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Chapter 4

# Cerebellar involvement in autism and ADHD

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**Abstract**

The cerebellum has long been known for its importance in motor learning and coordination. However, increasing evidence supports a role for the cerebellum in cognition and emotion. Consistent with a role in cognitive functions, the cerebellum has emerged as one of the key brain regions affected in nonmotor disorders, including autism spectrum disorder and attention deficit-hyperactivity disorder. Here, we discuss behavioral, postmortem, genetic, and neuroimaging studies in humans in order to understand the cerebellar contributions to the pathogenesis of both disorders. We also review relevant animal model findings.

## INTRODUCTION

Early lesion studies by Rolando and Flourens (Flourens, 1822) in the 19th century revealed the importance of the cerebellum in motor action and movement coordination, leading Flourens to suggest the cerebellum as a seat for motor learning. Since then, recent findings have shown that the cerebellum expresses a range of different functions in addition to motor action, including working memory, emotion regulation, response timing, action planning, and attentional control (for review, see Ito, 2012). Interestingly, a disruption of these functions and dysfunctional cerebellar neuroanatomy has been shown in several neurodevelopmental disorders, including autism spectrum disorder (ASD) and attention deficit-hyperactivity disorder (ADHD) (Stoodley, 2016). Both disorders are highly comorbid with each other (Sinzig et al., 2009), overlap in genetic vulnerability (Ronald et al., 2008), and share similar patterns of social impairment and increased nonsocial behavior such as repetitive behavior (Nijmeijer et al., 2009).

ASD is a lifelong neurodevelopmental condition characterized by deficits in social communication and social interaction, as well as increased repetitive behaviors (American Psychiatric Association, 2013), all functions where cerebellar involvement has been well described (Stoodley and Schmahmann, 2009). While it is highly heritable, ASD is also very heterogeneous and current estimates suggest that up to 1000 risk genes carry de novo coding mutations (Willsey and State, 2015). Furthermore, autism-like behavior is highly present in a number of genetic syndromes including tuberous sclerosis (TSC), Rett syndrome (RTT), and fragile X syndrome (FXS) (Hampson and Blatt, 2015).

ADHD is one of the most common neurodevelopmental disorders (Faraone et al., 2003), defined by age-inappropriate inattention, impulsiveness, and hyperactivity (American Psychiatric Association, 2013), and is associated with deficits in attention, working memory, and timing (Rubia et al., 2014), all functions of cerebellar contribution (Ito, 2012). ADHD is also highly heterogeneous, but in contrast to ASD, its symptoms are treatable. However, when left untreated, it can lead to adverse consequences in adult life, including depression and drug dependency (Leo and Gainetdinov, 2013), underlining the importance of early diagnosis and treatment of ADHD.

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In this chapter, we aim to review recent literature from behavioral, postmortem, genetic, and neuroimaging studies in order to understand the underlying cerebellar involvement in the pathophysiology of both disorders, ASD and ADHD.

## MOTOR IMPAIRMENT IN ASD AND ADHD

### Motor impairment in autism spectrum disorder

One of the main characteristics of ASD is increased stereotypic and repetitive behavior, which can be expressed through hand flapping, rhythmic rocking, and twirling objects. In children with ASD, repetitive behavior occurs more often and in longer bouts than in typical developing (TD) children, but is maintained with age, making it a pervasive feature of ASD (for review, see Leekam et al., 2011). In addition, patients without a cerebellar vermis (vermal agenesis) or diffuse cerebellar volume reduction (cerebellar hypoplasia) have shown an increase in ASD symptoms, including stereotypic and repetitive behavior, and repetitive behavior has also been shown in TSC patients as well as in in ASD animal models (for review, see Hampson and Blatt, 2015).

In addition, children with ASD often display deficits in fine and gross motor skills, lack of coordination, and poor performance in postural stability. Up to 80% of children with autism show motor coordination deficits and these are highly correlated with autism severity and IQ (Becker and Stoodley, 2013). Moreover, motor impairments are among the earliest identifiable clinical abnormalities in ASD and have been argued to be included as core ASD features (Mosconi and Sweeney, 2015). Motor impairments in ASD have been extensively reviewed recently (Downey and Rapport, 2012; Becker and Stoodley, 2013; Mosconi and Sweeney, 2015). Here, we will focus specifically on postural impairments in ASD.

