

Review

Duchenne muscular dystrophy: A cerebellar disorder?

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Abstract

Cyrulnik, S.C., and V.J. Hinton. Duchenne muscular dystrophy: A cerebellar disorder? *NEUROSCI. BIOBEHAV. REV.* Duchenne muscular dystrophy (DMD) is a genetic disorder that is often associated with cognitive deficits. These cognitive deficits have been linked to the absence of dystrophin, a protein product which is normally found in multiple tissues throughout the body. In the current paper, we argue that it is the absence of dystrophin in the *cerebellum* that is responsible for the cognitive deficits observed. We begin by reviewing data that document structural and functional abnormalities in the brains of individuals with DMD and *mdx* mice. We briefly review the cognitive deficits associated with DMD, and then present neuroimaging and neuropsychological evidence to indicate that the cerebellum is involved in the same aspects of cognition that are impaired in children with DMD. It is our contention that the development of brain pathways in the cerebellum (e.g., cerebro-cerebellar loops) without dystrophin may result in altered brain function presenting as cognitive deficits in DMD.

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Contents

1. Introduction	486
2. Dystrophin and the brain: possible neural substrates of cognitive deficits	487
3. Of <i>mdx</i> mice and mazes	488
4. Cognitive deficits in DMD	488
5. The cerebellum: structure and function	489
5.1. The cerebellum and verbal working memory: evidence from neuroimaging.	490
5.2. The cerebellum and verbal working memory: evidence from neuropsychological studies	490
5.3. The cerebellum and reading: evidence from neuroanatomical and neuroimaging studies	491
5.4. The cerebellum and reading deficits: evidence from neuropsychological studies	492
6. Summary	492
References	493

1. Introduction

Duchenne muscular dystrophy (DMD) is a genetic disorder caused by a mutation in a single gene on the X chromosome. This mutation disrupts the production of dystrophin, a protein product normally concentrated at the

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neuromuscular junction. The resulting absence of dystrophin causes structural and signaling defects, which result in the gradual breakdown of muscle fiber. Over time, children and adolescents with DMD exhibit deterioration in muscle strength and function. The primary result of this mutation is progressive, and ultimately fatal, muscular weakness.

In addition to progressive muscular weakness, children with DMD often exhibit cognitive deficits. The absence of dystrophin, which studies have documented is normally present in the central nervous system (including the cerebral and cerebellar cortices), likely underlies the cognitive deficits observed. In the current paper, we hypothesize that the absence of dystrophin during brain development specifically disrupts the efficiency of the cerebro-cerebellar pathways, resulting in the cognitive deficits observed in DMD. Put simply, we argue that DMD is a cerebellar disorder.

2. Dystrophin and the brain: possible neural substrates of cognitive deficits

The absence of dystrophin in the muscle fiber is pathognomonic of DMD. Although less well known, dystrophin is also absent from the central nervous system (CNS) in individuals affected with the disorder. In fact, since brain-type dystrophin is normally as abundant as muscle-type dystrophin (Lederfein et al., 1992), its absence likely reflects a significant alteration in brain structure. These alterations in brain structure impact brain function, and likely underlie the cognitive deficits seen in children with DMD. We begin by presenting evidence that DMD is associated with altered brain structure and function.

Some of the most valuable localization data to date has been collected from the *mdx* mouse, a mouse model of DMD which is dystrophin-deficient. Immunohistochemical studies of normal mouse brain have demonstrated that dystrophin is localized to the cerebral cortex, the hippocampus, and the cerebellum. In the *mdx* mouse brain, however, these areas are lacking in dystrophin (Lidov et al., 1990, 1993; Huard and Tremblay, 1992; Kim et al., 1992). Further, among these three brain areas, dystrophin is normally most abundant in the cerebellum (Lidov et al., 1990). Dystrophin also localizes to certain cell types and cell areas. In both the cerebral cortex and cerebellum, dystrophin normally localizes to neurons (Chelly et al., 1990; Lidov et al., 1990). Within the cerebellum, it localizes specifically to Purkinje cells, and does not localize to other structures or processes (i.e., granule cells, stellate cells, basket cells, etc.) (Huard and Tremblay, 1992; Lidov et al., 1990, 1993). A more detailed analysis reveals that dystrophin is highly enriched at post-synaptic structures, thus prompting speculation that is involved in synaptic functioning (Lidov et al., 1990; Tian et al., 1996; Kim et al., 1992; Kamakura et al., 1994; Górecki et al., 1998). Furthermore, there is evidence to suggest that within the post-synaptic densities, dystrophin normally co-localizes with the GABA_A receptors (Knuesel et al., 1999).

The cellular data described above have been partially verified in human studies. Autopsy studies have documented the absence of dystrophin in the post-synaptic densities of the cerebral cortex in individuals diagnosed with DMD (Kim et al., 1995). The normally “highly enriched” dystrophin proteins found in a control brain were “undetectable” in the brain of a boy with DMD (Kim et al., 1995). In another series of autopsy studies, patients with DMD and known “intellectual disturbances” were examined; the investigators found a complete absence of dystrophin in cerebral and cerebellar neurons (Uchino et al., 1994a, b). In addition to these cellular anomalies, limited autopsy data have also revealed disordered connections and architectural anomalies (Rosman, 1970). Structural MRI has revealed mild atrophy in some individuals with DMD (Al-Qudah et al., 1990). Thus, there is evidence to indicate altered brain structure in humans with DMD, both on the cellular level and on the gross structural level.

In both mice and humans, dystrophin expression appears to be developmentally regulated. In mice, for example, dystrophin isoforms are involved in many different types of developing tissue, and that activity seems to increase before birth (Sarig et al., 1999). Kim et al. (1992) found differences in the expression of dystrophin and its isoforms during development in mice, with the brain-type dystrophin exhibiting dramatic increases from day 7 to day 10 of development (Kim et al., 1992). This is in contrast to the muscle-type dystrophin, which appears to plateau much more rapidly in the fetal mouse (Chelly et al., 1990). Similarly, Sogos and colleagues (2002) have documented the presence of dystrophin very early in human fetal development, and noted an increase in its expression until approximately week 15. Morris and colleagues, using post-mortem brain tissue samples from an adult (60 year-old) and fetus (3.5 months), found that there are dramatic decreases in dystrophin isoforms after birth (Morris et al., 1995).

In addition to structural abnormalities, there is evidence to indicate altered brain functioning in humans and animals with DMD (for a review, see Anderson et al., 2002). In humans, DMD is associated with metabolic abnormalities of the brain (Tracey et al., 1995). Furthermore, reduced glucose metabolism has been found in areas normally rich in dystrophin, including the cerebellum, medial temporal structures, sensorimotor area, and temporal neocortex (Lee et al., 2002).

In *mdx* mice, similar functional brain abnormalities have been reported: *mdx* mice exhibit impairments in glucose metabolism and other metabolic abnormalities (Rae et al., 2002a; Tracey et al., 1996). Of interest is that functional abnormalities have been detected on the cellular level in brain tissue slices of *mdx* mice. Specifically, marked reductions in the number of GABA_A receptor clusters immunoreactive for $\alpha 1$ and $\alpha 2$ subunits at the post-synaptic density have been noted in *mdx* mouse brain (Knuesel et al., 1999). Although this may have broad implications, in

the cerebellum it has been noted that the reduction in GABA_A receptor clusters at inhibitory synapses is associated with decreased amplitude and frequency of spontaneous miniature inhibitory post-synaptic currents (mIPSCs) in Purkinje cells of the *mdx* mouse when compared to littermate controls (Anderson et al., 2003). Furthermore, synaptic plasticity is also disrupted in cerebellar Purkinje cells of the *mdx* mouse, as demonstrated by a substantial reduction in long-term depression (LTD). The blunting of LTD occurred in the presence of pharmacological blockers of GABA, indicating that the consequences of an absence of dystrophin are not restricted to GABAergic-related functions (Anderson et al., 2004). Finally, it has been shown that hippocampal pyramidal neurons prepared from the *mdx* mouse are less likely to recover following hypoxic injury than slices prepared from control mice (Mehler et al., 1992). Thus, the dystrophin-deficient brain appears to be less resilient to adverse environmental influences than the normally developed brain.

