Published in final edited form as:
Semin Fetal Neonatal Med. 2016 October ; 21(5): 356–364. doi:10.1016/j.siny.2016.04.010.

Structure–function relationships in the developing cerebellum: evidence from early-life cerebellar injury and neurodevelopmental disorders

Catherine J. Stoodley[a,*] and **Catherine Limperopoulos**[b]

[a]Department of Psychology and Center for Behavioral Neuroscience, American University, Washington DC, USA

[b]Diagnostic Imaging and Radiology, Children's National Health Systems, Washington DC, USA

SUMMARY

The increasing appreciation of the role of the cerebellum in motor and non-motor functions is crucial to understanding the outcomes of acquired cerebellar injury and developmental lesions in high-risk fetal and neonatal populations, children with cerebellar damage (e.g. posterior fossa tumors), and neurodevelopmental disorders (e.g. autism). We review available data regarding the relationship between the topography of cerebellar injury or abnormality and functional outcomes. We report emerging structure–function relationships with specific symptoms: cerebellar regions that interconnect with sensorimotor cortices are associated with motor impairments when damaged; disruption to posterolateral cerebellar regions that form circuits with association cortices impact long-term cognitive outcomes; and midline posterior vermal damage is associated with behavioral dysregulation and an autism-like phenotype. We also explore the impact of age and the potential role for critical periods on cerebellar structure and child function. These findings suggest that the cerebellum plays a critical role in motor, cognitive, and social–behavioral development, possibly via modulatory effects on the developing cerebral cortex.

Keywords

Cerebellum; Fetal; Preterm; Autism; Developmental diaschisis; Cognition

1. Introduction

There is an increasing appreciation of the importance of the contributions of the cerebellum to the developing brain. Emerging evidence from fetal, neonatal and pediatric populations

*Corresponding author. Address: Department of Psychology and Center for Behavioral Neuroscience, American University, 4400 Massachusetts Ave. NW, Washington, DC 20016, USA. Tel.: +1 (202) 885-1785; fax: +1 (202) 885-1023. stoodley@american.edu (C.J. Stoodley).

Conflict of interest statement
None declared.

supports the existence of a regional functional topography of the cerebellum, and provides testable hypotheses for clarifying the role of the developing cerebellum in motor, cognitive, and social/behavioral development. Here, we review data from very preterm infants following early-life cerebellar injury, infants with cerebellar malformations, older children with cerebellar injury (e.g. pediatric posterior fossa tumors), and neurodevelopmental disorders to clarify the potential importance of cerebellar structure–function relationships in the developing brain.

Cerebellar development follows a highly orchestrated series of developmental processes. Between 20 and 40 weeks of gestation, the cerebellum undergoes an exuberant period of growth, during which time the rapid growth of the cerebellum is unparalleled by that of any other cerebral structure [1,2]. This developmental pattern suggests strongly the presence of a critical period for cerebellar development, which in turn is central to both the cerebellum's vulnerability and the developmental repercussions of injury, which are capable of disrupting this highly regulated, programmed developmental course.

At the systems level, disrupted or aberrant cerebellar growth could have significant effects on the developing cerebral cortex [3]. As described below, the cerebellum is richly interconnected with regions of the cerebral cortex supporting movement, cognition, and affective regulation [4]. The cerebellum is thought to modulate these cerebro-cerebellar circuits to support the optimization of behavior, with a particular role in procedural learning and skill acquisition. It is therefore possible that during early development – a period of intense skill acquisition – the cerebellum serves to optimize both structure and function in the cerebral cortex (see [5] for discussion). We argue that early disruption of the cerebellum – be it due to preterm birth, prenatal cerebellar developmental lesions (i.e. malformations), cerebellar posterior fossa tumors in early childhood, or developmental disorders – could exert significant, long-lasting, and wide-ranging changes in the structure and function of cerebro-cerebellar systems, with long-term effects on behavior.

2. Cerebellar anatomy and functional topography

The cerebellum is located in the posterior fossa and comprises ~10% of the volume of the brain. It is connected to the brainstem via the cerebellar peduncles: the superior peduncle contains fiber tracts carrying information from the cerebellum to the cerebral cortex via the thalamus; the middle peduncle consists of fiber tracts which travel from the cerebral cortex to the cerebellum via the pontine nuclei; and the inferior peduncle carries both afferent and efferent fiber tracts connecting the cerebellum with the vestibular system and spinal cord, as well as incoming projections to the cerebellum from the inferior olive. The cerebellum itself consists of two cortex-covered hemispheres connected by the midline vermis, with a core of white matter in which the deep cerebellar nuclei are embedded. The cerebellar cortex is divided into ten lobules (I–X based on nomenclature detailed in [6]; see Fig. 1): lobules I–V make up the anterior lobe of the cerebellum; lobules VI–IX the posterior lobe; and lobule X the flocculonodular lobe. The projections from the cerebellar cortex to the deep nuclei are organized such that the midline vermis projects to the most medial deep nuclei, the fastigial nuclei; the medial, paravermal regions of the hemispheres project to the interpositus nuclei (which consist of the globose and emboliform nuclei), and the cortex in the lateral hemispheres projects to the dentate nuclei. The deep nuclei then send projections to the cerebral cortex via the thalamus and to the spinal cord via brainstem nuclei. In this way, the cerebellum forms closed-loop circuits with the spinal cord and cerebral cortex: for example, the cerebellum projects via the thalamus to sensorimotor cortices, and these regions project back to the cerebellum via the pons. The organization of these anatomical connections within the cerebellum form the basis of cerebellar functional topography, whereby different regions of the cerebellum process information routing from different regions of the cerebral cortex and the spinal cord.

