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Local and long-range circuit elements for cerebellar function

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The view of cerebellar functions has been extended from controlling sensorimotor processes to processing 'contextual' information and generating predictions for a diverse range of behaviors. These functions rely on the computation of the local cerebellar microcircuits and long-range connectivity that relays cerebellar output to various brain areas. In this review, we discuss recent work on two of the circuit elements, which are thought to be fundamental for a wide range of non-sensorimotor behaviors: The role for cerebellar granule cells in multimodal integration in the cerebellar cortex and the long-range connectivity between the deep cerebellar nuclei and the basal ganglia. Lastly, we discuss how studies on synapses and circuits of the cerebellum in rodent models of autism-spectrum disorders might contribute to our understanding of the pathophysiology of this class of neurodevelopmental disorders.

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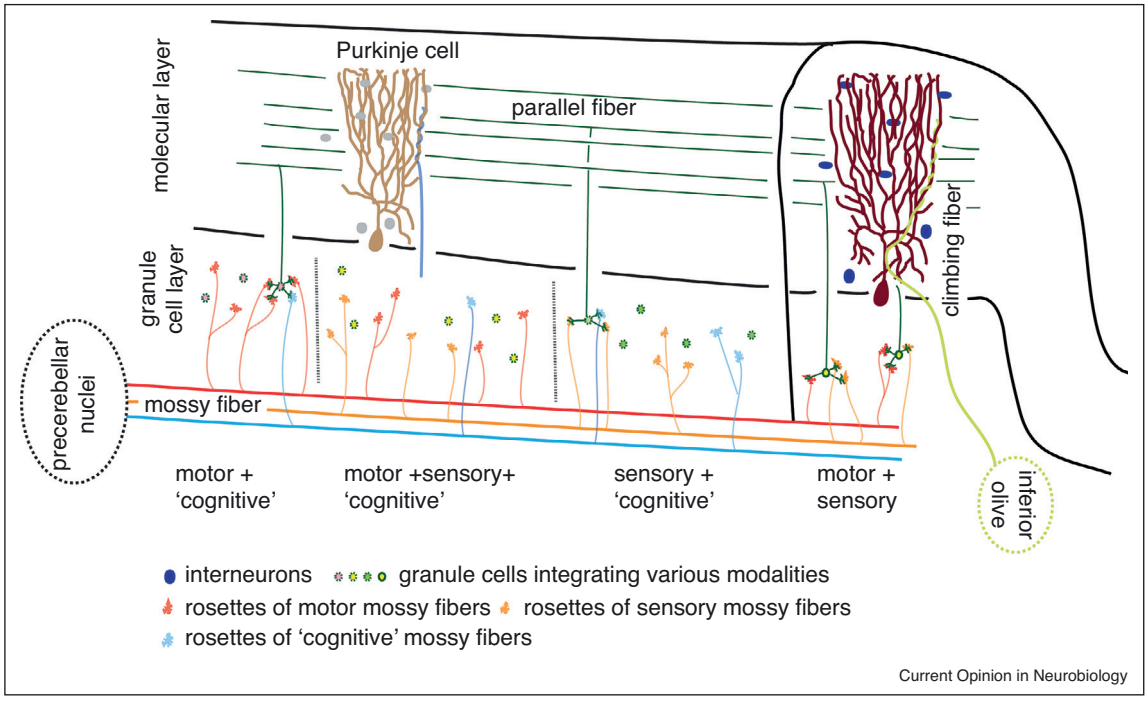
Introduction

The cerebellum has classically been viewed as being dedicated to the control of motor behavior through outputs routed towards primary motor cortex and the descending rubrospinal tract. The cerebellar cortex is composed of a dense array of parallel microcircuit modules whose cellular components and synapses have been well characterized (Figure 1). Maybe the most remarkable aspect of cerebellar anatomy is the abundance of granule cells (tens of billions in the human brain) which are densely packed in the cerebellar cortex. Each granule cell receives through a few short dendrites (3–7, depending on the species), input from mossy fibers (one per dendrite) through so-called mossy fiber 'rosettes'. These inputs carry different sensory and motor information, or equivalent sensory information from different body parts, possibly enabling a single granule cells to integrate various modalities and to represent specific associations. Parallel fibers, the axons extending from granule cells, relay this integrated mossy fiber information to Purkinje cells, the sole output of the cerebellar cortex. In addition to parallel fiber synapses, Purkinje cells receive excitatory climbing fiber inputs from the inferior olivary nucleus that are thought to relay error signals associated with ongoing behaviors. Output axons of the inhibitory Purkinje cells converge onto a group of deep cerebellar nuclei (DCN) with a ratio of ~40:1 per cell, and the synchrony of Purkinje cell axons can elicit a time-locked firing response of DCN neurons [1•]. Therefore, DCN neurons code information by both spike timing and frequency. In classical studies, the cerebellum has been proposed to act as a 'supervised motor learning' machine. The 'internal state' of the cerebellum is constantly modified by the mossy fiber 'command' signals, as well as the climbing fiber 'error' signals from peripheral sensory or locomotor feedback. The synaptic plasticity (mainly long-term depression) between parallel fibers and Purkinje cells has been proposed as one mechanism for cerebellum-based motor learning [2–4]. However, several other sites of synaptic plasticity have been identified for contributing to cerebellum-dependent learning processes [5].

