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Emerging connections between cerebellar development, behavior, and complex brain disorders

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Abstract

The human cerebellum has a protracted developmental timeline compared to the neocortex, expanding the window of vulnerability to neurological disorders. As the cerebellum is critical for motor behavior, it is not surprising that most neurodevelopmental disorders share motor deficits as a common sequela. However, evidence gathered since the late 80's suggests that the cerebellum is involved in motor as well as non-motor function, including cognition and emotion. More recently, evidence indicates that major neurodevelopmental disorders such as intellectual disability, autism spectrum disorder, attention-deficit hyperactivity disorder, and Down syndrome have potential links to abnormal cerebellar development. Out of recent findings from clinical and preclinical studies the concept of the 'cerebellar connectome' has emerged that can be used as a framework to link the role of cerebellar development to human behavior, disease states, and the design of better therapeutic strategies.

Keywords

cerebellum; developmental disorders; ASD; behavior; connectome; trajectory

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Author contributions

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Introduction

The cerebellum controls both motor and non-motor behaviors [1-4]. Although the relationship between motor skills and intellectual ability in early childhood has long been known[5], the idea that complex developmental brain disorders (with both motor and non-motor deficits) are linked to dysfunctional cerebellar development is a much more recent proposal[6,7]. Cumulative evidence implicates cerebellar development as an important process regulating the onset of a broad range of behaviors. The most direct form of evidence in support of this idea comes from the clinical characterization of non-motor deficits in domains such as executive function, memory, and language in children who have malformations restricted to the cerebellum[8] or those who underwent cerebellar tumor resection[9]. Evidence has also indicated that risk factors that impair cerebellar growth, such as neonatal brain injury are correlated to poor overall neurodevelopmental outcomes at later stages[6]. The co-occurrence of early behavioral deficits in most neurodevelopmental disorders (NDDs) - spanning motor, sensory, cognitive, and emotional domains - indicates that abnormal cerebellar development is a major determining factor for disease. One primary reason for increased susceptibility of the cerebellum is due to its protracted developmental trajectory[10]. The cerebellum is among the first brain structures to begin cellular differentiation, and one of the last to fully mature[11]. As such, the developing cerebellum is vulnerable to dysfunction due to genetic and epigenetic factors, toxic *in utero* environment, focal or global neonatal brain injury, or some combination of aforementioned stressors. This complexity of risk factors acting over the course of development thus results in a broad range of cellular, morphological, and circuit abnormalities.

Cerebellum and NDDs

An extensive network of connections are formed between the cerebellum and the cerebral cortex (Figure 1a)[12]. Cerebellar dysfunction during critical periods of circuit formation could further lead to altered development and dysfunction of cortical targets[13,14]. In trying to understand complex developmental brain disorders, it is essential to address the development of both local cerebellar circuitry, as well as cerebello-cortical circuitry, or the ‘cerebellar connectome’. NDDs are, however, often defined in terms of behavior. Thus, the path from understanding to treatment lies in identifying the ‘neural implementation’ of the behavior in typically developing individuals, and altered or deficient implementation in patients with a neurodevelopmental disorder. In the context of developmental disorders with a cerebellar locus, this would involve defining both a developmental trajectory of cerebellar-dependent behavioral tasks[15], as well as cellular, physiological, and circuitry-level correlates of developmental disease[16].

In the present review article, we focus on the link between cerebellar development and complex brain disorders that emerge during development, rather than those that primarily appear in adulthood. Specifically, for the purposes of this review, we will be emphasizing findings in developmental brain disorders which are characterized by the presence of abnormal cerebellar development, altered cerebello-cortical connectivity, and the absence of a clear hereditary etiology. Spinocerebellar ataxias (SCAs), which are a group of movement disorders characterized by progressive loss in motor coordination due to dysfunction of

cerebellar and cortical areas - are beyond the scope of this review since the majority of SCAs have onsets in adulthood, and have a defined hereditary basis[17]. Although a small subset of SCAs are childhood-onset or early-onset, developmental aspects of these SCAs have not yet been well-characterized at the cellular and physiological levels. Finally, although cerebellar dysfunction can result in cognitive deficits as a secondary consequence of motor deficits[18], our specific focus in this review is on brain disorders for which a preponderance of evidence points to disruption of cerebellar development affecting both motor and non-motor circuits.

Cerebellar development in mammals

Previous reviews have covered morphological aspects of cerebellar development[16,19,20], however, for our specific focus, we will limit our description to cellular and circuit aspects. From a cellular standpoint (Figure 1b), the principal cells of the cerebellum – Purkinje cells (PCs) are born at the beginning of the 7th gestational week, until the PC plate is formed by the 13th gestational week[21] (Figure 1c). The external germinal zone appears as a separate layer between the 10th – 11th week. By 16 weeks, the PC layer consists of several rows, but by the 28th week the PC layer assumes its stereotypical monolayer organization and the PC soma increase in size. The 28th week of human gestation corresponds to P0 or birth in the mouse cerebellar developmental timeline. Around this time (28 weeks in humans and P0 in mice), PCs develop extensive complexity in dendritic length and arborization. This coincides with the thickening of the molecular layer, which extends from just before birth (38 weeks) to 1 year postnatal[21]. In the mouse, the first two postnatal weeks are critical to major developmental processes in the cerebellum, including synapse formation, the completion of PC axon targeting to cerebellar and vestibular nuclei, and synaptic pruning[22]. Additionally, around this window, per rodent models, inhibitory interneurons in the cerebellar white matter (WM) differentiate and migrate to the cerebellar cortex[23] (Figure 1d).

In both mice and humans, granule cell (GC) layer expansion rapidly increases in the postnatal period. In mice, GC development involves proliferation in the external granule layer (EGL) at E17.5[24] up to P16[25], followed by postmitotic migration of GCs into the internal granule layer (IGL), which continues until P20. EGL formation in humans begins at the 10th gestational week, continuing until the first few postnatal months[26], peaking at the 4th postnatal month[27]. This is followed by a concomitant increase in IGL volume which likely continues beyond the 11th postnatal month[27]. Beyond the first postnatal year and into infancy and childhood, human cellular data on cerebellar growth is scarce. However, structural imaging indicates that cerebellar size increases until late childhood to adolescence[28,29]. In summary, cerebellar maturation is protracted over a broad time window, putting the developing cerebellum at increased risk for genetic and environmental disruption. Thus, we propose that one of the overarching goals in the study of complex brain disorders should involve the identification of molecules and cellular mechanisms critical to different stages of cerebellar development, and developmental alterations leading to cellular, physiological, and behavioral abnormalities.

Mechanisms of developmental signaling

Tight spatiotemporal coordination of developmental signaling is crucial to building the characteristic shape, morphology and connectivity of the cerebellum. Sonic hedgehog (Shh) signaling is a major player during both pre- and postnatal stages of cerebellar development[30]. PCs constitute the major source of mitogenic Shh, which is transported from the PC dendrites onto Shh-responsive granule cell precursors (GCPs) in the EGL, as well as in the IGL[31]. On a larger scale, the onset of Shh signaling correlates with the formation of fissures, contributing to macro-level features of cerebellar morphology, since the regulation of GC number and orientation is a key factor controlling this process[32]. As the temporal range of Shh signaling is considerably wide, spanning the perinatal period, studies using mouse models of neonatal injury suggest that disruption of Shh signaling is related to morphological and structural abnormalities in the cerebellum[33]. In humans, studies from autopsy tissue indicates that premature birth is correlated to decreased Shh expression in PCs, along with decreased EGL and IGL thickness[34]. Interestingly, a clinically relevant model of neonatal brain injury recapitulates this abnormality at both the cellular as well as folia level[35]. PCs also seem to be altered when Shh signaling is disrupted, the reasons for which seem unclear[31]. It is possible that bi-directional signaling between GCs and PCs could mediate this process[20]. Although morphogens such as Shh regulate macro-level features such as foliation and patterning, ample evidence indicates that other molecules such as neurotrophins regulate fine-level features such as dendrite and synapse formation[36]. Evidence indicates that the spatiotemporal expression of these molecular factors correlates with the formation and refinement of key aspects of cerebellar circuitry[22].