In a pioneering study, Kohen-Raz and colleagues (1992) demonstrated that children with ASD were significantly more unstable than control children when placed on a platform. Since then, several other studies have reported postural instability of ASD children when sensory inputs were available. In particular, larger displacement of the center of pressure (CoP) was reported in children with ASD compared to TD children (Molloy et al., 2003; Chang et al., 2010; Fournier et al., 2010, 2014; Bucci et al., 2013; Memari et al., 2013; Radonovich et al., 2013; Travers et al., 2013; Chen and Tsai, 2015; Smoot Reinert et al., 2015). Furthermore, velocity of the CoP was also found to be significantly larger in children with ASD compared to TD children (Gepner et al., 1995; Bucci et al., 2013; Memari et al., 2013; Radonovich et al., 2013; Fournier et al., 2014; Graham et al., 2015).

Other studies have reported similar changes in displacement and/or velocity of the CoP in the absence of visual inputs (Kohen-Raz et al., 1992; Gepner et al., 1995; Molloy et al., 2003; Minshew et al., 2004; Chen and Tsai, 2015; Graham et al., 2015). However, these results have not consistently been confirmed (Gepner and Mestre, 2002; Greffou et al., 2012; Travers et al., 2013; Smoot Reinert et al., 2015).

Similarly, several studies reported larger displacement of the CoP in children with ASD when compared to TD children during a visual motion condition, such as during looking at a video of visual stimuli, sway reference surround, or a virtual reality scene (Gepner et al., 1995; Gepner and Mestre, 2002; Minshew et al., 2004; Greffou et al., 2012; Price et al., 2012; Doumas et al., 2015).

Postural control has also been evaluated in quiet standing during altered somatosensory inputs, for instance on a sway reference surface, standing on foam, or wearing a vibrating device around the neck region (Kohen-Raz et al., 1992; Molloy et al., 2003; Minshew et al., 2004; Doumas et al., 2015; Morris et al., 2015; Smoot Reinert et al., 2015). All of these studies reported a significantly larger body sway displacement and/or faster sway velocity in subjects with ASD compared to their TD peers. Finally, a recent study showed that the instability observed in ASD children with respect to the TD group was even more significant when vision was unavailable or perturbed and when somesthesic information was misled (Goulème et al., 2017).

Taken together, the findings presented suggest that postural impairment found in ASD children might be due to cerebellar deficiencies, consistent with the hypothesis that abnormal cerebellar function may play an important role in ASD. As sensorimotor problems often emerge in infancy and well before other features of ASD (Mosconi and Sweeney, 2015), a better understanding of the pathophysiology underlying the sensorimotor impairments might provide important clues about the neural mechanisms contributing to social and cognitive features of ASD.

### Motor impairment in attention deficit-hyperactivity disorder

Similarly to ASD, ADHD is also associated with increased stereotyped and repetitive behavior, which seems to be highly heritable amongst siblings (Nijmeijer et al., 2009). Such stereotypic and repetitive behavior can be often noted as repeatedly knocking with the hand on an object or touching the face and is believed to assist the child to maintain an optimal state of arousal (Zentall and Zentall, 1983) or to reduce external distraction by channeling thoughts and actions into movements (Hutt, 1970), thus trying to direct attention.

Furthermore, individuals with ADHD display poor gross and fine motor control abilities (Pitcher et al., 2003). Motor problems occur in 30–50% of children with ADHD and were found to correlate with worse outcomes (Goulardins et al., 2017). Several studies have reported poor postural sway in ADHD children. In particular, poor postural sway has been reported when ADHD children were asked to stand on a stable platform with eyes open (Zang et al., 2002; Kooistra et al., 2009; Hassan and Azzam, 2012; Shorer et al., 2012; Bucci et al., 2014). CoP sway velocity was significantly higher in ADHD children under various testing conditions (e.g., standing with the eyes closed, standing on a foam pad) than in the control group (Zang et al., 2002; Wang et al., 2003). Such postural deficit was even more pronounced in more difficult standing conditions, such as when having the eyes closed and/or by manipulating the visual surround response (Buderath et al., 2009; Shum and Pang, 2009; Hassan and Azzam, 2012).

Taken together, balance control function seems to be compromised in the ADHD children most likely because it requires the capability to integrate inputs from various sensory systems (i.e., somatosensory, visual, vestibular) in order to maintain body equilibrium. Since sensorimotor integration and balance regulation rely on the cerebellum, these studies suggest that poor balance in children with ADHD could stem from suboptimal cerebellar function (Shum and Pang, 2009). A study by Hove et al. (2015) reported that higher sway was associated with larger cerebellar regional volume in posterior motor areas, providing additional support for cerebellar involvement in the pathophysiology of ADHD.

