

Evolution of Cerebellum-Like Structures

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Key Words

Cerebellum · Cerebellum-like structures · Evolution · Homology · Convergence · Syngeny

Abstract

All vertebrate brains have a cerebellum, and most of them have one or more additional structures that are histologically similar to the cerebellum. The cerebellum-like structures include the medial octavolateral nucleus in most aquatic vertebrates; the dorsal octavolateral nucleus in many aquatic vertebrates with an electrosensory system; the marginal layer of the optic tectum in ray-finned fishes; electrosensory lobes in the few groups of advanced bony fish with an electrosensory system; the rostromedial nucleus of the thalamus in a few widely scattered groups of bony fish; and the dorsal cochlear nucleus in all mammals except monotremes. All of these structures receive topographically organized sensory input in their deep layers. Purkinje-like cells receive the sensory input near their cell bodies. These cells extend apical dendrites up into the molecular layer where they receive synaptic input from parallel fibers. The cerebellum itself can be included within this characterization by considering the climbing fiber as at least in part a conveyor of sensory information and by recalling that climbing fibers in more basal vertebrates terminate on smooth dendrites close to the soma. Physiological findings from three different systems suggest the hypothesis that cerebellum-like structures remove predictable features from the sensory inflow. Phylogenetic homology can explain

the similarities across different taxa for some types of cerebellum-like structures, but similarities within other types cannot be explained in this way. Moreover, phylogenetic homology cannot explain the similarities among different types of cerebellum-like structures. Evolutionary convergence provides the best explanation for all these similarities that cannot be explained by homology. The convergence is almost surely constrained by the availability of a genetic-developmental program for creating cerebellum-like circuitry and by the need within many different systems for the type of information processing that cerebellum-like circuitry can provide.

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Introduction

The cerebellum is present in all vertebrate brains [Nieuwenhuys, 1967; Larsell, 1967], and most vertebrate brains also have additional structures that are histologically similar to the cerebellum. The cerebellum and cerebellum-like structures vary widely among the different vertebrate taxa and neural systems, but their basic architecture is distinct and easily recognized. The distinctiveness of the architecture and the similarity across so many different taxa and systems lead naturally to an inquiry into the evolutionary and developmental origins of the similarities, and make cerebellum-like structures an attractive subject for such an inquiry. The most basic issue is whether the similarities among these structures are best explained by homology, that is by evolution from a com-

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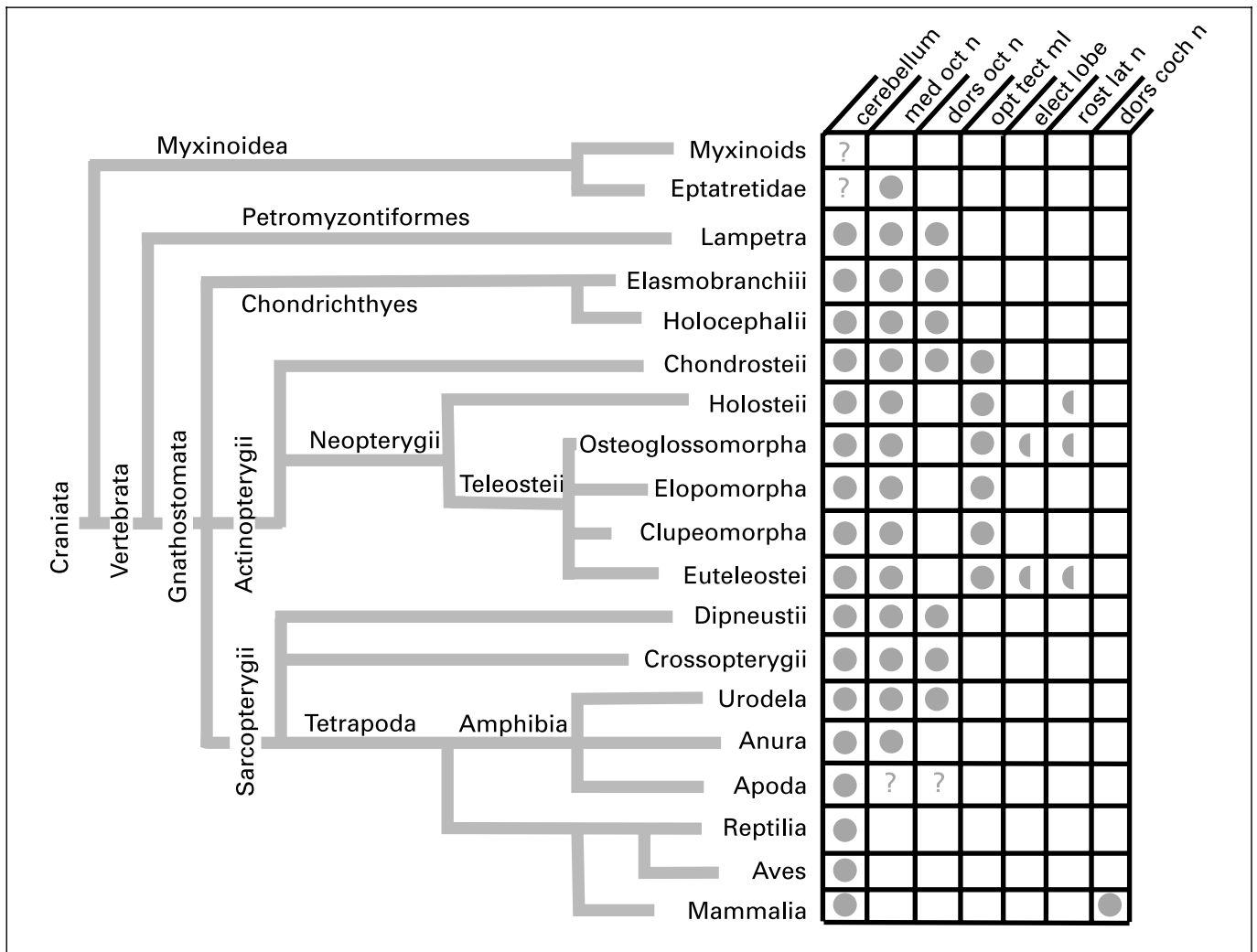


