A comparative approach to cerebellar function: insights from electrosensory systems

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Abstract

Despite its simple and highly-ordered circuitry the function of the cerebellum remains a topic of vigorous debate. This review explores connections between the cerebellum and sensory processing structures that closely resemble the cerebellum in terms of their evolution, development, patterns of gene expression, and circuitry. Recent studies of cerebellum-like structures involved in electrosensory processing in fish have provided insights into the functions of granule cells and unipolar brush cells--cell types shared with the cerebellum. We also discuss the possibility, supported by recent studies, that generating and subtracting predictions of the sensory consequences of motor commands may be core functions shared by both cerebellum-like structures and the cerebellum.

Introduction

The circuitry of the cerebellum is remarkably simple, containing just a handful of cell types connected in an orderly way[1;2]. Purkinje cells, the sole output neurons of the cerebellar cortex, receive just two classes of excitatory input. Parallel fibers, the axons of granule cells, form many, weak synaptic connections with each Purkinje cell (on the order of hundreds of thousands). Granule cells themselves receive a wide variety of sensory and motor signals from many parts of the brain and distribute this information widely, i.e. each parallel fiber travels long distances, contacting many Purkinje cells. In addition, each Purkinje cell receives a single powerful climbing fiber input from the inferior olivary nucleus in the brainstem. Early theorists found this architecture highly suggestive. They speculated that the climbing fiber conveys elemental motor commands[3] or error signals[4] and serves to instruct plasticity at parallel fiber to Purkinje cell synapses. By virtue of this mechanism Purkinje cells were believed to act as powerful computational devices for learning to automate or correct movements. Though these early theories remain influential and have received much experimental support, including experimental verification of plasticity at parallel fiber synapses[5], we still have little or no idea what most parts of the mammalian cerebellum actually do.

One reason for this is that most regions of the cerebellum are neither directly connected to the sensory periphery nor do they directly control muscles. Hence inputs to the cerebellum are typically complex, highly-processed signals and the effects of most regions of the cerebellum on behavior are indirect and typically not well understood. This situation greatly complicates efforts to understand the input-output transformation(s) performed by cerebellar circuitry[6]. A traditional approach to understanding cerebellar function has been to sidestep these issues by focusing on carefully selected regions of the cerebellum, e.g. those involved in eye movement control, which do receive relatively simple inputs and which are directly involved in motor control[7-9]. This brief review focuses on an alternative approach that takes advantage of the fact that cerebellum-like circuitry is not only located within the cerebellum but is also found at the initial stage of sensory processing for the electrosensory, mechanosensory lateral line, auditory, and visual systems in numerous vertebrate groups[10;11]. Understanding the function of these cerebellum-like sensory structures is made easier because they are just one synapse away from the sensory periphery.

The numerous similarities as well as the differences between cerebellum-like structures and the cerebellum with respect to their evolution, development, gene expression, and circuitry have been discussed at length elsewhere[10-12]. For the purposes of this review similarities and differences in circuitry are the most important (**Figure 1**). Many circuit elements are shared between cerebellum-like structures and the cerebellum including: mossy fibers, granule cells (GCs), parallel fibers, Golgi cells,

unipolar brush cells (UBCs), molecular layer interneurons, and equivalents of both Purkinje cells and deep nuclear cells. Like Purkinje cells, principal cells in cerebellum-like structures receive input from parallel fibers. However, instead of a climbing input from the inferior olive they receive a direct input from the sensory periphery.

What are these cerebellum-like circuits doing at initial stages of sensory processing? Extensive studies of cerebellum-like structures at the initial stage of electrosensory processing in fish indicate that these structures function to predict and cancel out self-generated sensory input. *In vivo* recordings have shown that pairing an electrosensory stimulus with signals related to the fish's own behavior, e.g. a motor command or proprioceptive input related to a passive movement of the body, results in a gradual reduction in the response to the stimulus[13-15]. Removing the stimulus reveals effects of the motor command or passive movement that resemble highly-specific negative images of the effects of the previously paired (and now predicted) stimulus. The mechanisms of negative image formation have been investigated using a combination of *in vitro*, *in vivo*, and theoretical approaches for over three decades[16;17]. Parallel fibers convey rich information about the fish's own behavior, including motor corollary discharge and proprioceptive signals. Moreover, their synapses with principal cells exhibit an anti-Hebbian form of synaptic plasticity[18]. Increases in principal cell firing that occur together with (i.e., can be predicted by) parallel fiber input are opposed and eventually cancelled by weakening of parallel fiber synapses. Conversely, predictable decreases in principal cell firing are opposed by increases in parallel fiber synaptic strength. As will be discussed below, these mechanisms closely parallel those thought to underlie motor learning in the mammalian cerebellum.

