muscle tissue and activation of the complement system (Haslett et al. 2002), which is an important effector arm of both the innate and adaptive divisions of the immune system. The inflammatory response is due, in part, to the secretion of cytokines from damaged dystrophin-deficient muscle fibers (De Paepe and De Bleecker 2013; Porter et al. 2002). Consistent with this, DMD muscle biopsies display altered cytokine profiles with elevated levels of pro-inflammatory mediators such as TNFα (Kuru et al. 2003; Porreca et al. 1999), IL-1β (Evans et al. 2009), IL-6 (Messina et al. 2011; Rufo et al. 2011) and IL-17 (De Pasquale et al. 2012).

Whilst cytokines have a well characterized role in the response of tissues to infection, these signaling molecules also have neuromodulatory actions. In addition to immune cells, neurons, glia and the endothelial cells of the microvasculature in the CNS secrete cytokines and also express receptors for these immune mediators. There is significant crosstalk between the immune and nervous systems, as cytokines can have indirect effects on neuronal activity by stimulating secretion of neuromodulatory molecules from glia or endothelial cells (Allan and Rothwell 2001; Montgomery and Bowers 2012). Moreover, they can bind directly to receptors on neurons, where their neuromodulatory actions can subsequently influence cognitive function. The hippocampus, a structure upon which the acquisition of new declarative memories is absolutely dependent, expresses receptors for IL-1β (Gardoni et al. 2011), TNFα (Sairanen et al. 2001), and IL-6 (Schobitz et al. 1993).

Cytokines can promote neurite outgrowth, neurogenesis and neuronal survival, in addition to being able to regulate synaptic transmission and synaptic plasticity (Marin and Kipnis 2013). However, chronically elevated levels of inflammatory cytokines can result in neuronal dysfunction. For example, IL-1 (Terrando et al. 2010) and IL-6 (Sparkman et al. 2006) have been implicated in lipopolysaccharide (LPS) -evoked cognitive dysfunction and TNF receptor 1 facilitates memory deficits associated with sepsis (Calsavara et al. 2015; Haslett et al. 2002). IL-17 is also a central regulator of CNS inflammatory responses and works synergistically with TNF and IL-1 under inflammatory conditions (Gaffen 2009). It is upregulated in hippocampal neurons following stimulation with LPS, indicating a role for it in neuroinflammation and the associated cognitive impairment (Sun et al. 2015). Disease states associated with such pathophysiology include epilepsy, stress-related disorders and neurodegenerative diseases (Allan et al. 2005; Glass et al. 2010; Griffin 2006; Nguyen et al. 1998; Vezzani et al. 2011). As neuro-immune interactions promote homeostasis of the nervous system (Marin and Kipnis 2013), chronic inflammation may also be a contributory factor in cognitive dysfunction exhibited by dystrophin-deficient DMD patients.

Expression of dystrophin in the CNS.

The dystrophin gene has many independent, and tissue-specific, promoters for brain and skeletal muscle cells (Blake et al. 2002). Within the brain, dystrophin expression is only one tenth of that found in muscle. However, brain tissue exhibits much greater variability in the protein products that are generated from the dystrophin gene. Included are the full length protein (Dp427), which this review will focus on, and shorter proteins (Dp71, Dp260, Dp140 and Dp116) (Gorecki and Barnard 1995). Quantitatively, Dp71 is the main dystrophin gene product in the brain and its location, around perivascular astrocyte endfeet (Haenggi et al. 2004; Tadayoni et al. 2012), suggest a role in blood brain barrier (BBB) function (Amiry-

Moghaddam et al. 2004), which may be a consideration in the ability of peripheral inflammatory molecules gaining access to the brain.

In the CNS, Dp427 is only found in neurons, and only within specific regions of the brain such as the hippocampus, amygdala, cerebellar Purkinje cells and neocortex (Anderson et al. 2002; Bies et al. 1992; Chamberlain et al. 1988; Chelly et al. 1990; Comim et al. 2011; Cyrulnik and Hinton 2008; Knuesel et al. 2000; Lidov 1996; Sekiguchi et al. 2009). Similar to its function in striated muscle, dystrophin in neurons and glia associates with the DAPC of membrane-spanning proteins that link the intracellular cytoskeleton to the extracellular matrix. However, the DAPC in the brain is unlikely to act as a mechanotransducer as it does in skeletal muscle (Hendriksen et al. 2015). Further, several variants of brain DAPC exist due to both the variety of CNS dystrophin protein products and the fact that they can also associate with DAPC components which are absent from skeletal muscle cells, such as β-dystrobrevin, ε-sarcoglycan, and the γ-syntrophins (Waite et al. 2012; Waite et al. 2009). It is likely however, that this interaction of Dp427 with the DAPC in neurons does play a critical role in the formation and maintenance of new synaptic connections (Rodius et al. 1997).

Changes in the structure and function of dystrophic brains

DMD patients

Considerable debate continues as to whether loss of Dp427 alters the architecture of DMD brains, with some investigators noting relatively minor changes in DMD brains (al-Qudah et al. 1990; Bresolin et al. 1994; Dubowitz and Crome 1969; Rae et al. 1998) and others reporting a range of brain abnormalities including neuronal loss, neurofibrillary tangles, dendritic changes and cortical atrophy (Itoh et al. 1999; Jagadha and Becker 1988; Lv et al. 2011; Rosman 1970; Rosman and Kakulas 1966; Septien et al. 1991; Yoshioka et al. 1980).

Indeed, no clear correlations have been made between the different types of brain abnormalities observed in DMD patients and the degree of intellectual impairment suffered. Moreover, investigations into possible biochemical and neuromodulatory mechanisms underlying the dystrophin-associated cognitive deficits in human DMD are relatively limited. The brains of DMD boys have been reported to be hypometabolic in their use of glucose (Bresolin et al. 1994; Lee et al. 2002), a phenomenon which occurs in other conditions with known associated cognitive deficits, and may be related to reduced synaptic activity (Jueptner and Weiller 1995).

Mdx mice

The functional role of specific proteins within the CNS is usually made much easier with the development of transgenic knockin or knockout mouse models. Therefore, the fortuitous generation of the *mdx* mouse (Bulfield et al. 1984), which is deficient in Dp427 (Blake and Kroger 2000) due to a nonsense mutation occurring in exon 23 of the dystrophin gene (Arechavala-Gomeza et al. 2010), provided an opportunity for more functional studies on DMD to be carried out. *Mdx* mice are genetically comparable to human DMD and recapitulate striated muscle dysfunction, where skeletal muscle fibres progress through cycles of degeneration and regeneration until functional myofibres are replaced by collagen and adipocytes. Degeneration and regeneration of myofibres is associated with muscle inflammation (Grounds et al. 2008), but fibrosis and loss of limb muscle function is not as severe in *mdx* mice as in humans (Dangain & Vrbova 1984; Coulton et al. 1988), possibly due to compensatory mechanisms (Manning and O'Malley 2015). Nonetheless, consistent with human studies (al-Qudah et al. 1990; Bresolin et al. 1994; Dubowitz and Crome 1969; Rae et al. 1998), most studies in *mdx* mice failed to note any gross abnormalities in brain structure (Bulfield et al. 1984; Miranda et al. 2009; Torres and Duchen 1987; Yoshihara et al.

2003). However, changes in cell number, size and/or shape were noted in regions of the cerebral cortex and brainstem of *mdx* mice (Carretta et al. 2004; Carretta et al. 2001; Carretta et al. 2003; Minciacchi et al. 2010; Sbriccoli et al. 1995) and enlargement of the lateral ventricles, possibly due to grey matter atrophy has also been reported (Xu et al. 2015). Similar to findings in DMD patients, muscle levels of IL-6, TNFα and IL-1β are elevated in *mdx* mice (Huang et al. 2009; Huynh et al. 2013; Kurek et al. 1996), however changes in circulating or CNS levels of inflammatory mediators in this mouse model has not yet been reported.

Hippocampal dysfunction in mdx mice

The neurobehavioral profile of *mdx* mice is characterised by deficits in cognitive function (Chaussenot et al. 2015; Muntoni et al. 1991; Perronnet et al. 2012; Vaillend et al. 2004; Vaillend et al. 1995), behaviors which are linked to dysregulation of hippocampal and amygdalar function. For example, the *mdx* mouse exhibits deficits in its capacity to learn and store spatial memories relative to controls (Vaillend et al. 2004; Vaillend et al. 1995) and it also displays deficiencies in associative learning as well as in general processes of memory consolidation which are dependent upon both the hippocampus and the amygdala (Chaussenot et al. 2015). Changes in long- and short-term memory formation and consolidation have been associated with altered synapse morphology and plasticity linked to a loss of Dp427 (Miranda et al. 2009; Vaillend et al. 2004; Vaillend et al. 1995). Interestingly, other *in vivo* and *in vitro* hippocampal-dependent functions, such as spatial learning, CA1 NMDA-dependent long term potentiation (LTP), and its converse, long term depression (LTD), have either been found to be intact (Sesay et al. 1996) or actually enhanced relative to controls (Dallerac et al. 2011; Vaillend and Billard 2002; Vaillend et al. 1998; Vaillend et al. 2004; Vaillend et al. 1999).

Dysregulated synaptic receptor clustering in the mdx mouse

$GABA_A$ receptors

Within the hippocampus, alterations in the number and localisation of several receptor types having been noted in the absence of Dp427. Dp427 is exclusively expressed post-synaptically in dense puncta on neuronal cell membranes of hippocampal inhibitory synapses (Brunig et al. 2002; Kim et al. 1992; Knuesel et al. 2000; Knuesel et al. 1999; Levi et al. 2002; Sakamoto et al. 2008). Here, through its interaction with components of the DAPC, it makes a crucial contribution to synapse structure and function (for reviews see Haenggi and Fritschy 2006; Hendriksen et al. 2015; Perronnet and Vaillend 2010; Waite et al. 2012). This is likely to be facilitated through interactions between the syntrophin-dystrobrevin sub complex (Compton et al. 2005; Matsumura et al. 1992), β-dystroglycan and the synaptic cell-adhesion molecules, neurexin and neuroligin (Craig and Kang 2007; Graf et al. 2004; Kang et al. 2008; Sudhof 2008; Sugita et al. 2001; Waite et al. 2012; Zhang et al. 2010), all of which may be critically involved in anchoring GABAergic (for review see Fritschy et al. 2012), and other neurotransmitter receptors or channels, in place at specific points in the post-synaptic membrane (Krasowska et al. 2014). Thus, loss of dystrophin leads to the generation of malformed synapses (Knuesel et al. 1999; Knuesel et al. 2001; Kueh et al. 2008; Miranda et al. 2011; Miranda et al. 2009), which will significantly alter how affected neurons respond to afferent stimuli (Graciotti et al. 2008). This will inevitably disrupt the precise and coordinated spatiotemporal and stratified neural network activity that is critical for normal hippocampal function and cognition (for review see Cohen et al. 2015).