Methylphenidate is frequently used as medication to treat ADHD patients (Wilens et al., 2002) and successful treatment has been shown to reduce alterations in walking ability (Leitner et al., 2007), balance and stepping disorders (Buderath et al., 2009), improve motor performance (Flapper et al., 2016) and postural ability even while performing a demanding memory attention task (Jacobi-Polishook et al., 2009). Examining eventual treatment effects of methylphenidate on spatial and temporal CoP, a recent study demonstrated significant spectral power index, surface area, and mean CoP velocity reduction (Bucci et al., 2016). This suggests reduction of needed body energy to control body stability and thus posture.

Interestingly, such changes were more relevant for postural conditions in which children had to integrate sensory information (visual, vestibular, and somatosensory) in order to obtain postural stability. This was particularly noticeable when children were placed on an unstable platform, when somatosensory inputs were missing, or visual inputs were absent and/or disturbed by optokinetic stimulation, suggesting that cerebellar processing is needed for deficit compensation and efficient postural control.

This is consistent with the hypothesis put forward by Peterka (2002), that when sensory inputs are defective, other subsystems compensate for the impairment by playing a more important role, i.e., the sensory system is reweighted via cerebellar activity. Czerniak et al. (2013) and Ivanov et al. (2014) suggested that the improvement of cerebellar processing in children with ADHD after methylphenidate treatment might be the basis for their clinical recovery, which could in turn improve postural stability.

Together, sensorimotor problems including postural impairments are a common feature of ASD and ADHD, strongly suggesting cerebellar deficiencies in these conditions. Although important, behavioral studies provide only indirect measures of cerebellar activity. More direct evidence for cerebellar involvement in ASD comes from neuropathologic, neuroimaging, and preclinical studies in ASD that are discussed below.

## CEREBELLAR PATHOLOGY

### Cerebellar abnormalities in ASD postmortem studies

Histopathologic changes in the cerebellum have been frequently observed in postmortem studies of ASD brains (for review, see Becker and Stoodley, 2013; Hampson and Blatt, 2015). In particular, the loss of cerebellar Purkinje cells has been consistently described in ASD brains compared to controls. This is widely distributed throughout the cerebellar folia and mainly observed in lateral hemispheres, with fewer studies reporting Purkinje cell loss in the vermis. Because of the absence of glial hyperplasia in ASD cerebellum, it has been argued that loss of Purkinje cells likely occurs early on during development (Allen, 2005). Moreover, widespread dysplasia that has been observed in 62% of studied autistic brains suggests very early cerebellar developmental deficits in ASD (Wegiel et al., 2010). However, the preservation of basket and stellate cells in the presence of reduced Purkinje cell numbers in some ASD brains suggests that in some cases Purkinje cells die mostly after normal migration (Whitney et al., 2009).

In addition to cell loss, reduced packing density and a reduction in size of Purkinje cells have been reported in ASD brains (Fatemi et al., 2002; Palmen et al., 2004). A systematic sampling approach examined the regional alterations in Purkinje cell density in ASD brains (Skefos et al., 2014). Purkinje cell density was found to be most affected in crus I and II, an area heavily interconnected with the prefrontal cortex in both males and females, while Purkinje cell density was reduced in lobule X in affected males only, a region associated with

vestibular regulation and gaze coordination. Indeed, Purkinje cell density in lobule X was found to correlate with the patient's use of social eye contact (Skefos et al., 2014). These findings suggest that regional Purkinje cell pathology may contribute to selected clinical features of the ASD phenotype.

In addition, deep cerebellar nuclear cells to which Purkinje cells project have been shown to enlarge during childhood and reduce again during adolescence and adulthood in ASD (Bauman, 1991). Other cerebellar pathologies have also been described, including a reduction in the number of granule cells and cells in the cerebellar nuclei (Allen, 2005), as well as glial reactivity (Hampson and Blatt, 2015). It remains to be explored whether these are secondary changes caused by the developmental loss of Purkinje cells or independent pathologies.

## Structural neuroimaging in ASD

Studies investigating structural differences in the cerebellum in vivo using magnetic resonance imaging (MRI) have confirmed that abnormal cerebellar development and injury contribute to the development of ASD. Specifically, disruption of prenatal cerebellar development during specific developmental "sensitive periods" can lead to key autism features and in turn affect maturation of both cerebellar structures and connected cerebral regions (Wang et al., 2014).

