Cerebellum-Like Structures and Their Implications for Cerebellar Function

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forward model, synaptic plasticity, electric fish, cerebellum

Abstract

The nervous systems of most vertebrates include both the cerebellum and structures that are architecturally similar to the cerebellum. The cerebellum-like structures are sensory structures that receive input from the periphery in their deep layers and parallel fiber input in their molecular layers. This review describes these cerebellum-like structures and compares them with the cerebellum itself. The cerebellum-like structures in three groups of fish act as adaptive sensory processors in which the signals conveyed by parallel fibers in the molecular layer predict the patterns of sensory input to the deep layers through a process of associative synaptic plasticity. Similarities between the cerebellum-like structures and the cerebellum suggest that the cerebellum may also generate predictions about expected sensory inputs or states of the system, as suggested also by clinical, experimental, and theoretical studies of the cerebellum. Understanding the process of predicting sensory patterns in cerebellum-like structures may therefore be a source of insight into cerebellar function.

Contents

LOCAL CIRCUITRY, GENE EXPRESSION, AND EVOLUTION OF CEREBELLUM-LIKE STRUCTURES

General Features

A distinctive molecular layer is a key identifying feature of all cerebellum-like structures (**Figure 1**). The molecular layer is composed of parallel fibers together with the dendrites and cell bodies on which the fibers terminate. The parallel fibers are numerous and closely packed. The granule cells that give rise to the parallel fibers in cerebellum-like structures are morphologically similar to cerebellar granular cells (Mugnaini et al. 1980a,b) but are usually located in an external granule cell mass rather than in a granule cell layer beneath the molecular layer as in the cerebellum. Unipolar brush cells and Golgi cells similar to those present in the granular layer of the cerebellum are also present in some cerebellum-like structures (Campbell et al. 2007, Mugnaini et al. 1997).

Functionally, the parallel fibers convey a rich variety of information from other central structures, which includes corollary discharge information associated with motor commands, information from higher levels of the same sensory modality represented in the deep layers, and information from other sensory modalities. In general, the types of signals conveyed by parallel fibers are signals that are likely to be associated with changes in the sensory input to the deep layers and that can therefore serve to predict such sensory input ("predictive inputs" in **Figure 1**).

The parallel fibers terminate on the dendritic spines of principal cells and on the smooth dendrites of inhibitory stellate cells in a manner very similar to the termination of parallel fibers on Purkinje cells and molecular layer interneurons of the cerebellum. We use the term principal cells to refer to large cells with spine-covered dendrites that extend throughout the molecular layer. Some of these principal cells are excitatory efferent cells that project to higher levels of the sensory system, whereas others are inhibitory neurons that terminate locally on each other and on the efferent cells. The latter are sometimes referred to as "Purkinje-like." The cell bodies of principal cells are usually located in a separate layer below the molecular layer, like the Purkinje cell layer of the cerebellum.

Afferent input from the periphery terminates in the deep layers of cerebellum-like structures, on basilar dendrites of principal

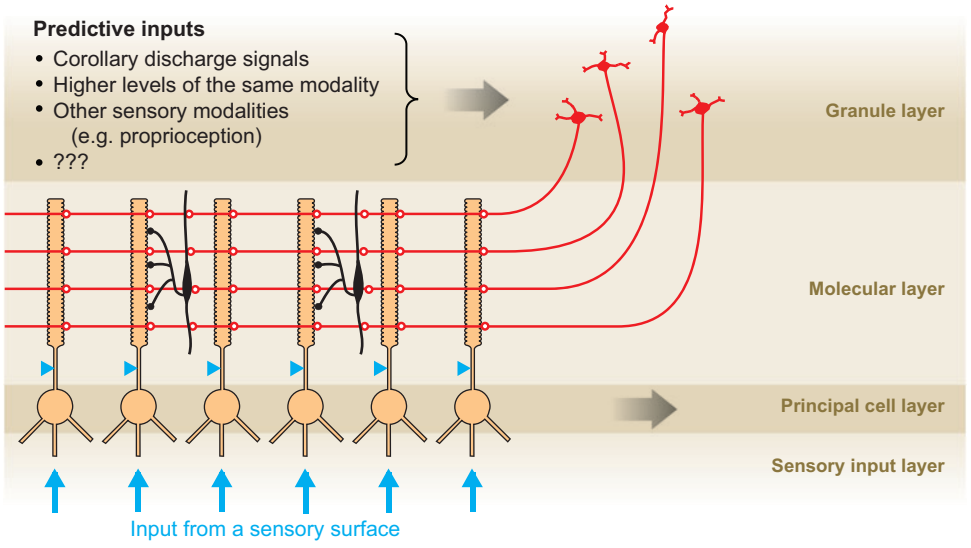

Figure 1

Schematic drawing showing major features of cerebellum-like sensory structures. Inhibitory stellate cells of the molecular layer are shown in black. Blue upward arrows indicate afferent input from the periphery terminating in the sensory input layer. In some cerebellum-like structures the afferent input also terminates on the smooth proximal portion of the apical dendrites as indicated by the small blue arrowheads.

cells, on proximal apical dendrites of principal cells, or on interneurons that relay the information from the periphery to the principal cells. Some of the interneurons of the deep layers are inhibitory, allowing for a change of sign, whereby excitation in the periphery is converted into inhibition of some principal cells. The peripheral input to the deep layers forms a map of a sensory surface, such as the skin surface, the retina, or the cochlea.

Local Circuitry of Different Cerebellum-Like Structures

The brains of all major groups of craniates except reptiles and birds have cerebellum-like structures (**Figures 2** and **3**). The similarities among the different cerebellum-like structures are clear, but so are the differences. Different structures may have different types of cells in addition to the principal cells, stellate cells, and granule cells that are present in all cerebellum-like structures. Moreover, some structures have additional inputs besides the inputs from the periphery and the parallel fibers.

This review describes major features of the different cerebellum-like structures of craniates but is not exhaustive. Recent reviews (Bell 2002, Bell & Maler 2005, Montgomery et al. 1995) and the original papers on individual structures, as provided below, should be consulted for more complete descriptions. Some of the structures are also much better known than others, which is reflected in the level of detail in the following descriptions.

Medial octavolateral nucleus. The medial octavolateral nucleus (MON) processes primary afferent input from the mechanical lateral line system and, in some fish, from eighth nerve end organs (Bell 1981b, McCormick 1999). It is present in all basal aquatic craniates with mechanical lateral line sensory systems (**Figures 2**, **3a–d**, **4a**). Myxinoids (atlantic hagfish; C.B. Braun, personal communication) and aquatic amniotes (reptiles, birds, and mammals; Montgomery et al. 1995) do not have lateral line systems and do not have an MON.