Recent work highlights that cerebellar function in integrating information and generating an 'internal-state' might extend beyond sensorimotor control and may be a major contributor to disorders of multi-modal integration for motor, language and even social behaviors [6–8]. Schmahmann and Sherman proposed the '*Cerebellar cognitive affective syndrome*' (CCAS) based on clinical observations [9]. Thus, lesions of the cerebellum not only result in motor dysfunction such as ataxia, dysmetria, dysarthria, and oculomotor abnormalities but can also result in impairments in executive function, visual–spatial processing, and affective dysregulation. These observations resonate with recent progress made by studies in rodents employing anatomical tracing, functional imaging, and disease models. In essence, the function of the cerebellum might be leveraged to regulate precision and timing of an array of non-sensorimotor functions by the same computational processes that mediate its motor control functions. In this review, we will first discuss integration of information within the cerebellar circuit. Second, we will discuss the long-range output connections between cerebellum, thalamic nuclei, and basal ganglia, as this represents one example for how cerebellar information

Figure 1



Cellular components and multimodal integration of the cerebellar cortex. The Purkinje cells are the centre around which the circuit is organized. They receive inhibition from interneurons in the molecular layer, and two major excitatory inputs, the climbing fibers from the inferior olive and parallel fibers from granule cells. The mossy fibers from various precerebellar nuclei project to granule cells and form mossy-fiber 'rosettes', carrying various modalities such as 'motor', 'sensory', 'cognitive'. Granule cells in different zones are specialized in integrating information of various modalities from mossy fibers.

might be impacting non-sensorimotor behaviors. Lastly, we will discuss how cerebellar circuits have been implicated in non-sensorimotor phenotypes of rodent models for autism-spectrum disorders.

Granule cells integrate locomotive, sensory, and 'cognitive' information

Granule cells receive mossy fibers carrying information of various modalities (Figure 1). For example, mossy fibers forming synapses onto a single granule cell can originate from the pontine nuclei (carrying 'command signals' from the cortex) and from the external cuneate nucleus (carrying proprioceptive information of the body) [10•]. Therefore, individual granule cells could be a site of multimodal integration. Since a single mossy fiber synapse ('rosette') can code sensory or locomotor information by the frequency of transmitter release [11,12], and granule cell firing transmits the mossy fiber information with high fidelity *in vivo* [13,14], it is interesting to investigate how single granule cells compute the summation of different mossy fiber inputs, depending on their arrival time and duration [15].

With the technical advances in two-photon brain imaging and ultra-fast Ca^{2+} indicators, recent studies have challenged several classic views about granule cell activity. Initially, it had been hypothesized by Albus and Marr that granule cells are sparsely activated *in vivo* and code for only a specific combination of sensorimotor inputs [2]. By contrast, recent studies demonstrated that a large fraction of granule cells responds to a simple stimulus. Thus, in larval zebrafish, approximately 50% of granule cells respond to changes in luminance, whereas approximately 25% respond to moving gratings. In the mouse cerebellum, more than 80% of granule cells are active during locomotion [16••]. During eyeblink conditioning, a learning paradigm that is cerebellum-dependent, about 65% of the imaged granule cells became active after the delivery of a conditioning stimulus [17••]. Most remarkably, a subset of granule cells in mice was found to code for reward-related signals [18••]. About 5% of imaged granule cells peaked in activity upon the consumption of a reward, 10% of cells peaked right before the consumption of reward, and 10% of granule cells were found to be active upon reward omission [18••]. Taken together, these studies demonstrated that a substantial number of granule cells is active simultaneously in response to environmental stimuli and/or during self-locomotion. Moreover, specific sub-populations of granule cells are recruited by non-sensorimotor tasks, supporting the hypothesis that cerebellar functions extend beyond motor control.