This feature of dystrophin function has been particularly well described for inhibitory α2 subunit-containing $GABA_A$ receptors in CA1 and CA3 regions of the hippocampus (Knuesel

et al. 1999; Knuesel et al. 2001). Indeed, the fact that $GABA_A$ receptor clustering in dendritic and pyramidal layers of *mdx* mice can be restored to normal levels by administering specific antisense oligonucleotides, established for the first time a direct link between receptor clustering and Dp427 expression (Vaillend et al. 2010). Furthermore, the proposed cellular correlate of new memory formation, NMDA-dependent LTP, can be restored in *mdx* mice using the same treatment. This evidence supports the suggestion that clustering of GABAergic neurotransmitter receptors at inhibitory synapses is essential for normal neuronal excitability and synaptic transmission (Dallerac et al. 2011).

More recently, the *Wnt* intracellular signalling pathway has emerged as an important player in the development and maintenance of normal neuronal structures within the CNS as well as in modulating synaptic plasticity and cognitive function (for reviews see Inestrosa and Arenas 2010; Oliva et al. 2013). Significantly, Fuenzalida et al. (2016) demonstrated that the aforementioned deficiency in GABAergic signalling within hippocampal CA1 neurons of *mdx* mice can be restored by stimulating the non-canonical *Wnt-5a* pathway, which serves to increase the number of inhibitory synapses and $GABA_A$ receptors in CA1 without any attendant increase in GABA release probability or release sites.

Nicotinic acetylcholine receptors (nAChRs)

Alterations in the expression, distribution and function of other receptor subtypes have also been noted in dystrophic brains. For example, behavioral studies reporting a reduced response to nicotine in a passive avoidance memory task, suggested altered nAChR expression or responsivity (Coccurello et al. 2002), work that has been supported by *in vitro* research demonstrating a reduction of hippocampal α3 nAChR mRNA (Wallis et al. 2004) and α7 nAChR binding sites (Ghedini et al. 2012). However, these alterations, which would be expected to lead to decreased nicotinic cholinergic synaptic signalling, appear to be

compensated for by an upregulation in nAChR-mediated cholinergic transmission in the same brain region (Parames et al. 2014). However, the fact that the expression of hippocampal muscarinic receptors is unchanged in dystrophic mice (Yoshihara et al. 2003) indicates that dystrophin does not exert a generalised effect on the expression of all cholinergic receptor subtypes. Nonetheless, a reduction in acetylcholinesterase activity in the hippocampus of *mdx* mice may be illustrative of a non-receptor dependent form of compensation for an overall reduction in cholinergic signalling in the CNS of dystrophic mice (Cohen et al. 2015; Comim et al. 2011).

Kainic acid (KA)/AMPA receptors

Yoshihara et al (2003) demonstrated that KA/AMPA receptor density was significantly reduced in several brain regions, including the hippocampus, in the *mdx* mice relative to WT animals. However this may reflect another homeostatic compensatory mechanism, this time for increased glutamatergic input (Miranda et al. 2011; Miranda et al. 2009).

In the context of this review it is interesting to note that changes in neuromodulatory cytokines such as IL-6, IL-1β and TNFα are known to effect both pre-synaptic and post-synaptic channels and receptors (Vezzani and Viviani 2015). Indeed, as previously mentioned, circulating levels of these proinflammatory cytokines are elevated in DMD patients (Chahbouni et al. 2010) but, as yet there is no evidence that brain levels of these neuromodulatory cytokines are altered.

Changes in hippocampal synaptic function in mdx mice

Consistent with reduction in the size and number, but not function (Kueh et al., 2008), of post-synaptically-localised neuronal $GABA_A$ receptor clusters in *mdx* mice (Anderson et al.

2002; Knuesel et al. 1999; Knuesel et al. 2001; Kueh et al. 2011; Kueh et al. 2008; Vaillend et al. 2010), one might expect reduced inhibitory input to the neuron to be manifested as a measurable increase in overall neuronal excitability in affected regions of the brain. However, the picture emerging from electrophysiological studies is not quite so straightforward. Whilst NMDA-induced Schaffer collateral - CA1 LTP in *mdx* hippocampus is abnormally enhanced in a bicuculline-sensitive manner which would tally with reduced inhibitory input onto the CA1 neurons (but see Sesay et al. 1996; Vaillend et al. 1998; Vaillend et al. 2004; Vaillend et al. 1999), a significant increase in the frequency of spontaneous miniature inhibitory post-synaptic currents (mIPSCs) has been recorded from *mdx* CA1 hippocampal neurons. This is likely due to increased neurotransmitter release probability from somatic inhibitory synapses contacting CA1 pyramidal neurons (Graciotti et al. 2008), due to an increased number of inhibitory synapses innervating the *mdx* CA1 neurons (Miranda et al. 2009; Perronnet and Vaillend 2010). This suggestion was supported by a contemporaneous study by Del Tongo *et al.* (2009) in which a significant increase in the number of parvalbumin-expressing GABAergic interneurons in the dorsal hippocampus of the *mdx* mouse was observed.

The increase in hippocampal GABAergic innervation associated with absence of dystrophin may have arisen as a systemic compensation for impaired GABAergic synaptic clustering and function but still appears to be insufficient to fully restore GABA concentrations within the hippocampus (Xu et al. 2015). Graciotti et al. (2008) speculated that an increase in inhibitory transmitter release specifically onto CA1 neurons may also occur *via* a retrograde signalling system, possibly involving pre-synaptically expressed scaffolding proteins such as neurexins (Craig and Kang 2007; Kang et al. 2008; Pilgram et al. 2010; Sudhof 2008; Sugita et al. 2001; Zhang et al. 2010). Not only do neurexins form direct structural links with the DAPC,

which, in turn, facilitates the post-synaptic clustering of $GABA_A$ receptors (Fritschy et al. 2012; Graf et al. 2004; Krasowska et al. 2014; Kueh et al. 2008), but they also modulate pre-synaptic release of neurotransmitters and vesicle cycling (Futai et al. 2007; Olsen et al. 2006; Sugita et al. 2001; Tanaka et al. 2000). Evidence for such a retrograde signalling mechanism has emerged from studies on *Drosophila*, where dystrophin isoforms retrogradely regulate pre-synaptic transmitter release from both inhibitory as well as excitatory synapses (Bogdanik et al. 2008; Fradkin et al. 2008; van der Plas et al. 2006; Wairkar et al. 2008). However, conclusive evidence for the existence of such a retrograde signalling mechanism occurring specifically at mammalian inhibitory synapses, where Dp427 is exclusively expressed, remains elusive. Tantalisingly, Vaillend and colleagues have demonstrated that dystrophin loss affects pre-synaptic ultrastructural organisation in hippocampal excitatory glutamatergic synapses, by increasing not only the size of their PSDs (Miranda et al. 2009) but also the density of docked vesicles (Miranda et al. 2011). Such a change in the density of docked vesicles, possibly in conjunction with reduced dendritic inhibition (Vaillend and Billard 2002; Vaillend et al. 1999), is likely to alter excitatory synapse physiology and may account for the facilitated induction of NMDA-dependent LTP observed at Schaffer collateral-CA1 synapses in *mdx* mice (Vaillend and Billard 2002). Moreover, such a potentiation of excitatory output could, at least partially, account for the increase in mIPSC frequency observed in CA1 of *mdx* mice (Graciotti et al. 2008) as it is well established that hippocampal inhibitory interneurons are directly innervated by glutamatergic excitatory projections emanating from the pyramidal cell layer (Gulyas et al. 1993; McBain and Dingledine 1993). It is as yet unclear how a cytoskeletal protein expressed exclusively at inhibitory CA1 synapses can exert such an effect on excitatory synapses, but dysregulation of calcium homeostasis (Hopf and Steinhardt 1992; Tuckett et al. 2015), defective brain vascular permeability (Goodnough et al. 2014; Nico et al. 2004) and/or dysbindin

relocalization (Miranda et al. 2011) have been posited as possible mechanisms for this phenomenon.

A role for immune molecules in synaptic transmission

Although not yet investigated in dystrophin-deficient models, it is interesting to note that receptors for immune molecules in the CNS have expression patterns that bear similarities to the synaptic receptors discussed previously. The major histocompatibility complex class I (MHCI) is a complex molecule which provides the cellular signature that allows the immune system to differentiate between self and non-self. MHCI is expressed in neurons (Corriveau et al. 1998) of the thalamus, hippocampus, cortex and cerebellum (Marin and Kipnis 2013), the latter three showing overlap with brain regions expressing DP427 (Anderson et al. 2002; Bies et al. 1992; Chamberlain et al. 1988; Chelly et al. 1990; Comim et al. 2011; Cyrulnik and Hinton 2008; Knuesel et al. 2000; Lidov 1996; Sekiguchi et al. 2009). MHCI is upregulated in skeletal muscle from muscular dystrophy patients (Nagappa et al. 2013) but it is not yet known if there are changes in expression of this immune molecule in the CNS of DMD patients. However, MHCI has been detected clustered at the post-synaptic density of synapses of hippocampal neurons, (Goddard et al. 2007), the site of expression of post-synaptic receptors which are altered in dystrophic hippocampal neurons. Furthermore, hippocampal neurons from a MHCI knockout mouse display enhanced synaptic plasticity and potentiated LTP (Goddard et al. 2007; Huh et al. 2000), features which bear a striking similarity to those reported in *mdx* mice (Dallerac et al. 2011; Vaillend and Billard 2002; Vaillend et al. 1998; Vaillend et al. 2004; Vaillend et al. 1999).

Cytokines represent another class of immune molecules which are crucial to the homeostatic function of the nervous system and, given the chronic elevations in their secretion in

dystrophinopathies, they are discussed below in relation to their potential role in the changes in hippocampal structure and function in dystrophic neurons.

