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Contributions of the cerebellum for predictive and instructional control of movement

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The cerebellum with its layered structure and stereotyped and conserved connectivity has long puzzled neurobiologists. While it is well established that the cerebellum functions in regulating balance, motor coordination and motor learning, how it achieves these end results has not been very clear. Recent technical advances have made it possible to tease apart the contributions of cerebellar cell types to movement in behaving animals. We review these studies focusing on the three major cerebellar cell types, namely: granule cells, Purkinje neurons and the cells of the deep cerebellar nuclei. Further, we also review our current understanding of cortico-cerebellar and basal ganglia-cerebellar interactions that play vital roles in motor planning and motor learning.

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Introduction

The cerebellum is among the oldest parts of the vertebrate brain and is conserved from fish to mammals [1–3]. Though originally postulated to function in motor control and motor learning, it is now clear that the cerebellum is also involved in higher level cognitive processing [4–6]. The modular organization of the cerebellum (Figure 1a) gave rise to speculation that the cerebellum could be performing similar computations on different inputs. Yet, the nature of these computations is still a matter of intense research. Studying cerebellar control of movements offers us the best paradigm for understanding cerebellar computation, as movements can be stereotyped and are quantifiable. Indeed much progress has been achieved in this regard. Though the exact behavioral module studied and recording techniques may vary from one study to another, a few common principles of cerebellar function emerge from these studies.

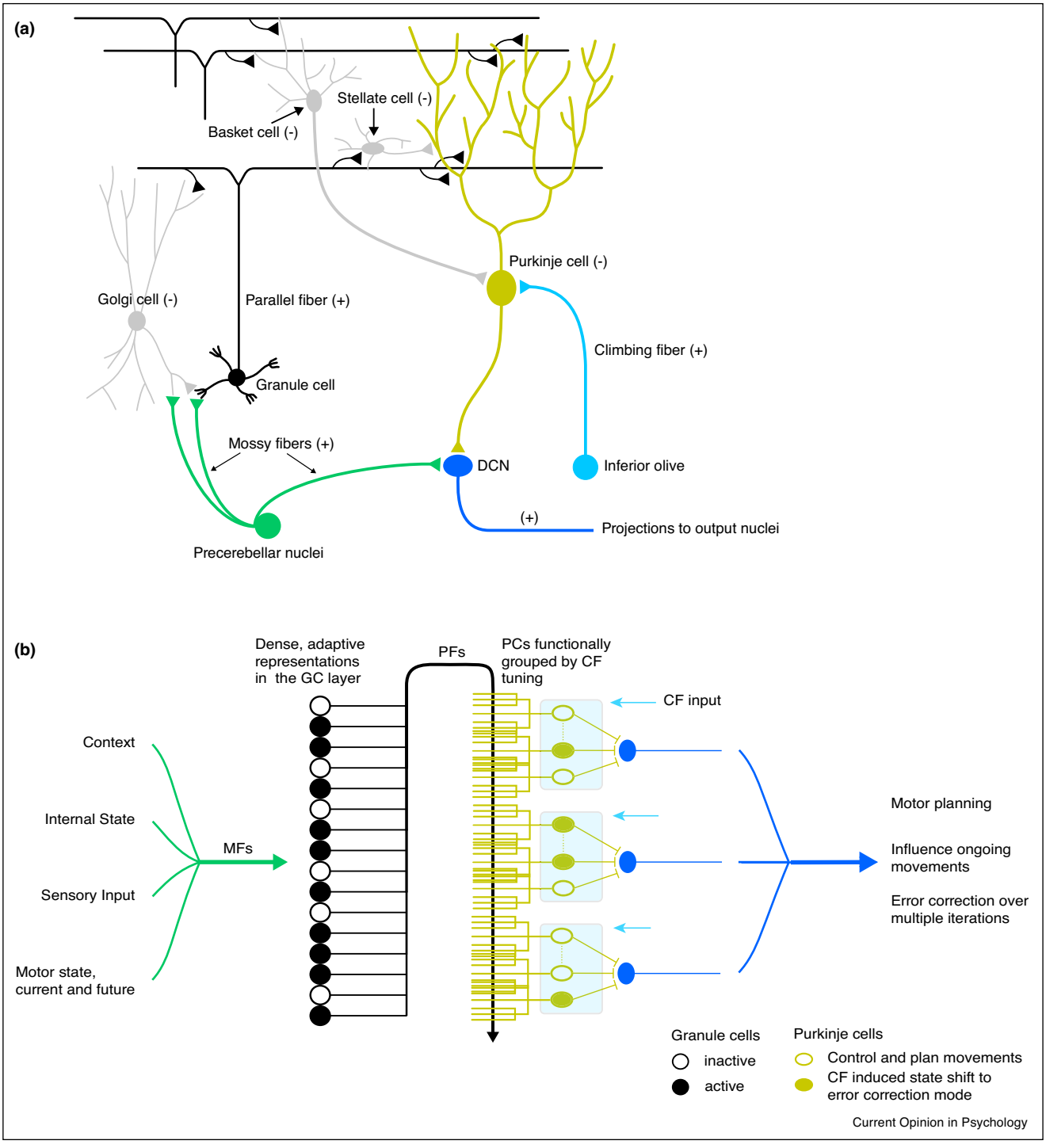
Dense, adaptive representations in granule cells