Functional subregions of the human cerebellum have been established based on the aforementioned anatomical connections and more recent neuroimaging investigations (for more detailed review, see [4]). Briefly, the anterior lobe (extending into medial lobule VI) and lobule VIII contain sensorimotor homunculi of the body, evident both in electrophysiological studies in animals and in neuroimaging studies in humans [7]. These regions are active during motor performance [8] and show resting-state functional connectivity with sensorimotor cortices [9]. By contrast, the majority of the cerebellar posterior lobe interconnects with association cortices, including the prefrontal cortex (for review, see [4]), and are engaged during a range of cognitive tasks [8]. Cerebellar regions interconnected with limbic networks are thought to involve the posterior vermis, including parts of lobule IX.

These broad functional subregions of the cerebellum provide a framework for understanding the role of the developing cerebellum in movement, cognition, and behavior. Consistent with cerebral cortical developmental trajectories, sensorimotor regions of the cerebellum mature earlier than posterolateral cerebellar regions, which interconnect with later-maturing regions of the cerebral cortex [10]. The similar developmental trajectories within cerebro-cerebellar loops suggest that early cerebellar injury could have a significant impact on the developing cerebral cortex, in a way that may depend on the location of injury within the cerebellum and on the age at which the lesion occurred.

3. Contribution of the cerebellum to the developing brain: optimization of structure and function?

The cerebellum is thought to support implicit/procedural skill learning via the formation and error-driven modification of internal models of behavior. For higher-level motor, cognitive and behavioral tasks, the cerebellum provides this modulatory function via cerebro-cerebellar loops with sensorimotor, association, and limbic regions of the cerebral cortex. In this way, the cerebellum is well positioned to drive the optimization of cerebral cortical circuits as skills are acquired and made fluent throughout childhood and into adolescence. In a recent review, Wang and colleagues argued that early cerebellar damage may lead to significant deleterious effects on the regions of the cerebral cortex to which the cerebellum projects, a concept termed “developmental diaschisis” [3]. Drawing from the evidence in preterm infants, newborns diagnosed with developmental cerebellar lesions, children with cerebellar lesions, and in children with neurodevelopmental disorders, there is growing evidence to support a crucial role of the cerebellum for the optimization of both structure and function in the developing cerebral cortex [3,5,11,12].

Indeed, our own work examining whether a specific regional pattern of cerebral growth restriction could be defined after isolated cerebellar injury in our cohort of ex-premature infants demonstrated significant long-term decreases in regional cerebral cortical volume. Specifically, when compared to the cerebral hemisphere ipsilateral to the injured cerebellar hemisphere, we described significant volume reductions of both gray and white matter of the contralateral dorsolateral prefrontal, premotor, sensorimotor, and inferior occipital regions of the cerebral hemisphere [12]. Conversely, children with bilateral cerebellar injury showed symmetrical reductions in cerebral hemispheric volumes. Factors associated with this impaired cerebral growth included lower gestational age, severity of the initial cerebellar injury, and age at magnetic resonance imaging (MRI). Our data suggest that early-life cerebellar injury in extremely premature infants results in disruption of selective supratentorial neural systems that are critical for normal development. Similarly, in a case–control study of infants diagnosed with isolated cerebellar malformations in the fetal and/or postnatal period, we reported that cerebellar malformations were associated with impaired regional cerebral growth in the parieto-occiptal, subgenual and midtemporal cortical gray and white matter, as well the deep gray nuclei, suggesting deactivation of principal cerebello-cerebral pathways [13]. When we further examined the relationship between these remote regional impairments of cerebral volumetric growth and domain-specific functional deficits in ex-preterm children with cerebellar hemorrhagic injury [14], we found that each unit increase in the corresponding regional cerebral volume was associated with lower odds of abnormal outcome score, adjusted for age at MRI and contralateral cerebellar volume. This was the first report linking secondary impairment of remote cerebral cortical growth and functional disabilities in survivors of prematurity-related cerebellar injury.

Early cerebellar damage can also lead to structural alterations beyond the fetal and neonatal period. In children with posterior fossa tumors, whereas it has been established that radiation therapy may lead to white matter damage (which in turn is associated with poorer cognitive function [15]), more specific neuroanatomical effects of pediatric cerebellar tumor resection have been examined using tractography [15,16]. Law et al. [15] report reduced fractional anisotropy and increased mean diffusivity, both indicators of reduced integrity of cerebello-thalamic-frontal white matter tracts. These white matter metrics for the right cerebellar–left frontal tract were associated with poorer working memory performance, especially in patients that had received radiation therapy [15]. Supporting the data from preterm populations, there were indications that these were long-term effects – longer time since diagnosis was associated with poorer integrity of the right cerebello-thalamic-frontal tract [15]. Soelva and colleagues [16] performed fronto-cerebellar tractography in children with cerebellar mutism, and reported reduced volumes in the superior cerebellar peduncles and midline cerebellum in the group with mutism compared with cerebellar patients without mutism and healthy controls. Children without mutism had reduced volumes relative to the control group in vermal and paravermal white matter. Both patient groups showed reduced fractional anisotropy in frontal white matter and the superior cerebellar peduncles relative to controls [16]. These changes in white matter tracts connecting the cerebellum with frontal cortices provide a potential neuroanatomical substrate for long-range effects on the developing cerebral cortex following cerebellar tumor resection.