Role of cytokines in hippocampal function

IL-1β

IL-1β is crucial for the generation of NMDA-dependent LTP in hippocampal CA1 neurons (Schneider et al. 1998), and reduced signalling through the IL-1 receptors results in impaired learning (Goshen et al. 2007). However, overexpression, or elevated levels of IL-1β also results in memory deficits (Moore et al. 2009) and decreased synaptic strength (Ross et al. 2003). In terms of its effects on post-synaptic receptors, IL-1β can increase the surface expression of hippocampal $GABA_A$ receptors and potentiate GABA-evoked inhibitory currents (Wang et al. 2012), features that have been observed in *mdx* hippocampal neurons (Graciotti et al. 2008). A relationship between IL-1β and cholinergic signalling in the hippocampus has also been postulated as IL-1β caused a reduction in extracellular acetylcholine in this brain region (Rada et al. 1991) an effect that was also correlated with memory defects (Taepavarapruk and Song 2010). This could perhaps be compared to the reduced sensitivity of the *mdx* hippocampus to cholinergic agonists (Coccurello et al. 2002) due to decreased nAChR binding sites (Ghedini et al. 2012)

IL-6

Local increases in hippocampal IL-6 are observed following intense synaptic or neuronal activity such as that induced by LTP protocols (Balschun et al. 2004; Jankowsky et al. 2000). However, in contrast to the effects of IL-1β, Balschun *et al.* found that inhibition of IL-6-mediated signalling in 'healthy' brains actually improved long-term memory, suggesting a possible negative regulatory role for IL-6 on LTP by limiting memory acquisition (Balschun

et al. 2004; Li et al. 1997). These findings correlate with *in vivo* behavioral studies which have demonstrated that neutralisation of IL-6 improved long term spatial memory in rats (Balschun et al. 2004), and that IL-6 knockout mice displayed an enhanced capacity for learning and memory (Braida et al. 2004). However, conversely, another study found that hippocampus-dependent learning was impaired in IL-6 knockout mice (Baier et al. 2009). Over-expression of IL-6 results in alterations in both inhibitory and excitatory synapses, and abnormal dendritic spine formation. These structural alterations are associated with impairments in cognitive abilities and deficits in learning, similar to symptoms exhibited by individuals with autism (Wei et al. 2012). This is an interesting finding as a significant number of boys with DMD also display behaviors on the autistic spectrum (Banihani et al. 2015).

Prenatal exposure to IL-6 in rats leads to increased levels of IL-6 in the hippocampus which are associated with altered expression of NMDA and $GABA_A$ receptors and deficits in spatial learning (Samuelsson et al. 2006). This has led to the proposal that exposure to pathological levels of IL-6 during critical stages of neurodevelopment may contribute to deficits in cognitive function. Although it is currently unknown if IL-6 is elevated locally in brain regions such as the hippocampus in *mdx* mice, given that elevated IL-6 levels are a hallmark of dystrophin-deficiency and are elevated in *mdx* plasma (Pelosi et al. 2015), it is possible that this may be a factor in dystrophinopathy-associated hippocampal dysfunction.

TNFα

TNFα concentration is elevated in both DMD patients and in *mdx* mice, with glial cells representing a likely sources of endogenous TNF (Stellwagen and Malenka 2006). Interestingly, in an *mdx* IL-6 mouse, where IL-6 levels are elevated, TNFα levels are also

potentiated (Pelosi et al. 2015). Activation of hippocampal TNF 1 receptors increases the frequency and amplitude of mEPSCs, which stimulates an increase in the expression of AMPA receptors and an overall increase in synaptic strength (Beattie et al. 2002; Dummer et al. 2002). Weakening of inhibitory synaptic input also contributes to the excitatory effects of TNFα on hippocampal neurons, which may be due to a persistent decrease of inhibitory synaptic strength caused by downregulation of membrane expressed $GABA_A$ receptors (Pribiag and Stellwagen 2013). While not consistent with the changes in electrophysiological properties of dystrophin deficient hippocampal neurons, it remains to be elucidated whether this inflammatory molecule may have a compensatory role in cognitive dysfunction in dystrophinopathies.

Other possible contributory factors in DMD-related cognitive dysfunction

Nitric oxide (NO)

In a manner similar to that proposed for elevated levels of peripherally-released cytokines altering hippocampal function, others have discovered that peripherally released NO, which is decreased in DMD, also exerts neuromodulatory effects. DMD patients and *mdx* mice display up to an 80% reduction of nitric oxide synthase (NOS) activity as loss of dystrophin leads to a secondary loss of nNOS from muscle (Brenman et al. 1995; Chang et al. 1996). As muscle is the primary source for systemic NO, and this is reduced in DMD patients, Deng and colleagues investigated if this impacted upon hippocampal neurogenesis in the *mdx* mouse. Adult neurogenesis within the hippocampus is a proposed means by which alterations in synaptic plasticity and memory formation may occur. They found that neurogenesis was disrupted in *mdx* hippocampal tissue (Deng et al. 2009). However, normal neurogenesis was restored by increasing muscle, and subsequently serum, NO levels (Deng et al. 2009),

evidence that further supports the potential role of peripheral molecules in hippocampal dysfunction in dystrophinopathies.

Mitochondrial dysfunction

Loss of dystrophin in skeletal muscle results in structurally unstable fibres which are more porous to the extracellular environment resulting in excessive influx of calcium. Poor calcium handling and subsequent activation of proteases and/or lipases leads to calcium overload in the cellular mitochondria and subsequent muscle degeneration. As mitochondrial ATP is crucial to a myriad of physiological functions, dysregulation of cellular energy homeostasis is likely to contribute to dystrophinopathy-associated pathophysiology, including impaired intracellular calcium signalling in skeletal muscle and in the brain (Timpani et al. 2015). Tracey *et al.* (1996) found evidence of raised inorganic phosphate ratio, relative to ATP, phosphocreatine and phosphomonomers, in DMD brains (Tracey et al. 1995) and there is also evidence that the concentration of choline-containing compounds is increased in DMD brains (Kato et al. 1997; Rae et al. 1998), which is usually interpreted as being due to increased membrane turnover and degradation, or decreased membrane stability, also seen in a number of other brain disorders (Anderson et al. 2002). Although in contrast, a more recent study showed a deficit in total choline in the brains of DMD patients (Kreis et al. 2011).

The *mdx* mouse has raised hippocampal choline-containing compounds (Rae et al. 2002; Xu et al. 2015), inorganic phosphate, pH and reduced total creatine (Tracey et al. 1996). The fact that these metabolic changes are also detected in muscle (Tracey et al. 1996) suggest bio-energetic similarities in other tissues that lack dystrophin. Uptake of glucose in *mdx* mice is increased relative to controls, reflecting an increase in metabolism, a finding which may indicate increased brain activity due to decreased GABA-evoked inhibition (Rae et al. 2002).

The fact that the GABA agonist muscimol, had a reduced dampening effect on glucose metabolism in *mdx* brains (Rae et al. 2002) is consistent with this theory in addition to the reduction and abnormal clustering of synaptically-located $GABA_A$ receptors in the hippocampus, cerebellum, amygdala and cerebral cortex (Knuesel et al. 1999; Knuesel et al. 2001; Kueh et al. 2011; Kueh et al. 2008; Perronnet and Vaillend 2010; Sekiguchi et al. 2009). A recent study has demonstrated a significant deficit in the amount of GABA within the hippocampal region of *mdx* mice and raised concentrations of the anti-oxidant molecule glutathione (Xu et al. 2015), a likely compensatory development against the increased quantity of reactive oxygen species produced by increased metabolism.

Such alterations in cellular metabolism, energy requirements and redox status in *mdx* brain tissue might also be expected to influence neuronal responses to hypoxia in dystrophic brain tissue. And indeed, this has proved to the case, with CA1 hippocampal neurons displaying particular sensitivity to hypoxic insults, with greater and more rapidly developing decreases in synaptic transmission relative to control brain slices at Schaffer collateral – CA1 synapses (Godfraind et al. 2000; Mehler et al. 1992). This altered response to hypoxia of *mdx* mouse hippocampal neurons may be due to a combination of factors including reduced $GABA_A$ receptor clustering in dystrophic neurons, as $GABA_A$ receptor activation exacerbates oxygen-glucose deprivation-induced neuronal injury (Muir et al. 1996). However, Godfraind et al., (2000) hypothesised that the more rapid failure of nerve conduction in the dystrophic tissue under hypoxic conditions was due to 'excessive leakiness' of nerves and poor regulation of ionic homeostasis, possibly due to Na-K and/or calcium ATPase activity. Disrupted cellular calcium ATPase activity, with a knock on effect on cellular calcium homeostasis, has been well described in dystrophic muscle and also seems to be mirrored in certain neural tissues. Although studies have not shown that elevated intracellular calcium levels or the number of

calcium-positive neurons were actually associated with frank neuronal loss *per se* in the *mdx* mouse (Tuckett et al 2014), modulation of synaptic plasticity (both LTP and LTD) is a calcium-dependent process that is absolutely contingent upon tight spatiotemporal control of intracellular neuronal calcium concentration (for review see Baker et al. 2013; Malenka and Bear 2004). Therefore, any dysregulation of calcium homeostasis or calcium signalling pathways would undoubtedly disrupt both short- and long-term plasticity in affected neurons and may at least partially account for some of the cognitive deficits observed in the *mdx* mice.

Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are a large family of zinc-dependent extracellular and membrane-bound endopeptidases that can cause proteolysis of selected components of the extracellular matrix in skeletal muscle. MMP-9 is one member of the family that is expressed at low levels under basal conditions but which can be induced by numerous factors, including inflammatory cytokines (Hu et al. 2007). MMP-9 is also important in synaptic plasticity, thereby contributing to learning and memory. For example, MMP-9 knockout mice exhibited deficits in particular components of CA1 LTP and spatial learning (Nagy et al. 2006). Furthermore, pharmacological inhibition of MMP-9 resulted in destabilization of LTP (Wojtowicz and Mozrzymas 2010). MMP-9 is a key molecule in the regulation of dendritic spine morphology and has been implicated in several neurological disorders (Stawarski et al. 2014). In the context of the dystrophinopathies, MMP-9 is elevated in *mdx* skeletal muscle (Kherif et al. 1999; Li et al. 2009). Thus, MMP-9 represents a possible molecule, possibly secondary to raised cytokine levels, which could be an important contributory factor in hippocampal dysfunction in DMD patients.

