A comparative approach to cerebellar function: insights from electrosensory systems

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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.

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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 of variety of sensory and motor signals from many parts of the brain and distribute this information widely, that is, 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, for example, 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.

Figure 1
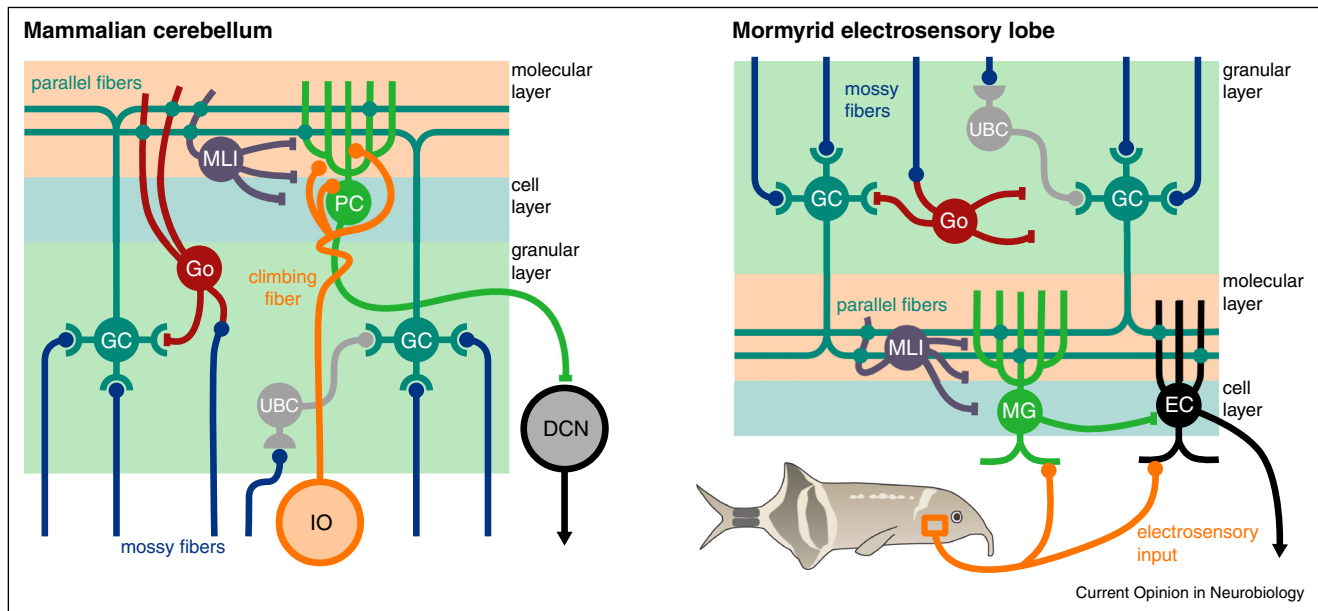
Circuitry of the mammalian cerebellum and the mormyrid ELL. Granular and molecular layer circuitry is similar in cerebellum-like structures such as the mormyrid ELL (right) and the mammalian cerebellum (left). The major difference between cerebellum-like structures and the cerebellum is the climbing 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.

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, for example, 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 long-standing idea that GCs respond selectively to combinations of mossy fiber inputs [23]. Individual GCs were shown to integrate separate mossy fibers inputs conveying electric organ corollary discharge inputs related to the