3. Of *mdx* mice and mazes

The structural and functional deficits documented above have been hypothesized to underlie the cognitive deficits seen in mice and humans. *Mdx* mice, for example, exhibit memory impairments on tasks such as the T-maze (Vaillend et al., 1995). These learning and memory deficits have been described as “specific” rather than global, and relate to the *mdx* mouse’s ability to retain novel information (Vaillend et al., 1995). Furthermore, the experimenters argue that these cognitive deficits cannot be attributed solely to motor or emotional variables, as young *mdx* mice (<6 months) do not exhibit impaired motor function or coordination (Vaillend et al., 1995). Other aspects of learning and visuo-spatial skills do not appear to be impaired in *mdx* mice (Sesay et al., 1996).

4. Cognitive deficits in DMD

Duchenne himself, when characterizing the disorder, commented on the cognitive deficits apparent in some children with DMD, observing that they presented with “*intelligence obtuse*” (Duchenne, 1868). However, the children he observed appeared to have a wide range of intellectual functioning, ranging from idiocy to precocity (e.g., “*idiotisme*,” “*peud’intelligence*,” “*intelligence ordinaire*,” “*facultés intellectuelles très-développées*,” and “*son intelligence était précoce*”). Duchenne’s observations based on case studies were supported by early experimental research investigating the cognitive deficits in DMD (primarily assessing general IQ levels). Considerable data now indicate that the mean IQ in children with DMD is significantly lower than in the normal population, and a meta-analysis reveals that it is on average one standard deviation below the mean (Cotton et al., 2001). These scores appear to be normally distributed, and, as Duchenne

observed in the 1800s, there is considerable variability in the presentation of children with this disorder (Cotton et al., 2001).

We have previously argued that there is a core cognitive deficit in DMD, and we have referred to it as “limited verbal span” (Hinton et al., 2004). Research indicates that children with DMD have difficulty on tests which require attention to and repetition of verbal material. For example, deficits have been noted on tests of story recall (Billard et al., 1992; Hinton et al., 2000, 2001; Wicksell et al., 2004), sentence repetition (Billard et al., 1992; Hinton et al., 2007), and recall of digits (Billard et al., 1998; Hinton et al., 2000, 2001; Ogasawara, 1989; Wicksell et al., 2004). Indeed, one of the most consistent findings when investigating cognition in children with DMD is that scores on the Digit Span subtest of the Wechsler Intelligence Scales (WIS) are depressed (Anderson et al., 1988; Billard et al., 1998; Dorman et al., 1988; Hinton et al., 2000, 2001, 2004; Sollee et al., 1985; Ogasawara, 1989; Whelan, 1987; Wicksell et al., 2004). This finding remains consistent regardless of whether children with DMD are compared to normal controls, their siblings, or children with other degenerative muscle diseases. These deficits cannot be attributed to more general delays in the acquisition of language skills, as other areas of language and memory are intact (Hinton et al., 2001, 2007). The verbal deficits appear across all intellectual levels (Hinton et al., 2000), while other areas of cognition are generally spared (Hinton et al., 2001).

Deficits in verbal span have been linked to impairments in the acquisition of phonological knowledge and single-word vocabulary (Adams and Gathercole, 2000; Gathercole et al., 1997). Thus, it comes as no surprise that children with DMD also exhibit deficits in phonological processing and reading (Billard et al., 1992, 1998; Dorman et al., 1988; Hendriksen and Vles, 2006; Hinton et al., 2001, 2004; Leibowitz and Dubowitz, 1981; Worden and Vignos, 1962). Indeed, when compared to children with another fatal and progressive muscular disorder, spinal muscular atrophy (SMA), on measures of academic achievement, 40% of children with DMD were not yet fluent readers, whereas all children with SMA were fluent readers (Billard et al., 1992).

When compared to their unaffected siblings, children with DMD consistently perform more poorly on tests of phonological awareness and phonological memory (Hinton et al., 2005). Dorman and colleagues (1988) examined reading and phonological processing skills in a cohort of older children with DMD and found that they had significant difficulty on a test of phonological manipulation called “sound deletion” (e.g., say “stand” without the “t” sound), in which they had to isolate a particular sound. Qualitative analyses revealed that the children with DMD were particularly impaired on this task, often deleting adjacent phonemes, or struggling to reconstitute the word after deleting the target sound (Dorman et al., 1988). Indeed, even when children with DMD are compared to

control children who are equivalent in terms of their reading age, children with DMD make more phonological errors when reading non-words (Billard et al., 1998). Thus it appears that children with DMD present with a form of developmental dyslexia, with a particular impairment in phonological processing (Hinton et al., 2004). These types of deficits are consistent with what one would predict given their verbal span limitations.

5. The cerebellum: structure and function

Structurally, the cerebellum is one of the most elegantly designed regions of the brain. Although its name derives from Latin for *little cerebrum*, this “little” structure contains a staggering number of neurons. “The total number of cells in the cerebellar cortex exceeds four times the number of cells in the cerebral cortex” (Andersen et al., 1992). These neurons are arranged in a three-cell layer—the molecular, Purkinje cell and granule cell layer. Neurons from these layers form self-contained units, each consisting of one Purkinje cell and associated molecular and granule cell neurons. Known as “cerebellar cortical modules,” these modular circuits are arranged in an orderly array throughout the entire cerebellum, resulting in a lattice-like configuration (O’Hearn and Molliver, 2001). These modular circuits have been conceptualized as the modern equivalent of micro-chips, capable of processing large amounts of information (Leiner et al., 1991, 1995). The primary member of this module is the Purkinje cell neuron, which analyzes most of the incoming information, and is responsible for all of the output from the module (O’Hearn and Molliver, 2001). As the Purkinje cell is the primary output neuron, developmental anomalies in the structure of the Purkinje cell will likely result in widespread disruptions to signaling efficiency.

Functionally, the cerebellum is divided into three distinct regions with corresponding sets of connections. We will focus primarily on the cerebro-cerebellar loops, which connect the lateral parts of the cerebellar hemisphere with the cerebral cortex, and are traditionally responsible for the coordination of movement (Ghez, 1991). From an evolutionary perspective, the lateral parts of the cerebellum (along with the dentate nucleus), have enlarged significantly in humans, and some have argued that these structural changes represents a functional expansion of the cerebro-cerebellar loops (Leiner et al., 1991, 1993).