Stress

Immune cells respond not only to tissue damage and infection by secreting cytokines, but also to stress, both physical and psychological in nature. Thus, stress may also indirectly contribute to inflammatory-related hippocampal dysfunction in DMD patients. However, the hippocampus is also directly affected by stress factors and is, in fact, susceptible to damage by acute psychological stress, resulting in difficulties in memory retrieval and the acquisition and storage of new memories (Sapolsky 1996). In DMD patients the contributory effects of chronic corticosteroid exposure on behavior is controversial. Long-term treatment with corticosteroids, used in DMD to suppress chronic inflammation, is associated with changes in mood, memory and attention (Brown et al. 2008), although not all studies detected such changes (Banihani et al. 2015). Nonetheless, DMD patients do exhibit an increased incidence of anxiety and depression (Banihani et al. 2015; Fitzpatrick et al. 1986; Pangalila et al. 2015). *Mdx* (Manning et al. 2014) and also *mdx*3cv (Vaillend and Ungerer 1999) mice, which lack Dp427, Dp71 and Dp140 display stress-related behaviors comparable to symptoms of depression and anxiety, although not all behavioral assessments detected signs of anxiety in dystrophic mice (Sekiguchi et al. 2009). Enhanced freezing behavior in response to restraint stress, which is not painful but induces a psychological stress, was also observed in *mdx* mice but it should be noted that this was not associated with any change in corticosteroid levels (Yamamoto et al. 2010). Nonetheless, we have observed the efficacy of the tricyclic anti-depressant, amitriptyline in alleviating depressive and anxiety-like behaviors displayed by *mdx* mice, changes that were linked to altered levels of hippocampal neurotransmitters (Manning et al. 2014). It remains to be seen if loss of dystrophin from the CNS contributes directly to a heightened stress responses or if these effects are secondary to the disease itself. Moreover, further research must be carried out to determine if cross talk between the stress axis and the immune system are important in cognitive dysfunction in DMD.

Conclusions

DMD is a devastating disease characterized by a progressive loss of physical function and premature death in affected boys. Despite the continuing absence of an effective cure, palliative treatments, including prednisone and respiratory ventilation, are extending the life expectancy and life quality of patients. As such, investigation into the cognitive deficits and co-morbid CNS disorders associated with loss of dystrophin from neurons in the CNS is an emerging area of research. Boys with DMD exhibit non-progressing cognitive dysfunction, with deficits in verbal, short-term and working memory. In the genetically comparable dystrophin-deficient *mdx* mouse model of DMD, specific deficits in synaptogenesis and channel clustering at synapses is evident and deficits in some, but not all, types of learning and memory have been identified. Key changes underlying hippocampal dysfunction in dystrophin-deficient models are alterations in the number and clustering of post-synaptic receptors. The absence of dystrophin results in malformed and dysfunctional synapses which are likely to disturb the precise and coordinated neural network activity crucial to the formation and consolidation of memories in the hippocampus. Indeed, loss of inhibitory input in the *mdx* hippocampus was associated with abnormally enhanced NMDA-induced Schaffer collateral - CA1 LTP, which was sensitive to a $GABA_A$ antagonist. It is as yet unclear how enhanced LTP in a dystrophin-deficient hippocampus results in deficits in learning and memory. However, other studies have revealed that loss of neuronal dystrophin is associated with alterations in cellular metabolism, energy requirements and redox status, resulting in hippocampal neurons being particularly vulnerable to hypoxic insults, all of which may contribute to hippocampal dysfunction. Furthermore, psychological stress can negatively impact upon hippocampal function resulting in difficulties in memory retrieval and the storage of new memories. We have also identified the potential importance of inflammatory

mediators, which are chronically elevated in peripheral tissue and plasma of DMD patients and *mdx* mice, in hippocampal function. Key pro-inflammatory cytokines such as IL-1β, TNFα and IL-6 exert neuronmodulatory effects on the hippocampus and have been linked to altered capacities for learning and the formation of memories. This novel research avenue may reveal the importance of neuroimmune interactions in the CNS of dystrophin-deficient patients. Whilst this is a research area still in its infancy, our understanding of both normal cognitive function in healthy brains, as well as specific cognitive deficits in the brains of those suffering from DMD will be improved by continuing research in this field.

References

al-Qudah AA, Kobayashi J, Chuang S, Dennis M, and Ray P. Etiology of intellectual impairment in Duchenne muscular dystrophy. *Pediatr Neurol* 6: 57-59, 1990.

Allan SM, and Rothwell NJ. Cytokines and acute neurodegeneration. *Nature reviews* 2: 734-744, 2001.

Allan SM, Tyrrell PJ, and Rothwell NJ. Interleukin-1 and neuronal injury. *Nature reviews Immunology* 5: 629-640, 2005.

Amiry-Moghaddam M, Frydenlund DS, and Ottersen OP. Anchoring of aquaporin-4 in brain: molecular mechanisms and implications for the physiology and pathophysiology of water transport. *Neuroscience* 129: 999-1010, 2004.

Anderson JE, Ovalle WK, and Bressler BH. Electron microscopic and autoradiographic characterization of hindlimb muscle regeneration in the mdx mouse. *The Anatomical record* 219: 243-257, 1987.

Anderson JL, Head SI, Rae C, and Morley JW. Brain function in Duchenne muscular dystrophy. *Brain : a journal of neurology* 125: 4-13, 2002.

Arechavala-Gomeza V, Kinali M, Feng L, Guglieri M, Edge G, Main M, Hunt D, Lehovsky J, Straub V, Bushby K, Sewry CA, Morgan JE, and Muntoni F. Revertant fibres and dystrophin traces in Duchenne muscular dystrophy: implication for clinical trials. *Neuromuscular disorders : NMD* 20: 295-301, 2010.

Baker KD, Edwards TM, and Rickard NS. The role of intracellular calcium stores in synaptic plasticity and memory consolidation. *Neuroscience & Biobehavioral Reviews* 37: 1211-1239, 2013.

Balschun D, Wetzel W, Del Rey A, Pitossi F, Schneider H, Zuschratter W, and Besedovsky HO. Interleukin-6: a cytokine to forget. *FASEB J* 18: 1788-1790, 2004.

Banihani R, Smile S, Yoon G, Dupuis A, Mosleh M, Snider A, and McAdam L. Cognitive and Neurobehavioral Profile in Boys With Duchenne Muscular Dystrophy. *Journal of child neurology* 30: 1472-1482, 2015.

Barbujani G, Russo A, Danieli GA, Spiegler AW, Borkowska J, and Petrusewicz IH. Segregation analysis of 1885 DMD families: significant departure from the expected proportion of sporadic cases. *Hum Genet* 84: 522-526, 1990.

Beattie EC, Stellwagen D, Morishita W, Bresnahan JC, Ha BK, Von Zastrow M, Beattie MS, and Malenka RC. Control of synaptic strength by glial TNFalpha. *Science (New York, NY* 295: 2282-2285, 2002.

Bies RD, Phelps SF, Cortez MD, Roberts R, Caskey CT, and Chamberlain JS. Human and murine dystrophin mRNA transcripts are differentially expressed during skeletal muscle, heart, and brain development. *Nucleic acids research* 20: 1725-1731, 1992.

Blake DJ, and Kroger S. The neurobiology of duchenne muscular dystrophy: learning lessons from muscle? *Trends in neurosciences* 23: 92-99, 2000.

Blake DJ, Weir A, Newey SE, and Davies KE. Function and genetics of dystrophin and dystrophin-related proteins in muscle. *Physiological reviews* 82: 291-329, 2002.

Bogdanik L, Framery B, Frolich A, Franco B, Mornet D, Bockaert J, Sigrist SJ, Grau Y, and Parmentier ML. Muscle dystroglycan organizes the postsynapse and regulates presynaptic neurotransmitter release at the Drosophila neuromuscular junction. *PLoS One* 3: e2084, 2008.

Braida D, Sacerdote P, Panerai AE, Bianchi M, Aloisi AM, Iosue S, and Sala M. Cognitive function in young and adult IL (interleukin)-6 deficient mice. *Behavioural brain research* 153: 423-429, 2004.

Brenman JE, Chao DS, Xia H, Aldape K, and Bredt DS. Nitric oxide synthase complexed with dystrophin and absent from skeletal muscle sarcolemma in Duchenne muscular dystrophy. *Cell* 82: 743-752, 1995.

Bresolin N, Castelli E, Comi GP, Felisari G, Bardoni A, Perani D, Grassi F, Turconi A, Mazzucchelli F, Gallotti D, and et al. Cognitive impairment in Duchenne muscular dystrophy. *Neuromuscul Disord* 4: 359-369, 1994.