The cerebellar cortex receives two major inputs: one input comprises the mossy fiber (MF) system which relays sensory information from various pre-cerebellar nuclei to GC dendrites, which then propagate this information via unmyelinated T-shaped axons, collectively called parallel fibers (PF)[22] (Figure 1 b). Another input source is from the climbing fiber system (CF). CFs originate from the inferior olive and ‘climb’ onto PC dendrites. Information relayed to PCs via CFs is critical for cerebellar forms of associative learning[37,38]. The MF-PF system and the CF system together constitute the excitatory input onto PCs. PCs receive inhibitory input from local GABAergic molecular layer interneurons (MLIs). MLIs in turn receive synaptic input from PFs. In addition, the excitatory input of GCs is modulated by Golgi cells (GoCs), which are inhibitory neurons located in the GC layer. GoCs also receive input from MFs[39]. This adult circuitry is a product of synaptic refinement and pruning or elimination which occurs over the course of postnatal development[22].

Similar to their action in other brain regions[40], neurotrophins play an important role in synapse development in the cerebellum. Brain-derived neurorotrophic factor (BDNF) plays a role in inhibitory synapse formation in GoCs, MLIs, and PCs[36,41]. More recent reports have shown that BDNF is also involved in the maturation of CF-PC synapses[42-45]. Although these studies showed that BDNF-TrkB signaling is prevalent in the developing cerebellum, the question of cellular specificity of BDNF was still undefined. In a very recent study, Choo and colleagues demonstrated that in a PC-specific BDNF knockout mouse line, synapse elimination is altered in the last phase of refinement[46], i.e. beyond the first two postnatal weeks, thus increasing the window of vulnerability for disrupted development in the case of

disease. Interestingly, signaling between BDNF and its receptor TrkB, is reduced in monogeneic mouse models of ASD[47]. Furthermore, peripheral blood levels of BDNF are increased in children with ASD[48], which may potentially correlate to an increase of this neurotrophin in the brain[49]. Thus, molecular mechanisms altered in complex brain disorders result in developmental disruption of cerebellar connectivity.

Cerebellar genesis to vulnerability

The developmental trajectory of the cerebellar connectome may be defined by the interaction of temporal and spatial factors[50], as well as 'information' factors[51,52] (Figure 2). Temporal factors include phases of cellular genesis, stages of cell migration, and onset of dendritogenesis, axonogenesis, and synaptogenesis. Spatial factors include circuit topography, distance of axonal targeting, cell density, and effective distance of secreted molecules involved in developmental signaling. Information factors involve the processing and transmission of information at the level of cells and circuits, such as spontaneous neuronal activity, synchronicity, and plasticity.

Whereas much of neocortical neurogenesis occurs prenatally[53], cerebellar neurogenesis continues until the 11th postnatal month[26], with 85% of GCs being generated after birth[27]. The formation of cerebellar synapses, dendrites, and axons also spans the perinatal period, with a considerable proportion of these events occurring postnatally. In terms of spatial considerations, the cerebellum quadruples in volume between the 24th and 38th gestational weeks, and its cortical surface increases thirty times[54]. Compared to other subcortical regions, the postnatal increase in cerebellar size is significantly higher[55]. Whereas the hippocampus increases in size by 47% over the first 90 days after birth, the cerebellum increases by 108%, effectively doubling in size. This increase in size is underscored by an increase in cell density, with cerebellar neurons comprising 80% of all neurons in the adult brain[56]. GCs alone make up about 75% of all neurons in the brain. PCs, which have large somata (50-80 micron) and dendritic trees with tens of thousands of synapses (Box 1), receive dense input from GCs. Consequently, the cerebellum displays extensive connectivity with cortical and sub-cortical regions, with a considerable portion of the cerebellum scoring in the upper 5% in global brain connectivity indices[57]. Thus, developmental disruption resulting in cerebellar atrophy could affect cerebello-cortical connectivity. Disruption in cerebello-cortical connectivity has also been shown in the context of neonatal brain injury due to risk factors such as premature birth[58]. Significantly, preclinical animal models of ASD such as the PTEN[59] and Tsc1 model[60] show abnormal PC dendritic morphology, which mirror morphological changes in human induced pluripotent stem cells (iPSCs) derived from ASD patients[61]. Thus, synaptic and morphological defects of PCs are potentially a key feature of developmental disorders with cerebellar dysfunction (Box 1).

In conjunction with an increase in cell number and onset of differentiation, specific physiological programs turn on at the cellular and circuit level, which provide a basis for tuning the computational properties of the cerebellum. Intrinsic spontaneous activity[62,63], synaptic pruning[64] and experience-dependent plasticity[65], contribute to defining the mature form of cerebellar circuitry. At the cellular level, PCs display unique firing properties, necessitating high metabolic demand[66] and increased vulnerability to external factors such

as hypoxia-ischaemia[67] resulting in free radical formation. In addition, exceptionally large Ca^{2+} influx into PCs due to CF inputs[68], enrichment of voltage-gated Ca^{2+} channels in PC dendrites, and Ca^{2+} regulation in postnatal development[69,70] increase susceptibility to excitotoxicity and neuronal injury[71]. Recent evidence indicates that synchronicity between spontaneously active PCs at early developmental stages is critical for synaptic pruning and CF-PC circuit maturation[72]. Optimal CF-PC synaptic pruning is necessary for normal long-term depression (LTD). As a result, sub-optimal CF-PC pruning causes impaired long-term depression[73], resulting in deficits in associative motor learning. Importantly, deficits in synchronicity at the systems level are found in persons with Down syndrome (DS) [74], and impaired LTD at the synapse level is found in preclinical models of autism spectrum disorder (ASD)[65]. Thus, linking cerebellar development to disease requires an integrated understanding of the underlying spatial, temporal, and information factors at play.

Cerebellar dysfunction in NDDs

Evidence from imaging studies

Brain imaging studies have shed light on cerebellar structural abnormalities in NDDs, including ASD, attention deficit hyperactive disorder (ADHD), Intellectual disability (ID), communication disorders, and childhood motor disorders[75,76]. Imaging has further provided direct evidence of differences in functional connectivity (distinct from structural connectivity) between the cerebellum and neocortex - as well as subcortical structures - during atypical development[77]. Both grey and WM changes have been reported in the cerebellum of children as well as adults with NDDs. These changes include regional volume changes with concomitant deviations in cell density, and alterations in WM microstructure[78].

In ASD, both structural and functional abnormalities are commonly found in the cerebellum[79] (Box 2). Specific regions of the cerebellum, such as the posterior vermis, are more prone to ASD-related structural abnormalities (Figure 3a). Studies employing voxel based morphometry (VBM) and comparative volumetric analysis of ASD and typically developing brains indicate that posterior lobules VI in addition to Crus I and Crus II (both part of lobule VII) show significant structural differences[80-83], although some studies suggest heterogeneity in structural changes[84], potentially correlated to within-spectrum differences in cohorts[85,86]. A recent meta-analysis, however, challenges the strength of the association between structural changes in the cerebellum and ASD[87]. The authors analyzed whole-brain and lobule-wise differences between ASD and typical developing (TD) brains reported in 30 studies, and observed that there was no conclusive evidence for differences between ASD and TD cerebella. Analysis of studies where '$p < 0.05$' was reported for total change in cerebellar volume did not indicate *p*-hacking. Nevertheless, the authors did find evidence for heterogeneity in the data, emphasizing the need for standardization. However, modest structural changes do not preclude functional differences between ASD and TD cerebella. Indeed, topography studies suggest significant functional differences between ASD and TD cerebello-cortical connectivity. In particular, differences in cerebellar activation measured by fMRI are seen during both motor and non-motor tasks. Using a finger-sequencing task, Mostofsky and colleagues found decreased cerebellar activation, but increased activation in pre-motor cortical brain regions in a cohort of children with high-

functioning autism[88]. An overall decrease in functional connectivity between the cortex and the cerebellum was also observed[88]. Importantly, reduced motor performance as measured using this paradigm is associated with altered connectivity in autism[89]. Within the non-motor domain, children and adults with ASD have been reported to show atypical fMRI activation of cerebro-cerebellar networks during tasks involving biological motion perception[90] and perception of social interaction[91].

