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# Regional functionality of the cerebellum

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### **Regional functionality of the cerebellum** Laurens Witter<sup>1,2</sup> and Chris I De Zeeuw<sup>1,3</sup>



Over the recent years, advances in brain imaging, optogenetics and viral tracing have greatly advanced our understanding of the cerebellum and its connectivity. It has become clear that the cerebellum can be divided into functional units, each connected with particular brain areas involved in specific tasks, allowing afferent and efferent pathways to process taskspecific information. The activity patterns in these pathways can be widely different among cerebellar areas. Therefore, it is expected that each cerebellar module is tailored to interpret inputs with a specific activity profile. In this paper we will review the evidence for region-specific inputs, region-specific connectivity with the rest of the brain, and region-specific processing within the cerebellum.

### Addresses

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### Introduction

The cerebellum plays a pivotal role in several behaviors that range from reflexive and planned motor coordination to emotional and cognitive processes. This wide range of behaviors all need to be processed by the same basic cerebellar circuitry. The cerebellar cortical circuitry is highly stereotyped. Mossy fibers synapse onto granule cells and Golgi cells in the granule cell layer. Granule cells in turn give rise to parallel fibers that traverse large portions of the cerebellar cortex to synapse onto Golgi cells, molecular layer interneurons and Purkinje cells. Climbing fibers synapse onto Purkinje cells and molecular layer interneurons to provide learning or instructive signals. Golgi cells provide feedforward and feedback inhibition to granule cells, whereas molecular layer interneurons provide feedforward inhibition to Purkinje cells. Ultimately, all information passes through Purkinje cells to reach neurons in the cerebellar nuclei from where signals are sent to a myriad of brainstem and midbrain nuclei.

Over recent years evidence has emerged that the cerebellum can be subdivided into several specialized regions to facilitate control of specific behaviors. Below we identify the basis of cerebellar zonation and its interconnectedness with the rest of the brain, we lay out what information is relayed to the cerebellum and how activity in various mossy fiber pathways differs between cerebellar partitions, and finally, we highlight evidence that different zones in the cerebellum are adapted to process differential information in their afferents.

# The cerebellum is divided into functional zones

The cerebellar vermis and hemispheres can be subdivided into ten lobules. Classically, each lobule has been considered to be responsible for a particular sensorymotor function [1]. However, over the past decades it has become clear that a lobule should not be considered as the main functional unit, since many cerebellar control functions can span multiple lobules. For example, one eyeblink region in the mouse cerebellum has recently been identified at the base of the primary fissure in the hemispheric extensions of lobules V and VI, implicating that parts of both lobules may be involved in eyeblink conditioning in mice [2<sup>••</sup>,3]. In addition, transsynaptic tracing of the eyeblink circuits in mice suggests that their cerebellar cortex contains also various other eyeblink regions, dispersed over lobules in not only the hemispheres, but also vermis and paravermis [4,5]. This potential multi-lobule organization of cerebellar eyeblink control is supported by electrophysiological stimulations and recordings of the eyeblink regions in cat [6]. Thus, even though specific functionalities might still be attributed to particular regions in different lobules, it is difficult to sustain the view that a lobule forms the main functional unit.

In mediolateral direction the cerebellum can be divided into functional stripes delimited by zebrin. Stripes of Purkinje cells expressing zebrin are alternated with Purkinje cells negative for this protein. Each stripe seems to work more or less on its own, since dendrites and axons of most types of cerebellar neurons have been shown to not cross zebrin borders [7,8]. Moreover, in most cases the climbing fiber input and frequently also the mossy fiber input appear to respect the zebrin borders [9,10]. In general, the zebrin-organization of the cerebellum is highly conserved throughout phylogeny in that it can be observed not only in mammals, but also in for example pigeon, catfish, goldfish, mormyrid fish, star-nosed mole and echidna [9,11–14]. Interestingly, in pigeon the zebrin identity of Purkinje cells in the uvula and flocculus has been shown to be associated with a preferred activity encoding a particular optic flow such as contraction, translation or rotation  $[12^{\circ}]$ . Finally, at a more detailed level zebrin zones can be even further divided into microzones, which are characterized by a particular functional response of climbing fibers firing in synchrony [15,16].