Cerebellar granule cells, the most numerous neuronal type in the vertebrate brain, receive inputs from mossy fibers originating primarily from the pontine nuclei and send long axons called parallel fibers into the molecular layer, where they make excitatory synapses onto the elaborate dendrites of Purkinje neurons (PNs; Figure 1a). Classical theories of cerebellar computation predicted that, as a population, granule cells must encode mossy fiber input sparsely such that each granule cell is highly selective in the combination of inputs that it is activated by and relays this particular combination of inputs to PNs [7,8]. Granule cells, however, have been difficult to record from, owing to their small size, dense packing and relatively less accessible anatomical location. Recent advances have enabled optical and electrical recording of granule cell activity in awake, behaving animals and have yielded unexpected results [9,10•,11••,12–14]. Dense representations of sensory, motor or a combination of sensory and motor variables were observed in granule cells of larval zebrafish [11••] and in rodents during classical [9] or operant [12] conditioning. During the course of training, granule cell activity evolved to predict the conditioned response [9], suggesting that the association between CS and US is present even at the input stage of the cerebellum. In an operant conditioning task, granule cells were shown to encode the expectation of a reward while still other granule cells reported the presence or omission of the reward [12].

Recordings from single granule cells during locomotion [15] or whisking [16] revealed that individual granule cell firing patterns follow mossy fiber input with high fidelity. In mice that were walking on a cylindrical treadmill, both mossy fiber-evoked EPSPs and granule cell firing contained a robust representation of gait during voluntary locomotion. The step cycle of the mice could be predicted from granule cell firing rate or mossy fiber EPSPs using a probabilistic model [15]. This suggests that a locomotor code already exists in mossy fiber input and is encoded by individual granule cells in a rich manner.

Further, mossy fiber inputs could themselves signal context or serve a modulatory role. This was illustrated in a study where mice were trained in a delay eyeblink conditioning task while they moved on a treadmill in a self-paced manner. Increased locomotor activity

Figure 1



(a) Circuit organization of the cerebellum. **(b)** Schematic showing flow of information through the cerebellum. Granule cells encode a rich and dense representation of a variety of input streams present in the mossy fibers. Purkinje cells employ both rate and temporal codes to encode highly convergent input from granule cells. Both granule cell and Purkinje cell activity is modulated by context and internal state as well as learning over longer timescales. Convergent, tuned Purkinje cell input to cells of the DCN regulates spike timing in the DCN, which influences ongoing and future movements.
CF, climbing fiber; DCN, deep cerebellar nucleus; GC, granule cell; PF, parallel fiber; PC, Purkinje cell.

correlated with faster learning and greater conditioned response amplitude. This effect could be reproduced by enforcing different speeds of locomotion or by simulating locomotor activity by low-intensity background stimulation of mossy fibers [17•], indicating that the observed effect is due to modulation of cerebellar computation by a change in internal state induced by background locomotor activity.

These studies have uncovered a new dimension to cerebellar computation at the granule cell layer that could vastly expand the repertoire of functions performed within the cerebellum. They show that even at the level of the cerebellar input layers, significant correlates of motor kinematics, associative learning and behavioral context are present (Figure 1b). It remains to be seen how such rich and dense information is processed further by downstream cell types in the cerebellum.