Functions of granular layer circuitry

Mossy fiber inputs to the cerebellum are recoded in a much larger number of GCs. Early theories discussed above as well as more recent models[19;20] posit that GCs provide a rich basis for cerebellum-dependent learning. However the practical difficulties involved in recording *in vivo* from these small, densely packed neurons have long thwarted experimental tests[21;22]. The cerebellum-like electrosensory lobe (ELL) of weakly electric mormyrid fish has proven a valuable system to perform such tests, in part because of the relative ease of recording GC responses to behaviorally relevant stimuli in an awake preparation. *In vivo* intracellular recordings from GCs in mormyrid fish provided the first evidence for the longstanding idea that GCs respond selectively to combinations of mossy fiber inputs[23]. Individual GCs were shown to integrate separate mossy fiber inputs conveying electric organ corollary discharge inputs related to the fish's electric organ discharge (EOD) and proprioceptive input related to the position of the tail. Such integration allowed GCs to fire action potentials only when the tail was in a particular position and an EOD command had just occurred. Such highly selective GC representations are just what would be needed to allow principal cells to cancel out changes in electrosensory input due to the fish's own movements—a capacity that was demonstrated experimentally. Though originally questioned[24;25], a strong case for multimodal integration in granule cells has now also been established for the rodent cerebellum. Anatomical studies in mouse used genetic labeling to demonstrate widespread convergence of motor-related pontine mossy fibers and sensory-related external cuneate mossy fibers onto individual granule cells[26]. More recently, direct electrophysiological evidence for multimodal convergence in GCs in rodent cerebellum has been obtained both *in vitro*[27] and *in vivo*[28].

Another hypothesized function of the cerebellar granular layer is to generate temporal representations. For example, learning appropriately timed conditioned responses (CRs) in delay eyelid conditioning is hypothesized to rely on temporally diverse granule cell responses (**Figure 2A**). In delay eyelid conditioning a neutral CS, typically a light or tone, is repeatedly paired with an unconditioned stimulus (US), typically a periorbital shock or airpuff to the eye. CS information is conveyed to the cerebellar cortex by granule cells and US information by climbing fibers. CRs are believed to be due, at least in part, to “learned” pauses in Purkinje cell firing[29]. The timing of such pauses is matched to the CS-US delay and bears a systematic relationship to the eyelid CR[30-33]. Leading models of eyelid conditioning suggest that the pauses emerge as a result of plasticity at parallel fiber synapses[34;35]. Critically, adaptive timing only emerges from such models if there is temporal diversity in GC responses,

e.g. if different GCs are active at different delays or with different patterns relative to the CS onset. However, to date there is no direct evidence for temporal representations in mammalian cerebellar GCs and models which depend on them have been called into question[36;37]. An alternative hypothesis has been proposed which involves a timing mechanism intrinsic to the Purkinje cells themselves[38]. Recent studies of the ELL of weakly electric mormyrid fish have shed light on these issues.