Fig. 1. Occurrences of cerebellum-like structures in different vertebrate groups. A filled circle means the structure is present in all or almost all the members of that group. A filled half circle means the structure is present only sporadically in that group. A question mark means that presence of the structure in that group is either unclear or controversial. Med oct n = medial octavolateral nucleus; dors oct n = dorsal octavolateral nucleus; opt tect ml = optic tectum marginal layer; elect lobe = electrosensory lobe; rostr lat n = rostralateral nucleus of thalamus; dors coch n = dorsal cochlear nucleus.

mon ancestral cerebellum-like structure, or are best explained by convergent evolution as constrained perhaps by available genetic mechanisms and by the need for similar types of information processing.

This review describes the different cerebellum-like structures of craniates and explores the issue of their evolutionary origin. The category ‘craniates’ includes the vertebrates and the myxinoids (hagfish) (see fig. 1). The myxinoids were once classified as vertebrates, but are now considered to be a sister group of the vertebrates [Liem et al., 2001]. The new classification scheme replaces an ear-

lier one in which the class Vertebrata was divided into two groups, the Agnatha (‘jawless’ animals) and the Gnathostomata (‘jawed’ animals). The ‘Agnatha’ included the myxinoids and petromyzontids (lampreys). The ‘Gnathostomata’ included all other vertebrates. The new classification scheme reflects current phylogenetic thinking which places the petromyzontids and gnathostomes together as vertebrates and considers the myxinoids as a separate group.

The cerebellum-like structures included in this review are as follows: the *medial octavolateral nucleus* (MON),