Cerebellar injury in preterm infants has been associated with ASD symptom onset, with most severe deficits connected to vermal injury (Limperopoulos et al., 2007). Underdevelopment of the cerebellar vermis (vermal hypoplasia) has been detected in ASD patients as young as 2 years (Courchesne et al., 2011), as well as in adults diagnosed with infantile autism (Scott et al., 2009). Furthermore, meta-analyses discovered vermal hypoplasia to be restricted to the posterior vermis (lobules VI–VII) in later childhood (Courchesne et al., 2011), and cerebellar undergrowth, particularly in the vermis, has been associated with increased frontal lobe volume (Carper and Courchesne, 2000) and increased repetitive behavior in autistic children (Pierce and Courchesne, 2001).

In addition to posterior vermal hypoplasia, an anatomic likelihood estimate meta-analysis identified reduced volume of the right crus I and left VIIIb to be ASD-specific across developmental stages (Stoodley, 2014); differences in shape (Bruchhage et al., 2017), and reduced right crus I/II volume were increasingly pronounced with ASD symptom severity in children with autism (D'Mello et al., 2015), paralleling postmortem findings of reduced Purkinje cell density in lobules crus I and II (Skefos et al., 2014). In addition, tuberculosis patients with cerebellar lesions exhibited more severe ASD features than those without cerebellar lesions (Eluvathingal et al., 2006) and increased volume of lobules VI–VII has been shown in FXS with comorbid ASD, but not without the double diagnosis (Kaufmann et al., 2003).

These cerebellar gray matter differences are accompanied by white matter microstructural alterations of the middle (Shukla et al., 2010; Sivaswamy et al., 2010) and superior cerebellar peduncle (Catani et al., 2008; Sivaswamy et al., 2010), with the latter being associated with decreased motor functioning in children with ASD (Hanaie et al., 2013) and social impairment in adults with Asperger syndrome (Catani et al., 2008). However, the cerebellar gray and white matter differences found might be part of more global abnormal brain development patterns in ASD characterized by an initial white matter peak, quickly followed by an increase in gray matter (Courchesne et al., 2011). This is proposed to be the product of abnormal synaptogenesis and pruning (Bourgeron, 2015), thus affecting not only structure but possibly function of the brain regions involved.

Indeed, functional MRI (fMRI) studies indicate that neuropathologic differences in ASD are accompanied by abnormalities in cerebellar functioning and connected circuits. Investigating activation patterns during challenging activities for autistic participants, decreased activity within cerebrocerebellar motor networks during finger sequence tapping (Mostofsky et al., 2009), but increased activation of the cerebellothalamic circuitry during a visually guided saccade task (Takarae et al., 2008), were demonstrated in individuals with ASD when compared to TD controls.

Further exploring higher cognitive functioning, studies demonstrated reduced cerebrocerebellar connectivity related to verb generation (Verly et al., 2014), as well as reduced activation in crus I during facial and vocal stimuli processing (Wang et al., 2007) and executive functioning (Solomon et al., 2009). When participants were asked to stay in a restful position with their eyes open (resting-state fMRI) to compare their functional brain connectivity patterns, predominant cerebrocerebellar overconnectivity (Khan et al., 2015) and lowered functional connectivity in the left crus I and right lobule VI consistently across development (Long et al., 2016) were reported.

Together, these findings indicate abnormal local structural and functional abnormalities in ASD of the posterior lateral cerebellar gray matter, cerebrocerebellar functional connectivity, and white matter microstructure. However, neuroanatomic differences in ASD are not solely expressed in the cerebellum, but also in several cortical structures (Ecker et al., 2013).

By using its white matter pathways, the cerebellum communicates with the cerebral cortex via polysynaptic circuits and closed-loop connections (for review, see Ramnani, 2006). This enables separate regions of the cerebellum to be functionally connected to distinct cortical regions, forming a complex somatomotor and association