In recent years, resting state functional connectivity MRI (rs-fcMRI)[92] has been used to address differences between motor and non-motor cerebellar connectivity motifs[93]. Along these lines, functional abnormalities detected in different brain regions fall under two distinct, but overlapping categories – sensorimotor and supramodal[94]. Abnormalities that fall under the sensorimotor domain are related to changes in connectivity between the cerebellum and sensory regions of the cortex. By contrast, supramodal abnormalities comprise connectivity changes between the cerebellum and higher-order cortical regions such as pre-frontal and posterior-parietal cortex[94]. However, this classification was described in adults. Using the same technique, Khan and colleagues confirmed the presence of a similar distinction of connectivity in children, and extended their analysis to compare children and adolescents with ASD versus TD subjects[95]. The authors contend that, in children and adolescents with ASD, there is an ‘overconnectivity’ in the sensorimotor domain, and reduced connectivity in the supramodal domain. It is thus possible that these connectivity changes may be related and complementary, resulting in both cognitive impairments and repetitive motor behavior.

It is important to emphasize that the causes of ASD are indeed complex, encompassing genetic, environmental, as well as genome-environment interaction[96,97]. As the leading risk-ratio for an ASD diagnosis - besides twin-sibling diagnosis - is perinatal cerebellar injury[13], evidence from studies involving these patients can be broadly insightful in identifying the connection between cerebellar dysfunction and developmental disability. Limperopoulos and colleagues have consistently shown that perinatal cerebellar injury leads to volume reduction not only in cerebellar gray matter, but also cerebellar WM and remote neocortical regions[58,98,99]. This suggests that grey matter volume changes in the cerebellum could be linked to volume changes in the neocortex, implying that changes in early cerebellar activity affects both cerebellar development and also activity of neocortical brain regions. Alternatively, coordinated deficits in the cerebellum and cortex could arise due to a common molecular and/or environmental insult rather than co-dependence between structures. Finally, as proper myelination is regulated by activity-dependent mechanisms[100], WM volume change could reflect altered activity and delayed development in both cerebello-cortical as well as cortico-cerebellar connections.

Structural changes in the cerebellum are also a key feature of DS, which is the most prevalent developmental disability with a known genetic basis[101]. Individuals with DS have smaller total cerebellar volumes[102], in addition to smaller frontal and temporal lobes, and smaller hippocampal volumes[103]. Reduced overall cerebellar volumes remains significant even after adjusting for total intracranial volume and microcephaly[104]. Similar to ASD, WM structural changes are also observed in the adult DS brain[105,106]. In a volumetric MRI study of children and adolescents with DS, both grey matter and WM reductions were observed

compared to controls[107]. However, when the DS cohort was split into two groups - one with DS only and the other with co-occurring ASD, significant WM hypoplasia was observed in the DS + ASD group, suggesting shared cerebello-cortical connectivity deficits in the diagnoses of DS and ASD[108].

Evidence from animal models

Preclinical animal models have proven indispensable to identify links between cerebellar development and disorders (Supplementary table 1). Many ASD mouse models have been developed – as inbred strains, or lines in which a specific gene or stretches of chromosomal DNA have been targeted[109]. The *SFARI Gene* database[110] currently lists a total of 1083 ASD-associated lines. With such a multiplicity of lines, it is essential to systematize the main effects and draw out trends. A recent attempt at addressing this problem used hierarchical clustering on neuroanatomical data from 26 ASD models[111]. Bootstrapping performed on brain regions as well as within ASD models revealed that the cerebellum featured consistently across the data. Using regional bootstrapping data, the authors note that in terms of circuitry, only localized cerebellar circuits are perturbed. However, in the bootstrapping results within models, the data suggests heterogeneity (among the 19 models across two of the three groups, significantly involving cerebellar anatomical differences), with one group showing volume decrease in cerebellar cortex and another group showing an increase in the cerebellum overall[111]. The latter group also showed a decrease in the thalamus. This large-scale analysis of multiple ASD mouse models captures the heterogeneity in cerebellar structural changes alluded to in the human structural MRI data mentioned in earlier sections.

Human cerebellar structural deficits are also recapitulated in mouse models of DS[112]. The most prominent DS model, the Ts65Dn mouse, which is trisomic for a distal portion of mouse chromosome 16 (orthologous to human chromosome 21), closely mirrors the human phenotype[113]. The Ts65Dn model has been shown to have significantly and disproportionately reduced cerebellar volume[114]. The GC layer appears to be particularly reduced in volume[115], suggesting that the MF-GC-PF circuitry is disrupted in this model. Although Ts65Dn cerebella do not show obvious volume differences compared to euploid controls at birth, there is significant hypoplasia observed at postnatal day 6 (P6), which persists until adulthood[116]. Behaviorally, although there is conflicting evidence on basic locomotor functional abnormalities in Ts65Dn mice[117,118], experiments using the vestibulo-ocular reflex (VOR) adaptation paradigm suggest that cerebellum-specific learning deficits are quite prominent in this model. This closely matches the human phenotype wherein persons with DS show VOR adaptation deficits[119], thus indicating that the Ts65Dn model is a robust model to study cerebellum-related developmental disruption in DS. Another emerging group of DS mouse models targeting the *Dyrk1a* gene also exhibit cerebellar structural deficits[120], but the connection to cerebellar behavior remains undefined. Structural cerebellar alterations that result in cerebellum-specific behavioral alterations are thus an important feature recapitulated in established models of complex developmental brain disorders.

In addition to macro-level features, which can be recapitulated to match phenomenology in human data, mouse models also allow insight into morphological, physiological and molecular mechanisms in the cerebellum and its connecting brain regions. In a pioneering study, Tsai and colleagues demonstrated that ASD-like pathologies can be observed in mice in which PCs have been selectively altered[60]. The authors genetically targeted PCs and selectively knocked out *Tsc1*, a gene implicated in *Tuberous sclerosis complex* – a genetic disorder in which human patients have high rates of ID and co-occurring ASD. The resulting selective Tsc1 knockout mice showed significant abnormalities in grooming, social approach, and reversal learning – behaviors with human correlates in ASD. The authors also observed reduction in PC number – a neuropathological correlate to reduction in PC number in post-mortem cerebellar tissue of ASD patients[121]. The reduction in PC number in the selective Tsc1 knockout mice did not occur until well into adulthood, consistent with behavioral tests that were conducted mostly in adult mice. However, the one exception to this was the ultrasonic vocalization tests which were conducted on pups from P5-P12. Mutant mice displayed significantly higher rate of vocalizations compared to control mice as early as P7, indicating early postnatal deficits in cerebellar circuitry and behavior even though PC morphological deficits are not obvious. Electrophysiologically, the input to PCs via PFs and CFs was normal, however PCs in adult mutant mice had lower spontaneous firing rate and were less excitable than normal mice, indicating that PC dysfunction was the major contributing factor in behavioral abnormalities in this *Tsc1* model of ASD. Other models, including global genetic KO models of ASD (as discussed below), do not show reduced firing rate or excitability in PCs, but instead show firing irregularities or synaptic deficits.

Shank2 KO mice, which are an ASD model for human Shank-mutation related ASD[122], show normal PC mean firing frequency as well as normal PC excitability, but exhibit irregular firing patterns and abnormal intrinsic plasticity following long-term potentiation (LTP) via PF stimulation[123]. By contrast, ASD models such as the 15q11-13 duplication mouse (*patDP/+*)[124], Fragile X mouse (*Fmr1* global KO and PC-selective *Fmr1* KO)[125] and the *Nlgn3* KO mouse[126] all display abnormal PF-LTD. Thus, both PF-LTP and PF-LTD may play critical roles in determining the contribution of PCs to dysfunction in ASD at the adult stage. More cellular and physiological data are necessary to define the developmental processes that give rise to abnormalities in adult LTP or LTD. However, in *patDP/+* mice, it was shown that there is a disruption in surplus CF elimination. This is a key result, since the CF-PC circuit element, which is critical to cerebellar-dependent forms of learning, undergoes extensive synaptic pruning in the first two postnatal weeks in mice.