Another key conclusion from these recent imaging studies was that granule cells activated by specific tasks are organized into anatomically-defined zones in coding sensory and motor information, but not necessarily into zones for coding 'contextual' information. In the larval zebrafish cerebellum, granule cell clusters responding to changes in illumination, motion-direction, or electrical shock were preferentially distributed in distinct anatomical zones. Moreover, visual stimulus-responsive granule cells had a topographical organization related to their receptive fields [16••]. These observations align with the classic view that mossy fiber inputs are organized into zones according to their anatomical source and modalities [19]. By contrast, granule cells activated by reward-related signals were widely distributed across various cerebellar lobules, including vermis V, VIa, VIb and simplex. This indicates a more dispersed distribution of mossy fibers carrying non-sensorimotor (possibly cognitive) information [18••] (and see [20]). Recent more detailed functional mapping experiments also indicated stereotyped spatial patterns of granule cell-Purkinje cell connectivity beyond anticipated anatomical boundaries [21]. These selective connections between distant cerebellar modules might further facilitate the integration of diverse modalities at the level of Purkinje cells. Taken together, while there is an anatomical organization of granule cells into cerebellar sub-domains representing motor and sensory functions, the rules for location–function correlations might be more complex for cognitive aspects.

The multimodal integration conducted by a single granule cell is preferentially one copy of 'motor' information conveyed by cortico-ponto-cerebellar mossy fibers and one copy of sensory information from self or the environment, rarely two sensory inputs with different modalities [16••]. This integrative configuration is thought to generate an 'internal-model' and predictions for behaviors by combining information of self-motion and sensory inputs. The discovery that granule cell activities code for reward-related signals, could be explained by the possibility that they receive cortico-ponto-cerebellar mossy fibers from cortical areas other than motor and visual cortex. However, this needs experimental validation. Thus, the 'internal-model' hypothesis could be applied not only to sensorimotor-function but also the non-motor functions. How cortico-ponto-cerebellar connections carrying such information are anatomically organized remains an important question. Moreover, it raises questions about how cerebellar outputs are relayed to cortical and sub-cortical structures that control cognitive processes.

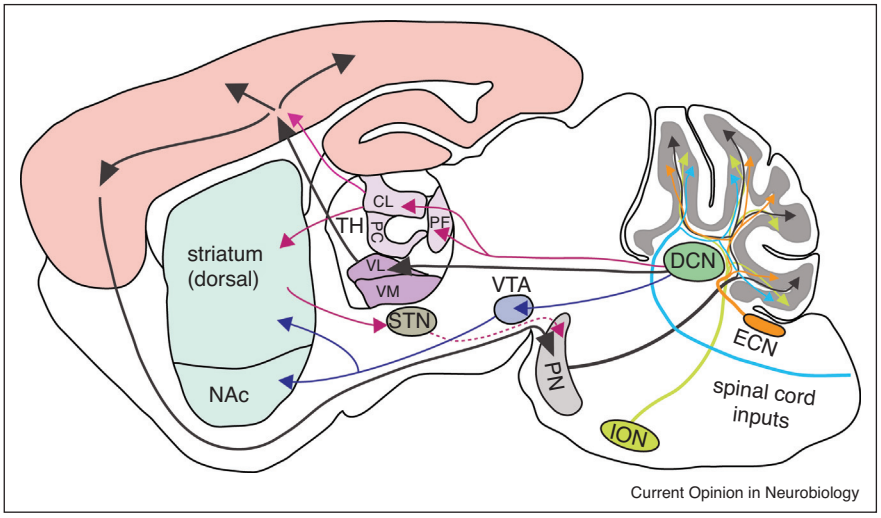
Interconnection between cerebellum, cerebrum, and basal ganglia

In primates, reciprocal connectivity 'loops' between the cerebellum and cerebrum have been extensively characterized by anatomical tracing and functional imaging [22•,23]. These studies highlighted connectivity of the cerebellum with several cortical areas, most prominently the motor and sensory cortex. However, such connectivity loops also exist for non-sensorimotor areas in the cortex. In fact, the primate cerebellum is regarded to be functionally divided into an anterior motor division (lobule I–V) and posterior non-motor division (remaining lobules). Thus, the anterior cerebellum is interconnected with sensory and motor cortices whereas the posterior cerebellum is more densely connected with the association cortex. In humans, Crus I, II of the cerebellum are interconnected with area 46, which is important for language [24,25] and, indeed, one of the key symptoms in patients with Crus I and II lesions are language deficits [23]. These observations support processing of non-sensorimotor information in the primate cerebellum.