Combining various cerebellar maps may thus result in a finely parcellated cerebellar cortex consisting of putative functional units. If these delineated units indeed represent functional units, it is expected (A) that each unit is connected in a specific manner to the rest of the brain, (B) that the activity observed in each unit sub-serves the function of that unit, and (C) that adaptive processing in that unit is tailored towards the function of the unit (Fig. 1). These three predictions will be further elaborated upon in the next sections.

### The cerebellum forms closed loops with the rest of the brain

Output from Purkinje cells is processed by neurons in the cerebellar nuclei, from where it is sent off to various

#### Fig. 1



The cerebellum can be divided into the anterior region (red), posterior region (green) and vestibular region (blue). Each region has its own set of afferent and efferent projections. The activity profiles of these afferent projections influence cerebellar activity and processing, ultimately influencing the firing frequency and regularity of Purkinje cells. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

nuclei in the midbrain and hindbrain [17,18]. Each functional unit of the cerebellar cortex is connected to a specific subnucleus of the cerebellar nuclei [19,20], with the most lateral parts of cerebellar cortex connected to the lateral or dentate nucleus, intermediate parts of cortex being connected to the interposed nucleus and most medial parts connected to the medial or fastigial cerebellar nucleus [15]. A similar scheme can be observed for climbing fiber projections from the inferior olive to the cerebellar cortex and nuclei [21]. Inhibitory connections from the cerebellar nuclei to the inferior olive close the olivo-cerebellar loop, thus enabling Purkinje cells in cerebellar cortex to regulate their own climbing fiber discharge [22°,23°].

Excitatory outputs from the cerebellar nuclei project for example to the thalamus and thereby indirectly influence neocortex, striatum and hippocampus [22°,24,25,26°°]. The projection to the thalamus is sufficiently robust to instantaneously stop generalized seizures in the cerebral cortex following optogenetic stimulation of the cerebellar nuclei [27]. Similarly, blocking a prominent cerebellostriatal connection has recently been shown to alleviate motor symptoms in a mouse model for cerebellar-induced dystonia [26<sup>••</sup>,28], further highlighting the relevance of the connectivity of the neocerebellum with the neocortex. Lobules I through V seem to be mostly involved with sensorimotor cortex, whereas lobules VI through part of lobule IX are more connected with association cortices [29,30,31,32°,33,34,35°°,36]. In contrast, no prominent connections have been found between lobule X (vestibulocerebellum) and cerebral cortex. The functional connectivity with cerebral cortex coincides with the connectivity between the cerebellum and pontine nuclei, thus creating additional, closed and topographically organized loops [31,32<sup>•</sup>,33,37,38]. Moreover, the connectivity to the cerebral cortex coincides largely with that to afferent nuclei in the brainstem. For example, sensory nuclei, such as the external cuneate nucleus, project mainly to the sensorimotor parts of the cerebellum [39-42], pontine nuclei converge mainly on the central and posterior zones of cerebellar cortex [41<sup>••</sup>], and vestibular nuclei project mainly to lobules IX and X [43]. Thus, the cerebellum is involved in many closed loop circuitries including not only those of the olivocerebellar modules, but also those of the cerebral cortex.

## Regional differences in input dictate cell physiological responses

Activities in afferent nuclei to the cerebellum have not been investigated in great detail yet, but seem to differ in their firing pattern. Neurons in sensory nuclei in the brainstem (e.g. cuncate nucleus) often respond with a bursting response upon peripheral stimulation [39,40]. Cerebellar projecting neurons in the lateral reticular nucleus can show similar bursting behavior [39,40], but also clock-like activity with profound pausing upon peripheral stimulation [44,45]. Interestingly, the pontine nuclei contain various types of neurons, which can show different levels of tonic activity intermingled with bursts of activity [46,47]. Neocortex drives activity in cerebellum and blocking activity in neocortex during slow wave activity blocks slow wave activity in cerebellum [48]. This relation seems especially strong between primary sensory cortex and cerebellum [49]. The cerebral-pontine-cerebellar connection therefore seems of particular importance for binding cerebral and cerebellar activities.