Brown ES, Wolfshohl J, Shad MU, Vazquez M, and Osuji IJ. Attenuation of the effects of corticosteroids on declarative memory with lamotrigine. *Neuropsychopharmacology* 33: 2376-2383, 2008.
Brunig I, Suter A, Knuesel I, Luscher B, and Fritschy JM. GABAergic terminals are required for postsynaptic clustering of dystrophin but not of GABA(A) receptors and gephyrin. *J Neurosci* 22: 4805-4813, 2002.
Bulfield G, Siller WG, Wight PA, and Moore KJ. X chromosome-linked muscular dystrophy (mdx) in the mouse. *Proc Natl Acad Sci U S A* 81: 1189-1192, 1984.
Calsavara AC, Soriani FM, Vieira LQ, Costa PA, Rachid MA, and Teixeira AL. TNFR1 absence protects against memory deficit induced by sepsis possibly through over-expression of hippocampal BDNF. *Metabolic brain disease* 30: 669-678, 2015.
Carretta D, Santarelli M, Sbriccoli A, Pinto F, Catini C, and Minciacchi D. Spatial analysis reveals alterations of parvalbumin- and calbindin-positive local circuit neurons in the cerebral cortex of mutant mdx mice. *Brain Res* 1016: 1-11, 2004.
Carretta D, Santarelli M, Vanni D, Carrai R, Sbriccoli A, Pinto F, and Minciacchi D. The organisation of spinal projecting brainstem neurons in an animal model of muscular dystrophy. A retrograde tracing study on mdx mutant mice. *Brain Res* 895: 213-222, 2001.
Carretta D, Santarelli M, Vanni D, Ciabatti S, Sbriccoli A, Pinto F, and Minciacchi D. Cortical and brainstem neurons containing calcium-binding proteins in a murine model of Duchenne's muscular dystrophy: selective changes in the sensorimotor cortex. *The Journal of comparative neurology* 456: 48-59, 2003.
Chahbouni M, Escames G, Venegas C, Sevilla B, Garcia JA, Lopez LC, Munoz-Hoyos A, Molina-Carballo A, and Acuna-Castroviejo D. Melatonin treatment normalizes plasma pro-inflammatory cytokines and nitrosative/oxidative stress in patients suffering from Duchenne muscular dystrophy. *Journal of pineal research* 48: 282-289, 2010.
Chamberlain JS, Pearlman JA, Muzny DM, Gibbs RA, Ranier JE, Caskey CT, and Reeves AA. Expression of the murine Duchenne muscular dystrophy gene in muscle and brain. *Science (New York, NY)* 239: 1416-1418, 1988.
Chang WJ, Iannaccone ST, Lau KS, Masters BS, McCabe TJ, McMillan K, Padre RC, Spencer MJ, Tidball JG, and Stull JT. Neuronal nitric oxide synthase and dystrophin-deficient muscular dystrophy. *Proceedings of the National Academy of Sciences of the United States of America* 93: 9142-9147, 1996.
Chaussenot R, Edeline JM, Le Bec B, El Massioui N, Laroche S, and Vaillend C. Cognitive dysfunction in the dystrophin-deficient mouse model of Duchenne muscular dystrophy: A reappraisal from sensory to executive processes. *Neurobiology of learning and memory* 124: 111-122, 2015.
Chelly J, Hamard G, Koulakoff A, Kaplan JC, Kahn A, and Berwald-Netter Y. Dystrophin gene transcribed from different promoters in neuronal and glial cells. *Nature* 344: 64-65, 1990.
Coccurello R, Castellano C, Paggi P, Mele A, and Oliverio A. Genetically dystrophic mdx/mdx mice exhibit decreased response to nicotine in passive avoidance. *Neuroreport* 13: 1219-1222, 2002.
Cohen EJ, Quarta E, Fulgenzi G, and Minciacchi D. Acetylcholine, GABA and neuronal networks: A working hypothesis for compensations in the dystrophic brain. *Brain Research Bulletin* 110: 1-13, 2015.
Comim CM, Moraz T, Abreu I, Fraga DB, Ghedim FV, Mildner N, Tuon L, Vainzof M, Zugno AI, and Quevedo J. Reduction of acethylcolinesterase activity in the brain of mdx mice. *Neuromuscul Disord* 21: 359-362, 2011.
Corriveau RA, Huh GS, and Shatz CJ. Regulation of class I MHC gene expression in the developing and mature CNS by neural activity. *Neuron* 21: 505-520, 1998.
Craig AM, and Kang Y. Neurexin-neuroligin signaling in synapse development. *Current opinion in neurobiology* 17: 43-52, 2007.
Cyrulnik SE, and Hinton VJ. Duchenne muscular dystrophy: a cerebellar disorder? *Neuroscience and biobehavioral reviews* 32: 486-496, 2008.

Dallerac G, Perronnet C, Chagneau C, Leblanc-Veyrac P, Samson-Desvignes N, Peltekian E, Danos O, Garcia L, Laroche S, Billard JM, and Vaillend C. Rescue of a dystrophin-like protein by exon skipping normalizes synaptic plasticity in the hippocampus of the mdx mouse. *Neurobiol Dis* 43: 635-641, 2011.
de Brouwer AP, Nabuurs SB, Verhaart IE, Oudakker AR, Hordijk R, Yntema HG, Hordijk-Hos JM, Voesenek K, de Vries BB, van Essen T, Chen W, Hu H, Chelly J, den Dunnen JT, Kalscheuer VM, Aartsma-Rus AM, Hamel BC, van Bokhoven H, and Kleefstra T. A 3-base pair deletion, c.9711_9713del, in DMD results in intellectual disability without muscular dystrophy. *Eur J Hum Genet* 22: 480-485, 2014.
De Paepe B, and De Bleecker JL. Cytokines and chemokines as regulators of skeletal muscle inflammation: presenting the case of Duchenne muscular dystrophy. *Mediators of inflammation* 2013: 540370, 2013.
De Pasquale L, D'Amico A, Verardo M, Petrini S, Bertini E, and De Benedetti F. Increased muscle expression of interleukin-17 in Duchenne muscular dystrophy. *Neurology* 78: 1309-1314, 2012.
Del Tongo C, Carretta D, Fulgenzi G, Catini C, and Minciacchi D. Parvalbumin-positive GABAergic interneurons are increased in the dorsal hippocampus of the dystrophic mdx mouse. *Acta neuropathologica* 118: 803-812, 2009.
Deng B, Glanzman D, and Tidball JG. Nitric oxide generated by muscle corrects defects in hippocampal neurogenesis and neural differentiation caused by muscular dystrophy. *The Journal of physiology* 587: 1769-1778, 2009.
Dubowitz V, and Crome L. The central nervous system in Duchenne muscular dystrophy. *Brain* 92: 805-808, 1969.
Dummer W, Niethammer AG, Baccala R, Lawson BR, Wagner N, Reisfeld RA, and Theofilopoulos AN. T cell homeostatic proliferation elicits effective antitumor autoimmunity. *The Journal of clinical investigation* 110: 185-192, 2002.
Evans NP, Misyak SA, Robertson JL, Bassaganya-Riera J, and Grange RW. Immune-mediated mechanisms potentially regulate the disease time-course of duchenne muscular dystrophy and provide targets for therapeutic intervention. *PM & R : the journal of injury, function, and rehabilitation* 1: 755-768, 2009.
Felisari G, Martinelli Boneschi F, Bardoni A, Sironi M, Comi GP, Robotti M, Turconi AC, Lai M, Corrao G, and Bresolin N. Loss of Dp140 dystrophin isoform and intellectual impairment in Duchenne dystrophy. *Neurology* 55: 559-564, 2000.
Fitzpatrick C, Barry C, and Garvey C. Psychiatric disorder among boys with Duchenne muscular dystrophy. *Dev Med Child Neurol* 28: 589-595, 1986.
Fradkin LG, Baines RA, van der Plas MC, and Noordermeer JN. The dystrophin Dp186 isoform regulates neurotransmitter release at a central synapse in Drosophila. *J Neurosci* 28: 5105-5114, 2008.
Fritschy JM, Panzanelli P, and Tyagarajan SK. Molecular and functional heterogeneity of GABAergic synapses. *Cellular and molecular life sciences : CMLS* 69: 2485-2499, 2012.
Fuenzalida M, Espinoza C, Perez MA, Tapia-Rojas C, Cuitino L, Brandan E, and Inestrosa NC. Wnt signaling pathway improves central inhibitory synaptic transmission in a mouse model of Duchenne muscular dystrophy. *Neurobiol Dis* 86: 109-120, 2016.
Futai K, Kim MJ, Hashikawa T, Scheiffele P, Sheng M, and Hayashi Y. Retrograde modulation of presynaptic release probability through signaling mediated by PSD-95-neuroligin. *Nature neuroscience* 10: 186-195, 2007.
Gaffen SL. Structure and signalling in the IL-17 receptor family. *Nature reviews Immunology* 9: 556-567, 2009.
Gardoni F, Boraso M, Zianni E, Corsini E, Galli CL, Cattabeni F, Marinovich M, Di Luca M, and Viviani B. Distribution of interleukin-1 receptor complex at the synaptic membrane driven by interleukin-1beta and NMDA stimulation. *Journal of neuroinflammation* 8: 14, 2011.

Ghedini PC, Avellar MC, De Lima TC, Lima-Landman MT, Lapa AJ, and Souccar C. Quantitative changes of nicotinic receptors in the hippocampus of dystrophin-deficient mice. *Brain Res* 1483: 96-104, 2012.
Glass CK, Saijo K, Winner B, Marchetto MC, and Gage FH. Mechanisms underlying inflammation in neurodegeneration. *Cell* 140: 918-934, 2010.
Gloss D, Moxley RT, Ashwal S, and Oskoui M. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 86: 465-472, 2016.
Goddard CA, Butts DA, and Shatz CJ. Regulation of CNS synapses by neuronal MHC class I. *Proceedings of the National Academy of Sciences of the United States of America* 104: 6828-6833, 2007.
Godfraind JM, Tekkok SB, and Krnjevic K. Hypoxia on hippocampal slices from mice deficient in dystrophin (mdx) and isoforms (mdx3cv). *J Cereb Blood Flow Metab* 20: 145-152, 2000.
Goodnough CL, Gao Y, Li X, Qutaish MQ, Goodnough LH, Molter J, Wilson D, Flask CA, and Yu X. Lack of dystrophin results in abnormal cerebral diffusion and perfusion in vivo. *NeuroImage* 102 Pt 2: 809-816, 2014.
Gorecki DC, and Barnard EA. Specific expression of G-dystrophin (Dp71) in the brain. *Neuroreport* 6: 893-896, 1995.
Goshen I, Kreisel T, Ounallah-Saad H, Renbaum P, Zalzstein Y, Ben-Hur T, Levy-Lahad E, and Yirmiya R. A dual role for interleukin-1 in hippocampal-dependent memory processes. *Psychoneuroendocrinology* 32: 1106-1115, 2007.
Graciotti L, Minelli A, Minciacchi D, Procopio A, and Fulgenzi G. GABAergic miniature spontaneous activity is increased in the CA1 hippocampal region of dystrophic mdx mice. *Neuromuscular Disorders* 18: 220-226, 2008.
Graf ER, Zhang X, Jin SX, Linhoff MW, and Craig AM. Neurexins induce differentiation of GABA and glutamate postsynaptic specializations via neuroligins. *Cell* 119: 1013-1026, 2004.
Griffin WS. Inflammation and neurodegenerative diseases. *The American journal of clinical nutrition* 83: 470S-474S, 2006.
Gulyas AI, Miles R, Sik A, Toth K, Tamamaki N, and Freund TF. Hippocampal pyramidal cells excite inhibitory neurons through a single release site. *Nature* 366: 683-687, 1993.
Haenggi T, and Fritschy JM. Role of dystrophin and utrophin for assembly and function of the dystrophin glycoprotein complex in non-muscle tissue. *Cellular and molecular life sciences : CMLS* 63: 1614-1631, 2006.
Haenggi T, Soontornmalai A, Schaub MC, and Fritschy JM. The role of utrophin and Dp71 for assembly of different dystrophin-associated protein complexes (DPCs) in the choroid plexus and microvasculature of the brain. *Neuroscience* 129: 403-413, 2004.
Haslett JN, Sanoudou D, Kho AT, Bennett RR, Greenberg SA, Kohane IS, Beggs AH, and Kunkel LM. Gene expression comparison of biopsies from Duchenne muscular dystrophy (DMD) and normal skeletal muscle. *Proceedings of the National Academy of Sciences of the United States of America* 99: 15000-15005, 2002.
Hendriksen RGF, Hoogland G, Schipper S, Hendriksen JGM, Vles JSH, and Aalbers MW. A possible role of dystrophin in neuronal excitability: A review of the current literature. *Neuroscience & Biobehavioral Reviews* 51: 255-262, 2015.
Hinton VJ, De Vivo DC, Nereo NE, Goldstein E, and Stern Y. Poor verbal working memory across intellectual level in boys with Duchenne dystrophy. *Neurology* 54: 2127-2132, 2000.
Hinton VJ, De Vivo DC, Nereo NE, Goldstein E, and Stern Y. Selective deficits in verbal working memory associated with a known genetic etiology: the neuropsychological profile of duchenne muscular dystrophy. *Journal of the International Neuropsychological Society : JINS* 7: 45-54, 2001.
Hinton VJ, Fee RJ, De Vivo DC, and Goldstein E. Poor facial affect recognition among boys with duchenne muscular dystrophy. *Journal of autism and developmental disorders* 37: 1925-1933, 2007.