The efferent cells of the MON extend their spiny apical dendrites up into a molecular

MON: medial octavolateral nucleus

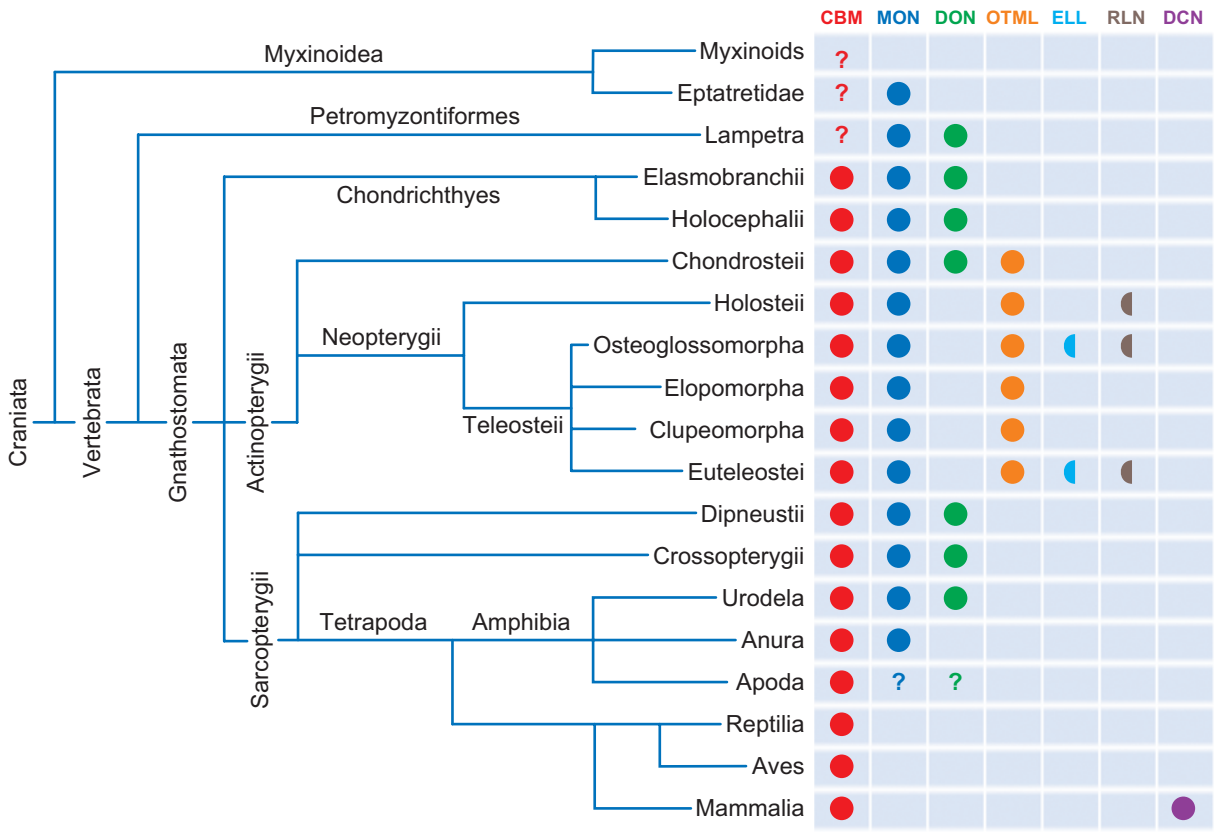

Figure 2

Distribution of cerebellum-like structures and the cerebellum in different craniate groups. A filled circle means the structure is present in all or almost all the members of that group. A filled half circle means the structure is present only sporadically in that group. A question mark means that presence of the structure in that group is controversial. CBM, cerebellum; DCN, dorsal cochlear nucleus; DON, dorsal octavolateral nucleus; ELL, electrosensory lobe; MON, medial octavolateral nucleus; OTML, marginal layer of the optic tectum; RLN, rostrolateral nucleus of thalamus.

layer known as the cerebellar crest (**Figure 3a–d**). The parallel fibers of the cerebellar crest descend from an anterior granule cell mass known as the lateral granular mass in elasmobranchs and the eminentia granularis in other fish. The inputs to these granule cells include lateral line primary afferents (Bodznick & Northcutt 1980), eighth nerve primary afferents (Puzdrowski & Leonard 1993), input from the spinal cord (Schmidt & Bodznick 1987), and descending input from higher-order lateral line and acoustic centers (Bell 1981c, McCormick 1997, Tong & Finger 1983). The basilar dendrites of MON efferent cells are affected by primary afferent input.

DON: dorsal octavolateral nucleus

Dorsal octavolateral nucleus (DON). The dorsal octavolateral nucleus (DON) processes primary afferent input from electroreceptors and is present in many basal vertebrates with an electrosense (**Figures 2**, **3*a***) Electroreception is a vertebrate sense that may have originated as early as the lateral line or vestibular senses (Bullock et al. 1983). The Myxinoidea do not have electroreceptors and do not have a DON (Ronan 1986). Electroreception was lost during the evolution of neopterygian bony fish, and these fish do not have a DON. Electroreception reappeared independently at least twice during the evolution of the teleost radiation: once during the evolution of the two

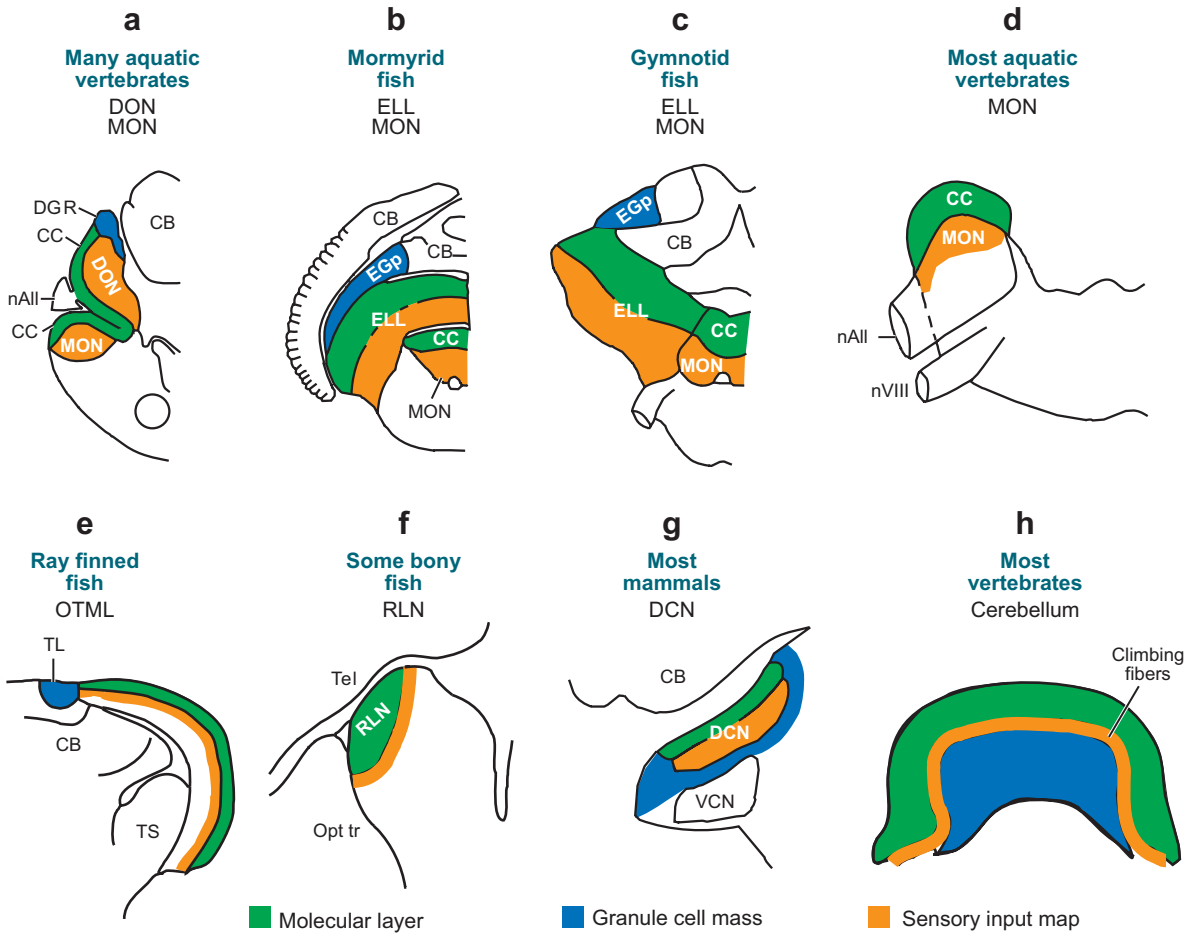

Figure 3

Cerebellum-like structures in different vertebrate groups. The molecular layer, granule cell mass, and sensory input map are shown in different colors, as indicated at the bottom of the figure. The climbing fiber input to the cerebellum is shown here as a sensory input (*see text*). CB, cerebellum; CC, cerebellar crest; DCN, dorsal cochlear nucleus; DGR, dorsal granular ridge; DON, dorsal octavolateral nucleus; EGp, eminentia granularis posterior; ELL, electrosensory lobe; gran, granular layer; MON, medial octavolateral nucleus; mol, molecular layer; nAll, anterior lateral line nerve; nVIII, eighth nerve; Opt tr, optic tract; RLn, rostrolateral nucleus; Tel, telencephalon; TL, torus longitudinalis; TS, torus semicircularis; VCN, ventral cochlear nucleus.