Representation of locomotor kinematics in PNs

PNs receive thousands of weak synapses from parallel fibers and a single strong excitatory synapse from climbing fibers, which are axons from the inferior olive (Figure 1a). PNs are spontaneously active and generate two kinds of output: simple spikes (SS) and complex spikes (CS). While parallel fiber excitation can increase SS rates, climbing fiber inputs initiate CS consisting of several spikelets riding on top of a depolarization [18]. In addition, PNs have been shown to exhibit membrane potential bistability in larval zebrafish [19••] and rodents [20]. At depolarized membrane potentials or 'up' states, PNs generate tonic SS and at hyperpolarized membrane potentials or 'down' states, they generate bursts of SS.

Recordings of PNs during routine movements, sensorimotor recalibrations or during classical conditioning have thrown up interesting insights and questions. One question is whether PNs use a rate code or temporal code and the answer seems to be both. In monkeys performing saccades, PNs were shown to multiplex rate codes and temporal codes by using the firing rate to linearly encode movement kinematics and firing pauses to represent the timing of movement onset [21]. A second question is whether PN outputs represent a forward model which predicts movement or sensory consequences of it or an inverse model which instructs movement to achieve a desired goal [22,23]. Although this is still the subject of intense research, one possibility is that PN firing could represent forward or inverse models in a task-dependent or context-dependent manner [22–24]. PNs have been shown to represent a mixture of kinematic variables [25••,26–32] as well as performance errors [32–34] in their SS and CS activity. New studies also show motor context-dependent modulation of SS by olivary inputs [29].

In monkeys trained to perform directed saccades, errors were induced by moving the target after saccade onset. PNs showed increased probability of CS error signals if the error was in their preferred direction. When PNs were grouped according to their preferred error direction, SS responses of such ensembles could predict saccade direction and velocity [35]. The timing of the directionally tuned CS error signal determined how simple spikes and behavior were modulated in subsequent trials. When the CS occurred in a window around 110 ms after saccade end, irrespective of whether there was an actual error, SS rate was reduced and saccade velocity in the direction of the error was increased [36••]. Taken together, these recent studies suggest anatomical segregation of PNs and their pre-motor targets based on the olivary input they receive, serving as a mechanism for SS modulation readout.

If modulation of SS affects subsequent behavioral output can manipulations of SS firing rate modulation rescue coordination and locomotion deficits in cerebellar mutants? Ataxic *tottering* mutant mice show prolonged swing phases and poor coordination of limbs. Synchronous optogenetic activation of PNs in these mutants during rest initiated stepping or whole body twitches while the same stimulation during locomotion inhibited stepping, suggesting that timed and synchronous activation of ensembles of PNs can rescue cerebellar deficits [37]. Such approaches could form the basis for therapeutic interventions in cerebellar ataxic patients in the future.

Cerebellar nuclei instruct ongoing movements

PNs inhibit their downstream targets in the deep cerebellar nucleus (DCN; Figure 1a). The DCN, broadly subdivided into the dentate, interposed and fastigial nuclei, are the primary output from the cerebellum and send long-range projections to several regions in the brain. When activity in DCN neurons was perturbed pharmacologically, optogenetically or by mutations, increased latencies or irregular movements were observed [31,38–40]. Genetic ablation of one particular subtype of DCN cells recapitulates these results. The urocortin3 positive large glutamatergic neurons of the anterior interposed nucleus ($IntA^{ucn3}$) are concerned with forelimb movement and project to the cerebellar cortex as well as to the motor thalamic and motor cortical forelimb regions. Ablation of these cells resulted in over reaching errors in a reach task and in abnormal limb kinematics during free walking. Abnormal limb kinematics were also seen when $IntA^{ucn3}$ neurons were photostimulated during free walking [41]. This suggests a role for temporal specificity in DCN regulation of locomotion. In a further exploration of this idea, two papers investigate DCN activity during locomotion and whisker movements. Sarnaik and Raman [42••] performed video recordings of hindpaw movements of mice on a treadmill while simultaneously optogenetically stimulating PNs and recording from DCN neurons in the interposed nucleus. They showed that light stimuli expected to cause asynchronous firing of PNs, and therefore, asynchronous inhibition of

DCN neurons produce greater frequency of locomotor 'slips' such as arrested movement, prolonged paw movements or incomplete strides. Synchronous inhibition also resulted in locomotor slips but at a relatively lower frequency. By measuring DCN firing rates during slip and non-slip trials, Sarnaik and Raman showed that when inhibition allowed the expression of the natural stride-related spike rate modulation, locomotor slips were not seen. However, when inhibition disrupted the normal cyclical rate modulation, locomotor slips occurred [42••]. In the second study, reflexive whisker movements were shown to be driven by rapid and brief elevations of DCN firing rate, sculpted by inhibition from PNs [31]. These findings demonstrate clearly that DCN neurons are likely to instruct movements via the timing of their spikes with respect to intended movement.