Hinton VJ, Nereo NE, Fee RJ, and Cyrulnik SE. Social behavior problems in boys with Duchenne muscular dystrophy. *Journal of developmental and behavioral pediatrics : JDBP* 27: 470-476, 2006.
Hopf FW, and Steinhardt RA. Regulation of intracellular free calcium in normal and dystrophic mouse cerebellar neurons. *Brain Res* 578: 49-54, 1992.
Hu J, Van den Steen PE, Sang QX, and Opdenakker G. Matrix metalloproteinase inhibitors as therapy for inflammatory and vascular diseases. *Nat Rev Drug Discov* 6: 480-498, 2007.
Huang P, Zhao XS, Fields M, Ransohoff RM, and Zhou L. Imatinib attenuates skeletal muscle dystrophy in mdx mice. *FASEB J* 23: 2539-2548, 2009.
Huh GS, Boulanger LM, Du H, Riquelme PA, Brotz TM, and Shatz CJ. Functional requirement for class I MHC in CNS development and plasticity. *Science (New York, NY* 290: 2155-2159, 2000.
Huynh T, Uaesoontrachoon K, Quinn JL, Tatem KS, Heier CR, Van Der Meulen JH, Yu Q, Harris M, Nolan CJ, Haegeman G, Grounds MD, and Nagaraju K. Selective modulation through the glucocorticoid receptor ameliorates muscle pathology in mdx mice. *The Journal of pathology* 231: 223-235, 2013.
Inestrosa NC, and Arenas E. Emerging roles of Wnts in the adult nervous system. *Nature reviews Neuroscience* 11: 77-86, 2010.
Itoh K, Jinnai K, Tada K, Hara K, Itoh H, and Takahashi K. Multifocal glial nodules in a case of Duchenne muscular dystrophy with severe mental retardation. *Neuropathology* 19: 322-327, 1999.
Jagadha V, and Becker LE. Brain morphology in Duchenne muscular dystrophy: a Golgi study. *Pediatr Neurol* 4: 87-92, 1988.
Jankowsky JL, Derrick BE, and Patterson PH. Cytokine responses to LTP induction in the rat hippocampus: a comparison of in vitro and in vivo techniques. *Learning & memory* 7: 400-412, 2000.
Jueptner M, and Weiller C. Review: does measurement of regional cerebral blood flow reflect synaptic activity? Implications for PET and fMRI. *NeuroImage* 2: 148-156, 1995.
Kang Y, Zhang X, Dobie F, Wu H, and Craig AM. Induction of GABAergic postsynaptic differentiation by alpha-neurexins. *The Journal of biological chemistry* 283: 2323-2334, 2008.
Kato T, Nishina M, Matsushita K, Hori E, Akaboshi S, and Takashima S. Increased cerebral choline-compounds in Duchenne muscular dystrophy. *Neuroreport* 8: 1435-1437, 1997.
Kherif S, Lafuma C, Dehaupas M, Lachkar S, Fournier JG, Verdiere-Sahuque M, Fardeau M, and Alameddine HS. Expression of matrix metalloproteinases 2 and 9 in regenerating skeletal muscle: a study in experimentally injured and mdx muscles. *Dev Biol* 205: 158-170, 1999.
Kim TW, Wu K, Xu JL, and Black IB. Detection of dystrophin in the postsynaptic density of rat brain and deficiency in a mouse model of Duchenne muscular dystrophy. *Proc Natl Acad Sci U S A* 89: 11642-11644, 1992.
Knuesel I, Bornhauser BC, Zuellig RA, Heller F, Schaub MC, and Fritschy JM. Differential expression of utrophin and dystrophin in CNS neurons: an in situ hybridization and immunohistochemical study. *The Journal of comparative neurology* 422: 594-611, 2000.
Knuesel I, Mastrocola M, Zuellig RA, Bornhauser B, Schaub MC, and Fritschy JM. Altered synaptic clustering of GABAA receptors in mice lacking dystrophin (mdx mice). *The European journal of neuroscience* 11: 4457-4462, 1999.
Knuesel I, Zuellig RA, Schaub MC, and Fritschy JM. Alterations in dystrophin and utrophin expression parallel the reorganization of GABAergic synapses in a mouse model of temporal lobe epilepsy. *The European journal of neuroscience* 13: 1113-1124, 2001.
Koenig M, Hoffman EP, Bertelson CJ, Monaco AP, Feener C, and Kunkel LM. Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals. *Cell* 50: 509-517, 1987.
Krasowska E, Zablocki K, Gorecki DC, and Swinny JD. Aberrant location of inhibitory synaptic marker proteins in the hippocampus of dystrophin-deficient mice: implications for cognitive impairment in duchenne muscular dystrophy. *PloS one* 9: e108364, 2014.

Kreis R, Wingeier K, Vermathen P, Giger E, Joncourt F, Zwygart K, Kaufmann F, Boesch C, and Steinlin M. Brain metabolite composition in relation to cognitive function and dystrophin mutations in boys with Duchenne muscular dystrophy. *NMR in biomedicine* 24: 253-262, 2011.
Kueh SL, Dempster J, Head SI, and Morley JW. Reduced postsynaptic GABAA receptor number and enhanced gaboxadol induced change in holding currents in Purkinje cells of the dystrophin-deficient mdx mouse. *Neurobiol Dis* 43: 558-564, 2011.
Kueh SL, Head SI, and Morley JW. GABA(A) receptor expression and inhibitory post-synaptic currents in cerebellar Purkinje cells in dystrophin-deficient mdx mice. *Clinical and experimental pharmacology & physiology* 35: 207-210, 2008.
Kurek J, Bower J, Romanella M, and Austin L. Leukaemia inhibitory factor treatment stimulates muscle regeneration in the mdx mouse. *Neuroscience letters* 212: 167-170, 1996.
Kuru S, Inukai A, Kato T, Liang Y, Kimura S, and Sobue G. Expression of tumor necrosis factor-alpha in regenerating muscle fibers in inflammatory and non-inflammatory myopathies. *Acta neuropathologica* 105: 217-224, 2003.
Lee JS, Pfund Z, Juhasz C, Behen ME, Muzik O, Chugani DC, Nigro MA, and Chugani HT. Altered regional brain glucose metabolism in Duchenne muscular dystrophy: a pet study. *Muscle & nerve* 26: 506-512, 2002.
Levi S, Grady RM, Henry MD, Campbell KP, Sanes JR, and Craig AM. Dystroglycan is selectively associated with inhibitory GABAergic synapses but is dispensable for their differentiation. *J Neurosci* 22: 4274-4285, 2002.
Li AJ, Katafuchi T, Oda S, Hori T, and Oomura Y. Interleukin-6 inhibits long-term potentiation in rat hippocampal slices. *Brain research* 748: 30-38, 1997.
Li H, Mittal A, Makonchuk DY, Bhatnagar S, and Kumar A. Matrix metalloproteinase-9 inhibition ameliorates pathogenesis and improves skeletal muscle regeneration in muscular dystrophy. *Human molecular genetics* 18: 2584-2598, 2009.
Lidov HG. Dystrophin in the nervous system. *Brain pathology* 6: 63-77, 1996.
Lidov HG, Byers TJ, and Kunkel LM. The distribution of dystrophin in the murine central nervous system: an immunocytochemical study. *Neuroscience* 54: 167-187, 1993.
Lidov HG, Byers TJ, Watkins SC, and Kunkel LM. Localization of dystrophin to postsynaptic regions of central nervous system cortical neurons. *Nature* 348: 725-728, 1990.
Lv SY, Zou QH, Cui JL, Zhao N, Hu J, Long XY, Sun YC, He J, Zhu CZ, He Y, and Zang YF. Decreased gray matter concentration and local synchronization of spontaneous activity in the motor cortex in Duchenne muscular dystrophy. *AJNR American journal of neuroradiology* 32: 2196-2200, 2011.
Malenka RC, and Bear MF. LTP and LTD: an embarrassment of riches. *Neuron* 44: 5-21, 2004.
Manning J, Kulbida R, Rai P, Jensen L, Bouma J, Singh SP, O'Malley D, and Yilmazer-Hanke D. Amitriptyline is efficacious in ameliorating muscle inflammation and depressive symptoms in the mdx mouse model of Duchenne muscular dystrophy. *Experimental physiology* 99: 1370-1386, 2014.
Manning J, and O'Malley D. What has the mdx mouse model of Duchenne muscular dystrophy contributed to our understanding of this disease? *Journal of muscle research and cell motility* 36: 155-167, 2015.
Marin I, and Kipnis J. Learning and memory ... and the immune system. *Learning & memory* 20: 601-606, 2013.
McBain CJ, and Dingledine R. Heterogeneity of synaptic glutamate receptors on CA3 stratum radiatum interneurones of rat hippocampus. *The Journal of physiology* 462: 373-392, 1993.
Mehler MF, Haas KZ, Kessler JA, and Stanton PK. Enhanced sensitivity of hippocampal pyramidal neurons from mdx mice to hypoxia-induced loss of synaptic transmission. *Proc Natl Acad Sci U S A* 89: 2461-2465, 1992.
Messina S, Vita GL, Aguennouz M, Sframeli M, Romeo S, Rodolico C, and Vita G. Activation of NF-kappaB pathway in Duchenne muscular dystrophy: relation to age. *Acta myologica : myopathies and cardiomyopathies : official journal of the Mediterranean Society of Myology / edited by the Gaetano Conte Academy for the study of striated muscle diseases* 30: 16-23, 2011.