related groups, Mormyriformes and Xenomystinae, and a second time during the evolution of the other two related groups, Gymnotiformes and Siluriformes (Bullock et al. 1983). However, the more recently derived electroreceptors and associated electrosensory central structures of teleosts are quite different from those of other aquatic vertebrates (see electrosensory lobe below).

The DON is located just dorsal to the MON and is similar to the MON in its structure and connections. Primary afferent input from electroreceptors terminates on the basilar dendrites of efferent cells and inhibitory neurons of the deep layers, as in the MON (Bodznick & Northcutt 1980, Puzdrowski & Leonard 1993). The spine-covered apical dendrites of efferent cells extend up into the overlying cerebellar crest.

Parallel fibers of the DON cerebellar crest arise from the dorsal granular ridge, which receives proprioceptive input, recurrent

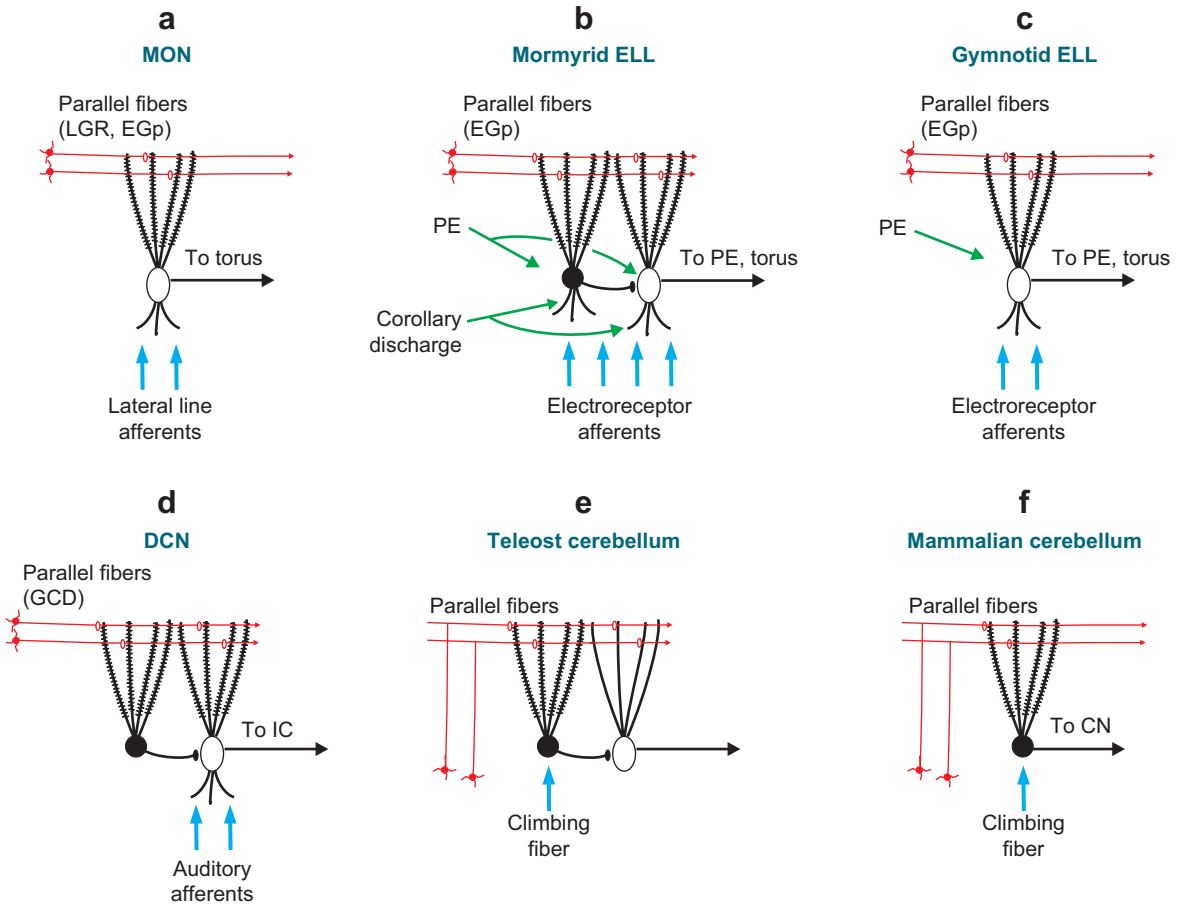

Figure 4

Local circuits of some cerebellum-like structures, the teleost cerebellum, and the mammalian cerebellum. Granule cells and parallel fibers are in red, afferent input from the periphery is in blue, and the additional inputs to the mormyrid and gymnotid ELLs are in green. The Purkinje-like cells of the mormyrid ELL and mammalian DCN as well as the Purkinje cells of the teleost and mammalian cerebellums are black. Excitatory efferent cells are white. IC, inferior colliculus; CN, cerebellar nucleus.

electrosensory input, and corollary discharge input associated with motor commands (Bodznick & Boord 1986, Conley & Bodznick 1994, Hjelmstad et al. 1996). All three types of input are active in relation to the fish's respiratory cycle. Electroreceptors in elasmobranchs are strongly affected by the fish's own respiration (Montgomery & Bodznick 1993). The activity in parallel fibers can therefore be used to predict the effect of these cyclic changes on electroreceptive input to the deep layers of DON (see Adaptive Processing in Cerebellum-Like Structures, below).

OTML: marginal layer of the optic tectum

Marginal layer of the optic tectum. The optic tectum of actinopterygian (ray-finned) fishes is distinctive in that its outer layers are cerebellum like (**Figures 2**, **3*e***) (Meek 1983, Vanegas et al. 1979). The external layer of the optic tectum in these fish is a molecular layer known as the optic tectum marginal layer (OTML). The cell bodies of principal cells, the type I neurons of Meek (1983), are located below the marginal layer. The type I neurons extend their spine-covered apical dendrites up into the marginal layer and input from the retina maps onto their basilar dendrites and

the smooth proximal portions of their apical dendrites.

The parallel fibers of the marginal layer arise from a medially located granule cell mass known as the torus longitudinalis. Granule cells of the torus longitudinalis respond to corollary discharge signals associated with the motor commands that evoke eye movements and respond to visual stimuli as well (Northmore et al. 1983). Parallel fiber activity driven by corollary discharge signals associated with eye movements could predict changes in retinal input to the deep layers, a possible interaction between the two types of input similar to that described above for the DON.

Electrosensory lobe (ELL). Electroreception is present in four groups of teleosts: Mormyriformes, an order of electric fish from Africa; Gymnotiformes, a superorder of electric fish from South America; Siluriformes, the order of catfish; and Xenomystinae, an African subfamily of the family Notopteridae (Bullock & Heiligenberg 1986). All these fish have a cerebellum-like electrosensory lobe (ELL) that receives primary afferent input from electroreceptors (**Figures 2**, **3*b*,*c***) (Bell & Russell 1978, Braford 1982, Finger & Tong 1984, Maler et al. 1981).