Cerebellar behavior and dysfunction

A pioneering study on language processing using positron emission tomography by Petersen and colleagues in 1989, demonstrated that the cerebellum was activated during a semantic association task in which subjects were asked to generate verbs that correspond to particular nouns (such as *eat*:*calzone* or *drive*:*car*)[127]. By subtracting the “motor control” activation related to subjects reading aloud just the nouns, the authors were able to associate an activation hotspot in the right lateral cerebellum to a cognitive function rather than a motor function[2,127]. Since then, multiple studies have demonstrated distinct cerebellar activation

profiles for non-motor tasks[2]. More recently, Peterburs and colleagues used fMRI on subjects performing a verbal working memory task, while also tracking eye movements and oculomotor activation[128]. When the authors took eye movements and the associated oculomotor processing in the superior colliculus into account, the increase in activation in lobule VI/Crus I and lobule VIIb remained significant, indicating that cerebellar activation during a cognitive task can be 'purely' cognitive, rather than a side-effect of motor processing. A converse question regarding motor and non-motor cerebellar function would be: in individuals with obvious 'non-motor' behavioral abnormalities, do 'pure' motor cerebellar abnormalities exist? Tran and colleagues used delay eyeblink conditioning, a cerebellar-dependent task, on a cohort of VPT children and young adults[129]. They found that in VPT children and adults, there were significant deficits in the acquisition of conditioned responses. This study suggests that, in the case of preterm birth, 'motor' cerebellar behavioral abnormalities co-exist with non-motor abnormalities.

Analogous to cerebellum-specific behavioral deficits in VPT individuals, children with ASD display abnormal conditioned responses in the delay eyeblink conditioning, but perform equally as well as TD children in a trace eyeblink conditioning paradigm, suggesting specificity in cerebellar dysfunction[130]. This effect is captured well in different mouse models of ASD, which show abnormal responses in delay eyeblink conditioning paradigm[131]. In spite of these findings, the mechanisms that result in cerebellar and cerebello-cortical deficits still largely remain uncharacterized. Below, we discuss potential developmental and physiological mechanisms, which may be disrupted in complex brain disorders resulting in cerbello-cortical deficits.

Disruption of cerebellar circuitry

Sensorimotor processing

The cerebellum is directly involved in motor coordination and associative motor learning[38]. Behavioral tests have probed this aspect of cerebellar control using motor reflexes such as the eyeblink reflex and the VOR. The cerebellum is also involved in sensorimotor control through adaptive learning via sensory prediction errors[132]. Further, a growing body of evidence indicates that the cerebellum is a key component of sensory processing circuitry[133]. Visual[134], auditory[135], tactile[136], and even olfactory[137] information is processed and integrated in the cerebello-cortical connectome. The cerebellar role in sensory integration is not surprising, given the range of inputs received by GCs and GoCs via the MF system (Figure 3b). However, the cells, circuits and mechanisms involved in this aspect of cerebellar function are only now being discovered.

Whisking behavior and the vibrissal system in rodents has been widely used as a model of sensorimotor processing. It has now been shown that the cerebellum is actively involved in both integration of sensory and motor information from the cortex, as well as control of the motor cortex via the ventrolateral thalamus[138]. Proville and colleagues used tetrode recordings to measure responses from hundreds of GoCs and PCs in Crus I following stimulation of the vibrissal M1 (vM1) and the vibrissal somatosensory cortex (vS1), showing that the integration of sensory and motor information occurs at the cellular level in GoCs and PCs.

Recent evidence indicates that there is an integration of somatosensory, visual, and auditory information via non-overlapping sets of MFs onto individual GCs[139,140] (Figure 3b). These GCs, which are also located in Crus I and Crus II, show an enhanced spike profile when multisensory information (such as tone stimulation + LED stimulation) is conveyed, compared to just a single type of sensory information (such as tone stimulation only), indicating a form of gain control at this step of the cortico-cerebellar circuit. Thus, individual GCs may function as sites of multimodal sensory input and processing. Translation of these results into humans is yet to be systematically performed, but a very recent behavioral case study from a patient with a rare case of cerebellar agenesis where – except for the cerebellum – no other brain region was significantly structurally impaired, showed deficits in multisensory integration compared to a group of healthy adults[141]. Similar to mouse data, fMRI evidence from humans shows increased activation in Crus I when both visual and auditory stimuli are provided simultaneously[142] rather than individually. Thus, multisensory integration can be considered a key feature of the cortico-cerebellar pathway.

It has been suggested that the language and social deficits observed in children with complex disorders are a consequence of deficits in multisensory integration[143]. Children with ASD have deficits in integrating auditory and visual information[144,145], resulting is reduced behavioral output. Evidence from a recent randomized controlled trial indicates that deficits in multisensory integration in children with ASD may occur due to deficits in perceiving the temporal relationship between distinct sensory components of complex audiovisual stimuli such as language[146]. In conclusion, it is quite likely that the altered developmental trajectory of the cortico-cerebellar connectome[78,147] resulting in higher-order deficits in language and social skills, is linked to lower-order deficits in multisensory integration.

Inter-regional morphogenesis

The cerebellar cortex surrounds three pairs of cerebellar nuclei that not only provide the major efferent output projections of the cerebellum but also receive collateral afferent input[148]. CFs and MFs project mainly to the cortex, although they also provide an extensive network of collateral projections to each of the cerebellar nuclei[148]. It is not entirely clear what the functional and behavioral role of the collaterals is, although some inputs may be sparse and functionally weak[149]. Interestingly, in certain pathways the afferent fiber projections to the cerebellar nuclei could constitute the main pathway to the cerebellum[150]. From medial to lateral, the three pairs of cerebellar nuclei are the fastigial, interposed (globose and emboliform in primates), and dentate. The cerebellar nuclei projections mainly target specific thalamic nuclei but also the red nucleus and numerous brain stem sites. Although the timing of afferent arrival into the cerebellum is understood with some level of clarity[151-157], the timing of how the cerebellar nuclei project and connect with their targets is unknown. However, it is interesting that the cerebellum and thalamus (the major cerebellar target) initiate neuronal differentiation at about the same time, around E10.5[158]. Neurogenesis continues throughout embryogenesis and progresses into early postnatal development in both structures[159-162]. Based on their common neurogenic timetables, it is interesting to speculate that extensive connectivity and matching of the developmental trajectories could indicate that early defects in the cerebellum might lead to structural and

wiring alterations in the thalamus. Indeed, there is experimental genetic evidence that loss of *En2* gene function in mice causes a significant anterior shift of the amygdala[163]. As the amygdala receives a robust innervation from the thalamus, we speculate that - if cerebellar development is altered - then it is possible that signals ultimately headed for the cerebral cortex are also abnormal.

Reduced growth and increased cell death in the hippocampus have also been reported in *En2*-null mice[164], as well as increased binocularity and reduced plasticity in the visual cortex[165]. At the behavioral level, loss of *En2* leads to motor[166] and non-motor autism-related[167] behavioral deficits. The various defects in the *En2* mice are not easy to interpret, because *En2* expression is dynamic and broad, although there is firm evidence that it is heaviest in the cerebellum[168]. Nevertheless, direct projections from the cerebellum to the cerebral cortex of developing and adult birds and mammals could provide a neural substrate for coordinated inter-regional development[169,170]. Using its direct and indirect projections, we propose that the cerebellum could also shape the formation and function of a number of other regions in the central nervous system. These regions include the inferior olive, basal ganglia, hypothalamus, periaqeductal gray, ventral tegmental area, locus coeruleus, septum, and even the spinal cord. The cerebellum could, in theory, interact with its targets using developmental cues that “match up” regions of connectivity[171,172]. For example, cerebellar communication with the developing thalamus might be mediated by chemoaffinity molecules such as Eph/Ephrins[173], which were previously shown to promote connectivity between the inferior olive and cerebellum. If such molecules and pathways exist for cerebellum-thalamus connectivity, then their role could be to establish a precise topography between sub-regions of the dentate nucleus and sub-nuclei of the thalamus[160,174,175]. However, we anticipate that before the identity of these molecular players is determined, a clear understanding of how each region of the thalamus is anatomically connected with each area of the cerebellum has to be systematically defined. Understanding the formation of these topographies in normal development as well as in the context of developmental disorders will hopefully enable targeted applications in both pharmacological and stimulation-based intervention strategies relevant to clinical settings.