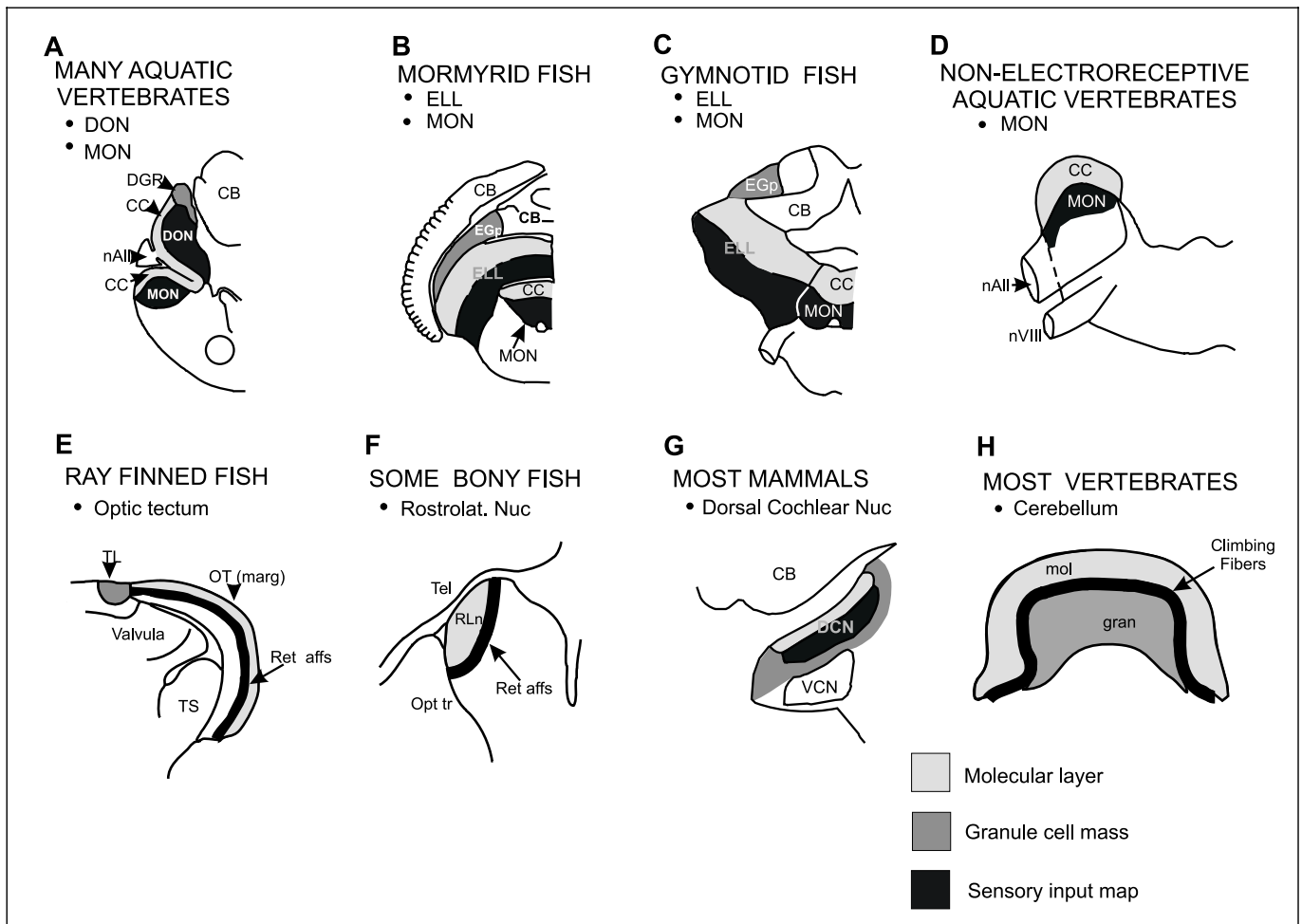


Fig. 2. Cerebellum-like structures in different vertebrate groups. The molecular layer, granule cell mass, and sensory input map are shown in different grayscale, as indicated at the lower right. CB = Cerebellum; CC = cerebellar crest; DCN = dorsal cochlear nucleus; DGR = dorsal granular ridge; DON = 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; OT (marg) = optic tectum, marginal layer; Ret affs = retinal afferents; RLn = rostralateral nucleus; Tel = telencephalon; TL = torus longitudinalis; TS = torus semicircularis; VCN = ventral cochlear nucleus.

present in most basal aquatic vertebrates and in some myxinooids; the *dorsal octavolateral nucleus* (DON), present in most of the same basal aquatic vertebrates as the MON, except for the bony fish (neopterygii), where it is entirely absent; the *marginal layer of the optic tectum*, present in all ray finned fish (actinopterygii); the *electrosensory lobe* (ELL), present in a few groups of advanced bony fish (teleostei); the *rostralateral nucleus* (RLN) of the thalamus, present in a few groups of bony fish; the *dorsal cochlear nucleus* (DCN), present in almost all mammals; and the *cerebellum* itself, present in all craniates, with the possible exception of the Myxinoidea

(fig. 1, 2). Note that the term ‘cerebellum-like structure’ when used in isolation in this paper includes the cerebellum itself. Similarly, the term ‘Purkinje-like cells’ includes the Purkinje cells of the cerebellum.