The Mormyriformes and Gymnotiformes are electric fish with electric organs as well as electroreceptors. The order Mormyriformes includes the family Mormyridae, all of which have electric organ discharges (EODs) that are brief and pulse like, and the single-species family Gymnarchidae, which has a continuous wave-like EOD. The order Gymnotiformes includes some families with wave-like EODs and other families with pulsatile EODs. The ELLs of pulsatile mormyrids and wave gymnotids have been studied most extensively, although some work has been done on the ELLs of wave mormyriforms (Kawasaki & Guo 1998, Matsushita & Kawasaki 2005) and pulse gymnotiforms (Caputi et al. 2002, Schlegel 1973).

The spine-covered apical dendrites of ELL principal cells extend up into the overlying molecular layer. Primary afferent fibers from electroreceptors in the skin map onto the deep layers, terminating on the basilar dendrites of principal cells or on interneurons (Bell & Maler 2005). The ELL efferent cells of mormyrid (Bell et al. 1997b), gymnotid (Saunders & Bastian 1984), and silurid fish (McCreery 1977) are of two main types: E-cells, which are excited by an increase in peripheral stimulus strength in the center of their receptive fields, and I-cells, which are inhibited by such an increase. These two functionally distinct cell types are also morphologically distinct; the E-cells have more extensive basilar dendrites.

Parallel fibers of ELLs arise from granule cells of the eminentia granularis posterior (EGp), which in mormyrids, at least, also contains Golgi cells and unipolar brush cells similar to the same cell types in the mammalian cerebellum (Campbell et al. 2007). The inputs to EGp in mormyrid and gymnotid fish include proprioceptive signals associated with bending of the body or the fins, recurrent electrosensory input from a higher levels of the system, and in mormyrids only, a corollary discharge signal associated with the motor command that elicits the electric organ (corollary) discharge (EOCD) (Bastian & Bratton 1990; Bell et al. 1992; Carr & Maler 1986; Szabo et al. 1979, 1990). These different inputs to EGp are relayed to ELL as parallel fiber inputs, where they can predict changes in electroreceptor input to the deep layers associated with tail movements, some other electrosensory input, or the EOD (see Adaptive Processing in Cerebellum-Like Structures).

The mormyrid (Bell et al. 1981), gymnotid (Carr & Maler 1986), and silurid (Tong 1982) ELLs receive additional input aside from the peripheral and parallel fiber inputs. They receive direct recurrent input from a higher-order electrosensory nucleus just rostral to ELL, the nucleus preeminentialis dorsalis (PE) (**Figures 4*b*,*c***). The deep layers of the mormyrid ELL also receive EOCD input directly from an EOD motor command–related nucleus (Bell & von der Emde 1995). This input is in addition to the EOCD input conveyed via parallel fibers.

ELL: electrosensory lobe

EOD: electric organ discharge

EOCD: electric organ corollary discharge

RLN: rostrolateral nucleus of the thalamus

DCN: dorsal cochlear nucleus

The ELLs of mormyrid and gymnotid fish have differences as well as similarities. Most important, the mormyrid ELL includes a principal cell that is not present in the gymnotid ELL (**Figures 4*b*,*c***), the medium ganglion cell (Meek et al. 1996). These cells are referred to as Purkinje-like because they are GABAergic with extensive spine-covered dendrites in the overlying molecular layer. However, they differ from Purkinje cells because they have basilar dendrites and do not receive climbing fiber input. The medium ganglion cells are interneurons that inhibit both nearby efferent cells and each other (**Figure 4*b***). They are more numerous than the efferent cells and have many more dendrites and spines in the molecular layer (Meek et al. 1996). They must therefore have a central role in the integration of peripheral and parallel fiber inputs in the mormyrid ELL. These and other differences between the mormyrid and gymnotid ELLs are consistent with their independent evolutionary origins.

Rostrolateral nucleus of the thalamus. The rostrolateral nucleus (RLN) (**Figures 2**, **3*f***) of the thalamus is a small, cerebellum-like structure found in the thalamus of a few widely scattered neopterygian fish (**Figure 2**) (Butler & Saidel 1992). The principal cells of RLN receive topographically organized direct input from the retina on the smooth proximal parts of their apical dendrites. The more distal apical dendrites are covered with spines and receive parallel fiber input from the torus longitudinalis.

Dorsal cochlear nucleus. All mammals possess a dorsal cochlear nucleus (DCN) (**Figures 2**, **3*g***, **4*d***). The DCN is laminated and cerebellum-like in marsupials and eutherian mammals but not in monotremes (Cant 1992, Nieuwenhuys et al. 1997). Fusiform cells are the major efferent cell type of the DCN. Their basilar dendrites are contacted by primary afferent fibers from the cochlea, which form a topographic map of the cochlea in the deeper layers below the molecular layer. The fusiform cells extend their spine-covered apical dendrites up into the molecular layer where they are contacted by parallel fibers. The parallel fibers arise from granule cells located around the margins of the nucleus. The parallel fibers course at right angles to the isofrequency bands in the deeper layers. Thus, parallel fibers cross through different frequency-specific regions of DCN.

The cartwheel cell is a second type of principal cell in the DCN (Cant 1992, Nieuwenhuys et al. 1997). These cells are Purkinje-like because they are GABAergic, have extensive spine-covered dendrites in the molecular layer, and inhibit the efferent fusiform cells. The cell bodies of cartwheel cells are in the molecular layer, and their dendrites are restricted to the molecular layer.

The local circuits of the DCN and the mormyrid ELL are very similar to the local circuit of the cerebellar cortex in actinopteryrian fish where most Purkinje cells are interneurons that terminate locally on efferent cells (**Figure 4*e***) (Finger 1978, Meek 1998). The parallel fibers of the DCN, the mormyrid ELL, and the actinopterygian cerebellum pass through and excite the dendrites of both efferent cells and Purkinje or Purkinje-like cells. In all three cases, the Purkinje cells or Purkinje-like cells inhibit nearby efferent cells (**Figures 4*b*,*d*,*e***). The efferent neurons of the actinopterygian cerebellum are equivalent to the cerebellar nucleus neurons of mammals (**Figure 4*f***).

The granule cells of the DCN receive various types of input: recurrent auditory input from the inferior colliculus (Caicedo & Herbert 1993) and auditory cortex (Weedman & Ryugo 1996); primary vestibular afferent input (Burian & Gstoettner 1988); input from the pontine nuclei (Ohlrogge et al. 2001); somatosensory input from the dorsal column nuclei (Weinberg & Rustioni 1987), the trigeminal nuclei (Zhou & Shore 2004), and the somatosensory cortex (Wolff & Kunzle 1997); and direct input from the cochlea via fine unmyelinated Type II afferents (Brown et al. 1988). DCN granule cells also receive input from brainstem nuclei associated with vocalization and respiration that

may convey corollary discharge signals (Shore & Zhou 2006). Proprioceptive input from the pinna has particularly strong effects on DCN granule cells in the cat (Kanold & Young 2001). Movements of the animal's pinna, head, or body have predictable effects on how the cochlea responds to an external sound source, and an animal's own vocalization and respiration will have predictable consequences on auditory input. Thus the signals conveyed by the parallel fibers in the DCN molecular layer could generate predictions about changes in afferent activity from the cochlea that arrive at the deep layers, as in other cerebellum-like structures.