Vestibular projections to the flocculo-nodular zone of the cerebellum have been extensively studied. Primary vestibular afferents can be subdivided into regular and irregular afferents. In anesthetized rodents, regular afferents show a remarkable linearity in their response to vestibular stimulation and short-term synaptic plasticity is virtually absent at physiological rates in these afferents. This facilitates a linear translation from vestibular afferent to vestibular nuclei neuron [50,51]. However, in awake behaving monkeys, non-linear translations can occur at this synapse when superimposed frequencies are used for vestibular stimulation [52]. Moreover, when the signals of regular and irregular afferents are integrated, vestibular nuclei neurons seem to show activity, which is even more irregular than that of irregular afferents, making them rely on averaging multiple neurons for reliable signaling [53]. By extension, mossy fibers arising from vestibular nuclei neurons in the anesthetized preparation show predominantly tonic activity, providing a regular drive to granule cells [54<sup>•</sup>], even though the level of variation in firing is presumably higher in awake behaving animals.

Clearly, each part of the cerebellum receives tailored inputs. Anterior cerebellum receives inputs mainly from sensory brainstem nuclei and sensorimotor afferents from forebrain that have a mixed bursting and tonic character. The central and posterior cerebellum is connected with association cortices, but virtually nothing is known about the activity in these pathways. Finally, the flocculonodular zone receives vestibular inputs that are probably predominantly tonically active.

## The cerebellum performs region-specific computations

Different from the firing frequency of climbing fibers, which does not reach far beyond a few spikes per second, the firing frequency of mossy fiber inputs can range from several up to several hundred spikes per second. Thus, in addition to the differences in firing patterns described above, mossy fiber activity is also characterized by an enormous diversity in firing rates. Since this can also vary among regions, it raises the question to what extent the diversity in mossy fiber inputs translates into different cell physiological response properties of the various cell types in the different cerebellar lobules and zones. Differences in mossy fiber input have to be interpreted by granule cells. There is considerable disagreement whether granule cell spiking can be elicited by a single mossy fiber input firing at low frequency [55] or whether several inputs at a high frequency are needed to generate granule cell output [56]. The reason for these discrepancies might in part be found in the fact that these experiments were performed in different parts of cerebellar cortex, medial anterior and lateral posterior lobe, respectively [55,56]. Possibly, the expression patterns of relevant conductances have been adapted during evolution to the local demands of the regions involved. Indeed, granule cells in lobule II (anterior lobe) and lobule IX (posterior lobe) differ in their expression of the CaV3-Kv4 complex, which regulates the responsiveness to bursts versus tonic inputs [57<sup>••</sup>]. Not surprisingly, granule cells in lobule II are more responsive to bursts of mossy fiber input, whereas granule cells in lobule IX are more sensitive to slow changes in mossy fiber input [57<sup>••</sup>]. This mechanism may present an elegant example where cell physiology is tuned to optimally interpret afferent inputs.

Activity in the granule cell layer directly affects the activity of molecular layer interneurons, which inhibit Purkinje cells, as well as that of Purkinje cells themselves, which form the sole output neuron of the cerebellar cortex. Indeed, we have recently shown that activity profiles from mossy fibers are transmitted through the cerebellar cortex. dictating firing regularity of interneurons and Purkinje cells [54<sup>•</sup>]. Purkinje cells express a tonic current that drives neurons to spike at 50-100 Hz in slice and in vivo, and at about 30 Hz in isolated culture [58]. This intrinsic tonic spiking, which in vivo can be influenced by excitatory input from granule cells and inhibition from molecular layer interneurons, has been investigated in slices in the absence of synaptic transmission [59,60,61°]. A comparison of Purkinje cells in the anterior cerebellum with those in the vestibulocerebellum revealed that lobule X Purkinje cells can sustain tonic firing rates longer with less adaptation compared with anterior lobe Purkinje cells [60]. At the same time lobule X Purkinje cells are generally less excitable and therefore show lower average firing rates than Purkinje cells in anterior cerebellum. In effect, Purkinje cells in lobule X may trade off their excitability to sustain constant or slowly modulated firing rates at higher input intensities. Purkinje cells in the anterior cerebellum on the other hand are better positioned to faithfully transmit short high-intensity inputs, like those arising from bursty granule cell-relayed mossy fiber inputs associated with the anterior cerebellum  $[54^{\circ}, 59]$ .