Models of negative image formation in the mormyrid ELL closely resemble those described above for delay eyelid conditioning (**Figure 2B**). Temporally-specific negative images, like timed pauses in Purkinje cells, are thought to be generated by synaptic plasticity acting on GC temporal representations[39]. In the case of the mormyrid ELL the question is how copies of motor commands to discharge the EOD, which are brief pulses lasting just a few milliseconds, could be used to predict and cancel responses in ELL neurons that last for up to 200 ms. This is a specific version of the more general question of how the brain transforms copies of motor commands into predictions of sensory events. A recent study recorded motor corollary discharge responses related to the EOD in hundreds of GCs along with the responses of mossy fibers and UBCs (the excitatory inputs to GCs) and Golgi cells (the inhibitory input to GCs)[40]. The main findings were: (1) that GC responses were more temporally diverse and delayed than those of mossy fibers and (2) that this temporal diversity appeared to be generated within UBCs. An important role for UBCs is intriguing. On the one hand, *in vitro* studies in the mammalian cerebellum and the cerebellum-like dorsal cochlear nucleus have reported intrinsic and synaptic properties of UBCs consistent with the generation of temporally diverse and delayed responses[41-48]. On the other, the distribution of UBCs varies widely in different parts of the cerebellum and past models of eyelid conditioning have focused on Golgi cells as the source of temporally diverse and delayed responses in GCs. Theoretical modeling showed that unexpected temporal features of negative images in ELL neurons could be explained by anti-Hebbian plasticity acting on the measured GC responses. Hence this study provides links between GC input representations, a measured form of synaptic plasticity, and adaptive function in a cerebellum-like circuit. Whether or not the generation of diverse temporal representations is a general feature of granular layer processing awaits additional studies, e.g. recordings of CS-evoked responses in the granular layer of regions of the mammalian cerebellum involved in eyelid conditioning.

Forward models and cancellation in cerebellum-like structures and the cerebellum

A leading hypothesis regarding the role of the cerebellum in motor control is that it acts to generate predictions of the sensory consequences of motor commands[49-53]. Such predictions, known as forward models, could allow for rapid, online correction of movements despite noise and delays in sensory feedback. Though this hypothesis is supported by numerous lines of evidence including human clinical[54-56] and primate electrophysiological studies[57], little is known about whether and how forward models are actually implemented in cerebellar circuitry. In this context, the demonstration that cerebellum-like structures generate predictions of the sensory consequences of motor commands provides a valuable proof-of-concept for the forward model idea. However, one question has been whether mechanisms for predicting the sensory consequences of motor commands related to simple, highly stereotyped behavior like the EOD are sufficient to solve the more complex problem of predicting the sensory consequences of motor commands for movements. Recent studies of mormyrid fish addressed this issue by demonstrating that in addition to corollary discharge signals related to the EOD, mossy fibers in mormyrid fish also convey a rich set of skeletomotor corollary discharge signals related to the fish's swimming movements[58;59]. ELL neurons were shown to be capable of simultaneously generating and storing two opposite negative images related to different movement commands, i.e. commands to move the tail in opposite directions. This study, together with previous work in electrosensory systems demonstrating negative images related to ventilatory motor commands and tail and trunk proprioception[15;60;61], suggest that cerebellum-like circuits in fish are capable of generating more complex internal models of movement consequences, akin perhaps to those thought to be generated within the mammalian cerebellum.

Numerous possible uses for forward models have been proposed[62]. Within cerebellum-like structures in fish forward model predictions are used to cancel self-generated sensory input. Interestingly, evidence for cancellation of self-generated inputs also exists for regions of the mammalian cerebellum. The work of Cullen and colleagues has shown that neurons in the rostral fastigial nucleus as well as the vestibular nucleus (both nuclei receive direct input from Purkinje cells) encode head velocity when such rotations are applied by the experimenter, i.e. the animal is passively rotated, but not when the identical head velocity results from a voluntary movement[63]. Vestibular afferents respond identically in the two conditions, suggesting that self-generated vestibular signals are cancelled centrally. Recently, Brooks et al. took these findings a step further by devising a motor adaptation paradigm that made it possible to track the cancellation of self-generated vestibular inputs in individual cerebellar neurons in real-time[64]. Initially neurons showed no response to self-generated head movements, consistent with previous findings. Next the sensory (i.e. vestibular) consequences of the monkey's motor commands were abruptly changed by applying a force that resisted the head movement. Cerebellar neurons robustly encoded the now unexpected vestibular consequences of movement. Over time the animals adapted their behavior by issuing larger motor commands so that the actual head movement was the same as before application of the force. Neural responses gradually declined, as if they came to expect the unexpected vestibular input. These findings are remarkably similar to those in the mormyrid ELL where neurons respond initially to electrosensory inputs paired with self-generated motor commands but over time these responses are cancelled out.