Comparison of the Local Circuitries of Cerebellum-Like Structures and the Cerebellum

Many similarities in cell types and local circuitry between the cerebellum and cerebellum-like structures have been described in the preceding section. The similar cellular elements include the granule cells, the Golgi cells, the unipolar brush cells, the parallel fibers, the stellate cells, and the spine-covered molecular layer dendrites of principal cells.

The most crucial similarity is that between the two inputs to cerebellum-like structures and the two inputs to cerebellar Purkinje cells. Cerebellum-like structures receive parallel fiber and peripheral input, whereas Purkinje cells of the cerebellum receive parallel fiber input and climbing fiber input. In both cases, one input, the parallel fibers, conveys a rich variety of information to an entire set of principal cells or Purkinje cells. In both cases, a second input—peripheral input for cerebellum-like structures and climbing fiber input for the cerebellum—conveys specific information that subdivides the set of Purkinje cells that share the same parallel fiber input.

Olivary input to Purkinje cells is more specific than the peripheral input to the deep layers of cerebellum-like structures insofar as it is conveyed by just a single climbing fiber. Efferent cells and Purkinje-like cells in cerebellum-like structures do not have such single fiber inputs. The cerebellums of different vertebrates can vary markedly, but all the cerebellums that have been closely examined have a specific input from the inferior olive that terminates as climbing fibers. We suggest that the presence of a climbing fiber is the defining characteristic of the cerebellum that distinguishes it from cerebellum-like structures.

Climbing fibers and the peripheral sensory input to cerebellum-like structures are similar in many respects. Climbing fibers signal rather specific sensory events in most of the cases where the information they convey has been identified. Such sensory signals include retinal slip in a particular direction (Maekawa & Simpson 1972), somatosensory stimulation within a small region of skin (Ekerot & Jorntell 2001, Robertson 1985), and vestibular stimulation with tilt in a particular direction (Barmack & Shojaku 1992). Moreover, the climbing fibers of vertebrates other than mammals do not terminate throughout the molecular layer as in mammals. They terminate instead on smooth, proximal dendrites at the base of the molecular layer (Nieuwenhuys et al. 1997) in a manner similar to that of retinal input onto the smooth, proximal dendrites of principal cells in the OTML and RLN. This is not to say that the inferior olive is a simple sensory relay. It is not. But clearly sensory stimuli have a strong influence on the inferior olive and on climbing fibers, a result consistent with the origin of the inferior olive from the embryo's alar or sensory plate. Devor (2002) has in fact suggested that the inferior olive has been interposed between peripheral sensory structures and the cerebellum to gate sensory signals by motor commands and by the inferior olive's own intrinsic rhythmicity.

As noted in the previous section, the parallel fibers of cerebellum-like structures convey information that is associated with sensory input changes to the deep layers and that can therefore predict such changes. The parallel fibers of the cerebellum similarly convey information that can predict the occurrence of climbing fiber input. Climbing fibers in the flocculonodular lobe of the mammalian cerebellum, for example, signal retinal slip (Maekawa

LTD: long-term depression

& Simpson 1972), and the parallel fibers in this region convey vestibular information about head movement (Lisberger & Fuchs 1974), corollary discharge information about eye movement (Noda & Warabi 1982), and proprioceptive information from the neck (Matsushita & Tanami 1987), all of which could be used to predict movement of an image on the retina.

The presence of a climbing fiber is perhaps the critical difference between the cerebellum and cerebellum-like structures. Other differences include the presence of basilar dendrites on most principal cells of cerebellum-like structures but not on Purkinje cells; the presence of planar dendritic trees in most Purkinje cells but not in most principal cells; the presence of cell types in cerebellum-like structures not present in the cerebellum; and the presence of other inputs besides parallel fibers and climbing fibers in cerebellum-like structures not present in the cerebellum, such as the preeminential input in electroreceptive teleosts (**Figures 4*b*,*c***).

Patterns of Gene Expression in Cerebellum-Like Structures and the Cerebellum

Similarities and differences between the different cerebellum-like structures and the cerebellum itself are also revealed in gene expression patterns. Some genes are expressed in many different cerebellar and cerebellum-like structures, whereas others are expressed in only a few of these structures (Bell 2002). Common patterns of gene expression between cerebellar Purkinje cells and cartwheel cells of the DCN are particularly prominent, and many mutations affect both cell types (Berrebi et al. 1990).

One gene, the *GluRdelta2* gene, may be expressed in most if not all cerebellum-like structures and also in the cerebellum, but not in other structures. This gene is structurally related to the ionotropic glutamate receptors but does not form ion channels (Yuzaki 2003). The gene is necessary for long-term depression (LTD) at the parallel fiber to Purkinje cell synapse (Yawata et al. 2006). In mammals, the *GluRdelta2* gene is expressed in Purkinje cells (Yuzaki 2003) and in the principal cells of the DCN (Petralia et al. 1996). In zebrafish, the *GluRdelta2* gene is expressed in the molecular layers of the cerebellum, the MON, and the OTML, but not elsewhere in the brain as shown for both the gene and the protein (Mikami et al. 2004). Similarly, in the mormyrid brain, the GluRdelta2 protein is present in the molecular layers of the cerebellum, the ELL, the MON, and the OTML, but not elsewhere in the brain (J. Zhang & C. Bell, unpublished observations). Expression of the *GluRdelta2* gene in still other cerebellum-like structures remains to be established.

Some genes are expressed in some of the cerebellum-like structures or the cerebellum in the adult but are expressed only in other such structures during development. The *zebrin II* gene, for example, is expressed only in Purkinje cells in adult mammals, birds, and fish (Hawkes & Herrup 1995, Lannoo et al. 1991) but is expressed transiently during development in the MON and in part of the ELL of gymnotid fish (Lannoo et al. 1992). Similarly, functional N-methyl-D-aspartate (NMDA) receptors are present on principal cells of the adult mormyrid and gymnotid ELLs (Grant et al. 1998, Berman et al. 2001), as well as principal cells of the adult DCN (Manis & Molitor 1996), but are present on cerebellar Purkinje only during development (Dupont et al. 1987).

The common features in the local circuitry and in the gene expression patterns suggest the presence of a shared genetic-developmental program in all craniates, a program that once activated can generate a cerebellum or cerebellum-like structure. Some findings from experimental embryology support this idea. Thus, ectopic cerebellum-like structures develop in the forebrain or midbrain of a chick embryo if beads are coated with fibroblast growth factor 8 and placed at those sites in the embryo (Martinez et al. 1999). Similarly, cerebellar tissue will develop ectopically in the midbrain and forebrain of a mouse embryo with a genome that is Otx1+/- and Otx2+/- (*Drosophila* orthodenticle protein, a transcription factor) (Acampora et al. 1997).

Evolution of Cerebellum-Like Structures and the Cerebellum

The similarities between all the different cerebellum-like and cerebellar structures cannot be explained solely by homology in the sense of historical or phylogenetic homology (Butler & Saidel 2000). In this usage of the term, a feature is considered homologous across different taxa if the taxa have inherited the feature from a common ancestor that also had the feature. However, some of the individual structures described here are homologous. Thus the most parsimonious explanation for the presence of a cerebellum in all vertebrates is that it was present in a common ancestor. A common ancestor is also the most parsimonious explanation for the presence of an MON, a DON, or a DCN in some groups of craniates. However, we find no evidence for an ancestral cerebellum-like structure from which the cerebellum, MON, DON, marginal layer of the tectum, ELL, RLN, and DCN all evolved. (See Bell 2002 for a more complete analysis of the evolution of cerebellum-like structures.)

How then can we explain the clear similarities among the different cerebellums and cerebellum-like structures? The best explanation may be the presence of a developmental-genetic program that can generate a cerebellum or cerebellum-like structure, as described previously, together with evolutionary pressure for the type of information processing that these structures can perform.