Two recent studies investigated the firing frequencies and regularity of Purkinje cells throughout the cerebellum in vivo  $[61^{\circ}, 62^{\circ}]$ . The most prominent land-mark feature of the output frequency of a cerebellar module seems to be expression of zebrin, but the actual determining factors are probably other zone-related proteins [61°]. Purkinje cells in zebrin-positive zones showed on average a lower firing frequency than those in zebrinnegative zones [61°,62°]. In accordance with the aforementioned in vitro studies, firing frequency decreased when moving from anterior cerebellum, which contains mostly zebrin-negative cells, to the vestibulocerebellum, which is dominated by zebrin-positive cells.

Interestingly, Zhou et al. [61<sup>•</sup>] found in awake mice a slight difference in regularity between the different zones of the cerebellum. The anterior zone showed lowest regularity, while PCs in the vestibulocerebellum were most regular. This difference however disappeared when looking at in vitro firing of Purkinje cells, highlighting the potential importance of mossy fiber inputs [54<sup>•</sup>]. In contrast, Xiao et al. [62<sup>•</sup>] found in anesthetized rats that PCs in zebrin-positive zones fired more irregularly than those in zebrin-negative zones. Both, Zhou et al. and Xiao et al., found a slight difference in complex spike firing rates and complex spike pause duration between PCs in zebrin-positive and -negative zones [61<sup>•</sup>,62<sup>•</sup>], highlighting homeostatic regulation of firing of inferior olivary neurons through the cerebellar cortical and nuclear loop [22<sup>•</sup>,23<sup>•</sup>].

### Conclusions and future directions

In this article we have reviewed evidence for the existence of functional cerebellar zones that are connected to other brain areas in a zone-specific manner. Evidence has emerged that functional zones of the cerebellum are specialized in their physiology to process specific kinds of inputs. Substantial circumstantial evidence indicates that mossy fiber systems, which often target lobule-oriented regions, will impact the firing behavior within a module and the potential for its adaptation (Fig. 1). Taken together, it seems that the precise physiological processing of a cerebellar module is adapted to its tasks and the mossy fiber sources involved and that the corresponding physiology can tell us about the functionality of the cerebellar module.

Before we can come to a full understanding of the relation between cerebellar function, cerebellar zonation, cerebellar interconnectivity and cerebellar connectivity, there are several issues that need to be resolved.

First, there is relatively little known about the physiology of pontine nuclei neurons during behavior. Some information is available on gaze information coded in these neurons, but many other modalities should be transmitted through the pontine nuclei to the cerebellum [26<sup>••</sup>,31,37,41<sup>••</sup>,63]. Understanding what information exactly is relayed to the cerebellum will prove essential for the understanding of cerebellar function in relation to the rest of the brain.

Second, although some is known about cerebellar projections to the thalamus, the full extent of cerebellar impact on processing in the mid- and forebrain remains to be elucidated. A thorough understanding of what information is relayed and which areas are affected is necessary to advance our understanding of cerebellar processing.

Third, evidence about region-specific processing in the cerebellum is now emerging slowly but steadily. The cerebellar cortex is much less stereotyped than classically described [64]. Investigations into signal processing of specific areas of the cerebellar cortex will help us understand how the cerebellum integrates information from diverse sources and how its output is relevant for its target structures. Also, insight in different ways inputs are treated will help us understand the computations the cerebellum performs.

Finally, all these issues need to converge into a greater scheme: What does the cerebellum compute exactly? What do specific inputs contribute to cerebellar computations? And how are downstream areas influenced by the outcomes of cerebellar processing?

### **Conflict of interest statement**

Nothing declared.

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