Treating cerebellar abnormalities

Studying NDDs as a function of the developmental trajectory of the cerebellar connectome offers unique avenues in clinical intervention. Recent efforts have aimed at exploring both stimulation-based paradigms (invasive and non-invasive), as well as the targeting of therapeutics to molecular signaling pathway that are involved in cerebellum-related disorders.

Non-invasive stimulation

Non-invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS), have become increasingly popular as therapeutic approaches for cerebellar disorders. tDCS allows for direct modulation of neuronal excitability through the skull by delivering low-amplitude electrical current through scalp electrodes[176]. The directionality of current flow used in tDCS guides its effect on neuronal excitability (anodal stimulation –

excitation, cathodal stimulation – inhibition)[177]. Recent studies have illuminated the implications of cerebellum-targeted tDCS on a variety of motor and non-motor functions, ranging from procedural learning to adaptive postural control[178-180].

Anodal cerebellar tDCS (ctDCS) has been reported to improve posture, gait, and reflexive symptoms in patients with cerebellar ataxias, compared to patients in a control group who received sham stimulation[181,182]. Patients suffering from focal dystonia have also experienced enhanced kinematics after receiving anodal ctDCS[183]. Furthermore, long-term treatment of cathodal ctDCS has been reported to significantly improve symptoms in patients with essential tremor[184,185], as well as help stroke patients recover hand and limb function[186]. Healthy individuals have also demonstrated motor improvements after receiving ctDCS – a recent study showed that individuals receiving anodal stimulation were able to better maintain and regain a balanced, steady standing posture after Achilles tendon perturbations, compared to individuals who received sham[179].

Although clinically effective, mechanistic bases for improvement in non-motor functions following ctDCS are largely unknown. Recent studies have used tDCS to study healthy cerebellar processing, yielding insights into applicability in disease contexts. Consequently, tDCS has been used to successfully disrupt or enhance non-motor processing including language and working memory[176]. As more insight is gained into the exact mechanisms of how tDCS acts on healthy cerebellar circuits, and as clinical safety standards become standardized, teams will be better equipped to use tDCS in small patient cohorts. Along these lines, it was reported that a small cohort with schizophrenia showed significant improvements on multiple neuropsychological scales including improvement in emotional mood and working memory after tDCS[187]. Together, these findings implicate non-invasive cerebellar neuromodulation as a therapeutic tool with the potential to benefit patients across a wide range of motor and non-motor function abnormalities.

Invasive stimulation

Deep brain stimulation (DBS) is an invasive stimulation approach that continues to gain attention due to its increasing success in the clinic[188]. DBS is a surgical approach that involves the delivery of either high- or low-frequency stimulation into deep structures using implanted electrodes (Figure 4a)[189]. Typically, the thalamus, subthalamic nucleus, and the internal segment of the globus pallidus are targeted[190] (Figure 4b). DBS is extensively used in Parkinson’s disease, dystonia, and essential tremor. It may also be beneficial in obsessive-compulsive disorder (OCD), Tourette’s, epilepsy, and chronic pain[191], all of which can involve abnormal cerebellar function[192]. This raises the hypothesis that perhaps cerebellar stimulation could also be beneficial in a number of motor and possibly even non-motor conditions. The hypothesis was recently put to test in a genetic mouse model of dystonia. Indeed, in that model, DBS of the interposed cerebellar nuclei dramatically improved motor function (Figure 4 c)[193]. This was not the first indication that cerebellar directed DBS could be beneficial in disease, or that DBS was considered for diseases not typically associated with the cerebellum. In fact, the initial discovery of the DBS technique targeted the cerebellum in epilepsy and related disorders[194-197]. Using modern DBS approaches, stimulation of the dentate nucleus showed remarkable promise in a rat model of stroke[198].

The systems level mechanism of action in this particular paradigm may involve microstructural plasticity and cortical reorganization[198]. However, the cellular and circuit mechanisms of how DBS works are unclear[190,199]. Optogenetics has shown promise to delineate mechanisms of DBS[200]. Recently, optogenetic-targeting of the dentate nuclei showed equivalent recovery in a mouse stroke model[201]. Authors reported that cerebellar-induced cortical plasticity is mediated through an increase in growth-associated protein 43 (GAP-43)[201] expression.

Considering the extensive connectivity of the cerebellum with diverse brain regions - including the thalamus, basal ganglia, hippocampus, hypothalamus, and amygdala - it will be interesting to see whether different molecular programs mediate the DBS effects in each cerebellar target region. The efficacy of cerebellar DBS could therefore be linked to how the inter-regional connections form during development, the molecules that are expressed, the precise afferent-target innervation patterns, and the functions that each circuit performs.

Molecular therapies

As complex brain disorders with a cerebellar locus follow different developmental trajectories, it is crucial to tailor molecular therapies to specific cell types and drug targets. Pharmacological interventions may involve molecular networks associated with activity-based processes regulating synaptogenesis and plasticity and developmental signaling[202,203].

Activity-based mechanisms are directly regulated by the excitatory-inhibitory (E/I) balance. Molecular therapies have thus been targeted towards regulating this balance[204]. Clinical trials involving drugs such as riluzole[205], which potentiates $GABA_A$ receptors have shown promise at altering the E/I balance in patients with autism. Targeting NMDA receptors in preclinical animals in early postnatal development, is also a promising approach, however translation to the clinic has not yielded consistent results[206]. A promising direction in E/I therapy in developmental disorders involves targeting the GABA system. In a randomized controlled trial, Lemonnier and colleagues found that bumetanide, a benzodiazepine, reduced ASD-related behaviors in a cohort of children[207]. Along the same lines, in a recent study, we have shown that Tiagabine, a GABA-reuptake inhibitor partially rescues behavioral as well as electrophysiological aspects of cerebellar function in a clinically relevant mouse model of neonatal brain injury[208]. However, it is important to note that GABA serves different roles based on developmental stage in both cellular-specific and region-specific manners. As GABA generally increases neuronal excitability in early development due to the developmental regulation of the Cl- ion gradient[209], it is also essential to consider the temporal aspect of therapy when targeting the GABA system in NDDs.

Ion gradient changes occur due to changes in the expression profiles of transporters and ion channels[210]. In addition to targeting the GABA system, it is instructive therefore to approach therapeutic targeting more broadly. Ion channel modulators have been used in pre-clinical animal models of SCA[211]. These ion channel modulators are targeted toward PCs by improving their firing patterns and consequently rescuing some aspects of cerebellar ataxia[212-214]. Specifically, drugs targeted toward K^+ channels[212,215] and the mGluR1 receptor[216] show considerable therapeutic potential in rescuing PC electrophysiological

deficits. As PCs serve as integrators within the cerebellar circuit, PC-targeted ion channel modulators may be a promising cross-over strategy in complex brain disorders. In fact, it has been recently proposed that mGluR1 may serve as a “hub” molecule onto which developmental (e.g. synaptic wiring) and biophysical (e.g. membrane excitability) characteristics of PCs may converge, making it an ideal starting point for rational drug design within a neurodevelopmental context.

Targeting ion channels and Ion channel modulators, while effective, may generally be limited to acute effects. A more straightforward strategy for sustained therapeutic effects includes leveraging developmental pathways. The BDNF and Shh pathways have shown therapeutic potential in mouse models of Rett Syndrome[217] and DS[115], respectively. As BDNF signaling is involved in multiple wiring steps within the cerebellum, targeting this pathway may serve to rescue multiple cellular and physiological processes. Importantly, BDNF signaling links sensory experience to neuronal activity and synaptic plasticity[218], providing a rationale for therapeutic application in disorders with sensory processing deficits. However, as a broad range of factors influence BDNF-TrkB signaling, including glucocorticoids[219] and environmental enrichment[220], more research is required to construct a comprehensive picture of cross-talk between factors. Interestingly, both glucocorticoids[221] and environmental enrichment[222] are viable intervention strategies for infants with neonatal brain injury. Further, early BDNF levels in infants with neonatal brain injury are correlated with long-term behavioral outcomes[223]. Future studies may specifically address BDNF-TrkB targeting in the developing cerebellum. Such strides have begun in DS research with regard to Shh signaling pathway in the Ts65Dn mouse model. Das and colleagues have used a small molecule – SAG – to rescue cerebellar size, specifically the size of the GC layer in Ts65Dn mice[115]. However, although SAG treatment rescues the gross morphology of the cerebellum, behaviorally, treated Ts65Dn mice continue to show abnormal responses in a vestibule-ocular reflex (VOR) paradigm, which is a cerebellum-dependent task.