Cerebellum-like structures may have evolved before the cerebellum itself. An MON is clearly present in some myxinoids, and both an MON and a DON are clearly present in lampreys, but the presence of a cerebellum is not well established in either of these groups. Some comparative anatomists affirm the presence of a cerebellum in myxinoids (Larsell 1967), whereas others deny it (Nieuwenhuys et al. 1997), and arguments have also been made both for (Larsell 1967, Nieuwenhuys et al. 1997) and against (Crosby 1969) the presence of a cerebellum in lampreys. As suggested previously, the identification of climbing fibers on putative Purkinje cells could indicate the presence of a cerebellum, but no efforts to identify climbing fibers have been made in myxinoids and lampreys. Purkinje cell–specific markers that do not stain cerebellum-like structures could also help determine the presence of a cerebellum. Thus the finding that the Zebrin II antibody does not stain cells in what some consider to be the lamprey cerebellum is of interest (Lannoo & Hawkes 1997) but is not conclusive because the Zebrin II antibody does not stain all Purkinje cells.

PREDICTIONS AND PLASTICITY IN CEREBELLUM-LIKE STRUCTURES AND THE CEREBELLUM

Predictions and Plasticity in Cerebellum-Like Structures

Cerebellum-like structures process information from peripheral sensory receptors in combination with an array of central signals conveyed by parallel fibers. If a common function exists among all cerebellum-like structures, it must involve the interaction between these two types of inputs. Progress toward understanding these interactions has been made in cerebellum-like structures concerned with the processing of electrosensory information in three distinct groups of fish: elasmobranchs, gymnotiform teleosts, and mormyrid teleosts. The cerebellum-like structures of these fish act as adaptive filters, removing predictable features of the sensory input (for reviews, see Bastian & Zakon 2005, Bell 2001, Bell et al. 1997a).

In these systems, the animals' own behavior strongly affects electroreceptors and could interfere with sensing weak electrosensory signals from the environment. In the passive electrosensory system of elasmobranch fish, for example, ventilatory movements modulate the fish's standing bioelectric field and can drive electroreceptor afferents through their entire dynamic range (Montgomery & Bodznick

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1999). In the active electrosensory systems of mormyrid and gymnotid fish, movements of the electric organ (located in the tail) relative to sensory surface cause large changes in EOD-evoked electroreceptor input that could overwhelm the small changes resulting from nearby objects.

Parallel fiber inputs to cerebellum-like structures involved in electrolocation convey proprioceptive, corollary discharge, and electrosensory signals that could be used to predict the electrosensory consequences of the animals' own behavior. Direct evidence for the generation of such predictions has been obtained from in vivo recordings from principal cells in the mormyrid and gymnotid ELL and elasmobranch DON (Bastian 1996a, Bell 1981a, Bell et al. 1997b, Bodznick et al. 1999). In each case, pairing artificial electrosensory stimuli with central predictive signals—a corollary discharge signal at a particular delay after the EOD motor command in the case of the mormyrid ELL (**Figure 5*a***), a proprioceptive signal at a particular tail angle in the case of the gymnotid ELL (**Figure 5*b***), and a proprioceptive or corollary discharge signal at a particular phase of the ventilatory cycle in the case of the elasmobranch DON (**Figure 5*c***)—results in a change in the response to the predictive signals alone that resembles a negative image of the response to the previously paired (and now predicted) stimulus. The negative images develop rapidly over the course of a few minutes of pairing and are specific to the sign as well as to the spatial and temporal patterns of activity evoked by the stimulus. On the basis of these results investigators suggested that cerebellum-like circuitry could operate as an adaptive filter by continually generating and updating sensory predictions on the basis of associations between central signals and current sensory inputs and subtracting these predictions from the neural response. Adaptive filtering could thus allow external electrosensory signals to be detected more easily.

Several lines of evidence confirm that formation of negative images is due, at least in large part, to plastic changes occurring within the cerebellum-like structures themselves (Bell 2001). Pairing predictive signals with intracellular current injections in vivo results in the formation of negative images in principal cells in all three groups of fish, indicating that the inputs to the recorded cell are plastic (Bastian 1996b, Bell et al. 1993, Bodznick et al. 1999). Given the types of predictive signals involved in negative image formation, synapses between parallel fibers and principal cells are the most natural candidates for the site of plastic changes. Negative image formation requires that the plasticity be anti-Hebbian in character, i.e., correlations between pre- and postsynaptic activity should decrease synaptic strength, and researchers have obtained evidence for anti-Hebbian plasticity at parallel fiber synapses with principal cells in all three classes of fish. Anti-Hebbian plasticity at parallel fiber synapses has also been shown recently in the DCN of mammals (Fujino & Oertel 2003, Tzounopoulos et al. 2004) but has not yet been connected to systems-level adaptive filtering.

Modeling studies have helped to link the properties of negative image formation with mechanisms of synaptic plasticity (Nelson & Paulin 1995, Roberts 1999, Roberts & Bell 2000). Temporal specificity is a key feature of negative image formation. In the mormyrid ELL, parallel fibers convey corollary discharge signals related to the motor command that drives the EOD. Pairing with electrosensory stimuli at various delays relative to the motor command results in negative images that are specific to the paired delay (Bell 1982). Results of modeling studies suggest that temporally specific negative images could be generated using an anti-Hebbian learning rule similar to that observed experimentally (see below) together with an array of parallel fiber inputs active at different delays following the motor command (Roberts 1999, Roberts & Bell 2000). The mechanisms for generating temporally specific negative images in this model are quite similar to those proposed for some forms of cerebellar learning, such as the learning of adaptively timed responses in classical eye-blink conditioning (Medina et al. 2000) or