Key next steps will be to attempt to reveal the circuit mechanisms underlying this cancellation in the cerebellum, e.g. by recording from Purkinje cells that target the rostral fastigial under the same experimental conditions. Along these lines, a recent study recording from rats during a balancing task reports changes in Purkinje cell responses consistent with the cancellation of predictable vestibular inputs[65]. Additional examples for cancellation should also be sought, for example in other regions of the cerebellum involved in processing sensory information[66]. Along these lines several recent studies have identified regions of the cerebellum that appear to process sensory and motor information related to the rodent whisker system[67-70] and computational models have suggested mechanisms via which the cerebellum could cancel out self-generated sensory signals related to whisker movement[71].

Finally, a possible role for the cerebellum in generating forward models and cancellation signals comes from a recent quantitative analysis of gait in mutant mice with selective degeneration of Purkinje cells[72]. The analysis suggested that gait ataxia in these animals can be understood in terms of a failure of forward model predictions. Of particular interest, the authors found that Purkinje cell degeneration mice were unable to cancel movements of one part of the body (i.e. swaying of the tail) that were passive consequences of active movements of other parts of the body (i.e. forward locomotion).

Conclusions

Recent studies of cerebellum-like structures in fish have provided unique insights into the function of cerebellar granular layer circuitry and important demonstrations of how cerebellar circuitry can function to predict and cancel the sensory consequences of motor commands. Despite obvious and important differences, some core operating principles appear to be shared between cerebellum-like structures and the cerebellum. The comparative approach offered by studies of electrosensory systems as well as other cerebellum-like sensory structures, such as the mammalian dorsal cochlear nucleus, are expected to be a continued source of insight into cerebellar function as well as into the broader question of how the brain integrates sensory information with internally generated predictive models.

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Figure legends

Figure 1. Circuitry of the mammalian cerebellum and the mormyrid ELL. Granular and molecular layer circuitry is similar in cerebellum-like structures such as the mormyrid ELL (right) and the mammalian cerebellum (left). The major difference between cerebellum-like structures and the cerebellum is the climbing fiber input from the inferior olive to the cerebellum (orange). Instead of a climbing fiber input cerebellum-like structures receive direct sensory input from the periphery (orange). Also, in cerebellum-like structures inhibitory Purkinje-like cells (green) synapse locally on glutamatergic efferent cells (labeled EC) whereas Purkinje cells in the mammalian cerebellum project to the cerebellar or vestibular nuclei. This is not a universal feature of the cerebellum however as Purkinje cells in the cerebellum of teleost fish are also interneurons that synapse locally on glutamatergic output cells. Small circles indicate excitatory synapses and lines indicate inhibitory synapses. Abbreviations: GC, granule cell; Go, Golgi cell; UBC, unipolar brush cell; MLI, molecular layer interneuron; PC, Purkinje cell; DCN, deep cerebellar nucleus; IO, inferior olive; MG, medium ganglion cell; EC, efferent cell.

Figure 2. Similarities between hypothesized mechanisms of eyelid conditioning in the cerebellum and negative image formation and sensory cancellation in the mormyrid ELL. **Left,** Purkinje cells (center, green) receive climbing fiber information about the unconditioned stimulus (US) (orange box, lower left) along with information about the conditioned stimulus (CS) conveyed by granule cells (green box, upper left). In eyelid conditioning animals learn to blink their eyes in anticipation of the US (Conditioned response, middle right). This conditioned response is thought to be due to timed pauses in Purkinje cell firing (lower right). Such pauses can be explained by an experimentally observed form of climbing fiber-induced plasticity (upper right) at synapses between granule cells and Purkinje cells but only if granule cells exhibit temporally diverse responses to the CS. Such responses have yet to be measured and represent a major unknown in models of eyelid conditioning (question mark, green). **Right,** MG cells (center, green) receive electrosensory input via electroreceptors (orange box, lower left) along with motor corollary discharge (CD) input related to the fish's own electric organ discharge (EOD) via granule cells (green box, upper left). In order to encode behaviorally relevant external events, the MG cell must cancel the sensory input due to the fish's EOD. Previous results have shown that this is accomplished by the generation and subtraction of a temporally-specific negative image of the effects of the EOD (lower right). An experimentally observed form of spike timing-dependent plasticity (upper right) at synapses between granule cells and MG cells together with temporally diverse corollary discharge responses in individual granule cells (green box, upper left) can explain how temporally-specific negative images are formed.

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Mammalian cerebellum

Figure 2

Cerebellum: eyelid conditioning

ELL: sensory cancellation