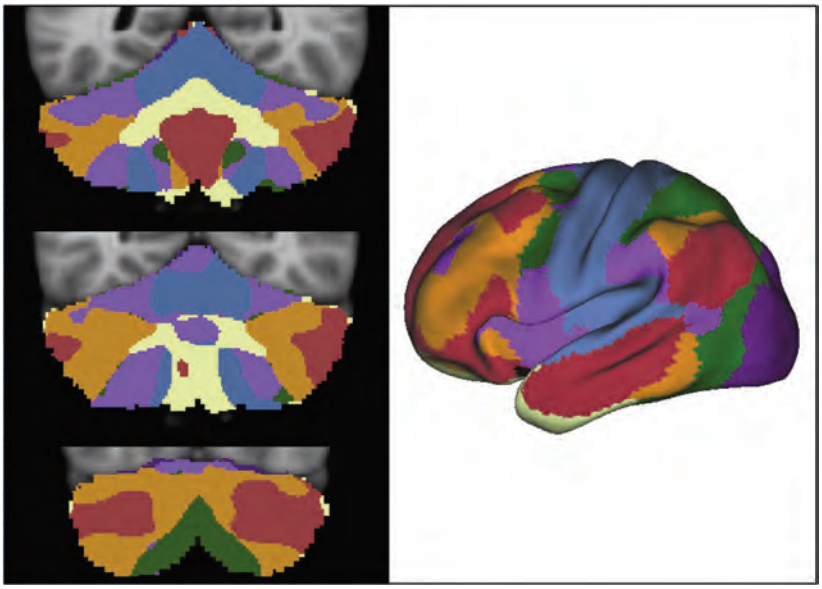

**Fig. 4.1.** Functionally coupled corticocerebellar networks. Multiple coronal sections are displayed through various levels of the cerebellum. The colored parcellation of the cerebellum (left) represents the most strongly functionally coupled networks of the cerebral cortex (right). Cerebellar regions in the anterior and posterior lobes (shown in blue) are strongly coupled to the cerebral somatomotor cortex. Most of the human cerebellum is linked to cerebral association networks, including an executive control network (shown in orange) and the default network (shown in red). These association networks each have multiple representations in the cerebellum (Buckner RL (2013). The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. Neuron 80: 807–815). See also Chapter 4. (C.J. Stoodley and J.D. Schmahmann (2018). Functional topography of the human cerebellum. In: M. Manto, T.A.G.M. Huisman (Eds.), The Cerebellum: From Embryology to Diagnostic Investigations, pp. 59–70.)

network topography (Buckner, 2013) (Fig. 4.1). Atypical cerebellar and cortical anatomy, connectivity, and function in ASD likely do not develop in isolation, but rather are the result of complex cerebrocerebellar interactions during development influenced by genetic and environmental factors. In order to build a comprehensive map of neural connections or a connectome of the ASD brain, several cohorts across the globe have agreed to share their data openly, such as in the Autism Brain Imaging Data Exchange initiative (Di Martino et al., 2016). These large-scale datasets are poised to make a valuable contribution to the field as they aim to disentangle and describe ASD heterogeneity and facilitate replications of previous findings across disciplines by aggregating resting-state functional connectivity and structural imaging data as well as phenotypic information.

## Cerebellar abnormalities in ADHD

Just as in ASD, structural cerebellar differences are one of the most consistent findings in ADHD (Valera et al., 2007). Specifically, reduced volume of the total cerebellum (Castellanos et al., 2002) and superior vermis (Mackie et al., 2007) persisting throughout ADHD development, right cerebellum (Durston, 2003), posterior vermis (e.g., Yang et al., 2008), posterior cerebellar lobules (e.g., Montes et al., 2011), with crus I and lobule IX specific to ADHD symptomatology (Stoodley, 2014), have been demonstrated.

However, in contrast to ASD, ADHD is not a lifelong disorder and can be treated. Methylphenidate is one of the most common pharmacologic treatments for ADHD and has been proposed to normalize differences in the ADHD brain (Schweren et al., 2013). Interestingly, treatment of ADHD with a single dose of methylphenidate leads to changes in cerebellar activation (Czerniak et al., 2013) and methylphenidate-treated children (chronic treatment) with ADHD did not show the same volume decrease in the posterior vermis as untreated ADHD children, suggesting a possible effect on development of the vermis (Bledsoe et al., 2009).

ADHD symptom severity has further been shown to increase with the degree of cerebellar vermis reduction (Castellanos et al., 2002; Bledsoe et al., 2011; Ivanov et al., 2014) as well as overall cerebellar volume (Rubia et al., 2009), and poorer clinical outcome has been associated with reduced posterior cerebellar volume (Mackie et al., 2007), underlining the central role of the cerebellum in ADHD symptomatology.

Furthermore, while some cortical but no cerebellar structural differences found in children with ADHD appear to normalize with age (Castellanos et al., 2002), it has been proposed that ADHD symptoms arise from dysfunction of noncortical structures such as the

cerebellum, with cortical compensations introducing remission to patients (Halperin and Schulz, 2006). This could be enabled through disturbances of white matter tracts connecting the cerebellum with the neocortex, as white matter volume reductions in the left cerebellum (Ashtari et al., 2005; van Ewijk et al., 2012) and microstructural differences in the middle cerebellar peduncle have been shown in ADHD (Ashtari et al., 2005; Bechtel et al., 2009).