Survey of Cerebellum-Like Structures

General Description of Cerebellum-Like Architecture

A molecular layer is the most universal feature of these structures, and might be taken as a defining feature. The molecular layer contains fine parallel fibers all of which

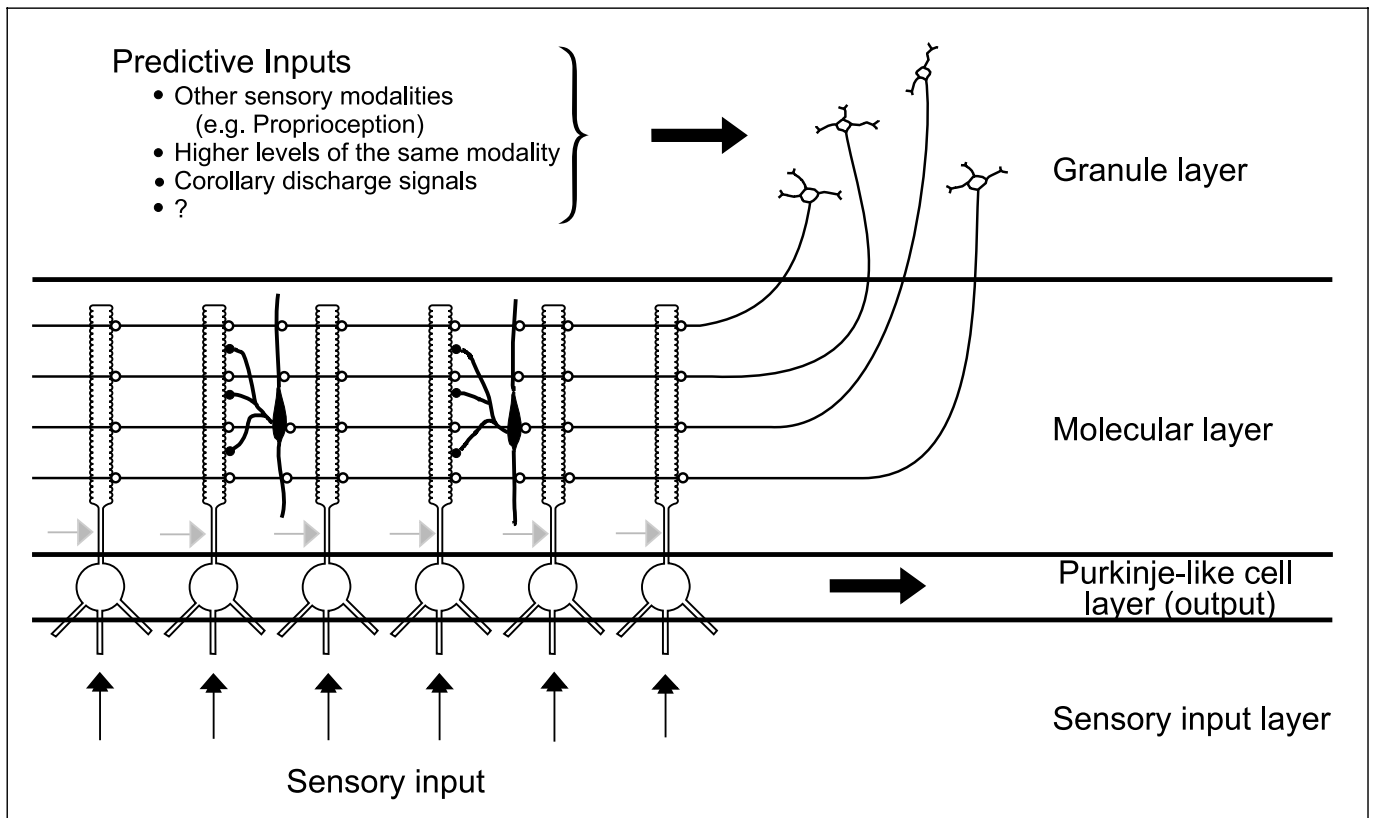


Fig. 3. Schematic drawing showing major features of cerebellum-like structures. Sensory input to the deeper layers may terminate on basal dendrites of Purkinje-like cells (black arrows) or on proximal apical dendrites of these cells (gray arrows).

course in approximately the same direction. Most cerebellum-like structures also have a cell body layer beneath the molecular layer that contains the somas of Purkinje-like cells. These cells have apical dendrites that extend up into an overlying molecular layer and are densely covered with spines. The spines receive synaptic input from parallel fibers (fig. 3). In a few cases, the cell bodies of Purkinje-like cells do not form a distinct layer but are embedded in the molecular layer itself. This occurs in the cerebellum of lampreys and the caudal (vestibulolateral) cerebellar lobe of some fish.