Summary and future directions

Pioneering work in the field has challenged the paradigm of cerebellum as primarily being involved in motor behavior[4] and has led to an increased interest in non-motor aspects of cerebellar function. However, the developmental mechanisms responsible for the cerebellum acquiring both motor and non-motor functional states remains poorly understood. Importantly, the protracted development of the cerebellum combined with its rapid growth in the perinatal period suggest that it may be uniquely vulnerable to developmental disruption. Vulnerability of the developing cerebellum is especially important to consider given that a rich network of connections form between the cerebellum and the cerebral cortex (Box 2). Evidence from imaging, behavioral, and pre-clinical animal model studies clearly point to both cerebellar development as well as development of cerebello-cortical connectivity as factors determining the onset and severity of childhood psychiatric diseases. Here we propose the developmental trajectory of the cerebellar connectome (Figure 2) as a unifying framework to study diverse complex brain disorder such as ASD, ADHD, and DS. This framework integrates the alterations in spatial, temporal, and information-related factors which result in disease. Finally, we review therapeutic strategies in complex brain disorders including DBS-based strategies and molecular targeting methods.

There is still much to be discovered about fundamental developmental mechanisms that lead to normal cerebellar function, including the role of early postnatal cues that enable synapse formation and maturation, and how different cell types within the cerebellum influence each other during key developmental processes. An approach with much potential for uncovering key insights involves linking postnatal cerebellar development with the fine-tuning of excitatory/inhibitory (E/I) balance. In the adult cerebellar cortex, E/I balance is maintained via feedforward circuits involving excitatory input from GCs and inhibitory input from MLIs and BGs that converge to regulate PC neuronal excitability[224,225]. Optimal E/I balance is a key contributing factor to the large dynamic range of PC firing and consequently cerebellar cortical output[226]. The formation of this E/I balance is in turn dependent on the development and refinement of synaptic communication between the major cell types of the cerebellar cortex, as well as on the intrinsic morphological and physiological properties of PCs.

An important implication of the maintenance of cerebellar E/I balance is that both multisensory integration via MFs and the cerebellar-nucleo-thalamic circuit may be affected. We think that the ‘E/I balance’ approach will encompass research questions that extend the connectivity question in a meaningful way. This can serve to integrate the mapping of E/I balance in connected brain regions in health and disease. For example, in Ts65Dn model, GCs display hyperexcitability[227], likely altering the overall E/I balance in the cerebellar cortex. Future studies may determine if GC hyperexcitability is uniform across the cerebellum or confined to specific functional modules or zones. Finally, in most complex brain disorders, the developing WM has received little attention. Evidence suggests that E/I imbalance via [Cl−] gradient disruption results in cellular and physiological alteration in the cerebellar WM[35].

Recent evidence also indicates that developmental delay - a hallmark of complex brain disorders - can be alleviated by shifting the E/I balance to normal levels[208,228]. Therapeutic efforts can thus be directed to the use of drugs which have been developed for adult neuropsychiatric diseases with E/I imbalance, however, the developmental context must be paid close attention to since excitatory or inhibitory drugs can have different and often undesired effects on developing neurons and circuits

Finally, as more mechanistic details are gleaned about the environmental risk factors for complex brain disorders, avenues for intervention can be expanded. Considering that factors such as premature birth is one of the leading risk factors for ASD and ID, and that the cerebellum is uniquely affected in this population, it is surprising that the role of the cerebello-cortical connectome in this context is still largely understudied. With the advance of new imaging technologies, sophisticated behavioral and physiological analyses, as well as large-scale sequencing methods, cracking the developmental code of the cerebellum and its complex and multiple connections to other regions of the brain is an exciting future avenue for neuroscience and developmental disease research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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GLOSSARY

Attention deficit hyperactivity disorder (ADHD):
A complex developmental brain disorder that is characterized by deficits in attentional processes, and increased frequency, intensity, and variability of motor behavior.

Autism spectrum disorder (ASD):
A broad range of neurodevelopmental conditions characterized by social skill deficits, repetitive motor behavior, and communication deficits.

Bootstrapping:
A statistical method used to measure how strong a given grouping or cluster is supported by the data.

Cerebellar connectome:
A map of neuronal connections within the cerebellum as well as that between the cerebellum and other CNS regions, including the cerebral cortex and subcortical regions.

Complex developmental brain disorders:
NDDs which affect multiple brain regions, gene loci, and behavioral domains. These disorders do not have a clearly defined hereditary basis.

Down syndrome (DS):
A neurodevelopmental disorder wherein persons have abnormalities associated with Chromosome 21. Persons with DS have have reduced muscle tone (hypotonia) during infancy, characteristic facial features, mild to moderate intellectual disability, and experience developmental delay, among other symptoms.

Finger-sequencing task:
A behavioral task to assess motor function wherein subjects are directed to tap their fingers, on either hand, in a particular sequence. This task is commonly used to identify motor-related regional activation during functional brain imaging.

Intellectual diability (ID):
A neurodevelopmental disorder/condition that often co-occurs with other disorders, and is characterized by reduced intellectual functioning (such as learning and abstract reasoning) and deficits in flexible or adaptive behaviors (such as social and motor behavior)

Neurodevelopmental disorders (NDDs):
Disorders that emerge during the course of central nervous system development, often having long-term effects on behavior.

***p*-hacking:**
The selective reporting of statistically significant results based on inappropriate, faulty, or loosely-defined data anlysis schemes.

Vestibulo-ocular reflex (VOR):
A reflex that generates eye movement in the opposite direction to head movement in order to stabilize vision. The cerebellar flocculus is an integral part of VOR circuitry, contributing to adaptive control of the VOR during trial-based learning.

Eyeblink conditioning paradigm:
An associative conditioned-learning paradigm wherein an acoustic or light stimulus (conditioning stimulus or CS) is paired with an air-puff stimulus (unconditioned stimulus or US) over multiple trials, to eventually yield anticipatory eyelid closure (conditioned response or CR) as soon as CS is presented, prior to US onset. Whereas delay eyeblink conditioning involves co-terminous CS and US, and is primarily cerebellar-dependent, trace eyeblink conditioning involves non-overlapping CS and US, and requires multiple brain regions including the hippocampus.

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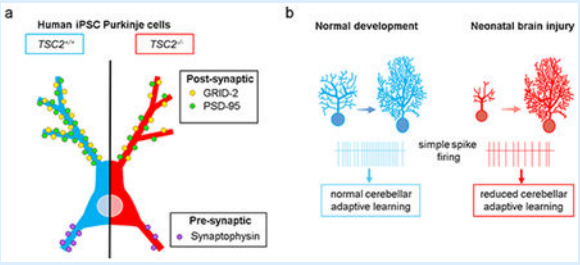
Box 1:

Synaptic match-up in development and disease

Previous comparisons of the neocortex and cerebellum mostly include morphometric analysis of size and volume. However, from a computational and functional standpoint, the synapse is an effective and crucial point of functional comparison. The synapse plays a fundamental role in neuron-neuron as well as neuron-glia communication, and many NDDs involve deficits in synapse formation, maturation, and function. While a “typical” pyramidal neuron in the neocortex has approximately 8000 synapses[229], it is estimated that a single PC may have more than twenty times this number, with around 200,000 synapses[230,231]. The large synapse numbers in PCs likely correlate to the larger dendritic tree arborization, which in turn may relate to the enormous number of PF inputs from GCs to PCs. In mouse models of ASD and patient-derived cerebellar iPSCs, morphological deficits resulting in altered number of synaptic connections are apparent. Interestingly, in a mouse model of neonatal brain injury, which is a risk factor for ASD, PC dendritic formation is delayed35 and spike patterns are altered208. Delayed development of PC dendritic arbors during the first two postnatal weeks likely causes alterations in PC circuitry and physiology, resulting in significant long-term learning deficits . Reduced numbers of synapses are a characteristic of many NDDs232. Recent Ca^{2+} imaging studies have shown GCs themselves encode a rich repertoire of sensory information[233,234]. Therefore, it is likely that synaptic deficits in PCs correlate to sensory processing deficits in NDDs. For example, mutations in the postsynaptic scaffolding protein family SHANK are strongly associated with ASD. PCs in Shank2KO mice fire simple spikes with altered regularity, and display synaptic plasticity deficits123. Future experiments may help determine specific synaptic PC deficits in neonatal brain injury models to address potential convergence with knockout and mutant models.