Minciacchi D, Del Tongo C, Carretta D, Nosi D, and Granato A. Alterations of the cortico-cortical network in sensori-motor areas of dystrophin deficient mice. *Neuroscience* 166: 1129-1139, 2010.
Miranda R, Nudel U, Laroche S, and Vaillend C. Altered presynaptic ultrastructure in excitatory hippocampal synapses of mice lacking dystrophins Dp427 or Dp71. *Neurobiol Dis* 43: 134-141, 2011.
Miranda R, Sebrie C, Degrouard J, Gillet B, Jaillard D, Laroche S, and Vaillend C. Reorganization of inhibitory synapses and increased PSD length of perforated excitatory synapses in hippocampal area CA1 of dystrophin-deficient mdx mice. *Cerebral cortex* 19: 876-888, 2009.
Montgomery SL, and Bowers WJ. Tumor necrosis factor-alpha and the roles it plays in homeostatic and degenerative processes within the central nervous system. *Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology* 7: 42-59, 2012.
Moore AH, Wu M, Shaftel SS, Graham KA, and O'Banion MK. Sustained expression of interleukin-1beta in mouse hippocampus impairs spatial memory. *Neuroscience* 164: 1484-1495, 2009.
Muir JK, Lobner D, Monyer H, and Choi DW. GABAA receptor activation attenuates excitotoxicity but exacerbates oxygen-glucose deprivation-induced neuronal injury in vitro. *J Cereb Blood Flow Metab* 16: 1211-1218, 1996.
Muntoni F, Mateddu A, and Serra G. Passive avoidance behaviour deficit in the mdx mouse. *Neuromuscular disorders : NMD* 1: 121-123, 1991.
Nagappa M, Nalini A, and Narayanappa G. Major histocompatibility complex and inflammatory cell subtype expression in inflammatory myopathies and muscular dystrophies. *Neurology India* 61: 614-621, 2013.
Nagy V, Bozdagi O, Matynia A, Balcerzyk M, Okulski P, Dzwonek J, Costa RM, Silva AJ, Kaczmarek L, and Huntley GW. Matrix metalloproteinase-9 is required for hippocampal late-phase long-term potentiation and memory. *J Neurosci* 26: 1923-1934, 2006.
Nardes F, Araujo AP, and Ribeiro MG. Mental retardation in Duchenne muscular dystrophy. *J Pediatr (Rio J)* 88: 6-16, 2012.
Nguyen KT, Deak T, Owens SM, Kohno T, Fleshner M, Watkins LR, and Maier SF. Exposure to acute stress induces brain interleukin-1beta protein in the rat. *J Neurosci* 18: 2239-2246, 1998.
Nico B, Paola Nicchia G, Frigeri A, Corsi P, Mangieri D, Ribatti D, Svelto M, and Roncali L. Altered blood-brain barrier development in dystrophic MDX mice. *Neuroscience* 125: 921-935, 2004.
Oliva CA, Vargas JY, and Inestrosa NC. Wnts in adult brain: from synaptic plasticity to cognitive deficiencies. *Frontiers in cellular neuroscience* 7: 224, 2013.
Olsen O, Moore KA, Nicoll RA, and Bredt DS. Synaptic transmission regulated by a presynaptic MALS/Liprin-alpha protein complex. *Current opinion in cell biology* 18: 223-227, 2006.
Pangalila RF, van den Bos GA, Bartels B, Bergen M, Stam HJ, and Roebroeck ME. Prevalence of fatigue, pain, and affective disorders in adults with duchenne muscular dystrophy and their associations with quality of life. *Archives of physical medicine and rehabilitation* 96: 1242-1247, 2015.
Parames SF, Coletta-Yudice ED, Nogueira FM, Nering de Sousa MB, Hayashi MA, Lima-Landman MT, Lapa AJ, and Souccar C. Altered acetylcholine release in the hippocampus of dystrophin-deficient mice. *Neuroscience* 269: 173-183, 2014.
Pelosi L, Berardinelli MG, Forcina L, Spelta E, Rizzuto E, Nicoletti C, Camilli C, Testa E, Catizone A, De Benedetti F, and Musaro A. Increased levels of interleukin-6 exacerbate the dystrophic phenotype in mdx mice. *Human molecular genetics* 24: 6041-6053, 2015.
Perronnet C, Chagneau C, Le Blanc P, Samson-Desvignes N, Mornet D, Laroche S, De La Porte S, and Vaillend C. Upregulation of brain utrophin does not rescue behavioral alterations in dystrophin-deficient mice. *Human molecular genetics* 21: 2263-2276, 2012.
Perronnet C, and Vaillend C. Dystrophins, utrophins, and associated scaffolding complexes: role in mammalian brain and implications for therapeutic strategies. *Journal of biomedicine & biotechnology* 2010: 849426, 2010.
Pilgram GS, Potikanond S, Baines RA, Fradkin LG, and Noordermeer JN. The roles of the dystrophin-associated glycoprotein complex at the synapse. *Molecular neurobiology* 41: 1-21, 2010.

Porreca E, Guglielmi MD, Uncini A, Di Gregorio P, Angelini A, Di Febbo C, Pierdomenico SD, Baccante G, and Cuccurullo F. Haemostatic abnormalities, cardiac involvement and serum tumor necrosis factor levels in X-linked dystrophic patients. *Thrombosis and haemostasis* 81: 543-546, 1999.
Porter JD, Khanna S, Kaminski HJ, Rao JS, Merriam AP, Richmonds CR, Leahy P, Li J, Guo W, and Andrade FH. A chronic inflammatory response dominates the skeletal muscle molecular signature in dystrophin-deficient mdx mice. *Human molecular genetics* 11: 263-272, 2002.
Pribiag H, and Stellwagen D. TNF-alpha downregulates inhibitory neurotransmission through protein phosphatase 1-dependent trafficking of GABA(A) receptors. *J Neurosci* 33: 15879-15893, 2013.
Rada P, Mark GP, Vitek MP, Mangano RM, Blume AJ, Beer B, and Hoebel BG. Interleukin-1 beta decreases acetylcholine measured by microdialysis in the hippocampus of freely moving rats. *Brain research* 550: 287-290, 1991.
Rae C, Griffin JL, Blair DH, Bothwell JH, Bubb WA, Maitland A, and Head S. Abnormalities in brain biochemistry associated with lack of dystrophin: studies of the mdx mouse. *Neuromuscul Disord* 12: 121-129, 2002.
Rae C, Scott RB, Thompson CH, Dixon RM, Dumughn I, Kemp GJ, Male A, Pike M, Styles P, and Radda GK. Brain biochemistry in Duchenne muscular dystrophy: a 1H magnetic resonance and neuropsychological study. *Journal of the neurological sciences* 160: 148-157, 1998.
Rodius F, Claudepierre T, Rosas-Vargas H, Cisneros B, Montanez C, Dreyfus H, Mornet D, and Rendon A. Dystrophins in developing retina: Dp260 expression correlates with synaptic maturation. *Neuroreport* 8: 2383-2387, 1997.
Rosman NP. The cerebral defect and myopathy in Duchenne muscular dystrophy. A comparative clinicopathological study. *Neurology* 20: 329-335, 1970.
Rosman NP, and Kakulas BA. Mental deficiency associated with muscular dystrophy. A neuropathological study. *Brain* 89: 769-788, 1966.
Ross FM, Allan SM, Rothwell NJ, and Verkhratsky A. A dual role for interleukin-1 in LTP in mouse hippocampal slices. *Journal of neuroimmunology* 144: 61-67, 2003.
Rufo A, Del Fattore A, Capulli M, Carvello F, De Pasquale L, Ferrari S, Pierroz D, Morandi L, De Simone M, Rucci N, Bertini E, Bianchi ML, De Benedetti F, and Teti A. Mechanisms inducing low bone density in Duchenne muscular dystrophy in mice and humans. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 26: 1891-1903, 2011.
Sairanen TR, Lindsberg PJ, Brenner M, Carpen O, and Siren A. Differential cellular expression of tumor necrosis factor-alpha and Type I tumor necrosis factor receptor after transient global forebrain ischemia. *J Neurol Sci* 186: 87-99, 2001.
Sakamoto T, Arima T, Ishizaki M, Kawano R, Koide T, Uchida Y, Yamashita S, Kimura E, Hirano T, Maeda Y, and Uchino M. Regions downstream from the WW domain of dystrophin are important for binding to postsynaptic densities in the brain. *Neuromuscul Disord* 18: 382-388, 2008.
Samuelsson AM, Jennische E, Hansson HA, and Holmang A. Prenatal exposure to interleukin-6 results in inflammatory neurodegeneration in hippocampus with NMDA/GABA(A) dysregulation and impaired spatial learning. *American journal of physiology Regulatory, integrative and comparative physiology* 290: R1345-1356, 2006.
Sapolsky RM. Stress, Glucocorticoids, and Damage to the Nervous System: The Current State of Confusion. *Stress (Amsterdam, Netherlands)* 1: 1-19, 1996.
Sbriccoli A, Santarelli M, Carretta D, Pinto F, Granato A, and Minciacchi D. Architectural changes of the cortico-spinal system in the dystrophin defective mdx mouse. *Neurosci Lett* 200: 53-56, 1995.
Schneider H, Pitossi F, Balschun D, Wagner A, del Rey A, and Besedovsky HO. A neuromodulatory role of interleukin-1beta in the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America* 95: 7778-7783, 1998.
Schobitz B, de Kloet ER, Sutanto W, and Holsboer F. Cellular localization of interleukin 6 mRNA and interleukin 6 receptor mRNA in rat brain. *The European journal of neuroscience* 5: 1426-1435, 1993.