Indeed, fMRI studies investigating deficits in ADHD have consistently demonstrated compensatory overactivation of the posterior cerebellum coupled with frontal lobe underactivation during attention tasks (Berquin et al., 1998; Mostofsky et al., 1998; Rubia et al., 2009; Hart et al., 2012; Cubillo et al., 2014) and decreased cerebellar activation in right crus I (Kobel et al., 2009; Wolf et al., 2009) and left lobule VI (Valera et al., 2005) while performing a working-memory task. Interestingly, this mirrors structural findings of reduced posterior cerebellar volume as well as abnormal frontal lobe anatomy and function in ADHD (Durston, 2003).

In addition, resting-state fMRI studies report abnormal cerebrocerebellar connectivity in ADHD patients (for review, see Konrad and Eickhoff, 2010) and ADHD treatment of methylphenidate was shown to mediate functional connectivity in cerebrocerebellar regions (Rubia et al., 2009; Czerniak et al., 2013). Thus, accumulating evidence has underlined the mediating effects of the cerebellum both locally and globally in ADHD in disease and treatment.

When taken together, the cerebellum plays an important role in both ASD and ADHD, demonstrating both overlapping differences in gray matter structure and abnormal functional activation influencing core symptomatology. Furthermore, these differences seem to also functionally affect broader cerebral networks even at a resting state. However, while most studies indicate modifiable cerebrocerebellar underconnectivity in ADHD, overconnectivity has been reported in studies on ASD and a meta-analysis contrasting both disorders has highlighted distinct neuroanatomic profiles for both (Stoodley, 2014). Thus, the resulting disrupted connectivity patterns could reflect a compensatory mechanism specific to the disorder and possibly developmental window.

## LESSONS FROM PRECLINICAL MODELS

### Cerebellar deficits in mouse models of ASD

Over the past several years and accelerated by recent genetic findings in ASD, an increasing number of rodent models of autism have been developed (for review, see Ellegood and Crawley, 2015; Hulbert and Jiang, 2017). In general, good animal models for ASD and other human disorders should possess three main attributes: (1) face validity, i.e., strong analogies to the endophenotypes of the human syndrome; (2) construct validity, i.e., the same underlying biologic dysfunction that causes the human disease; and (3) predictive value, i.e., an analogous response to treatments that prevent or reverse symptoms in the human disease (Silverman et al., 2010). ASD mouse models have been subjected to a comprehensive set of assays testing autism-relevant behaviors in rodents, including social behavior assays, ultrasonic vocalizations, and quantitative measures of spontaneous motor stereotypies and repetitive behavior, which have been summarized elsewhere (Ellegood and Crawley, 2015; Hulbert and Jiang, 2017). Interestingly, in addition to features relevant to the core symptoms of ASD, a number of the ASD mouse models also display specific cerebellar phenotypes (Becker and Stoodley, 2013). Mouse models for RTT display both cerebellar pathology and motor impairments. Cerebellar volume is significantly reduced in *Mecp2*-deficient mice (Belichenko et al., 2008), and the cell bodies of cerebellar granule cells are smaller and more densely packed (Chen et al., 2001).

Moreover, transcriptomic analysis revealed significant gene expression changes in the cerebellum of *MecP2* mutant mice (Ben-Shachar et al., 2009). Consistent with pathologic changes in the cerebellum, a number of RTT mouse models display motor impairments (Chen et al., 2001; Guy et al., 2001; Goffin et al., 2011). Similarly, *Fmr1*-deficient mice, a model for FXS, display cerebellar pathology and aberrant cerebellar function. Neuroimaging of these mice revealed anatomic changes only in the cerebellum, including decreased volume and neuronal loss in the deep cerebellar nuclei (Ellegood et al., 2010).

Purkinje cells in *Fmr1*-deficient mice were also found to exhibit abnormal morphology with longer dendritic spines (Koekkoek et al., 2005). Behaviorally, these mice are impaired in eye blink conditioning, a cerebellum-dependent form of associative learning, similar to FXS and ASD patients (Koekkoek et al., 2005; Tobia and Woodruff-Pak, 2009), and display significant cerebellum-dependent oromotor defects (fluid-licking deficits) that might be related to articulation deficits in humans with FXS (Roy et al., 2011).