Box 2:

Neuronal mechanisms of cerebro-cerebellar interactions

Recent evidence has indicated that a specific cerebellar cortical site is not just linked to one cerebral cortical site, but is rather an integral part of a large, brain-wide network consisting of multiple distributed structures that jointly control fundamental brain functions[93,235]. The cerebellum contains multiple distinct 'network nodes' that are part of different brain-wide functional networks including the somatomotor, limbic, attention and default mode networks[93,235,237]. Manipulation of a cerebellar network node changes functional connectivity throughout the entire functional network[236,238]. Halko and colleagues showed that stimulation of a cerebellar node not only increased the functional connectivity between the cerebellum and cerebral cortical nodes but also between the cerebral cortical nodes of the stimulated network[236]. This is consistent with the idea that the cerebellar cortex consists of arrays of parallel microcircuit modules or micro-complexes proposed as an organizing principle for spinocerebellar interactions[239,240], that may also underlie cerebro-cerebellar interaction in cognitive functions.

Autism spectrum disorder (ASD) and schizophrenia are two cognitive disorders that are strongly associated with cerebellar neuropathology[79,241,242] and with altered cerebro-cerebellar functional connectivity[78,243,244]. However, because of a possible crucial role of the cerebellum in the early development of the cerebral cortex[13,14], the causative chain of events that link the cerebellum to cognitive disorders may start during development[13]. Consistent with this assumption are the findings by Limperopoulos and colleagues, who have shown that local injury to the premature cerebellum is associated with subsequent impairment of growth in the contralateral cerebrum and a 40% increased risk for developing ASD[14]. In contrast to ASD, which manifests between the first and third year of life[245], schizophrenia manifests predominantly at a later age as either adolescent-onset or adult-onset schizophrenia[246]. Both forms are associated with gray matter loss in several cerebral cortical areas, but only adolescent-onset patients also showed gray matter loss in the cerebellum[246].

Box 3:

Regionalized information processing

Functional network nodes in the cerebellum are spatially segregated[93,235-237], and brain-wide networks associated with these nodes can be independently activated[236,238]. In view of the homogeneity of the gross network architecture of the cerebellar cortex, the specific functional role of a particular cerebellar node is likely determined by the functional properties of the local inputs. Detailed analysis of cerebellar integration in brain-wide functional networks using fcMRI shows a millimeter-scale regional segregation of function in the cerebellum[93,235-238]. Higher-resolution calcium-imaging studies even suggest functional segregation at the cellular level[233,234,247].

However, input-output relations are not solely determinative of regional functional properties. Underneath the gross morphological homogeneity exists a pattern of parasagittal zones which shape the cerebellar wiring diagram. These function-shaping zonal patterns are best revealed using molecular markers such as Zebrin II[248], although afferent terminal field organization, genetic mutations, and cell lineage all conform to the same plan[248,249].

PCs have zone specific firing properties[250,251] and classes of cerebellar interneurons respect the same zonal map, although they tend to form clusters[252]. These findings provide a link to local functional properties. The distinction between PC zones and interneuron clusters is based heavily on the strict planar orientation of the relatively “flat” and closely stacked PC dendrites. This is in contrast to the interneurons that tend to display somata and dendrites in more distributed orientations, forming clusters that are nonetheless topographically linked to zones.

At the functional level, localized information processing is revealed by spatial activation patterns. GCs specifically were shown to become activated in clusters in response to sensory stimulation or the performance of a motor task[233,234,247]. These clustered activation patterns are likely to reflect the spatial organization or topographical projection map of task-related MF inputs to GCs (see Figure 1 b). It is interesting to speculate that this functional topography respects the zonal plan.

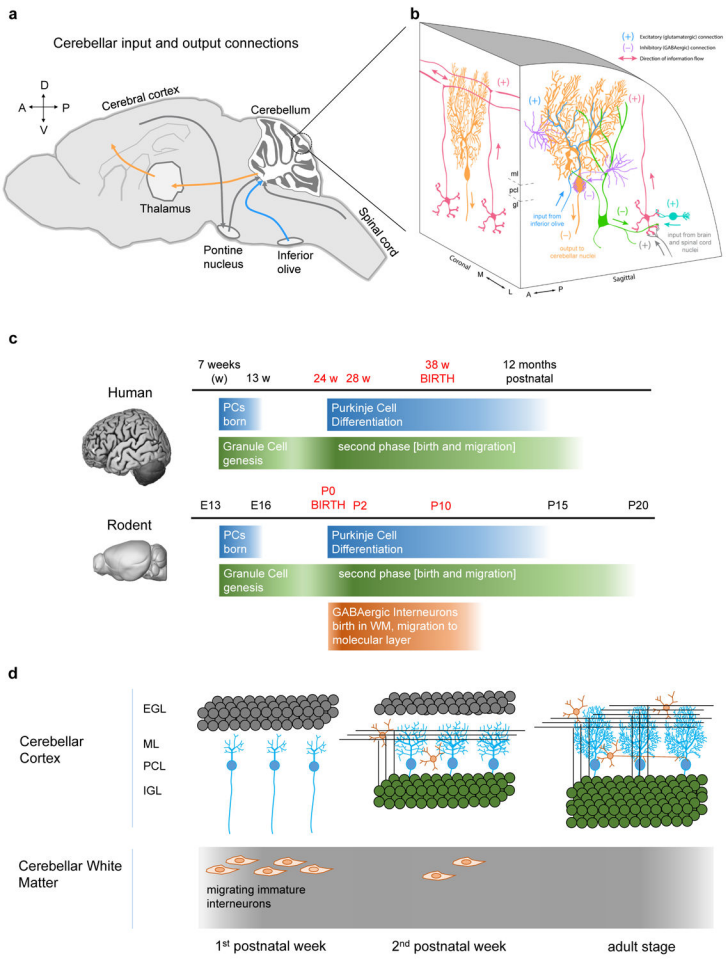


Figure 1. Essential features of cerebellar connections, circuitry and development

(a) General scheme of input and output connections to and from the cerebellum. Main inputs include spinal cord, inferior olive and pontine nucleus. Main outputs include connections from cerebellar nuclei to cerebral cortex via the thalamus. **(b)** Cellular anatomy and circuit connections within the cerebellar cortex. PCs are shown in orange, GCs in magenta, MLIs in purple, GoCs in green, unipolar brush cell interneuron in cyan, input from inferior olive is shown in blue, input from the brain and spinal cord is shown in grey **(c)** When the human and rodent timelines are aligned based on major cellular/developmental events in the cerebellum, in humans the window of vulnerability to injury (indicated by red numbers) is mostly late gestational, while in preclinical rodent models, it is mostly postnatal. **(d)** Cellular schematic of events depicted in the timeline in panel ‘a’ showing EGL expansion (grey), dendritic arborization (PCs blue), and white matter interneuron migration in the 1st postnatal week. Migration of GCs into the IGL (green) continues in the second postnatal week with concomitant reduction of EGL, and circuit formation. In the adult, cerebellar circuitry formation is completed, the EGL has disappeared, and MLIs (salmon) have been integrated into the cerebellar cortical circuitry.