In summary, evidence from structural neuroimaging studies indicates that early cerebellar injury resulting from preterm birth or tumor resection may impact adversely the development of both cerebro-cerebellar white matter pathways and the cortical gray matter volume of distal regions of the cerebral cortex to which the cerebellum projects. These data support the developmental diaschisis model proposed by Wang and colleagues [3]. Based on this model, and the functional topography of the cerebellum, we predict that these structural changes have specific functional consequences on behavior, depending on the pattern of regional damage within the cerebellum.

4. Structure–function relationships: motor performance

The classic cerebellar motor syndrome, consisting of ataxic and dysmetric movement and dysarthric speech, is evident in children following early cerebellar damage [17]. One would predict that damage to the cerebellum resulting in such motor deficits would involve sensorimotor regions of the cerebellum, with individual differences reflecting particular sites of damage (e.g. lesion-symptom mapping in adults has shown that dysarthria is more likely after damage to medial lobule VI [18]). This anatomical specificity might explain why, in a study of 23 children with cerebellar tumors, there was evidence of the cerebellar motor syndrome in only about half of the patients [19] – the other children may have had lesions outside the sensorimotor cerebellum.

More generally, there is also evidence for “cerebellar” motor deficits in children with neurodevelopmental disorders that are known to involve the cerebellum, though these deficits are subtle compared with those seen in clinical cerebellar populations. Delayed motor milestones, differences in postural stability, poorer fine and gross motor skills, and eye movement abnormalities have been associated with both autism and developmental dyslexia (see [20] for autism review; [21] for dyslexia review). Attention deficit hyperactivity disorder (ADHD) has also been associated with impaired fine and gross motor skills (see [22] for review). Similarly, motor impairments have been well described in survivors of extreme preterm birth following cerebellar parenchymal injury. Overall, the severity of cerebellar injury is associated with worsening and wide-ranging neuromotor disabilities including cerebral palsy, movement disorders and delayed motor skill acquisition [23–25].

Whereas detailed structure–function relationships between motor skills and specific cerebellar substrates are lacking in infants born prematurely, in children with cerebellar malformations and with neurodevelopmental disorders, clearer associations between site of damage and motor outcome have emerged from pediatric cerebellar lesion studies. One form of speech motor impairment following cerebellar damage in childhood is cerebellar mutism with subsequent dysarthria, which is one characteristic of posterior fossa syndrome (PFS) [26]. The other features of PFS – emotional and behavioral changes – are discussed below. The anatomical signature of PFS has yet to be definitively established, but there is evidence that a higher risk is associated with large, posterior midline lesions that involve surgical incision of the vermis [27– 29], damage to the dentate nucleus [27,30,31], and reduced integrity of white matter in cerebello-thalamic-cortical tracts [16,29]. Mutism has also been linked to right cerebellar hemisphere involvement [29] as well as extra-cerebellar damage, including brainstem invasion of the tumor [32]. Dysarthria following cerebellar surgery in both children and adults is associated with damage to medial lobule VI, although injury to this region in pediatric populations is not as frequent as the midline posterior lesions that are associated with PFS [33].

In adults, balance difficulties are generally associated with lesions involving medial regions of the cerebellum and the vestibulo-cerebellar system. Konczak and colleagues [34] report that loss of postural control (in the absence of visual input) was associated with damage to the fastigial nucleus (to which medial regions project) in children and adolescents following removal of a cerebellar tumor. Balance abnormalities were more strongly related to damage to the fastigial nuclei than to adjuvant radiotherapy treatment [34], suggesting that this is a robust anatomical predictor of impaired balance. In neurodevelopmental populations, postural stability has been used as a test of cerebellar function, although the deep nuclei are rarely, if ever, the focus of investigation in these populations. Some children with developmental dyslexia do show evidence of increased postural sway (for review, see [21]), although dyslexia is more often associated with reduced gray matter in regions of lobule VI that do not contribute to sensorimotor circuits [35]. Children with autism are also reported to have poorer balance and postural stability than age-matched typically developing children (for review, see [20]), though these difficulties have not been associated with specific neural correlates.

Problems with control of arm movement after cerebellar damage in adults and children are often evident in the form of dysmetria and intention tremor during reaching movements, reflecting a loss of cerebellar co-ordination of online movements. In pediatric populations, deficits have been reported on speeded motor tasks, such as pegboard tasks, and hand speed has been related to poorer cognitive outcomes [28]. In children who were >3 years post removal of cerebellar tumors, upper limb ataxia was associated with damage to the deep cerebellar nuclei, in this case the interpositus nucleus (which receives projections from medial cerebellar regions responsible for motor control) and the dorsal (motor-related) part of the dentate nucleus [34].