There is anatomical and physiological evidence to suggest that the cerebro-cerebellar loops are much more extensive than previously thought (Leiner et al., 1993; Schmahmann, 1991, 1996). The cerebellum receives input from multiple association areas of the cerebral cortex (including frontal, temporal and parietal areas) via the pontine nuclei which project to the cortex of the cerebellum (i.e., mossy fibers). The cerebellum also receives information from the association areas via the red nucleus and the inferior olive (i.e., climbing fibers). Indeed, the “cerebellum receives not only visual, auditory, and somatosensory

information from posterior lobes of the cerebral cortex, and not only motor information from the frontal lobe, but also highly processed multisensory information from some association areas” (Leiner et al., 1991, p. 120). Furthermore, the cerebellum can influence cerebral activity by projecting back to these areas through via the dentate nucleus (specifically, the phylogenetically newer part, the neodentate) and the thalamus. In fact, projections have been traced from the cerebellum to the dorsolateral prefrontal cortex that is separate from those cerebello-thalamocortical projections which innervate the motor cortex (Middleton and Strick, 1994). It seems that both the primary motor cortex and the dorsolateral prefrontal cortex receive different projections from distinct groups of Purkinje cells in the cerebellum. These projections appear to be part of “closed-loop circuits” which indicate that there are separate motor and non-motor channels between the cerebellum and the cerebral cortex which remain distinct as they traverse the brain (Kelly and Strick, 2003).

Several investigators have argued that the role of the cerebellum is not limited to the coordination of motor information, but that it extends to the coordination of certain types of cognitive information as well. (For arguments against the extended role of the cerebellum, see Glickstein, 1993, 2006.) The manner in which the cerebellum achieves this goal varies according to the theoretical perspective: automatization/skill learning perspective (Leiner et al., 1986, 1991, 1993), dynamics learning (Ito, 1993), the internal model hypothesis and the cerebellar microcomplexes (Ito, 2005, 1997), the dysmetria of thought hypothesis (Schmahmann, 1991, 1996, 2004), timing mechanisms (Ivry, 1997), and attentional and anticipatory mechanisms (Akshoomoff et al., 1997; Courchesne et al., 1994; Courchesne and Allen, 1997). Although the theoretical perspective may differ, all of the above theories agree that the cerebellum is responsible for the optimization and enhancement of cognitive performance in certain domains. The cerebro-cerebellar loops are perhaps responsible for “skilled mental performance” in the same way that other loops are responsible for “skilled motor performance” (Leiner et al., 1986).

If, indeed, the cerebellum is responsible for “skilled mental performance,” it follows logically that damage to the cerebellum will result in sub-optimal performance (and not necessarily frank deficits). Put differently, if our hypothesis regarding the disruption of cerebro-cerebellar circuits in DMD is correct, we should expect to see a pattern of sub-optimal performance on cognitive tasks in children with this disorder. In fact, we do indeed observe this pattern in our sample of children with DMD. They generally score within the normal range on standardized tests. It is only when compared to controls that the weaker performance of children with DMD becomes apparent (e.g., Hinton et al., 2001). Thus, there appears to be some preliminary evidence to support our contention that disruptions of the cerebro-cerebellar loops underlie the

cognitive phenotype of DMD. In the following sections, we present further evidence to indicate that the cerebellum is involved in cognitive functioning in certain domains (e.g., verbal working memory, phonological processing and reading).

5.1. *The cerebellum and verbal working memory: evidence from neuroimaging*

Cerebellar activation has been documented in numerous verbal tasks, and more importantly, is consistently activated in verbal working memory tasks (Jonides et al., 1997, 1998; Honey et al., 2000; Crottaz-Herbette et al., 2004; Glabus et al., 2003; Schumacher et al., 1996; Chen and Desmond, 2005; Fiez et al., 1996; Paulesu et al., 1993; Cabeza et al., 1997; Awh et al., 1996; Smith et al., 1996). The cerebellum does not appear to be involved in spatial working memory tasks (Smith et al., 1996), indicating a dissociation between the two types of working memory. Cerebellar activation appears in verbal working memory tasks regardless of input modality (Schumacher et al., 1996), and increases in response to task difficulty (Jonides et al., 1997). Cerebellar activation also cannot be attributed solely to speech production or to a motor response, as this is generally controlled for by the experimental design (i.e., subtraction or parametric methods). Thus, across methodologies, there appears to be a growing consensus that the cerebellum is part of the network of brain regions mediating verbal working memory.

In a review of 275 PET and fMRI studies on cognition, Cabeza and Nyberg (2000) note that the cerebellum is active in verbal working memory tasks, especially when phonological processing is involved. There is no consensus as to what aspect of phonological processing is mediated by the cerebellum; some argue for encoding (Ravizza et al., 2006; Chein and Fiez, 2001), others for articulatory control processes and phonological storage (Desmond, 2001; Chen and Desmond, 2005; Awh et al., 1996; Desmond et al., 1997), yet there is general agreement that the cerebellum is actively involved in processing phonological material.

5.2. *The cerebellum and verbal working memory: evidence from neuropsychological studies*

While neuroimaging studies demonstrate that the cerebellum is active when an individual engages in a certain cognitive task (e.g., verbal working memory), neuropsychological studies suggest that the cerebellum is not only active, but also necessary, for that task. In the case of verbal working memory, damage to the cerebellum has been shown to specifically disrupt verbal working memory in adults, but more general language skills in children. This is consistent with studies which demonstrate more diffuse neural representation of language in young children (for example, see Booth et al., 1999).

Following the resection of cerebellar tumors, language production in young children is often temporarily dis-

rupted; this is rarely observed in adults who undergo similar procedures (van Dongen et al., 1994). The pattern of language deficits exhibited by these children has sometimes been called “cerebellar mutism,” and generally resolves, in some cases to dysarthria (Pollack et al., 1995; Van Calenbergh et al., 1995). During post-surgical recovery children often exhibit abnormal voice quality, and peculiar alterations in tone, pitch, and loudness, in addition to bizarre behavioral abnormalities (Pollack, 1997, 2001; Pollack et al., 1995).

Recent evidence suggests that cerebellar mutism is not simply a disorder of muscle control and timing but is associated with a constellation of language impairments. After surgery, children exhibit deficits in naming, comprehension, and processing complex language (Riva and Giorgi, 2000). Another study documented impairments on measures of visual–spatial skills, expressive language, story recall, and sequencing and planning in children with cerebellar tumor resection who had not received radiation or chemotherapy (Levisohn et al., 2000). Some investigators believe that language impairments in cerebellar mutism are due to the destruction of dentate nuclei projections (Pollack et al., 1995), or perhaps to a more general disruption in cerebro-cerebellar pathways (Cole, 1994; Desmond, 2001; Pollack, 2001; Silveri et al., 1994). In either case, these studies point to an important role for the cerebellum in the maintenance of language in children.

In adults, damage to the cerebellum appears to disrupt more specific aspects of language processing, namely verbal working memory. In a recent study investigating working memory, patients with cerebellar damage exhibited deficits on measures of verbal, but not spatial, working memory; these deficits could not solely be accounted for by speech output problems (Ravizza et al., 2006). Furthermore, symptom severity was associated with performance on the verbal, but not spatial, memory task (Ravizza et al., 2006). When these patients were tested on measures of rehearsal (e.g., articulatory suppression and word-length effect), no significant impairments in these normal effects were found, indicating that rehearsal processes were intact. As such, Ravizza and colleagues (2006) hypothesized that the cerebellum mediates phonological encoding. Justus and colleagues (2005) reached a similar conclusion, when they tested adult patients with cerebellar damage on a verbal working memory task. They reported a reduced phonological similarity effect, indicating that the normal effect of similar phonemes on recall was reduced in cerebellar patients. This study provides evidence for a non-articulatory role for the cerebellum, perhaps for the phonological short-term store (Justus et al., 2005).

Silveri et al. (1998) present a case study of an 18-year-old Italian patient with a right cerebellar tumor. Silveri et al. utilized a battery sensitive to verbal working memory; specifically, measures designed to dissociate among different aspects of the phonological loop (e.g., phonological similarity effect, word-length effect, articulatory suppression

effect, recency effect, auditory vs. visual presentation of stimuli). The results of this patient's testing indicate that he suffered from a deficit in the rehearsal process, specifically the "phonological output buffer"; however, he displayed an intact phonological short-term storage system (Silveri et al., 1998). Silveri and colleagues hypothesized that the right cerebellum may be involved in the rehearsal process, particularly covert speech planning.