Sekiguchi M, Zushida K, Yoshida M, Maekawa M, Kamichi S, Yoshida M, Sahara Y, Yuasa S, Takeda S, and Wada K. A deficit of brain dystrophin impairs specific amygdala GABAergic transmission and enhances defensive behaviour in mice. *Brain* 132: 124-135, 2009.
Septien L, Gras P, Borsotti JP, Giroud M, Nivelon JL, and Dumas R. [Mental development in Duchenne muscular dystrophy. Correlation of data of the brain scanner]. *Pediatrie* 46: 817-819, 1991.
Sesay AK, Errington ML, Levita L, and Bliss TV. Spatial learning and hippocampal long-term potentiation are not impaired in mdx mice. *Neuroscience letters* 211: 207-210, 1996.
Snow WM, Anderson JE, and Jakobson LS. Neuropsychological and neurobehavioral functioning in Duchenne muscular dystrophy: a review. *Neuroscience and biobehavioral reviews* 37: 743-752, 2013.
Sparkman NL, Buchanan JB, Heyen JR, Chen J, Beverly JL, and Johnson RW. Interleukin-6 facilitates lipopolysaccharide-induced disruption in working memory and expression of other proinflammatory cytokines in hippocampal neuronal cell layers. *J Neurosci* 26: 10709-10716, 2006.
Stawarski M, Stefaniuk M, and Wlodarczyk J. Matrix metalloproteinase-9 involvement in the structural plasticity of dendritic spines. *Front Neuroanat* 8: 68, 2014.
Stellwagen D, and Malenka RC. Synaptic scaling mediated by glial TNF-alpha. *Nature* 440: 1054-1059, 2006.
Sudhof TC. Neuroligins and neurexins link synaptic function to cognitive disease. *Nature* 455: 903-911, 2008.
Sugita S, Saito F, Tang J, Satz J, Campbell K, and Sudhof TC. A stoichiometric complex of neurexins and dystroglycan in brain. *The Journal of cell biology* 154: 435-445, 2001.
Sun J, Zhang S, Zhang X, Zhang X, Dong H, and Qian Y. IL-17A is implicated in lipopolysaccharide-induced neuroinflammation and cognitive impairment in aged rats via microglial activation. *Journal of neuroinflammation* 12: 165, 2015.
Tadayoni R, Rendon A, Soria-Jasso LE, and Cisneros B. Dystrophin Dp71: the smallest but multifunctional product of the Duchenne muscular dystrophy gene. *Molecular neurobiology* 45: 43-60, 2012.
Taepavarapruk P, and Song C. Reductions of acetylcholine release and nerve growth factor expression are correlated with memory impairment induced by interleukin-1beta administrations: effects of omega-3 fatty acid EPA treatment. *Journal of neurochemistry* 112: 1054-1064, 2010.
Tanaka H, Shan W, Phillips GR, Arndt K, Bozdagi O, Shapiro L, Huntley GW, Benson DL, and Colman DR. Molecular modification of N-cadherin in response to synaptic activity. *Neuron* 25: 93-107, 2000.
Terrando N, Rei Fidalgo A, Vizcaychipi M, Cibelli M, Ma D, Monaco C, Feldmann M, and Maze M. The impact of IL-1 modulation on the development of lipopolysaccharide-induced cognitive dysfunction. *Critical care* 14: R88, 2010.
Timpani CA, Hayes A, and Rybalka E. Revisiting the dystrophin-ATP connection: How half a century of research still implicates mitochondrial dysfunction in Duchenne Muscular Dystrophy aetiology. *Medical hypotheses* 85: 1021-1033, 2015.
Torres LF, and Duchen LW. The mutant mdx: inherited myopathy in the mouse. Morphological studies of nerves, muscles and end-plates. *Brain* 110 (Pt 2): 269-299, 1987.
Tracey I, Dunn JF, and Radda GK. Brain metabolism is abnormal in the mdx model of Duchenne muscular dystrophy. *Brain* 119 (Pt 3): 1039-1044, 1996.
Tracey I, Scott RB, Thompson CH, Dunn JF, Barnes PR, Styles P, Kemp GJ, Rae CD, Pike M, and Radda GK. Brain abnormalities in Duchenne muscular dystrophy: phosphorus-31 magnetic resonance spectroscopy and neuropsychological study. *Lancet (London, England)* 345: 1260-1264, 1995.
Tuckett E, Gosetti T, Hayes A, Rybalka E, and Verghese E. Increased calcium in neurons in the cerebral cortex and cerebellum is not associated with cell loss in the mdx mouse model of Duchenne muscular dystrophy. *Neuroreport* 26: 785-790, 2015.
Vaillend C, and Billard JM. Facilitated CA1 hippocampal synaptic plasticity in dystrophin-deficient mice: role for GABAA receptors? *Hippocampus* 12: 713-717, 2002.

Vaillend C, Billard JM, Claudepierre T, Rendon A, Dutar P, and Ungerer A. Spatial discrimination learning and CA1 hippocampal synaptic plasticity in mdx and mdx3cv mice lacking dystrophin gene products. *Neuroscience* 86: 53-66, 1998.
Vaillend C, Billard JM, and Laroche S. Impaired long-term spatial and recognition memory and enhanced CA1 hippocampal LTP in the dystrophin-deficient Dmd(mdx) mouse. *Neurobiol Dis* 17: 10-20, 2004.
Vaillend C, Perronnet C, Ros C, Gruszczynski C, Goyenvalle A, Laroche S, Danos O, Garcia L, and Peltekian E. Rescue of a dystrophin-like protein by exon skipping in vivo restores GABAA-receptor clustering in the hippocampus of the mdx mouse. *Molecular therapy : the journal of the American Society of Gene Therapy* 18: 1683-1688, 2010.
Vaillend C, Rendon A, Misslin R, and Ungerer A. Influence of dystrophin-gene mutation on mdx mouse behavior. I. Retention deficits at long delays in spontaneous alternation and bar-pressing tasks. *Behavior genetics* 25: 569-579, 1995.
Vaillend C, and Ungerer A. Behavioral characterization of mdx3cv mice deficient in C-terminal dystrophins. *Neuromuscul Disord* 9: 296-304, 1999.
Vaillend C, Ungerer A, and Billard JM. Facilitated NMDA receptor-mediated synaptic plasticity in the hippocampal CA1 area of dystrophin-deficient mice. *Synapse* 33: 59-70, 1999.
van der Plas MC, Pilgram GS, Plomp JJ, de Jong A, Fradkin LG, and Noordermeer JN. Dystrophin is required for appropriate retrograde control of neurotransmitter release at the Drosophila neuromuscular junction. *J Neurosci* 26: 333-344, 2006.
Vezzani A, Maroso M, Balosso S, Sanchez MA, and Bartfai T. IL-1 receptor/Toll-like receptor signaling in infection, inflammation, stress and neurodegeneration couples hyperexcitability and seizures. *Brain, behavior, and immunity* 25: 1281-1289, 2011.
Vezzani A, and Viviani B. Neuromodulatory properties of inflammatory cytokines and their impact on neuronal excitability. *Neuropharmacology* 96: 70-82, 2015.
Wairkar YP, Fradkin LG, Noordermeer JN, and DiAntonio A. Synaptic defects in a Drosophila model of congenital muscular dystrophy. *J Neurosci* 28: 3781-3789, 2008.
Waite A, Brown SC, and Blake DJ. The dystrophin-glycoprotein complex in brain development and disease. *Trends in neurosciences* 35: 487-496, 2012.
Waite A, Tinsley CL, Locke M, and Blake DJ. The neurobiology of the dystrophin-associated glycoprotein complex. *Annals of medicine* 41: 344-359, 2009.
Wallis T, Bubb WA, McQuillan JA, Balcar VJ, and Rae C. For want of a nail. ramifications of a single gene deletion, dystrophin, in the brain of the mouse. *Frontiers in bioscience : a journal and virtual library* 9: 74-84, 2004.
Wang DS, Zurek AA, Lecker I, Yu J, Abramian AM, Avramescu S, Davies PA, Moss SJ, Lu WY, and Orser BA. Memory deficits induced by inflammation are regulated by alpha5-subunit-containing GABAA receptors. *Cell reports* 2: 488-496, 2012.
Wei H, Chadman KK, McCloskey DP, Sheikh AM, Malik M, Brown WT, and Li X. Brain IL-6 elevation causes neuronal circuitry imbalances and mediates autism-like behaviors. *Biochimica et biophysica acta* 1822: 831-842, 2012.
Wojtowicz T, and Mozrzymas JW. Late phase of long-term potentiation in the mossy fiber-CA3 hippocampal pathway is critically dependent on metalloproteinases activity. *Hippocampus* 20: 917-921, 2010.
Xu S, Shi D, Pratt SJ, Zhu W, Marshall A, and Lovering RM. Abnormalities in brain structure and biochemistry associated with mdx mice measured by in vivo MRI and high resolution localized (1)H MRS. *Neuromuscul Disord* 25: 764-772, 2015.
Yamamoto K, Yamada D, Kabuta T, Takahashi A, Wada K, and Sekiguchi M. Reduction of abnormal behavioral response to brief restraint by information from other mice in dystrophin-deficient mdx mice. *Neuromuscular disorders : NMD* 20: 505-511, 2010.
Yoshihara Y, Onodera H, Iinuma K, and itoyama Y. Abnormal kainic acid receptor density and reduced seizure susceptibility in dystrophin-deficient mdx mice. *Neuroscience* 117: 391-395, 2003.

Yoshioka M, Okuno T, Honda Y, and Nakano Y. Central nervous system involvement in progressive muscular dystrophy. *Archives of disease in childhood* 55: 589-594, 1980.
Zhang C, Atasoy D, Arac D, Yang X, Fucillo MV, Robison AJ, Ko J, Brunger AT, and Sudhof TC. Neurexins physically and functionally interact with GABA(A) receptors. *Neuron* 66: 403-416, 2010.