It is clear that the cerebellar motor syndrome in pediatric populations seems to be the outcome of damage involving cerebellar circuits supporting sensorimotor behaviors, including the motor-related deep nuclei. Disruption to these motor circuits early in development could have knock-on effects on the sensorimotor cortical areas that receive cerebellar projections. For example, gross motor scores were associated with the volume of sensorimotor cortices in preterm infants with early cerebellar damage [14]. It is less likely for such deficits to be associated with damage to lateral cerebellar regions that interconnect with prefrontal and parietal association areas of the cerebral cortex, or to the ventral dentate nucleus, which is involved in these non-motor circuits.

5. Structure–function relationships: cognitive performance

Schmahmann and Sherman [36] first described the cerebellar cognitive affective syndrome (CCAS) in adult cerebellar patients. The CCAS is a constellation of symptoms characterized by “dysmetria of thought” [37], and includes difficulties in language, visual–spatial performance, working memory, executive function and affective regulation. From the first investigation of the CCAS, these symptoms were associated with damage to the posterolateral cerebellum, rather than to the cerebellar regions that have been strongly associated with motor dysfunction [38]. In the pediatric population, cognitive deficits have been reported in a range of studies of children following cerebellar tumor resection, including effects on IQ, language, attention, verbal and visual memory, and executive functions [28,39–42] (see [43] for review). Poorer cognitive outcomes are sometimes associated with radiation therapy [44], but have also been reported in patients who have not received adjuvant radiation treatment [19]. Cerebellar hemorrhagic injury in preterm infants is also associated with a significantly higher prevalence of global developmental disabilities and cognitive deficits compared to premature age-matched control toddlers [23]. Available evidence suggests that in the years following very preterm birth, cerebellar volume (in the absence of direct cerebellar injury) is positively correlated with cognition [45,46]. Finally, cerebellar structural and functional differences have been associated with neurodevelopmental disorders, which present with a range of cognitive deficits, including developmental dyslexia (reading disorder), autism, and ADHD [11,35]. Aarsen et al. [19] reported that, in their sample of 23 children with cerebellar tumors, one child with a midline/ right hemisphere tumor had a diagnosis of Asperger’s syndrome; one with a midline vermal tumor had an ADHD diagnosis; and a child with a right hemisphere tumor had phonological agraphia. Taken together, these findings support a strong association between cerebellar abnormalities and symptoms (and even diagnosis) of these developmental disorders. Specific associations between cerebellar subregions and particular cognitive deficits in these populations are discussed below.

Although it can be argued that cognitive deficits in children with cerebellar lesions may be contaminated by poor motor performance (see [17] for review) or predicted by poor motor performance (e.g. pegboard [28]), neuroimaging studies (see [47] for review) and clinical studies in which motoric aspects of performance are controlled for [48] suggest that the posterolateral cerebellum is involved in various cognitive measures. In one pediatric tumor study, only about half of the children showed cerebellar motor deficits [19], and motor difficulties often dissociate from cognitive effects following cerebellar damage [39]. It is also possible to see a dissociation between motor deficits with preserved cognition and cognitive deficits without ataxia in cerebellar stroke patients (see case studies in [4]).

Here we focus on emerging and early structure–function relationships regarding cognitive deficits in fetal–neonatal cerebellar lesions, pediatric cerebellar damage (tumor patients and preterm populations), and neurodevelopmental disorders. Most studies of pediatric tumor patients to date have not systematically examined structure–function relationships in fine detail; the majority of studies that assess this issue tend to group cerebellar patients more broadly into hemisphere and vermal groups (right hemisphere, left hemisphere, vermis [19,41]). Whereas this is a crucial first step, these studies did not differentiate the regions of the cerebellum that we now know to be involved in cognitive functions (e.g. posterior lateral hemispheres including lobules Crus I and Crus II) from the regions involved in sensorimotor control (e.g. lobules I–V, lobule VIII). In the future, this level of analysis should parse the cerebellar regions that, when damaged, are more likely to produce poorer language, working memory, visual–spatial and executive functions, based on their anatomical connections and involvement in these functions. In ex-preterm infants, regional lateral cerebellar volume reductions have been associated with decreased executive and visuo-spatial function [49]. In a recent paper, Ranger et al. [50] used constrained principal component analysis to identify cerebellar subregional volumes that were maximally related to cognitive outcomes. The authors reported that decreased verbal comprehension, visual perception and perceptual reasoning were associated with smaller volumes in lobules IV–VI, VIIB, Crus I, Crus II, VIIIA, VIIIB, the vermis and flocculus in ex-preterm infants at age 7 years. Conversely, working memory was only related to decreased volumes of Crus I, Crus II, and VIIB, indicating some degree of anatomical specificity. These data suggest that local volume loss in the posterior cerebellum is linked to specific cognitive impairments in ex-preterm survivors. Finally, a meta-analysis of the cerebellar gray matter reductions reported in dyslexia, autism, and ADHD has shown that non-overlapping cerebellar regions are affected in each disorder [35]. We explore these specific structure–function relationships for different cognitive measures in more detail below.