While much attention has focused on cerebellar connections with cortical areas there is also a less-studied disynaptic connection between the deep cerebellar nuclei of the cerebellum and the basal ganglia that may provide insights into non-sensorimotor functions of the cerebellum (Figure 2). These connections were first mapped in primates using viral tracing. Thus, the dentate nucleus (a sub-structure of the DCN) connects to the striatum through the intralaminar thalamic nuclei [26]. In turn, the cerebellar cortex receives inputs from the subthalamic nucleus relayed by the pontine nuclei in the brain stem [27] creating a cerebellar–striatal circuit loop in primates. Throughout evolution, neuron numbers in cerebral and cerebellar cortex have undergone a significant coordinated increase, with highest numbers in primates [28]. Thus, whether analogous cerebellar loops, in particular, connectivity with non-sensorimotor areas are conserved across mammalian species is currently unclear.

In rodents, cerebello-striatal connectivity is only beginning to be investigated. Studies with chemical tracers [29] indicate that DCN-derived axons contact in the centrolateral thalamic nucleus cells that project to the dorsal striatum. The centrolateral nucleus (CL) is one of several intralaminar thalamic nuclei (also including paracentral nucleus (PC) and parafascicular (PF) nuclei) that receive inputs from the cerebellum and the spinal cord, and projects to striatum and neocortex [30]. Interestingly, intralaminar thalamic nuclei have been implicated in an array of non-sensorimotor behaviors, including arousal, social stress, and working memory [31,32]. In macaques, the firing of intralaminar neurons synchronizes with sensory stimuli [33]. Silencing or lesion of thalamostriatal pathways in mice lead to deficits in reversal learning and lever-pressing guided by visual discrimination [34,35]. Further, tracing and lesion studies in rodents suggest that motor-related information may be more reliant on the parafascicular nucleus whereas CL and part of CM might be more relevant for cognitive functions [32]. More

Figure 2



Interconnection between cerebellum and basal ganglia. The basal ganglia are a group of subcortical nuclei, including striatum (dorsal and ventral), pallidum, substantia nigra, subthalamic nuclei and ventral tegmental area (VTA). The deep cerebellum nuclei (DCN) forward inputs to the dorsal striatum via intralaminar nuclei in the thalamus (TH). Intralaminar thalamic nuclei include paracentral nucleus (PC), central lateral nucleus (CL), parafascicular nucleus (PF) and a few other nuclei. In addition, the ventral lateral thalamic nuclei (VL) receive inputs from DCN and forward them to the cortical areas. DCN neurons also connect to ventral tegmental area (VTA), which further project to the dorsal striatum, and ventral striatum (*nucleus accumbens*, NAc). The striatal outputs are relayed to the subthalamic nuclei (STN), which in turn project to the pontine nuclei (PN) (at least in primates). The PN neurons receive also cortical inputs beside the STN inputs, and send mossy fibers throughout the cerebellar cortex. Therefore, there are two long-range 'loops' related to the cerebellum: between cerebellum–thalamus–basal ganglia and cerebellum–thalamus–cortex. Note that in the illustration of the loops not all arrows represent direct connections. Additional types of mossy fibers, carrying proprioceptive information from the external cuneate nucleus (ECN), or spino-cerebellar fibers carrying somatosensory information converge in the cerebellar cortex. This mossy fiber information is further integrated with climbing fiber information from the inferior olivary nucleus. Thus, the local cerebellar circuit integrates 'command signals' from the cortex and sensory information from the body and surroundings.

recent experiments in mice have examined the impact of DCN-derived signals on striatal function with respect to motor function. Short-latency responses in ~70% of the dorsolateral striatal neurons were detected when DCN-derived axons were optogenetically stimulated in the thalamus [36••]. Moreover, optogenetic stimulation of DCN neurons can reverse the striatal long-term depression (LTD) induced by corticostriatal stimulation to long-term potentiation (LTP) [36••]. In addition, DCN neurons form synapses onto ventral tegmental area (VTA), and the latter project to both dorsal striatum and ventral striatum (*nucleus accumbens*) [37,38].