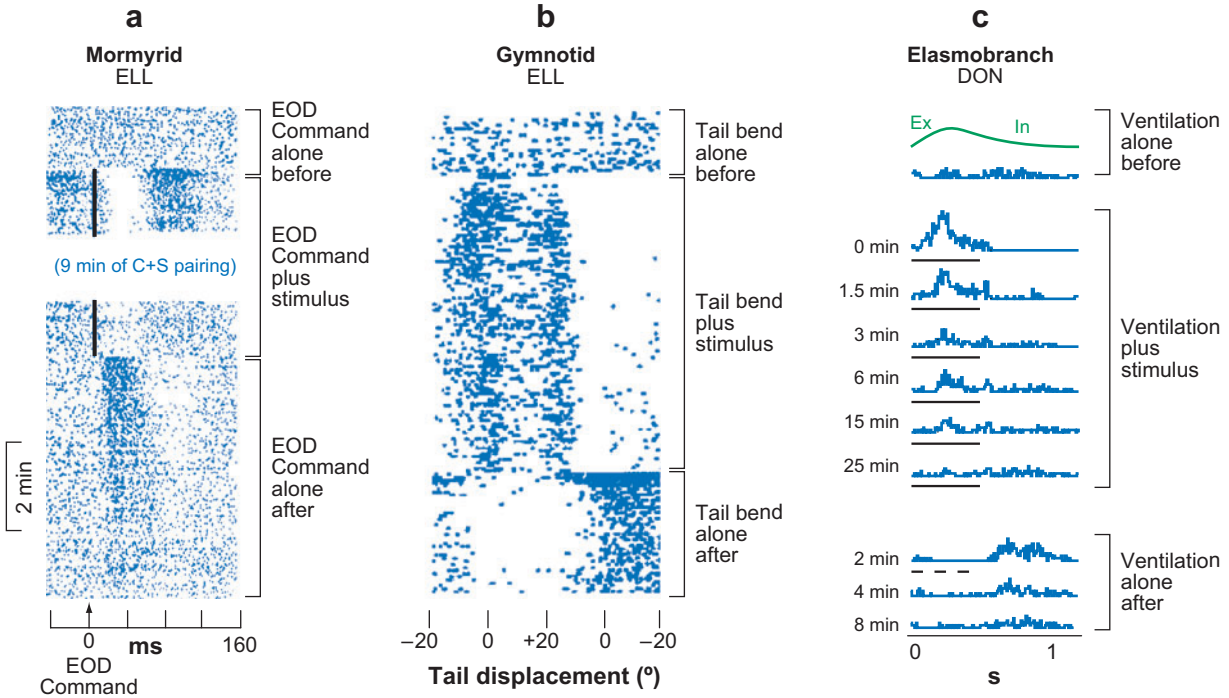

Figure 5

Formation of negative images of predicted sensory responses in three different cerebellum-like structures. (*a*) Raster display of the responses of a cell in the ampullary region of the mormyrid ELL. Each dot represents an action potential. The EOD motor command occurs at time 0. The command alone initially has no effect on the cell. An electrosensory stimulus (*vertical black line*) that evokes a pause-burst response is then paired with the command. After several minutes of pairing, the stimulus is turned off and a response to command alone is revealed, which was not present before the pairing and which is a negative image of the previously paired sensory response. From Bell 1986. (*b*) Raster display of responses of cell in the gymnotid ELL. The tail is moved back and forth passively. Each row of dots shows response to one movement cycle. Initially the tail bend has no effect on the cell. An electrosensory stimulus that evokes a burst-pause is then delivered in phase with the movement. The electrosensory stimulus is turned off after several minutes of pairing, which reveals a response to tail bending alone that was not present before the pairing and which is opposite to the previously paired sensory response. From Bastian 1995. (*c*) Histogram display of responses of a cell in the elasmobranch DON. Initially the cell does not respond to the exhalation (Ex)–inhalation (In) ventilatory cycle of the fish (*top histogram*). An electrosensory stimulus that evokes a burst-pause is then delivered in phase with the ventilatory cycle. The response to ventilation plus the electrosensory stimulus decreases during 25 min of pairing. Turning off the electrosensory stimulus after pairing reveals the presence of a response to ventilation alone, which was not present before and which is a negative image of the previously paired sensory response. From Bodznick 1993.

of appropriate phase relations in the vestibular ocular reflex (Raymond & Lisberger 1998).

The cellular properties of anti-Hebbian synaptic plasticity have been studied in some detail at synapses between parallel fibers and Purkinje-like medium ganglion cells in an in vitro preparation of the mormyrid ELL (Bell et al. 1997c, Han et al. 2000). Synaptic depression requires a postsynaptic dendritic spike and depends on the precise timing of the spike relative to the parallel fiber evoked excitatory postsynaptic potential (EPSP) onset. Depression develops when a postsynaptic dendritic spike occurs within 50 ms of EPSP onset, whereas other timing relations yield potentiation or no effect. Potentiation as measured in vitro is nonassociative and likely depends on simple repetition of the parallel fiber stimuli at a sufficiently high rate, although in vivo experiments suggest a spike timing–dependent component

to the potentiation (Bell et al. 1997b, Sawtell et al. 2007). The depression requires activation of NMDA receptors and changes in postsynaptic calcium. The potentiation can reverse the depression and vice versa, with both potentiation and depression having a presynaptic locus of expression. Plasticity at parallel fiber synapses onto Purkinje-like cartwheel cells of the DCN is also anti-Hebbian, spike timing–dependent, NMDA dependent, and presynaptically expressed (Tzounopoulos et al. 2004, 2007).

Investigators have observed both similarities and differences between plasticity in cerebellum-like structures and plasticity in the cerebellum itself. The depression of responses to signals conveyed by parallel fibers following the pairing of these signals with postsynaptic excitation in cerebellum-like structures is similar to the depression of responses to parallel fiber stimulation in the mammalian Purkinje cells following pairing with climbing fiber input or with postsynaptic depolarization (Ito 2001). Such depression has been linked to the formation of negative images of predicted sensory input in cerebellum-like structures and to motor learning in the mammalian cerebellum (Ito 1984). It is of interest in this regard that the timing of stimulus-driven parallel fiber–evoked simple spike activity is consistently close to the inverse of climbing fiber responses in almost all the systems where this relation has been examined (Barmack & Shojaku 1992, Ebner et al. 2002, Graf et al. 1988, Kobayashi et al. 1998, Stone & Lisberger 1990). Thus in many systems, simple spike activity is a kind of negative image of predicted climbing fiber activity. Plasticity at parallel fiber synapses may play a role in generating the antiphase relation, but it is only part of the explanation because the antiphase relation is still present when parallel fiber LTD is blocked (Goossens et al. 2004).

The timing constraints on parallel fiber plasticity may be more restrictive in cerebellum-like structures than in the cerebellum. LTD in the cerebellum-like structures where timing relations have been tested occurred only when the postsynaptic spike followed the presynaptic spike by 50 ms or less (Bell et al. 1997c, Tzounopoulos et al. 2004). In the cerebellum, however, depression of the parallel fiber synapse is present after pairings with climbing fiber input in which delays varied between occurrence of the climbing fiber 50 ms before the parallel fiber stimulus and occurrence of the climbing fiber 200 ms after the parallel fiber stimulus (Safo & Regehr 2007, Wang et al. 2000).

The mechanisms of synaptic plasticity are clearly not the same in the cerebellum and in the cerebellum-like structures where it has been studied. Plasticity at parallel fiber synapses onto efferent or Purkinje-like cells in the mormyrid ELL (Han et al. 2000) and the mammalian DCN (Tzounopoulos et al. 2004) depends on activation of NMDA receptors, but synaptic plasticity at parallel fiber synapses onto Purkinje cells does not (Ito 2001). However, some aspects of the plasticity mechanisms may be shared as indicated by the presence of the *GluRdelta2* gene in the cerebellum and in cerebellum-like structures, and by the involvement of this gene in plasticity at Purkinje cell synapses (Hirano et al. 1995).

Adaptive processes in the cerebellum appear similar to those in cerebellum-like structures. In cerebellum-like structures, the pairing of parallel fiber signals with excitatory input from the periphery results in such signals eliciting a predictive reduction in principal cell activity. In the cerebellum, the pairing of parallel fiber signals with climbing fiber input likely leads to such signals eliciting a reduction in the firing of Purkinje cells (but see Steuber et al. 2007 for a contrary view). If the climbing fibers convey some type of sensory signal, gated through the inferior olive, then the parallel fiber signals that are paired with the climbing fibers, and which predict their occurrence, will reduce Purkinje cell activity, as shown by Jirenhed et al. (2007) during eye-blink conditioning.

This review focuses on sensory predictions through mechanisms of associative synaptic plasticity and with those features of cerebellum-like structures that are particularly relevant to cerebellar function. Cerebellum-like structures are also excellent sites for addressing other

important issues in neuroscience, which cannot be discussed here because of space constraints. These include the roles of recurrent feedback from higher to lower levels of the same sensory system (Chacron et al. 2003, 2005; Doiron et al. 2003), the effects of motor commands on sensory processing (Bell & Grant 1992), the preservation and analysis of temporal information (Kawasaki 2005), and the neural processing of spectral cues for sound localization in the DCN (Young & Davis 2002).

Predictions in the Cerebellum

The many similarities between cerebellum-like structures and the cerebellum suggest that the cerebellum too may be involved in generating predictions concerning expected sensory input or states of the system (Bell et al. 1997a, Devor 2000), and a variety of experimental, clinical, and theoretical studies of the cerebellum support this hypothesis (Diedrichsen et al. 2007, Nixon 2001, Paulin 2005, Wolpert et al. 1998).