Language difficulties following cerebellar damage in pediatric populations include the aforementioned cerebellar mutism as well as anomia, difficulties with semantic and pragmatic language, and agrammatism [19] (see [51] for review). Perhaps the best-established relationship between location of damage and outcome in adult cerebellar patients is that right posterolateral cerebellar damage is associated with a range of language deficits [51]. The right posterolateral cerebellum interconnects with contralateral language regions of the cerebral cortex, providing a viable anatomical substrate for such deficits. Consistent with this, several studies have reported a variety of language deficits following right cerebellar damage in children [19,39–41]. Further, some children with PFS have agrammatical language after the mutism has resolved [41], suggesting that there is a linguistic as well as a motoric component to PFS. Riva and Giorgi [41] propose that agrammatical language in the context of PFS is associated with lesions that involve the right cerebellar hemisphere as well as the midline posterior vermis. Consistent with the link between the right cerebellum and broad language performance, it has been reported that children with developmental dyslexia have reduced rightward asymmetry of the cerebellum, and a region in right cerebellar lobule VI was shown to be the best predictor of dyslexia in adults (see [21] for review). Language impairment in autism has also been associated with right cerebellar dysfunction: reduced functional connectivity has been reported between right cerebellar Crus I and supratentorial language regions in language-impaired children in autism (discussed in [5]). In preterm populations, our work has shown that early cerebellar damage that specifically affected premotor and mid-temporal cerebral cortical volumes was associated with cognitive and expressive language scores [14]. Moreover, our studies in young children with cerebellar malformations diagnosed in the fetal and early postnatal period have reported that decreased volume in the right lateral cerebellum is associated with expressive language deficits [52]. These findings all suggest that damage or developmental abnormalities in the right cerebellum are related to later language deficits in a location-specific manner.

That said, others have not found signs of verb generation deficits or aphasia in children and adolescents following cerebellar lesions [53,54], even when right hemisphere lesions were examined. In the future, finer-grained analyses of the localization of damage within the cerebellum may aid to clarify these findings. Recent work in healthy adult populations suggests that different cerebellar regions are engaged during language tasks, depending on task demands [51].

Several studies have noted impaired performance on a range of visual–spatial measures following cerebellar lesions in children, including the block design from Wechsler Intelligence Scale for Children, copying and recall of Rey–Osterrieth complex figure, and mental rotation tasks [19,39,40]. Consistent with the contralateral connections between the cerebellum and the cerebral cortex, some studies report that children with left cerebellar lesions are more likely to show deficits on visual–spatial tasks [40,41], suggesting a potential association between lateralization of damage and visual–spatial performance.

Whereas deficits in executive functions (including working memory, digit span, Wisconsin Card Sorting Task, Stroop task) have been reported in pediatric cerebellar patients, not all studies reveal deficits in executive functions following cerebellar tumor removal (e.g. [34] found no verbal working memory deficit); differences between studies may reflect variations in the localization of cerebellar lesions. Supporting this, Kirschen and colleagues [42] investigated the neural substrates of verbal working memory in children after resection of pilocytic astrocytomas, finding that specific deficits were associated with damage to particular regions of the cerebellum. Although visual digit span was unaffected in the cerebellar patients, verbal working memory impairments were evident in reduced auditory digit span. Damage to left hemispheric lobule VIII was associated with reduced auditory digit span, whereas reduced effects of articulatory suppression were associated with damage to the vermis and bilateral lobules IV/V (which are associated with articulation). These authors suggest that left hemispheric lobule VIII is involved in encoding auditory stimuli into the phonological store during working memory tasks [42]. In a smaller study, performance on the Wisconsin Card Sorting Task was examined in four children with cerebellar hemisphere tumors; these children showed deficits using feedback to establish new rules on the task [55]. The authors suggest that the relationship between the cerebellar hemispheres and prefrontal cortex could mediate this finding. Among the neurodevelopmental disorders with established links to cerebellar dysfunction, executive function deficits are most characteristic of ADHD. A recent study indicated that ADHD participants with impaired working memory show hypoactivation in the anterior cerebellum [56] and that bilateral regions of Crus I were hypoactive in ADHD participants during a working memory paradigm [57]. Gray matter reductions have been reported in multiple cerebellar regions in ADHD [35], including those that are associated with dorsal and ventral attention networks, and reduced functional connectivity has been found in cerebellar regions involved in fronto-parietal networks in children with ADHD [58]. These findings implicate impaired cerebro-cerebellar circuits in ADHD, and notably in cerebellar regions that support performance on attention and executive function tasks.

6. Structure–function relationships: adaptive behaviors, autism spectrum, and neuropsychiatric disorders

Impaired adaptive behaviors [59] and a range of affective disturbances [39] have been reported in children following cerebellar tumor removal and in very preterm infants following cerebellar parenchymal injury [23]. The original description of the CCAS [36] included affective dysregulation in cerebellar patients; in children, this has also been reported as part of the CCAS [39], and emotional lability is also a defining characteristic of posterior fossa syndrome [26]. Recently, Schmahmann and colleagues have expanded their characterization of the neuropsychiatric consequences of cerebellar damage, describing dysregulation in five main domains: control of attention, control of emotion, social skill set, psychosis spectrum disorders, and autism spectrum disorders [60]. In each of these categories, the concept of dysmetria is applied to describe symptoms consistent with the idea of “overshoot” and “undershoot” – e.g. pathological laughter as an example of overshoot, and flat affect as an example of undershoot. The inclusion of autism spectrum disorder is of particular importance given the long-standing support for both structural and functional abnormalities in the cerebellum in autism (see [20] for review).