Therefore, anatomical and physiological studies confirm extensive coupling between the cerebellum and basal ganglia in primates and rodents (Figure 2). However, the cerebellar role in modulating striatum-dependent motor-behavior or/and non-motor behavior remains to be explored. The striatum is traditionally regarded as reinforcement-related circuit that regulates action selection whereas the cerebellum is regarded as error-detection/correction circuit. How could the two different types of circuit function together in motor and non-motor behaviors? One theoretical model proposed by Kenji Doya is that the cerebellar–striatal circuit performs a prediction-based evaluation of potential actions [39]. According to this model, the cerebellum would integrate sensory and non-sensory information, to predict an outcome/sensory state for a potential action and would forward this prediction to the striatum. The striatum would then evaluate current and predicted states to estimate the value of the action. Based on those predictions, a favorable action would be selected. This model needs to be experimentally tested. However, the recently identified anatomical and functional links between the cerebellum and reward systems provide a framework for how common principles of cerebellar computation can be applied to motor and non-sensorimotor functions.

Impact of cerebellar alterations in autism-related mouse models

The recent progress in understanding cerebellar connectivity and function has also greatly advanced our knowledge of how cerebellar alterations might contribute to neurodevelopmental disorders. A particular focus in recent years has been on autism spectrum disorders (ASDs). Notably, cerebellar injury in infants elevates risk for developing an ASD by about 40 fold [40]. Early [41], as well as more recent reports noted alterations in Purkinje cells in postmortem tissue from ASD patients [42]. Moreover, many autism genetic risk factors are highly expressed in the cerebellum (though none of them are

restricted to the cerebellum). The simple and well-defined cerebellar circuitry facilitated identification of synaptic alterations in mutant mice with deletions for genetic ASD risk factors. For example, knock-out mice lacking the synaptic adhesion and scaffolding proteins NLGN3 or SHANK2 respectively exhibit defects in parallel fiber synaptic transmission and plasticity [43–45]. Interestingly, several Autism-related mouse mutants (SHANK3, MECP2, CNTNAP2, TSC1, and 15q11-13 paternal duplication) exhibit common cerebellar-learning deficits [46,47]. Thus, in an eyeblink conditioning task, several mutants showed defects in various parameters, including timing, probability and amplitude of conditioned responses, strongly supporting common alterations in sensory processing resulting from molecularly distinct genetic risk factors.

Besides genetic risk factors, environmental challenges and maternal immune activation have been linked to increased ASD risk, possibly through the impact of cytokine signaling on neuronal development and synapse function [48]. While most studies in model systems have focused on cortical cells and circuits [49,50] there is evidence that some cytokines are elevated in granule cells in brain sections from ASD patients and that elevation of IL-6 in the rodent granule cells results in abnormalities [51–53]. It is still unclear to what extent these cerebellar alterations contribute to the etiology of ASD but cerebellar cells and function may indeed be vulnerable to cytokine-dependent perturbations.

An important opportunity afforded by rodent models is testing the impact of selective lesions in specific circuit elements to autism-relevant behavioral domains. Interestingly, several recent studies reported social interaction and stereotypic behavioral phenotypes for Purkinje cell — specific mutations, thus, resembling core autism behaviors. For example, Purkinje cell-specific *Tuberous Sclerosis 1* (TSC1) knock-out mice showed defects in social interactions, reversal learning, ultrasonic vocalization, as well as increased grooming [54•]. Moreover, Purkinje cell-specific SHANK2 mutant mice exhibits increased repetitive behavior (nose-poking) and decreased social interaction [44,45]. The functional contribution of the cerebellum is likely complex and further work is required to understand the circuit and synaptic mechanisms underlying these phenotypes. For example, it is puzzling that genetic Purkinje cell-specific lesions impair social behaviors whereas social interactions appear unchanged when the majority of the synaptic inputs onto Purkinje cells are disrupted [55]. Moreover, some of the behavioral findings diverge between individual studies. Regardless, the impact of cerebellum-specific lesions on a broad range of rodent behaviors, in particular social interactions and learning paradigms lends further support to the participation of cerebellar circuits in higher cognitive functions.

Conclusions

By combining genetic lesions and circuit level analysis, future work should uncover how cerebellar outputs specifically impact multi-sensory integration, reward-based action-selection, and cognitive flexibility — functional domains that are central to ASDs. One attractive hypothesis suggests that cerebellar dysfunction during a sensitive period could derail development of cerebellar–cerebral and cerebellar–basal ganglia circuitry [56]. The recent observations of reward-related activity patterns in the cerebellar cortex highlight the possibility that cerebellar dysfunction may not only result in altered sensorimotor integration. The cerebellar prediction of outcomes for an action may apply to a broad range of modalities. Finally, the cerebral–striatal connectivity represents a potential circuit substrate for directly linking cerebellar outputs to the evaluation of rewards and the selection of favorable actions. Probing the functional contribution of circuitry as well as its contribution to specific domains of autism phenotypes will be a formidable challenge for the future.

Conflict of interest statement

Nothing declared.

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