All of the cerebellum-like structures are derived from the alar or sensory plate of the embryo, and most of them can be described as processors of sensory information. Each structure, or in some cases different regions within a structure, processes a particular modality or type of sensory information. Afferent fibers that convey the type of sensory information for which the structure is responsible affect the basal regions of the Purkinje-like cells, either directly or via interneurons in the deeper layers of the

structure. The synapses conveying sensory input may be on basilar dendrites (vertical black arrows of fig. 3), on the proximal portion of apical dendrites (horizontal gray arrows of fig. 3), or on both. The afferent fibers usually terminate in a topographically organized manner, providing a map of a peripheral sensory surface such as the retina, the cochlea, or the electroreceptors of the skin.

The parallel fibers in the molecular layer generally arise from a mass of granule cells that is external to the cerebellum-like structure, although in the case of the cerebellum and the dorsal cochlear nucleus granule cells that give rise to parallel fibers are considered a part of the same structure. Neither parallel fibers nor the granule cells that give rise to them have been recorded *in vivo* in any cerebellum-like structure, and the exact information conveyed by these fibers is not known. Inputs to the granule cells have been described both anatomically and physiologically, however. Thus, the general types of information conveyed by parallel fibers are known in most cases, although the ways in which this information is integrated

and encoded by the granule cells are not known. Inputs to the granule cells include signals from sensory modalities other than the one that projects to the deeper layers, signals from higher central nervous system levels of the same sensory modality that projects to the deeper layers, and corollary discharge signals associated with motor commands. All of these parallel fiber signals are ones that are often associated with changes in the sensory modality that the structure is responsible for, allowing the parallel fiber signals to be used as predictors of changes in that modality. The inputs to the granule cells that give rise to parallel fibers are therefore indicated as 'predictive inputs' in figure 3. Other, as yet unidentified, types of predictive input to granule cells may also be present ('?' in fig. 3).

Figure 3 is a simplifying diagram that shows the common features of the different cerebellum-like structures. Each of the actual structures includes a rich variety of additional types of neurons and additional types of input from other central structures. The following descriptions of the different structures also emphasize the common features.

Medial Octavolateral Nucleus

The medial octavolateral nucleus (MON), also known as the intermediate octavolateral nucleus (fig. 2A–D), analyzes sensory input from mechanical lateral line and eighth nerve end organs [McCormick, 1999]. The MON is present in all aquatic craniates that possess mechanical lateral line receptors (fig. 1). Atlantic hagfish (myxinioids) do not have lateral line receptors and do not appear to have a MON [C.B. Braun, personal communication].

Purkinje-like cells of the MON, known as crest cells, have apical dendrites that extend into an overlying molecular layer known as the cerebellar crest. Basilar dendrites of the crest cells are affected by primary afferent fibers from lateral line and eighth nerve end organs [Puzdrowski and Leonard, 1993; McCormick, 1999]. Primary afferents from different sources terminate in different regions of the MON. In the mormyrid fish, for example, fibers from the anterior lateral line nerve, the posterior lateral line nerve, the utricle, the lagena, and the sacculus terminate within separate rostral-caudal strips of the MON [Bell, 1981a].

Parallel fibers of the cerebellar crest descend from an anteriorly located mass of granule cells known as the lateral granule mass in elasmobranchs and the eminentia granularis in other fish. The parallel fibers course in an anterior-to-posterior direction through the cerebellar crest and

synapse on the apical dendrites of crest cells. The inputs to these granule cells are not well known but include lateral line primary afferents [Bodznick and Northcutt, 1980], eighth nerve primary afferents [Bell, 1981a; Puzdrowski and Leonard, 1993], input from the spinal cord [Schmidt and Bodznick, 1987], and descending input from higher order lateral line and acoustic centers [Bell, 1981b; Finger and Tong, 1984; Schmidt and Bodznick, 1987; McCormick and Hernandez, 1996; McCormick, 1997].