In terms of specific structure–function relationships, damage to the posterior vermis is most often associated with behavioral dysregulation. Vermal lesions can lead to both flattened affect and disinhibited behavior [19,39], suggesting difficulty with modulation of affect. Aarsen et al. [19] reported that 15 of 19 children with midline or vermal tumors had problems with affect regulation, whereas none of the four children with cerebellar hemisphere tumors had difficulties regulating affect. Richter et al. [61] found that children with chronic cerebellar lesions showed both positive (thoughtful behavior, decreased aggression) and negative (anxiety, depression, aggression) behavioral symptoms. In line with the association between the vermis and behavioral regulation, volumetric reductions in the posterior vermis have been reported in both ADHD [62] and autism [20].

Consistent with Schmahmann’s description of the psychiatric effects of cerebellar damage [60], >50% of surviving preterm infants with cerebellar parenchymal injury demonstrate important functional limitations in socialization skills. Moreover, significant differences in social and behavioral measures have been reported, with particular social–behavioral deficits evident in attention, internalizing, affective, and pervasive sub-domains [23]. Noteworthy, a remarkable 42% of infants with cerebellar injury in the above study also tested positive for early signs of ASD using the Modified Checklist for Autism in Toddlers (M-CHAT). As in children with cerebellar lesions, social–behavioral deficits were more frequent and profound in preterm infants with injury to the vermis. This atypical social–behavioral profile in ex-preterm children following cerebellar parenchymal injury is strongly suggestive of an autism spectrum disorders profile. A similar social/behavior phenotype implicating the vermis has also been reported in young children with cerebellar developmental lesions [63], which, together with vermal abnormalities reported in autistic populations [20], suggest that the cerebellar vermis may be an important substrate for ASD. In addition, cerebellar right Crus I shows consistent differences in autism, which can be considered in the context of the broad spectrum of symptoms that comprise the ASD profile (see [5] for review). As we have argued before, early cerebellar developmental differences have distal effects on cerebro-cerebellar circuits, including multiple regions of the cerebral cortex to which the cerebellum projects [5]; in our preterm populations, we have found that autism in the context of cerebellar injury was associated with reduced volume in the dorsolateral prefrontal cortex [14].

Taken together, these data demonstrate that early life cerebellar injury in very preterm infants and infants diagnosed with developmental cerebellar lesions are associated with pervasive and wide-ranging neurodevelopmental disabilities which we have previously termed "developmental CCAS" [64]; cerebellar damage during childhood is also associated with the psychiatric symptoms of the CCAS. In neurodevelopmental disorders with behavioral dysregulation, including ADHD and autism, reduced volume of the posterior vermis has been reported. We have proposed that disruption in multiple cerebro-cerebellar circuits could give rise to the social, communication, and repetitive behavior/restricted interests that comprise the autism spectrum [5]; that said, the functional cerebellar topographic correlates of these intriguing social– behavioral impairments remain to be determined.

7. Effect of age at cerebellar injury on outcomes

The insight provided from preterm infants with early postnatal cerebellar injury, and from neurodevelopmental disorders in which cerebellar differences are thought to arise during prenatal development (e.g. cerebellar malformations), suggest that early cerebellar lesions (acquired or developmental) may have more pronounced and wide-ranging developmental consequences than cerebellar damage that occurs in adulthood [3] which likely represent a critical period for cerebellar development. Although this idea is not well established in the pediatric clinical literature, it is often confounded by a variety of issues, including tumor location, adjuvant treatments, and the presence of extra-cerebellar lesions, and complications of preterm birth [17]. That said, children with cerebellar injury have more long-term and persistent sequelae when compared with adults sustaining cerebellar lesions, where effects may be rather transient with improved recovery rates.

The potential importance of the cerebellum during early development is supported by the role of the cerebellum in learning [11]. The cerebellum is thought to be involved in building and optimizing internal models of behavior during implicit/procedural learning of motor, cognitive and behavioral information [65]. Adults with cerebellar damage show deficits in acquisition of a new skill [66], but may only show subtle deficits on already-acquired skills that are supported by well-established cerebral–cortical circuits. For example, the cerebellum is thought to be especially important early in learning [5], when the initial internal model of the information is being established. It has been proposed that impaired procedural learning is characteristic of both developmental dyslexia and autism [67]; children must overcome these deficits to acquire information explicitly, which is consistent with the approach of behavioral remediation programs for both dyslexia and autism. It is possible, therefore, that the cerebellar structural and functional differences in these neurodevelopmental disorders contribute to these procedural learning deficits. In young infants and children where these cerebellar circuits are more severely affected, we would predict that cerebellar injury could produce long-term effects on behavior, particularly for skills that have not yet been acquired. For example, a preterm infant with early-life cerebellar damage has yet to acquire and consolidate fundamental language skills, and evidence from typically developing populations has shown that gray matter concentration in the right posterior cerebellum at 7 months predicts receptive language abilities at 12 months [68]. These data, linking right posterior cerebellar structure with later language skills, also support another prediction: the effect of early cerebellar injury should be specific, such that damage to sensorimotor regions of the cerebellum would impact motor performance, whereas lesions involving posterior vermis may disrupt the optimal regulation of behavior within a given context. Here, we have provided some evidence that this is the case, but future research is needed to establish more fine-grained structure–function relationships in the developing cerebellum, and specifically address the impact of fetal–neonatal cerebellar injury on function using a longitudinal study design.