The probable involvement of the cerebellum in predictive or feedforward control through learning is well recognized (Bastian 2006, Ito 1984, Miall et al. 1993, Ohyama et al. 2003, Wolpert et al. 1998). Predictive control allows for prior knowledge to shape an action, as in knowing if a cup is full or empty before picking it up. Several studies indicate that predictive feedforward control is deficient in cerebellar patients (Morton & Bastian 2006, Smith & Shadmehr 2005). Such patients do not adapt their responses to predictable perturbations, although they respond quite well to sudden unpredictable perturbations of a movement, indicating that feedback control from the periphery is functional.

Theoreticians have proposed that the cerebellum may act in an adaptive and predictive manner through the generation of two types of models: forward models and inverse models (Wolpert et al. 1998). In a forward model, copies of a motor command are conveyed to the cerebellum together with information about the current state of the system such as positions and velocities of the limbs. The cerebellum then generates a prediction about the sensory consequences of the commanded motor act in the current context. In an inverse model, the desired goal of an action together with information about the current state are conveyed to the cerebellum, which then generates the precise motor commands that will yield the desired goal. Both types of models must be capable of plastic change or learning to adapt to changes in the task or in the system, such as changes in load or initial limb position.

Forward model: predicts the future state of the system on the basis of the current state and the motor command

Inverse model: generates an appropriate motor command that will cause a desired change in the state of the system

Forward models are particularly important in generating fast, coordinated movement sequences. Feedback from peripheral sensory receptors is slow. An appropriate command for one phase of a movement must often be issued before peripheral feedback can arrive about the consequences of a motor command that evoked a previous phase of the movement. A forward model that predicts the sensory consequences of a motor command, accounting for all that is known about the current state of the system, allows the next motor command in a sequence to be issued appropriately and in accord with the expected consequences of previous commands. Such a process allows for the chunking of separate components of a motor sequence and their automatization, as described by Nixon (2001). Moreover, classic symptoms of cerebellar damage such as decomposition of movement, slowness, and tremor can all be understood as due to the absence of predictive forward models and reliance on peripheral feedback (Bastian 2006, Nixon 2001).

What is required in such automatization of a sequence of movements is the predicted effect of the motor command: the sensory consequences or state that results from the action, not simply the motor command itself. Recent experiments by Pasalar et al. (2006) suggest that the Purkinje cell output from large regions of the cerebellar hemispheres is indeed more tightly coupled with predictions about consequences of the movement than with the motor commands themselves (but see Yamamoto et al. 2007). Pasalar et al. (2006) recorded from Purkinje cells over a wide area of the hemisphere in monkeys that had been trained to

control a cursor on a screen with a manipulandum and to make the cursor track a circularly moving stimulus. They then altered the forces required to move the manipulandum. The electromyograms in the arm muscles varied systematically with the changes in required forces, but Purkinje cell simple spike activity was unaffected by the changes in force. Purkinje cell simple spikes depended only on the position, direction, and velocity of the movement. Purkinje cell activity was phase advanced, that is, predictive of the movement parameters or state of the arm (T. Ebner, personal communication).

Pasalar et al. (2006) took their results as an argument against an inverse model in the cerebellum because Purkinje cell activity had little relation to the motor commands to the muscles. Although one could argue that the activity reflects a high-level motor command, in movement rather than muscle coordinates, the simpler explanation is that the Purkinje cell activity reflects a forward model of expected consequences, as required for the automatization of movement sequences. Their experiments suggest that not all sensory consequences are predicted; only those critical for accomplishing the task are predicted. Thus presumed changes in touch or muscle receptors associated with force changes were not predicted by Purkinje cell activity; only velocity and position of the limb were predicted.

Examples of what are, in effect, forward models in the cerebellum-like structures of mormyrid and elasmobranch fish are described in the previous section, showing that forward models can indeed be generated within structures such as the cerebellum. In these systems, corollary discharge signals come to elicit a prediction about the sensory input pattern that is expected to follow the motor command. The possibility of such corollary discharge effects in the OTML and DCN was also mentioned.

Cerebellum-like structures can generate predictions on the basis of other sensory inputs (Bastian 1996a, Bodznick et al. 1999), not just on the basis of motor commands, and the cerebellum may do so also. For example, in eye-blink conditioning, which is thought to involve the cerebellum, the timing of one sensory signal, an air puff to the cornea (signaled by the climbing fiber), is predicted from another sensory signal, a tone (signaled by mossy fibers) (Kim & Thompson 1997). Similarly, cerebellar modulation of the vestibular ocular reflex involves the prediction of one sensory stimulus, retinal slip (signaled by climbing fibers), by the occurrence of another sensory stimulus, vestibular input (signaled by mossy fibers). More broadly, Paulin (1993, 2005) has suggested that the cerebellum estimates future states of the organism or environment using a combination of sensory, motor, and possibly other types of information.

In simpler systems, such as the vestibular ocular reflex, in which Purkinje cell output is coupled quite directly with motor pathways, the adaptive alteration in Purkinje cell activity after pairing with the climbing fiber can be viewed as either a prediction about a sensory input or as a motor command. In more complex systems, where Purkinje cell output is less tightly coupled with motor pathways, as in the tracking task studied by Pasalar et al. (2006), the hypothesis of Purkinje cell activity as a predictor of consequences may provide a more useful perspective.

DIRECTIONS FOR FUTURE RESEARCH

Our understanding of adaptive processing in cerebellum-like structures is far from complete, and future work will be useful both for understanding the neural mechanisms of sensory processing and for understanding the cerebellum. Promising lines of research are outlined briefly below.

Activity Patterns in Granule Cells

How the different types of predictive inputs are combined and represented in the granule cells that are associated with cerebellum-like structures remains unclear, as is also the case for cerebellar granule cells.

Adaptive Filtering in Electrosensory Systems

Several aspects of adaptive filtering in cerebellum-like structures require further investigation, including (*a*) the behavioral consequences of adaptive filtering; (*b*) the effects of adaptive filtering on encoding naturalistic stimuli in the presence of self-generated interference; (*c*) the mechanisms of plasticity and the presence of plasticity at other sites, such as inhibitory synapses; and (*d*) the possible generation of more complex expectations such as those based on memories of entire scenes or sequences. The possibility of more complex expectations is suggested by the massive descending inputs that cerebellum-like structures receive from higher levels of the same sensory systems.

Adaptive Filtering in the DCN and Less-Studied Cerebellum-Like Structures

Recent studies have found synaptic plasticity at parallel fiber synapses onto Purkinje-like cartwheel cells and fusiform cells in the DCN in vitro. Yet very little is known at the systems level regarding the role of such plastic parallel fiber inputs in auditory processing. Similarly, very little is known about adaptive filtering in the MON or OTML.

Purkinje-Like Cells

The functional roles of Purkinje-like cells remain unclear. Recent work has shown that dendritic spikes that drive anti-Hebbian plasticity in Purkinje-like MG cells of the mormyrid ELL are strongly regulated by central signals, suggesting a parallel to supervised learning mediated by climbing fiber inputs to the cerebellum (Sawtell et al. 2007). In addition, the mormyrid ELL, the DCN, and the teleost cerebellum all provide excellent opportunities for examining interactions between Purkinje or Purkinje-like cells and neighboring efferent cells (analogous to deep cerebellar nuclear cells in the mammalian cerebellum).

Primitive Cerebellums

As discussed previously, the earliest craniates possess cerebellum-like structures, but it is not clear if they possess a cerebellum. Identification of a structure similar to the inferior olive in hagfish or lampreys would help to resolve this issue.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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