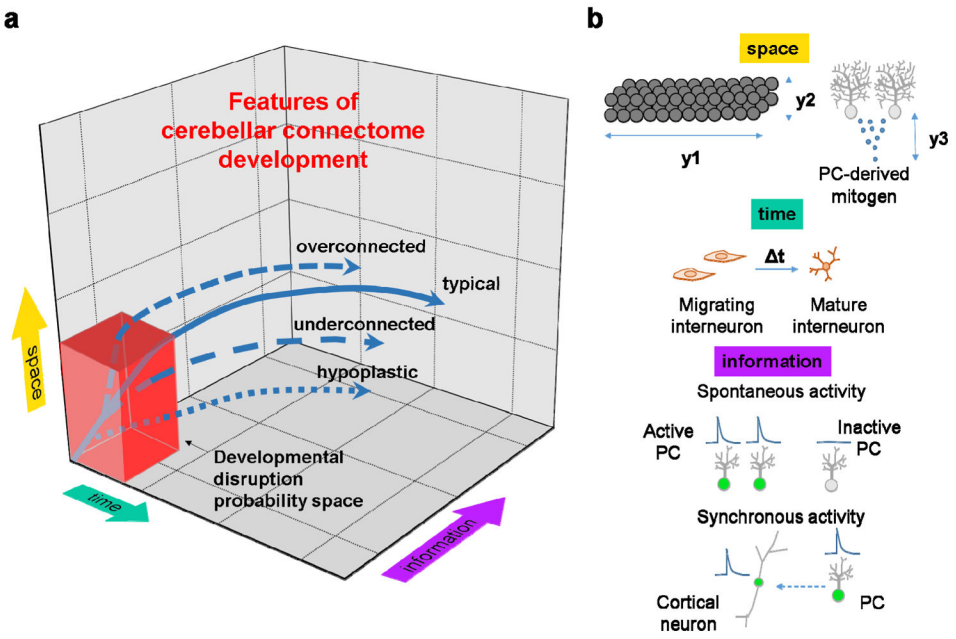


Figure 2. Features of the cerebellar connectome and dependent factors

(a) Cerebellar connectome developmental trajectories can be plotted along three dimensions – space (gold), time (turquoise), and information (purple). **(b)** Spatial factors include cell density and regional volumes (defined by y1 and y2), and effective distance of secreted molecules (defined by y3). Temporal factors include time of onset of developmental events such as interneuron migration (Δt), and information factors include cell-to-cell communication events such as spontaneous PC firing, and long range communication between PCs and cortical neurons. Cerebellar development is a protracted process, making this brain region particularly vulnerable to a broad range of abnormalities. This early vulnerability is represented by the probability space defined as a function of spatial, temporal and information factors (red box). While trajectories may start out as typically-developing (solid blue trajectory, TD), alterations in the developmental disruption probability space can cause altered paths resulting in overconnected connectomes (short space dashed trajectory, e.g. high functioning autism), underconnected connectomes (long space dashed trajectory, e.g. low functioning autism), or hypoplasticity (dotted trajectory, e.g. Down syndrome).

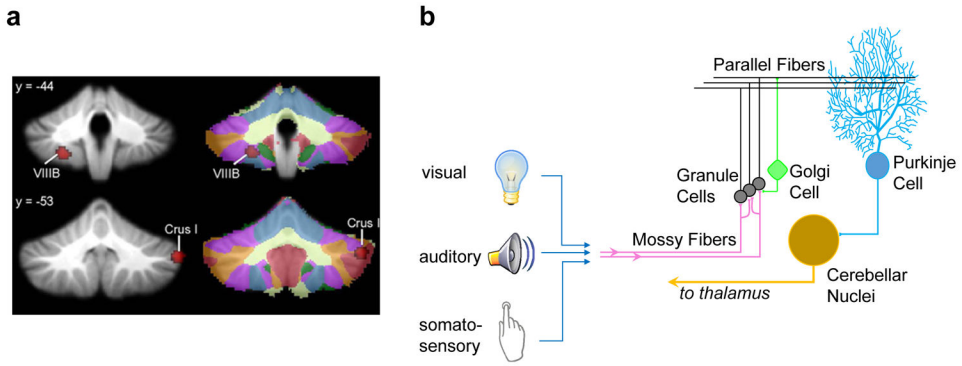


Figure 3. Regions of cerebellar developmental vulnerability and multisensory integration.

(a) Certain cerebellar regions are more vulnerable to abnormalities than others in the domain of complex disorders. Structural MRI images are from figure 2 in Ref. [80]. Images on the left show voxels (red) with significant structural changes associated with autism spectrum disorders, compared to typically developing controls. Images on the right are corresponding sections with functional connectivity map as described in Ref. 93. Colors denote networks, namely, blue – somatomotor, green – dorsal attention, violet – ventral attention, cream – limbic, orange – frontoparietal, red – default network (b) Granule cells (GCs) (grey) integrate sensory information (auditory, visual and somatosensory) resulting in multisensory integration. Golgi cells (GoCs, green) are also involved in modulation of sensory information flowing into the cerebellum. Integration of sensory information from complex stimuli such as speech is impaired in autism spectrum disorder.

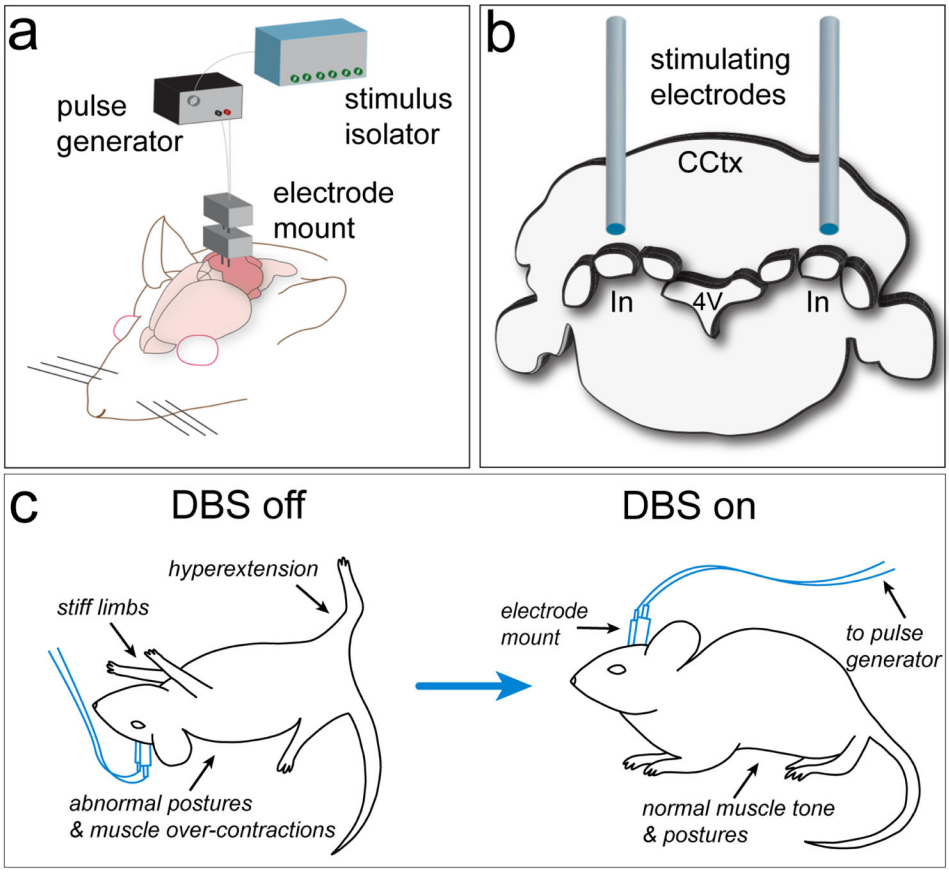


Figure 4. Deep brain stimulation of the cerebellum in mouse.

(a) Schematic illustrating the experimental set-up for stimulating cerebellar circuits in adult mice (b) Schematic of the tissue section (bottom) illustrates the targeting of the stimulating electrodes to the interposed nuclei (In), with reference to the overlying cortex (CCtx) and adjacent cerebellar nuclei. The fourth ventricle is labeled as 4V (c) Schematics illustrating a deep brain stimulation approach of the cerebellar circuit in a mouse model of dystonia. Mobility is immediately improved after stimulation begins (DBS on condition). Adapted with permission from Ref 193.