Although the conclusion drawn by Silveri et al. (1998) is not consistent with those drawn by Ravizza et al. (2006) and Justus et al. (2005), the hypotheses are not mutually exclusive, and all indicate cerebellar involvement in phonological processing. The studies differ in methodology (e.g., case vs. group study), etiology (e.g., tumor vs. stroke) and selective (e.g., right vs. left cerebellum), which may have differential effects on different aspects of phonological processing. Furthermore, there may be different areas of the cerebellum which are involved in storage and rehearsal. In fact, there is neuroimaging evidence to suggest that the frontal/superior aspects of the cerebellum are involved in articulatory processes, while the parietal/inferior aspects of the cerebellum are involved in phonological storage (Chen and Desmond, 2005).

Data from "natural experiments" (i.e., children and adults with acquired lesions in the area of interest) highlight two important points regarding language/verbal working memory processes when cerebro-cerebellar pathways are disrupted: In patients with acute cerebellar lesions, deficits in verbal working memory appear to be both *subtle* and *transient*. For example, in the case of cerebellar damage in children, language deficits normally resolve soon after surgery and, in most cases, are no longer apparent after four months (Pollack et al., 1995; van Dongen et al., 1994). Similarly, the deficit in verbal working memory in the Italian adolescent resolved within a few months after surgery. In adults with cerebellar damage, the deficits in verbal span are often subtle. Ravizza et al. (2006) observes: "the patients' verbal spans were quite good and fell within the normal range based on standardized norms...the deficit here was apparent in comparison to age- and education-matched control participants" (p. 310).

This is similar to the cognitive deficits seen in DMD, which are also both *subtle* and *transient*. As noted before, among individuals with DMD, performance on certain verbal working memory tasks often falls within the low-average to average range. Similar to Ravizza et al. (2006), the cognitive deficits in many children with DMD only become apparent when compared to well-matched controls. Furthermore, cross-sectional data suggest that verbal skills may improve with age in children with DMD (Cotton et al., 2005). However, these likely reflect modest gains, as children with DMD do not usually "recover" from their verbal deficits in the same way that children with cerebellar injury do. This may be attributed to the lack of plasticity that is frequently seen in developmental language disorders as compared to acquired language disorders.

5.3. The cerebellum and reading: evidence from neuroanatomical and neuroimaging studies

While considerably less plentiful than imaging data of verbal working memory, recent neuroanatomical and imaging studies have implicated the cerebellum in reading and developmental reading disorders. Post-mortem neuroanatomical data indicate differences in Purkinje cell size and distribution between dyslexic and non-dyslexic brains (Finch et al., 2002). Structural imaging studies have demonstrated an increased incidence of cerebellar abnormalities (e.g., symmetries) in individuals with reading disorders (Eckert et al., 2003; Leonard et al., 2001; Rae et al., 2002b). The degree of symmetry has been linked to performance on tests of phonological processing (Rae et al., 2002b). Furthermore, cerebellar abnormalities contribute significantly to discriminatory analyses which differentiate among subtypes of dyslexia (Leonard et al., 2001). Indeed, the cerebellum "is one of the most consistent locations for structural differences between dyslexic and control participants in imaging studies" (Eckert et al., 2003, p. 482).

Several functional imaging studies have documented cerebellar activation during component processes of reading, such as phonological processing (Paulesu et al., 1996; Xu et al., 2001; Zatorre et al., 1996) and single-word identification (Fiez et al., 1999; Herbster et al., 1997; Mechelli et al., 2003; Price et al., 1994); however, very few investigators comment upon this activation. An elegantly designed study by Fulbright and colleagues (1999) specifically investigated the role of the cerebellum in the different component processes of reading. A series of tasks were designed to investigate the role of the cerebellum in orthographic analysis, phonological analysis (word rhyme) and lexical semantic processing. Fulbright et al. (1999) found that cerebellar activation increased as cognitive demands involved in reading increase. Furthermore, different areas were engaged by the cerebellum in phonological processing as compared to lexical-semantic processing. The cerebellar activation in this study could not be attributed to motor control or strictly to covert articulation as the motor components were accounted for using a subtraction paradigm, and input (e.g., same/different judgment task) and output (e.g., yes/no button press) demands were kept constant across tasks.

The findings of cerebellar activation in reading are consistent with a putative role of the cerebellum in the optimization of certain cognitive skills. Other investigators have hypothesized that the cerebellum is generally responsible for the "skilled manipulation of symbols" (Leiner et al., 1991), a description which seems to perfectly capture the experience of fluent reading. This is consistent with theoretical models of reading which have suggested that for reading to develop successfully, many of the component skills involved must be mastered to the point of automaticity (Kitz and Tarver, 1989; LaBerge and Samuels, 1974; Shaywitz, 1998).

5.4. *The cerebellum and reading deficits: evidence from neuropsychological studies*

A group of researchers from the United Kingdom have proposed that the deficits associated with dyslexia are due to cerebellar involvement [for an historical overview of their research, the reader is referred to Nicolson and Fawcett (1999)]. Fawcett et al. (1996) tested children with dyslexia on measures of cerebellar functioning. They reported that the dyslexic children exhibited significant impairments on all of the cerebellar tests, both compared to age-matched controls and reading-matched controls (Fawcett et al., 1996). Moreover, the effect sizes associated with cerebellar impairment were greater than those associated with reading impairment. Finally, all dyslexic children, to various extents, exhibited impairments on these tasks, indicating that these results were not just representative of a few dyslexic children (Fawcett et al., 1996).

These findings were subsequently replicated in a later study (Fawcett and Nicolson, 1999). Dyslexic children exhibited deficits on several cerebellar tests (e.g., balance, posture and muscle tone), and the degree of severity was similar to that exhibited on tests of spelling and reading (Fawcett and Nicolson, 1999). A closer inspection of the data revealed that not only were these findings consistent at the group level, but they even were consistent when reduced to the individual level (i.e., a majority of dyslexic children showed signs of cerebellar dysfunction) (Fawcett and Nicolson, 1999).

Nicolson, Fawcett and colleagues present an intriguing perspective on dyslexia and reading difficulties, one which implicates cerebellar involvement. They posit that a developmental disorder of the cerebellum or cerebro-cerebellar loops is responsible for the reading difficulties in children with dyslexia (Nicolson et al., 2001). In particular, they suggest that early cerebellar dysfunction may cause mild motor and articulation difficulties; these articulation difficulties may prevent the acquisition of the phonological code, or may prevent its implementation in an automatic manner (this deficit may be reflected in impaired verbal working memory); phonological processing difficulties, in turn, may lead to the difficulties in the acquisition of fluent reading (Nicolson et al., 2001). While perhaps not mainstream, this theory neatly accounts for the various manifestations of dyslexia, and offers a plausible account of the manner in which cerebellar abnormalities may cause impairments in both phonological processing and reading. Furthermore, this theory offers a heuristic model for conceptualizing the reading difficulties seen in children with DMD. Their putative developmental description seems to perfectly describe the association of deficits seen in DMD children.