Dorsal Octavolateral Nucleus

The dorsal octavolateral nucleus (DON; fig. 2A) analyzes sensory input from electroreceptors and is found in aquatic vertebrates including lampreys, many fishes and salamanders [Bullock and Heiligenberg, 1986; Montgomery et al., 1995] (fig. 2). Electroreception is a basal vertebrate sense that may have originated as early as the lateral line or vestibular senses during evolution [Bullock et al., 1983]. The Myxinoidea (hagfish) are not electroreceptive and do not have a DON. Whether electroreception was lost in the evolution of the Myxinoidea, or whether an absence of electroreception is the ancestral craniate condition is not known. Electroreception was clearly lost, however, during the evolution of the bony fish (Neopterygii), and bony fish do not have a DON. Electroreception reappeared during the evolution of a few separate groups of advanced bony fish (Teleostei), but the more recently derived electroreceptors and associated central structures of teleosts (see below, 'Electrosensory Lobe of Electroreceptive Teleosts') are quite different from those of other aquatic vertebrates.

The DON is located just dorsal to the MON and is similar to the MON in its structure and connections. However, the deeper layers of DON receive primary afferent input from electroreceptors in the skin rather than from mechanical lateral line or eighth nerve receptors [Bodznick and Northcutt, 1980; Puzdrowski and Leonard, 1993]. The afferent projection to DON is topographically organized and forms a map of the electroreceptive surface of the skin. The basilar dendrites of DON crest cells are affected directly or indirectly by primary afferent input, as in the MON, and their apical dendrites extend up into an overlying cerebellar crest, where they are contacted by parallel fibers.

Parallel fibers of the cerebellar crest lying above the DON arise from a mass of granule cells known as the dorsal granular ridge. Anatomical studies show inputs to the dorsal granular ridge from the spinal cord and from other central structures, including ones that appear to be higher-order electrosensory nuclei [Bodznick and Boord, 1986;

Schmidt and Bodznick, 1987]. Inputs to the dorsal granular ridge have also been recorded physiologically in an elasmobranch [Conley and Bodznick, 1994; Hjelmstad et al., 1996]. These inputs fall into three main categories: 1) proprioceptive inputs driven by movements of the body, fins, and respiratory apparatus; 2) electrosensory inputs descending from a higher level electrosensory nucleus; and 3) corollary discharge signals associated with the motor commands that drive the respiratory movements of the fish. Fibers conveying all three types of input discharge in relation to the fish's respiratory cycle, with different fibers being active at different phases of the cycle. Electroreceptors are exquisitely sensitive in elasmobranchs and are strongly affected by the fish's own respiration [Montgomery and Bodznick, 1993]. The descending activity in parallel fibers can therefore be used to predict these cyclic changes in afferent input to the deeper layers of DON (see below, 'Possible Similarity of Function for Cerebellum-Like Structures').

Marginal Layer of the Optic Tectum in Teleosts

Afferent input from the retina terminates in the roof of the mesencephalon in all vertebrates with functional retinas. The region is known as the optic tectum in fish, amphibia, reptiles and birds, and as the superior colliculus in mammals. The optic tectum of actinopterygian (ray-finned) fishes is distinctive in that its outer layers are cerebellum-like [Vanegas et al., 1979; Meek, 1992a].

The most external layer of the actinopterygian tectum is a molecular layer known as the marginal layer (fig. 2E). The marginal layer is small in chondrosteian fish (sturgeons and paddle fish), but quite prominent in many holostean and teleost fish. Purkinje-like cells [Type I interneurons of Meek and Schellart, 1978] form a layer deep to the marginal layer. These cells extend their spine-covered apical dendrites up into the marginal layer. Input from the retina maps topographically onto basilar dendrites of the Purkinje-like cells and onto smooth proximal portions of the apical dendrites just above the cell bodies.

The parallel fibers of the marginal layer arise from a medially located granule cell mass known as the torus longitudinalis. The parallel fibers stream laterally away from the torus longitudinalis over the entire surface of the tectum, making synaptic contact with the spines of the Purkinje-like cells.