Facilitation of spiking in a subset of DCN neurons predicted the occurrence of a conditioned eyeblink response, approximately 25–50 ms later. Optogenetically suppressing spike facilitation in this temporal window abolished the conditioned eyeblink response [38]. Taken together, these studies suggest that though PNs and DCN neurons share most of their synaptic inputs, spike time in DCN neurons is determined by relief from synchronous PN inhibition, resulting in modulation of their basal firing rates in a specific temporal window. This modulated spike train provides critical information for the execution of ongoing learned and volitional movements (Figure 1b).

Instructional participation in motor planning and learning

It has been suggested that the cerebellum, basal ganglia, and motor cortex could be distributed processing modules controlling the selection and planning of movements [43]. The basal ganglia and cerebellum are both important motor centers in the vertebrate brain; yet, they were thought to provide independent and complementary streams of information to the cortex. Evidence is now mounting that in birds, rodents and non-human primates, the cerebellum and basal ganglia communicate with each other disynaptically [44–51,52••]. In songbirds, the disynaptic projection from the DCN to the basal ganglia region Area X, via the thalamus [44,45] was recently shown to be critical for song learning [44]. In mice, the DCN project to medium spiny neurons and cholinergic interneurons of the dorsal striatum through a disynaptic connection routed via the thalamus. Acute chemogenetic silencing of these cerebello-striatal projections led to deficits in reward-driven motor behavior [47].

When monkeys were trained to perform saccades after short, medium or long delay periods, neurons in the striatum ramped up their activity during the delay period such that the ramp-up started at the same time but the slope of the ramp decreased with increasing delays. During the same task, neurons in the cerebellar dentate nucleus also increased their activity but the timing of the ramp-up varied with different delays while the slope remained constant. Further, trial to trial variability in saccade initiation was reflected earlier on in cerebellar activity than in striatal activity. These results led the authors to conclude that while the striatum could function like a stop-watch, keeping track of elapsed time with respect to a desired interval, the cerebellar nuclei may be involved in the planning and execution of the desired motor response at the end of the interval [52••].

Other studies exploring information flow between the cerebral cortex and the cerebellum also reveal a role for the cerebellum in planning motor acts. Persistent activity in the anterior lateral motor cortex (ALM) is known to predict future movements and is, therefore, thought to represent motor planning [53]. The ALM projects to the fastigial nuclei via the pontine nuclei and the fastigial nuclei in turn project to the ALM via the thalamus. Persistent activity predictive of future movements was also observed in neurons of the fastigial nuclei. This activity in the ALM and in the fastigial nucleus occurs during a delay period when movement has not yet started. Photoinhibition of the fastigial nucleus during the delay period caused incorrect responses and also biased future movements. Concomitant with these behavioral outcomes, motor preparatory activity in ALM was abolished by photoinhibition of the fastigial nucleus. Likewise, photoinhibition of the ALM in the delay period abolished planning-related firing in the fastigial nucleus [54••]. These findings show that the cortico-cerebellar loop via the thalamus is integral to the planning of movements as opposed to the generally held view that the motor cortex is concerned with planning and the cerebellum, only with online error correction and coordination (Figure 1b).

Conclusions

Recent findings reviewed here show that the cerebellum is involved in multiple phases of motor control, including planning, execution and long term error correction. The role played by the cerebellum during any task is likely to be a combination of more than one of these functions performed in a task and context-dependent manner. Part of the answer to how the same microcircuits perform different functions could lie within the input output transformations performed by individual microcircuits aided by single neuronal dynamics like membrane potential bistability in PNs. Larger scale readouts of population activity in the cerebellum and regions it interacts with will help us form a more comprehensive understanding of the adaptability of the cerebellum and how the various functions it performs integrate together to shape motor output.

Conflict of interest statement

Nothing declared.

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