It is important to note that, while this section has focused on the “cerebellar deficit hypothesis,” every theory of dyslexia must account for the manner in which children normally acquire language and reading in a rapid and effortless fashion. Reading becomes automatic, nay ob-

ligatory, in most normal children and adults. Indeed, there appears to be general consensus that the acquisition of fluent reading involves mastery of a particular skill or subset of skills to the point of automaticity (Bruck, 1992; Chall, 1987; Felton et al., 1990; Kitz and Tarver, 1989; LaBerge and Samuels, 1974; Shaywitz, 1998; van Daal and van der Leij, 1999; van der Leij and van Daal, 1999). Theories of dyslexia which attribute reading impairments to basic deficits in temporal processing (Anderson et al., 1993; Tallal et al., 1993) emphasize that the core deficit involves difficulty processing rapidly changing stimuli. The efficiency with which children analyze fast and transient stimuli (on the order of tens of milliseconds) appears to be impaired in dyslexia (Anderson et al., 1993; Tallal et al., 1993). Thus, across theoretical perspectives, there is general agreement that efficiency and automaticity are paramount in the acquisition of reading skills. If, as we have argued, the cerebellum is responsible for helping to automatize cognitive skills, it stands as the perfect neural substrate to assist in this process.

6. Summary

We have argued that DMD is a “cerebellar” disorder. In the current paper, we have presented evidence to support our contention that disruptions of the cerebro-cerebellar pathways best account for the profile of cognitive deficits seen in children with DMD (e.g., limited verbal span, difficulty with phonological processing and reading). We have reviewed neuroimaging evidence suggesting that the cerebellum is involved in these same aspects of cognition and that damage to the cerebellum disrupts functioning in these domains. Although there are numerous other areas of the brain that are traditionally implicated in these types of deficits (and which may also play a role in DMD), we contend that the cerebro-cerebellar loops hypothesis provides the most parsimonious explanation for the cognitive effects associated with the disease. In fact, the hypothesis that disruptions of the cerebro-cerebellar loops cause cognitive deficits in children with a motor disorder is consistent with opinions that motor and cognitive development are closely interrelated (Diamond, 2000).

We have also argued, as have others, that the cerebellum serves to coordinate cognition in the same way that it operates to coordinate motor skills and learning; it helps to automatize and optimize performance in certain cognitive domains. Thus, damage to the cerebellum will likely result in sub-optimal performance and these decrements in performance may escape detection if not studied carefully. We have shown that children with DMD display the types of deficits that one would predict given a cerebellar injury, both in terms of the type of deficit and the quality of the deficit.

Finally, we have argued that these deficits are due to the genetic mutation in DMD, which disrupts the production of dystrophin. Brain pathways in the cerebellum develop without dystrophin, a crucial protein product. The lack of

dystrophin in the fetal brain may lead to the disruption of synapse formation and subsequent synaptic function. The cerebellar Purkinje cells that lack dystrophin have a substantial reduction in long-term depression, which may have broad consequences on learning. Disordered connections may result in inefficient signaling and transmission of information, especially in the domain of language. Indeed, microscopic cortical abnormalities have been implicated in language and reading disorders in some of the earliest studies investigating the neuro-anatomical locus of language disorders (Galaburda et al., 1985; Cohen et al., 1989; Humphreys et al., 1990), and many investigators believe that the lack of plasticity seen in developmental language disorders may be due to an inefficiently wired brain (Bishop, 2000).

As evidenced by the findings described above, DMD provides a unique window into the relationship between neuroanatomical structure and cognitive function. It offers investigators the opportunity to study brain development that occurs without the presence of a necessary protein, which is the result of a mutation on a single-gene. In short, DMD facilitates a rare opportunity for us to traverse the continuum from genotype to cognitive phenotype.

References

- Adams, A.-M., Gathercole, S.E., 2000. Limitations in working memory: implications for language development. *International Journal of Language and Communication Disorders* 35, 95–116.
- Akshoomoff, N.A., Courchesne, E., Townsend, J., 1997. Attention coordination and anticipatory control. In: Schmahmann, J.D. (Ed.), *The Cerebellum and Cognition*. Academic Press, San Diego, pp. 575–598.
- Al-Qudah, A.A., Kobayashi, J., Chuang, S., Dennis, M., Ray, P., 1990. Etiology of intellectual impairment in Duchenne muscular dystrophy. *Pediatric Neurology* 6, 57–59.
- Andersen, B.B., Korbo, L., Pakkenberg, B., 1992. A quantitative study of the human cerebellum with unbiased stereological techniques. *The Journal of Comparative Neurology* 326, 549–560.
- Anderson, J.L., Head, S.I., Rae, C., Morley, J.W., 2002. Brain function in Duchenne muscular dystrophy. *Brain* 125, 4–13.
- Anderson, J.L., Head, S.I., Morley, J.W., 2003. Altered inhibitory input to Purkinje cells of dystrophin-deficient mice. *Brain Research* 982, 280–283.
- Anderson, J.L., Head, S.I., Morley, J.W., 2004. Long-term depression is reduced in cerebellar Purkinje cells of dystrophin-deficient *mdx* mice. *Brain Research* 1019, 289–292.
- Anderson, K.C., Brown, C.P., Tallal, P., 1993. Developmental language disorders: evidence for a basic processing deficit. *Current Opinion in Neurology and Neurosurgery* 6, 98–106.
- Anderson, S.W., Routh, D.K., Ionasescu, V.V., 1988. Serial position memory of boys with Duchenne muscular dystrophy. *Developmental Medicine and Child Neurology* 30, 328–333.
- Awh, E., Jonides, J., Smith, E.E., Schumacher, E.H., Koeppel, R.A., Katz, S., 1996. Dissociation of storage and rehearsal in verbal working memory: evidence from positron emission tomography. *Psychological Science* 7, 25–31.
- Billard, C., Gillet, P., Signoret, J.L., Uicaud, E., Bertrand, P., Fardeau, M., et al., 1992. Cognitive functions in Duchenne muscular dystrophy: a reappraisal and comparison with spinal muscular atrophy. *Neuromuscular Disorder* 2, 371–378.
- Billard, C., Gillet, P., Barthez, M.-A., Hommet, C., Bertrand, P., 1998. Reading ability and processing in Duchenne muscular dystrophy and spinal muscular atrophy. *Developmental Medicine and Child Neurology* 40, 12–20.
- Bishop, D.V.M., 2000. How does the brain learn language? Insights from the study of children with and without language impairment. *Developmental Medicine and Child Neurology* 42, 133–142.
- Booth, J.R., MacWhinney, B., Thulborn, K.R., Sacco, K., Voyvodic, J., Feldman, H.M., 1999. Functional organization of activation patterns in children: whole brain fMRI imaging during three different cognitive tasks. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 23, 669–682.
- Bruck, M., 1992. Persistence of dyslexics' phonological awareness deficits. *Developmental Psychology* 28, 874–886.
- Cabeza, R., Nyberg, L., 2000. Imaging cognition II: an empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience* 12, 1–47.
- Cabeza, R., Grady, C.L., Nyberg, L., McIntosh, A.R., Tulving, E., Kapur, S., et al., 1997. Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomographic study. *The Journal of Neuroscience* 17, 391–400.
- Chall, J.S., 1987. Reading development in adults. *Annals of Dyslexia* 37, 240–251.
- Chein, J.M., Fiez, J.A., 2001. Dissociation of verbal working memory system components using a delayed serial recall task. *Cerebral Cortex* 11, 1003–1014.
- Chelly, J., Hamard, G., Koulakoff, A., Kaplan, J.-C., Kahn, A., Berwald-Netter, Y., 1990. Dystrophin gene transcribed from different promoters in neuronal and glial cells. *Nature* 344, 64–65.
- Chen, S.H.A., Desmond, J.E., 2005. Cerebrocerebellar networks during articulatory rehearsal and verbal working memory tasks. *NeuroImage* 24, 332–338.
- Cohen, M., Campbell, R., Yaghai, F., 1989. Neuropathological abnormalities in developmental dysphasia. *Annals of Neurology* 25, 567–570.
- Cole, M., 1994. The foreign policy of the cerebellum (editorial). *Neurology* 44, 2001–2005.
- Cotton, S., Voudouris, N.J., Greenwood, K.M., 2001. Intelligence and Duchenne muscular dystrophy: full-scale, verbal, and performance intelligence quotients. *Developmental Medicine and Child Neurology* 43, 497–501.
- Cotton, S.M., Voudouris, N.J., Greenwood, K.M., 2005. Association between intellectual functioning and age in children and young adults with Duchenne muscular dystrophy: further results from a meta-analysis. *Developmental Medicine and Child Neurology* 47, 257–265.
- Courchesne, E., Allen, G., 1997. Prediction and preparation, fundamental functions of the cerebellum. *Learning and Memory* 4, 1–35.
- Courchesne, E., Townsend, J., Akshoomoff, N.A., Saitoh, O., Yeung-Courchesne, R., Lincoln, A.J., et al., 1994. Impairment in shifting attention in autistic and cerebellar patients. *Behavioral Neuroscience* 108, 848–865.
- Crottaz-Herbette, S., Anagnoson, R.T., Menon, V., 2004. Modality effects in verbal working memory: differential prefrontal and parietal responses to auditory and visual stimuli. *NeuroImage* 21, 340–351.
- Desmond, J.E., 2001. Cerebellar involvement in cognitive function: evidence from neuroimaging. *International Review of Psychiatry* 13, 283–294.
- Desmond, J.E., Gabrieli, J.D.E., Wagner, A.D., Ginier, B.L., Glover, G.H., 1997. Lobular patterns of cerebellar activation in verbal working-memory and finger-tapping tasks as revealed by functional MRI. *The Journal of Neuroscience* 17, 9675–9685.
- Diamond, A., 2000. Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. *Child Development* 71, 44–56.
- Dorman, C., Hurley, A.D., D'Avignon, J., 1988. Language and learning disorders of older boys with Duchenne muscular dystrophy. *Developmental Medicine and Child Neurology* 30, 316–327.
- Duchenne, G.B.A., 1868. Recherches sur la paralysie musculaire pseudo-hypertrophique ou paralysie myosclerosique. *Archives of General Medicine* 11, 5–25.