8. Conclusion and future directions

Evidence from preterm infants with acquired cerebellar injury, infants with developmental cerebellar lesions, pediatric cerebellar tumor patients, and from neurodevelopmental disorders collectively suggests that the cerebellum plays a crucial role in motor, cognitive, and behavioral development. Further, the presence of discrete functional subregions of the cerebellum suggests that the consequences of early cerebellar injury may be predicted based on lesion location (see Table 1). Finally, evidence suggests that early cerebellar dysfunction may lead to significant, long-term effects on distal regions of the brain to which the cerebellum projects; this “developmental diaschisis” could impact both the function and structure of the cerebral cortical areas that may be optimized by the guidance of cerebellar input.

In summary, converging evidence from clinical and neuroimaging studies in newborns with acquired and developmental cerebellar lesions, as well as older children with cerebellar damage, point to a developmental form of CCAS. These novel insights into the expanded role of the cerebellum have improved our understanding of the role of early-life cerebellar lesions of cerebral development. These findings also begin to define the structural topography of functional outcome in pediatric cerebellar lesions, and should lead to greater accuracy in prognostication, anticipatory guidance, and timely and targeted early developmental interventions.

These data provide ample testable hypotheses for future research. First, whereas several studies have considered location of tumor in association with outcomes, there have been no pediatric studies to investigate the relationship between cerebellar lesion topography and clinical symptoms on a voxel level, using methods such as voxel-based lesion–symptom mapping. In adult cerebellar patients, these methods have successfully delineated important regions for the development of aspects of the cerebellar motor syndrome [69] and cognitive performance [70], but this has yet to be done in newborns and young children. These finer-grained studies are needed to better understand structure–function relationships in the developing cerebellum to improve clinical prognosis, early intervention services, and educational planning. In neurodevelopmental disorders, voxel-level analyses of the cerebellum provide testable hypotheses and regions of interest for clinical populations [35]. Another outstanding and potentially crucial question is the impact of age of injury on long-term outcomes following cerebellar injury to the developing brain. Further studies specifically addressing the role of a critical (sensitive) period for cerebellar maturation and its selective vulnerability to prenatal insults and associated perturbations are urgently needed. Developmental differences in the cerebellum, as seen in cerebellar malformations and neurodevelopmental disorders, are associated with life-long consequences on motor, cognitive and behavioral functions. Preterm infants with cerebellar injury have increased rates of cognitive and social–behavioral dysfunction, and pediatric cerebellar tumor patients have long-term motor, cognitive, and behavioral outcomes that cannot be fully explained by adjuvant therapies.

Large multicenter and longitudinal structure–function studies are needed to better delineate the impact of prenatal and postnatal cerebellar lesions on cerebral development and child function at key intervals across the lifespan. A final future direction concerns the potential translational significance of a better understanding of structure–function relationships in the developing cerebellum: Can we use this information to improve treatment outcomes? Certainly, improving our ability to predict the consequences of early cerebellar damage can aid in educational planning and clinical prognoses, as mentioned above. It is also possible that therapeutic interventions, such as cerebellar neuromodulation, could provide alternate treatment options in these populations. Improved knowledge of the relationship between cerebellar circuits and specific behaviors is necessary in order to optimize the timing and localization of such treatments. These crucial future directions may have a positive impact on the lives of the millions of children affected by cerebellar damage and developmental abnormalities.

Acknowledgments

The authors would like to thank Anila D'Mello, Darina Chudnovskaya, and Dr Manouchka Jean-Gilles for their helpful contributions to this article.

Funding sources

This work was supported by the National Institutes of Health under award number R15MH106957 (C.J.S.) and the National Institutes of Health (IDDRC, grant P30HD40677). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Practice points

- Cognitive and behavioral/psychiatric outcomes should be considered in clinical planning following cerebellar injury in newborns and young children.
- Topography of injury within the developing cerebellum is related to specific developmental deficits.
- Early-life cerebellar injury in the preterm infant and newborn with developmental cerebellar lesions is associated with greater risk for adverse outcomes.

Future directions

- Elucidating the role of specific cerebellar subregions in neurodevelopmental disorders.
- Delineating more specific structure–function relationships in young infants and children following cerebellar injury.
- Studying the effect of age and critical periods following early-life cerebellar injury on motor, cognitive, and psychiatric outcomes.
- Defining the effect of cerebellar injury/damage on structure and function of specific cerebro-cerebellar loops.
- Identifying the mechanisms by which the cerebellum contributes to motor, cognitive, and social–behavioral regulation in early infancy and childhood.