Granule cells of the torus longitudinalis are affected by signals that could serve to predict the visual input from the retina. Thus, these cells receive a projection from the oculomotor nuclei [Wulliman, 1994] and respond to eye movements in the dark [Northmore et al., 1983], suggest-

ing that they are affected by corollary discharge signals associated with the motor commands that evoke eye movements. Such corollary discharge signals could serve to predict the changes in retinal input evoked by the associated eye movements. The torus longitudinalis cells also receive visual input, possibly from the tectum [Northmore et al., 1983]. One type of visual stimulus will often be associated with another type of visual stimulus. Thus, visual responses of parallel fibers could also serve to predict some aspects of visual input from the retina.

Electrosensory Lobe of Electroreceptive Teleosts

Electroreception is present in four groups of teleosts: Mormyriiformes, 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 Notopteriidae [Bullock and Heiligenberg, 1986]. All of these fish have a cerebellum-like electrosensory lobe (ELL) that receives the afferent input from electroreceptors (fig. 2B, C) [Maler et al., 1981; Braford, 1982; Finger and Tong, 1984; Meek et al., 1999]. Mormyriiform and xenomystid fish are closely related taxa of the teleost cohort Osteoglossomorpha (fig. 2), and it is possible that electroreception evolved in a common ancestor but was subsequently lost in non-electroreceptive notopterid fish. Similarly, gymnotiform and siluriform fish are closely related taxa of a different teleost cohort, the Euteleostei, and it is possible that electroreception evolved in a common ancestor of these two euteleost groups; however, electroreception is rare in teleosts, and the many sister groups of the electroreceptive taxa within euteleost or osteoglossid cohorts are not electroreceptive. Thus, electroreception and its central pathways must have evolved independently at least twice within the teleost radiation.

The apical dendrites of ELL Purkinje-like cells extend up into an overlying molecular layer. Their basilar dendrites receive afferent input from electroreceptors, either directly or indirectly via interneurons. The afferent input is topographically organized, forming maps within ELL of the electroreceptive skin surface. The ELLs of mormyriiform and gymnotiform fish contain multiple maps. ELLs of the family Mormyridae have three maps, each receiving a different type of primary afferent [Bell and Szabo, 1986]. Gymnotiform ELLs have four maps, but the maps are formed in a different manner. Three of the maps in the gymnotiform ELL are formed by branching of the same afferent fibers. A fourth map receives a different type of electroreceptor afferent [Carr and Maler, 1986].

The basic cerebellum-like structure of ELL is similar in mormyrid and gymnotiform fish, but there are also important differences, in addition to the difference in how maps are formed. Purkinje-like cells in the mormyrid ELL are inhibitory interneurons that end locally on efferent neurons, which in turn convey the electrosensory information to the mesencephalon. In this regard, mormyrid Purkinje-like cells are like true Purkinje cells of the teleost cerebellum. Teleost Purkinje cells are also inhibitory interneurons that end locally on efferent neurons, which are equivalent to cells of the cerebellar nuclei in mammals [Meek, 1992b]. In contrast, Purkinje-like cells of the gymnotid ELL are not inhibitory and are themselves efferent cells projecting to the mesencephalon [Carr and Maler, 1986]. These and other differences between the ELLs of the two groups are consistent with their independent evolutionary origins.

The parallel fibers of the ELL molecular layer arise from the eminentia granularis posterior (EGp), a mass of granule cells that is continuous with the anterior eminentia granularis from which parallel fibers of the cerebellar crest arise in the same fish. The inputs to EGp have been most extensively studied in mormyrid and gymnotid fish. In mormyrid fish these inputs include corollary discharge signals associated with the motor command that elicits the electric organ discharge, proprioceptive signals associated with bending of the body or the fins, and descending input from higher levels of the electrosensory system [Bell et al., 1992]. Anatomical studies show that the mormyrid EGp also receives extensive input from the spinal cord via a tract that appears to be equivalent to the ventral spinocerebellar tract in mammals [Szabo et al., 1979]. The ventral spinocerebellar tract in mammals conveys corollary discharge information associated with motor activity generated in the spinal cord [Arshavskii et al., 1972]. Thus it is possible that the mormyrid EGp might also receive corollary discharge information associated with ordinary motor activity. The EGp of gymnotid fish also receives proprioceptive input and descending input from higher levels of the electrosensory system [Bastian, 1986]. All of these different types of signals are relayed to ELL as parallel fiber inputs, where they can serve to predict changes in the afferent activity from electroreceptors arriving in the deeper layers (see below, 'Possible Similarity of Function for Cerebellum-Like Structures').