- Eckert, M.A., Leonard, C.M., Richards, T.L., Aylward, E.H., Thomson, J., Berninger, V.W., 2003. Anatomical correlates of dyslexia: frontal and cerebellar findings. *Brain* 126, 482–494.
- Fawcett, A.J., Nicolson, R.I., 1999. Performance of dyslexic children on cerebellar and cognitive tests. *Journal of Motor Behavior* 31, 68–78.
- Fawcett, A.J., Nicolson, R.I., Dean, P., 1996. Impaired performance of children with dyslexia on a range of cerebellar tasks. *Annals of Dyslexia* 46, 259–283.
- Felton, R.H., Naylor, C.E., Wood, F.B., 1990. Neuropsychological profile of adult dyslexics. *Brain and Language* 39, 485–497.
- Fiez, J.A., Raife, E.A., Balota, D.A., Schwarz, J.P., Raichle, M.E., Petersen, S.E., 1996. A positron emission tomography study of the short-term maintenance of verbal information. *The Journal of Neuroscience* 16, 808–822.
- Fiez, J.A., Balota, D.A., Raichle, M.E., Petersen, S.E., 1999. Effects of lexicality, frequency, and spelling-to-sound consistency on the functional anatomy of reading. *Neuron* 24, 205–218.
- Finch, A.J., Nicolson, R.I., Fawcett, A.J., 2002. Evidence for a neuroanatomical difference within the olivo-cerebellar pathway of adults with dyslexia. *Cortex* 38, 529–539.
- Fulbright, R.K., Jenner, A.R., Mencl, W.E., Pugh, K.R., Shaywitz, B.A., Shaywitz, S.E., et al., 1999. The cerebellum's role in reading: a functional MR imaging study. *American Journal of Neuroradiology* 20, 1925–1930.
- Galaburda, A.M., Sherman, G.F., Rosen, G.D., Aboitiz, F., Geschwind, N., 1985. Developmental dyslexia: four consecutive patients with cortical anomalies. *Annals of Neurology* 18, 222–233.
- Gathercole, S.E., Hitch, G.J., Service, E., Martin, A.J., 1997. Phonological short-term memory and new word learning in children. *Developmental Psychology* 33, 966–979.
- Ghez, C., 1991. The cerebellum. In: Kandel, E.R., Schwartz, J.H., Jessell, T.M. (Eds.), *Principles of Neural Science*, third ed. Appleton & Lange, Norwalk, Connecticut, pp. 626–646.
- Glabus, M.F., Horwitz, B., Holt, J.L., Kohn, P.D., Gerton, B.K., Callicott, J.H., et al., 2003. Interindividual differences in functional interactions among prefrontal, parietal and parahippocampal regions during working memory. *Cerebral Cortex* 13, 1352–1361.
- Glickstein, M., 1993. Motor skills but not cognitive tasks. *Trends in Neurosciences* 16, 450–451.
- Glickstein, M., 2006. Thinking about the cerebellum. *Brain* 129, 288–290.
- Górecki, D.C., Łukasiuk, K., Szklarczyk, A., Kaczmarek, L., 1998. Kainate-evoked changes in dystrophin messenger RNA levels in the rat hippocampus. *Neuroscience* 84, 467–477.
- Hendriksen, J.G.M., Vles, J.S.H., 2006. Are males with Duchenne muscular dystrophy at risk for reading disabilities? *Pediatric Neurology* 34, 296–300.
- Herbster, A.N., Mintum, M.A., Nebes, R.D., Becker, J.T., 1997. Regional cerebral blood flow during word and nonword reading. *Human Brain Mapping* 5, 84–92.
- Hinton, V.J., De Vivo, D.C., Nereo, N.E., Goldstein, E., Stern, Y., 2000. Poor verbal working memory across intellectual level in boys with Duchenne dystrophy. *Neurology* 54, 2127–2132.
- Hinton, V.J., De Vivo, D.C., Nereo, N.E., Goldstein, E., Stern, Y., 2001. 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* 7, 45–54.
- Hinton, V.J., De Vivo, D.C., Fee, R., Goldstein, E., Stern, Y., 2004. Investigation of poor academic achievement in children with Duchenne muscular dystrophy. *Learning Disabilities Research and Practice* 19, 146–154.
- Hinton, V.J., Cyrulnik, S., Fee, R., 2005. Selective phonological processing deficits in children with Duchenne muscular dystrophy. In: *The 33rd Annual Meeting of the International Neuropsychological Society*, p. 114.
- Hinton, V.J., Fee, R.J., Goldstein, E.M., De Vivo, D.C., 2007. Verbal and memory skills in males with Duchenne muscular dystrophy. *Developmental Medicine and Child Neurology* 49, 123–128.
- Honey, G.D., Bullmore, E.T., Sharma, T., 2000. Prolonged reaction time to a verbal working memory task predicts increased power of posterior parietal cortical activation. *NeuroImage* 12, 495–503.
- Huard, J., Tremblay, J.P., 1992. Localization of dystrophin in the Purkinje cells of normal mice. *Neuroscience Letters* 137, 105–108.
- Humphreys, P., Kaufmann, W.E., Galaburda, A.M., 1990. Developmental dyslexia in women: neuropathological findings in three patients. *Annals of Neurology* 28, 727–738.
- Ito, M., 1993. Movement and thought: identical control mechanisms by the cerebellum. *Trends in Neurosciences* 16, 448–450.
- Ito, M., 1997. Cerebellar microcomplexes. In: Schmahmann, J.D. (Ed.), *The Cerebellum and Cognition*. Academic Press, San Diego, pp. 475–487.
- Ito, M., 2005. Bases and implications of learning in the cerebellum—adaptive control and internal model mechanism. *Progress in Brain Research* 148, 95–109.
- Ivry, R., 1997. Cerebellar timing systems. In: Schmahmann, J.D. (Ed.), *The Cerebellum and Cognition*. Academic Press, San Diego, pp. 555–573.
- Jonides, J., Schumacher, E.H., Smith, E.E., Lauber, E.J., Awh, E., Minoshima, S., et al., 1997. Verbal working memory load affects regional brain activation as measured by PET. *Journal of Cognitive Neuroscience* 9, 462–475.
- Jonides, J., Schumacher, E.H., Smith, E.E., Koeppe, R.A., Awh, E., Reuter-Lorenz, P.A., et al., 1998. The role of parietal cortex in verbal working memory. *The Journal of Neuroscience* 18, 5026–5034.
- Justus, T., Ravizza, S.M., Fiez, J.A., Ivry, R.B., 2005. Reduced phonological similarity effect in patients with damage to the cerebellum. *Brain and Language* 95, 304–318.
- Kamakura, K., Tadano, Y., Kawai, M., Ishiura, S., Nakamura, R., Miyamoto, K., et al., 1994. Dystrophin-related protein is found in the central nervous system of mice at various developmental stages, especially at the postsynaptic membrane. *Journal of Neuroscience Research* 37, 728–734.
- Kelly, R.M., Strick, P.L., 2003. Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. *The Journal of Neuroscience* 23, 8432–8444.
- Kim, T.W., Wu, K., Xu, J.L., Black, I.B., 1992. Detection of dystrophin in the postsynaptic density of rat brain and deficiency in a mouse model of Duchenne muscular dystrophy. *Proceedings of the National Academy of Sciences USA* 89, 11642–11644.
- Kim, T.W., Wu, K., Black, I.B., 1995. Deficiency of brain synaptic dystrophin in human Duchenne muscular dystrophy. *Annals of Neurology* 38, 446–449.
- Kitz, W.R., Tarver, S.G., 1989. Comparison of dyslexic and nondyslexic adults on decoding and phonemic awareness tasks. *Annals of Dyslexia* 39, 196–205.
- Knuessel, I., Mastrocola, M., Zuellig, R.A., Bornhauser, B., Schaub, M.C., Fritschy, J.-M., 1999. Altered synaptic clustering of GABA_A receptors in mice lacking dystrophin (*mdx* mice). *European Journal of Neuroscience* 11, 4457–4462.
- LaBerge, D., Samuels, S.J., 1974. Toward a theory of automatic information processing in reading. *Cognitive Psychology* 6, 293–323.
- Lederfein, D., Levy, Z., Augier, N., Mornet, D., Morris, G., Fuchs, O., et al., 1992. A 71-kilodalton protein is a major product of the Duchenne muscular dystrophy gene in brain and other nonmuscle tissue. *Proceedings of the National Academy of Sciences USA* 89, 5346–5350.
- Lee, J.S., Pfund, Z., Juhász, C., Behen, M.E., Muzik, O., Chugani, D.C., et al., 2002. Altered regional brain glucose metabolism in Duchenne muscular dystrophy: a PET study. *Muscle and Nerve* 26 (4), 506–512.
- Leibowitz, D., Dubowitz, V., 1981. Intellect and behavior in Duchenne muscular dystrophy. *Developmental Medicine and Child Neurology* 23, 577–590.
- Leiner, H.C., Leiner, A.L., Dow, R.S., 1986. Does the cerebellum contribute to mental skills? *Behavioral Neuroscience* 100, 443–454.
- Leiner, H.C., Leiner, A.L., Dow, R.S., 1991. The human cerebrocerebellar system: its computing, cognitive, and language skills. *Behavioral Brain Research* 44, 113–128.