Similar to the cerebellar phenotypes observed in *Fmr1*-deficient mice, mice lacking the ASD-implicated gene *Neuroligin-3* (*Nlgn3*) exhibit cerebellar-dependent motor incoordination and deficits in metabotropic glutamate receptor-dependent synaptic plasticity (Baudouin et al., 2012), suggestive of a shared cerebellar pathophysiology between syndromic and nonsyndromic forms of ASD. This hypothesis is consistent with more recent studies demonstrating alterations in motor coordination and eye blink conditioning as well as abnormal cerebellar

synaptic plasticity and pruning in the patDp/+ model of human 15q11-13 duplication, one of the most frequent genetic abnormalities in autism (Piochon et al., 2014). Defects in cerebellar associative sensory leaning were subsequently identified in a number of other syndromic and nonsyndromic mouse autism models, albeit to different extents (Kloth et al., 2015). It is worth noting that cerebellar deficits have also been identified in the valproate rat model, a nongenetic rodent model of autism (Reynolds et al., 2012; Becker and Stoodley, 2013).

MRI-based neuroanatomic phenotyping has been carried out on 26 mouse models related to ASD and identified the cerebellar cortex as one of the brain regions consistently found to be abnormal (Ellegood et al., 2015). The autism models were clustered in three groups based on neuroanatomic phenotypes. One of the groups including mouse mutants defective in *Fmr1* and *Shank3* displayed decreases in the cerebellar cortex, while increases in cerebellum were detected in another group including *Mecp2* mutants (Ellegood et al., 2015). It would be interesting to follow up on these studies to identify whether connectivity between the cerebellum and cognitive regions of the cerebral cortex might be impaired and, ultimately, compare the neuroanatomic changes in the mouse models to human neuroimaging findings.

Together, evidence from multiple mouse models of autism is consistent with findings in human studies and points to cerebellar defects in ASD. However, it has remained unclear whether cerebellar changes play a causal role in autism. Using the power of mouse genetics, several studies have begun to address this issue by asking whether cerebellar dysfunction by itself can generate abnormal autism-related behaviors in the mouse. To investigate the contribution of cerebellar TSC1 to autistic-like behavior in a mouse model, Tsai et al. (2012) created conditional mouse mutants with *Tsc1* deleted only in Purkinje cells ($Tsc1^{PC}$). These mice developed not only progressive ataxia but also autistic-like behaviors, including impaired social interaction, repetitive behavior, and abnormal ultrasonic vocalizations. Interestingly, $Tsc1^{PC}$ heterozygous mice, which more accurately mimic the human genetic condition, displayed no motor impairments but still social deficits, suggesting that motor deficits are not responsible for the abnormal social behavior. On a cellular level, *Tsc1*-deficient Purkinje cells exhibited abnormal spine density and reduced excitability (Tsai et al., 2012).

Similar findings were observed upon deletion of *Tsc2* specifically in Purkinje cells. Heterozygous $Tsc2^{PC}$ mutant mice displayed autistic-like behaviors, including increased repetitive behavior and social deficits, but no motor impairment (Reith et al., 2013). In both $Tsc1^{PC}$ and $Tsc2^{PC}$ mice, treatment with the mTOR inhibitor rapamycin prevented the behavioral deficits (Tsai et al., 2012; Reith et al., 2013). Based on this and other work, a placebo-controlled double-blind trial of mTOR inhibitors in patients with TSC and neurocognitive deficits has been carried out (ClinicalTrials.gov; NCT01289912) but results have not been reported yet.

In a different ASD mouse model, deletion of the *Pten* gene specifically in Purkinje cells resulted in abnormal Purkinje cell morphology and firing activity (Cupolillo et al., 2016). Moreover, these mice exhibited abnormal repetitive behavior and social deficits. Recently, Purkinje cell-specific deletion of the ASD-implicated *Shank2* gene has been reported in two mouse models. The results were inconsistent, with one study reporting abnormal social behavior and repetitive behavior only in the T-maze task (Peter et al., 2016), whereas another study reported no social deficits in mice with a Purkinje cell-specific *Shank2* deletion but reported that these mice displayed enhanced repetitive behavior in the hole board test as well as specific anxiety-related behaviors (Ha et al., 2016). These findings emphasize the importance of employing standardized and reproducible behavioral assays and warrant attention to the effects of genetic backgrounds of the mouse lines being studied.