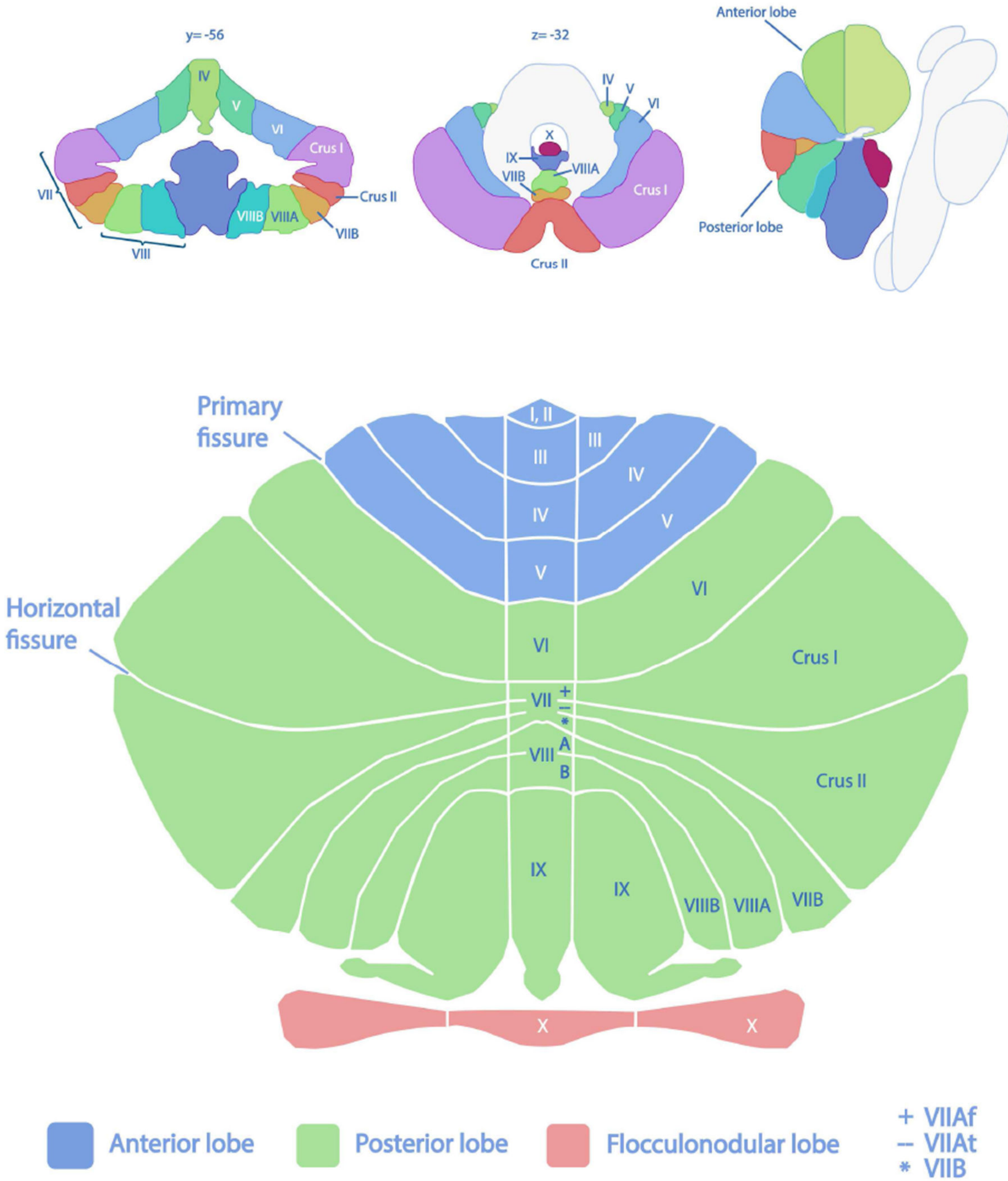

Fig. 1.

Cerebellar anatomy. (Upper) Cerebellar lobules shown in coronal, axial and sagittal slices from the spatially unbiased infra-tentorial template (SUIT) cerebellar atlas; individual lobules are labeled and color-coded. (Lower) Flattened cerebellum showing lobules I–X, including the subdivisions of lobule VII (Crus I, Crus II, VIIB) and lobule VIII (VIIIA and VIIIB); the anterior (lobules I–V; blue), posterior (lobules VI–IX; green), and flocculonodular (lobule X, red) lobes of the cerebellum are shown. Reproduced with permission from Schmahmann et al. [6].

Table 1

Structure–function relationships in the cerebellum.

Location	Anatomical connectivity	Tasks eliciting functional activation	Effects of damage	Associated neurodevelopmental disorder
"Sensorimotor" cerebellum				
Anterior lobe	Sensorimotor cortices	Sensorimotor	Cerebellar motor syndrome (ataxia, dysmetria)	Repetitive behaviors, motor symptoms in ASD
Medial lobules V–VI	Face area of sensorimotor cortices	Articulation	Dysarthria	
Vermal, paravermal and flocculonodular	Sensorimotor cortices; vestibular nuclei	Sensorimotor tasks	Postural instability	
"Cognitive" cerebellum				
Posterolateral cerebellar hemispheres	Fronto-parietal, default mode, dorsal and ventral attention networks	Cognitive tasks (e.g. language, theory of mind, working memory, mental rotation, executive function)	CCAS Cognitive impairments Social cognition deficits Language deficits (right cerebellum)	Developmental dyslexia ASD ADHD
Posterior vermis	Limbic networks		PFS Mutism Affective dysregulation Social deficits	ASD ADHD
Deep cerebellar nuclei				
Fastigial nuclei	Vestibular, oculomotor systems	Eye-blink conditioning	Postural instability Oculomotor deficits Gait ataxia	
Interpositus nuclei	Sensorimotor, spinal cord		Limb ataxia Gait ataxia	
Ventral (non-motor) dentate nuclei	Prefrontal, posterior parietal	Working memory	PFS	
Dorsal (motor) dentate nuclei	Sensorimotor, premotor	Sensorimotor tasks	PFS Limb ataxia	

ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; CCAS, cerebellar cognitive affective syndrome; PFS, posterior fossa syndrome.