- Leiner, H.C., Leiner, A.L., Dow, R.S., 1993. Cognitive and language functions of the human cerebellum. *Trends in Neurosciences* 16, 444–447.
- Leiner, H.C., Leiner, A.L., Dow, R.S., 1995. The underestimated cerebellum. *Human Brain Mapping* 2, 244–254.
- Leonard, C.M., Eckert, M.A., Lombardino, L.J., Oakland, T., Kranzler, J., Mohr, C.M., et al., 2001. Anatomical risk factors for phonological dyslexia. *Cerebral Cortex* 11, 148–157.
- Levisohn, L., Cronin-Golomb, A., Schmahmann, J.D., 2000. Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. *Brain* 123, 1041–1050.
- Lidov, H.G.W., Byers, T.J., Watkins, S.C., Kunkel, L.M., 1990. Localization of dystrophin to postsynaptic regions of central nervous system cortical neurons. *Nature* 348, 725–728.
- Lidov, H.G.W., Byers, T.J., Kunkel, L.M., 1993. The distribution of dystrophin in the murine central nervous system: an immunocytochemical study. *Neuroscience* 54, 167–187.
- Mechelli, A., Gorno-Tempini, M.L., Price, C.J., 2003. Neuroimaging studies of word and pseudoword reading: consistencies, inconsistencies, and limitations. *Journal of Cognitive Neuroscience* 15, 260–271.
- Mehler, M.F., Haas, K.Z., Kessler, J.A., Stanton, P.K., 1992. Enhanced sensitivity of hippocampal pyramidal neurons from *mdx* mice to hypoxia-induced loss of synaptic transmission. *Proceedings of the National Academy of Sciences USA* 89, 2461–2465.
- Middleton, F.A., Strick, P.L., 1994. Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science* 266, 458–461.
- Nicolson, R.I., Fawcett, A.J., 1999. Developmental dyslexia: the role of the cerebellum. *Dyslexia: An International Journal of Research and Practice* 5, 155–177.
- Nicolson, R.I., Fawcett, A.J., Dean, P., 2001. Developmental dyslexia: the cerebellar deficit hypothesis. *Trends in Neurosciences* 24, 508–511.
- Morris, G.E., Simmons, C., thi Man, N., 1995. Apo-dystrophins (Dp140 and Dp71) and dystrophin splicing isoforms in developing brain. *Biochemical and Biophysical Research Communications* 215, 361–367.
- Ogasawara, A., 1989. Downward shift in IQ in persons with Duchenne muscular dystrophy compared to those with spinal muscular atrophy. *American Journal on Mental Retardation* 93, 544–547.
- O'Hearn, E., Molliver, M.E., 2001. Organizational principles and microcircuitry of the cerebellum. *International Review of Psychiatry* 13, 232–246.
- Paulesu, E., Frith, C.D., Frackowiak, R.S.J., 1993. The neural correlates of the verbal component of working memory. *Nature* 362, 342–345.
- Paulesu, E., Frith, U., Snowling, M., Gallagher, A., Morton, J., Frackowiak, R.S.J., et al., 1996. Is developmental dyslexia a disconnection syndrome? Evidence from PET scanning. *Brain* 119, 143–157.
- Pollack, I.F., 1997. Posterior fossa syndrome. In: Schmahmann, J.D. (Ed.), *The Cerebellum and Cognition*. Academic Press, San Diego, CA, pp. 411–432.
- Pollack, I.F., 2001. Neurobehavioral abnormalities after posterior fossa surgery in children. *International Review of Psychiatry* 13, 302–312.
- Pollack, I.F., Polinko, P., Albright, A.L., Towbin, R., Fitz, C., 1995. Mutism and pseudobulbar symptoms after resection of posterior fossa tumors in children: incidence and pathophysiology. *Neurosurgery* 37, 885–893.
- Price, C.J., Wise, R.J.S., Watson, J.D.G., Patterson, K., Howard, D., Frackowiak, R.S.J., 1994. Brain activity during reading: the effects of exposure duration and task. *Brain* 117, 1255–1269.
- Rae, C., Griffin, J.L., Blair, D.H., Bothwell, J.H., Bubb, W.A., Maitland, A., et al., 2002a. Abnormalities in brain biochemistry associated with lack of dystrophin: studies of the *mdx* mouse. *Neuromuscular Disorders* 12, 121–129.
- Rae, C., Harasty, J.A., Dzendrowskyj, T.E., Talcott, J.B., Simpson, J.M., Blamire, A.M., et al., 2002b. Cerebellar morphology in developmental dyslexia. *Neuropsychologia* 40, 1285–1292.
- Ravizza, S.M., McCormick, C.A., Schlerf, J.E., Justus, T., Ivry, R.B., Fiez, J.A., 2006. Cerebellar damage produces selective deficits in verbal working memory. *Brain* 129, 306–320.
- Riva, D., Giorgi, C., 2000. The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. *Brain* 123, 1051–1061.
- Rosman, N.P., 1970. The cerebral defect and myopathy in Duchenne muscular dystrophy: a comparative clinicopathological study. *Neurology* 20, 329–335.
- Sarig, R., Mezger-Lallemand, V., Gitelman, I., Davis, C., Fuchs, O., Yaffe, D., et al., 1999. Targeted inactivation of Dp71, the major non-muscle product of the DMD gene: differential activity of the Dp71 promoter during development. *Human Molecular Genetics* 8, 1–10.
- Schmahmann, J.D., 1991. An emerging concept: the cerebellar contribution to higher function. *Archives of Neurology* 48, 1178–1187.
- Schmahmann, J.D., 1996. From movement to thought: anatomic substrates of the cerebellar contribution to cognitive processing. *Human Brain Mapping* 4, 174–198.
- Schmahmann, J.D., 2004. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *The Journal of Neuropsychiatry and Clinical Neurosciences* 16, 367–378.
- Schumacher, E.H., Lauber, E., Awh, E., Jonides, J., Smith, E.E., Koeppel, R.A., 1996. PET evidence for an amodal verbal working memory system. *NeuroImage* 3, 79–88.
- Sesay, A.K., Errington, M.L., Levita, L., Bliss, T.V.P., 1996. Spatial learning and hippocampal long-term potentiation are not impaired in *mdx* mice. *Neuroscience Letters* 211, 207–210.
- Shaywitz, S.E., 1998. Dyslexia. *The New England Journal of Medicine* 338, 307–312.
- Silveri, M.C., Leggio, M.C., Molinari, M., 1994. The cerebellum contributes to linguistic production: a case of agrammatic speech following a right cerebellar lesion. *Neurology* 44, 2047–2050.
- Silveri, M.C., Di Betta, A.M., Filippini, V., Leggio, M.G., Molinari, M., 1998. Verbal short-term store-rehearsal system and the cerebellum: evidence from a patient with a right cerebellar lesion. *Brain* 121, 2175–2187.
- Smith, E.E., Jonides, J., Koeppel, R.A., 1996. Dissociating verbal and spatial working memory using PET. *Cerebral Cortex* 6, 11–20.
- Sogos, V., Curto, M., Reali, C., Gremo, F., 2002. Developmentally regulated expression and localization of dystrophin and utrophin in the human fetal brain. *Mechanisms of Ageing and Development* 123, 455–462.
- Sollee, N.D., Latham, E.E., Kindlon, D.J., Bresnan, M.J., 1985. Neuropsychological impairment in Duchenne Muscular Dystrophy. *Journal of Clinical and Experimental Neuropsychology* 7, 486–496.
- Tallal, P., Miller, S., Fitch, R.H., 1993. Neurobiological basis of speech: a case for the preeminence of temporal processing. *Annals of the New York Academy of Sciences* 682, 27–47.
- Tian, M., Jacobson, C., Gee, S.H., Campbell, K.P., Carbonetto, S., Jucker, M., 1996. Dystroglycan in the cerebellum is a laminin alpha 2-chain binding protein at the glial-vascular interface and is expressed in Purkinje cells. *European Journal of Neuroscience* 8, 2739–2747.
- Tracey, I., Scott, R.B., Thompson, C.H., Dunn, J.F., Barnes, P.R.J., Styles, P., et al., 1995. Brain abnormalities in Duchenne muscular dystrophy: phosphorus-31 magnetic resonance spectroscopy and neuropsychological study. *Lancet* 345, 1260–1264.
- Tracey, I., Dunn, J.F., Radda, G.K., 1996. Brain metabolism is abnormal in the *mdx* model of Duchenne muscular dystrophy. *Brain* 119, 1039–1044.
- Uchino, M., Teramoto, H., Naoe, H., Miike, T., Yoshioka, K., Ando, M., 1994a. Dystrophin and dystrophin-related protein in the central nervous system of normal controls and Duchenne muscular dystrophy. *Acta Neuropathologica* 87, 129–134.
- Uchino, M., Teramoto, H., Naoe, H., Yoshioka, K., Miike, T., Ando, M., 1994b. Localisation and characterisation of dystrophin in the central nervous system of controls and patients with Duchenne muscular dystrophy. *Journal of Neurology, Neurosurgery, and Psychiatry* 57, 426–429.