Taken together, research in mouse models of autism strongly supports the hypothesis that cerebellar deficits play an important role in the pathogenesis of ASD. Future research in ever-advancing engineered rodent models will be key to further narrow down specific cerebellar regions, cell populations, and cerebrocerebellar circuitries, as well as sensitive developmental time periods that are critical to the involvement of the cerebellum in ASD. Importantly, the cerebellar macro- and microstructure is extremely well conserved between species (Apps and Hawkes, 2009), making findings in the mouse cerebellum highly relevant to humans.

## Cerebellar deficits in mouse models of ADHD

A number of rodent models of ADHD have been created, including genetic, toxic, and lesion models (for review, see Bari and Robbins, 2011; Leo and Gainetdinov, 2013; Homberg et al., 2016). However, as our understanding of the etiology of ADHD is limited, the construct validity of many of these models remains uncertain and a "gold standard" animal model has yet to be defined (Bari and Robbins, 2011). The inbred spontaneously hypertensive rat is one of the most widely studied rodent models of ADHD. In this model, motor impairments (vertical-pole task), loss of Purkinje cells, as well as astrocyte activation in the cerebellum have been described (Yun et al., 2014). Interestingly, these cerebellar deficits were rescued using treadmill exercise or treatment with methylphenidate. Recently, a new inbred mouse model of ADHD was

described, the high-active line, that exhibited abnormal motor performance on the Rotarod in addition to hyperactivity, as well as a trend towards increased c-Fos activation in the cerebellar granule cell layer (Majdak et al., 2016). One lesion model of ADHD is based on damaging the early postnatal cerebellum, resulting in hyperactivity (Ferguson, 1996).

Based on genetic findings in patients and available medication, most animal models that have been developed focused on candidate genes involved in the regulation of dopaminergic and serotonergic transmission (for review, see Leo and Gainetdinov, 2013). Cerebellar deficits have not been systematically evaluated in any of these models, although delays in some tests of complex motor skills, including righting reflex and bar holding, were described in the coloboma mutant mouse that harbors a deletion on chromosome 2 affecting 20 genes, including the synaptosomal-associated protein 25 (*SNAP-25*) gene (Heyser et al., 1995).

Thus, while cerebellar abnormalities are commonly described in ADHD patients, cerebellar deficits in rodent models of ADHD remain largely unexplored. Future studies in good preclinical ADHD models combining genetics, neuroimaging, and behavioral studies will be key to explore the potential functional link between cerebellar function and ADHD.

## CONCLUSIONS

Findings from human behavioral studies, neuropathology, neuroimaging and rodent models suggest a critical role for the cerebellum in the pathophysiology of ASD and ADHD. Early disruption of the cerebellum due to various genetic and/or environmental insults is likely to cause significant changes in the structure and function of closed-loop cerebrocerebellar circuitry, resulting in both sensorimotor and cognitive dysfunction, a concept described as developmental diaschisis (Wang et al., 2014). While symptoms of both disorders commonly emerge during childhood, brain abnormalities are often already established during early prenatal development and continue over a substantial period of time, resulting in long-lasting behavioral and physiologic deficits in both childhood and adulthood (Karmiloff-Smith, 1998). The cerebellum is one of the earliest brain regions to develop, continuing to grow until adulthood (Ito, 2012), making it a key brain region for identifying biomarkers in neurodevelopmental disorders such as ASD and ADHD.

In this chapter, we have reviewed shared genetic, behavioral and neuroanatomic profiles for both disorders. Specifically, both ASD and ADHD consistently show reduced right crus I volume and overlapping cerebrocerebellar dysfunction, impacting communication between brain structures. It is likely that, in both conditions, particular cerebellar circuits are affected during distinct developmental time windows, resulting in specific phenotypes in patients across disorders and perhaps even within subgroups of the same condition. However, the specific genetic and neural mechanisms as well as their acting time window during shared cerebellar and cortical development remain unclear.

Furthermore, in addition to shared features, both disorders display distinct symptomatic, neuroanatomic, and genetic profiles. It is important to acknowledge these differences as specific lobular differences might drive the stratification of both disorders.

In the future, it will be key to determine the (sub) regional specificity of cerebellar defects in ASD and ADHD, identify specific sensitive time periods, and test whether developmental phenotypes can be reversed or alleviated later on. In this context, a potential therapeutic role for cerebellar neuromodulation remains to be explored. Future studies involving longitudinal anatomic, physiologic, behavioral, and clinical testing of genetically stratified patient populations complemented with sophisticated rodent models are poised to provide important mechanistic and translational insights into ASD and ADHD and their therapy.

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