- Vaillend, C., Rendon, A., Misslin, R., Ungerer, A., 1995. 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.
- Van Calenbergh, F., De Laar, A.V., Plets, C., Goffin, J., Casaer, P., 1995. Transient cerebellar mutism after posterior fossa surgery in children. *Neurosurgery* 37, 894–898.
- van Daal, V., van der Leij, A., 1999. Developmental dyslexia: related to specific or general deficits? *Annals of Dyslexia* 49, 71–104.
- van der Leij, A., van Daal, V.H.P., 1999. Automatization aspects of dyslexia: speed limitations in word identification, sensitivity to increasing task demands, and orthographic compensation. *Journal of Learning Disabilities* 32, 417–428.
- van Dongen, H.R., Catsman-Berrevoets, C.E., van Mourik, M., 1994. The syndrome of ‘cerebellar’ mutism and subsequent dysarthria. *Neurology* 44, 2040–2046.
- Whelan, T.B., 1987. Neuropsychological performance of children with Duchenne muscular dystrophy and spinal muscular atrophy. *Developmental Medicine and Child Neurology* 29, 212–220.
- Wicksell, R.K., Kihlgren, M., Melin, L., Eeg-Olofsson, O., 2004. Specific cognitive deficits are common in children with Duchenne muscular dystrophy. *Developmental Medicine and Child Neurology* 46, 154–159.
- Worden, D.K., Vignos, P.J., 1962. Intellectual function in childhood progressive muscular dystrophy. *Pediatrics* 29, 968–977.
- Xu, B., Grafman, J., Gaillard, W.D., Ishii, K., Vega-Bermudez, F., Pietrini, P., et al., 2001. Conjoint and extended neural networks for the computation of speech codes: the neural basis of selective impairment in reading words and pseudowords. *Cerebral Cortex* 11, 267–277.
- Zatorre, R.J., Meyer, E., Gjedde, A., Evans, A.C., 1996. PET studies of phonetic processing of speech: review, replication, and reanalysis. *Cerebral Cortex* 6, 21–30.