Rostrrolateral Nucleus of the Thalamus in Some Holostean and Teleost Fish

The rostrrolateral nucleus (RLN, fig. 2F) of the thalamus is a small cerebellum-like structure found in the thalamus of a few widely scattered neopterygian fish (fig. 1).

The nucleus has been identified in 6 of the 16 different taxa in which it has been investigated [Butler and Saidel, 1992; Saidel and Butler, 1997]. The distribution in different fish is sporadic, and the structure is not present in sister groups of taxa in which it is present. The Purkinje-like cells of RLN do not have basilar dendrites but receive a direct input from the retina on the most proximal part of their apical dendrites (as shown by gray arrows in fig. 3). This input appears to be retinotopically organized [W.M. Saidel, personal communication]. The more distal apical dendrites are covered with spines and receive parallel fiber input from the torus longitudinalis. It is not known whether parallel fibers in the marginal layer of the tectum and the RLN arise from the same granule cells or from separate granule cells in the torus longitudinalis. The RLN has not yet been studied physiologically.

Dorsal Cochlear Nucleus of Mammals

All mammals possess a dorsal cochlear nucleus (DCN; fig. 2G). The DCN is laminated and cerebellum-like in marsupials and eutherian mammals but not in monotremes [Cant, 1992; Johnson et al., 1994; Nieuwenhuys et al., 1997]. The size of DCN varies greatly in different taxa, being rather small in humans and very large in some rodents [Merzenich et al., 1973]. Functional correlates of this variation in size are not known. Primary afferent fibers from the cochlea terminate in a tonotopically organized manner in the deeper cell layers of the structure (fig. 1G). An overlying molecular layer contains parallel fibers that 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, each parallel fiber passes through different frequency-specific regions of DCN.

The cells that are most similar to Purkinje cells in the DCN are the 'cartwheel' cells [Cant, 1992]. The dendrites of these cells are restricted to the molecular layer. Cartwheel cells are inhibitory interneurons that terminate locally on efferent neurons [Oertel and Wu, 1989], being similar in this respect to Purkinje cells of the teleost cerebellum and Purkinje-like cells of the mormyrid ELL. Cartwheel cells are different from most of the previously described Purkinje-like cells in that they do not have basilar dendrites and may not be directly affected by primary afferent input.

There is another cell type in the DCN, however; the fusiform cell is more similar to the previously described Purkinje-like cells in that it has both apical and basilar dendrites [Oertel and Wu, 1989; Cant, 1992]. The cell bodies of fusiform cells are in the deeper cell layer. Their

spine-covered apical dendrites extend up into the molecular layer where they are contacted by parallel fibers. Their basilar dendrites are in the cell layer where they are contacted by primary afferent fibers from the cochlea. The fusiform cells are efferent cells and project to the mesencephalon.

Various types of input to the granule cells of DCN have been identified including somatosensory input [Weinberg and Rustioni, 1987] and descending input from higher levels of the brain. The descending input comes from the auditory cortex [Weedman and Ryugo, 1996], somatosensory cortex [Wolff and Kunzle, 1997], and the inferior colliculus [Caicedo and Herbert, 1993]. Somatosensory input comes from the dorsal column nuclei as well as from the somatosensory cortex. Somatosensory input from the pinna has a particularly strong effect on cells of DCN [Kanold and Young, 2001], with proprioceptive input associated with pinna movement being much more effective than cutaneous input. The DCN granule cells also receive somatosensory input from the neck and forelimbs. Movements of the animal's pinna, head, or body will have strong and predictable effects on how the cochlea responds to an external sound source. Similarly, different sounds often occur together or in sequence so that one sound can predict another sound, as in a remembered melody. Thus, the somatosensory and auditory signals conveyed by the parallel fibers of DCN can serve to predict changes in afferent activity from the cochlea that arrives at the deeper layers.

Cerebellum

All vertebrates appear to have a cerebellum (fig. 2H), but the existence of a cerebellum is controversial in hagfish, with some anatomists saying it is present [Larsell, 1967] and others saying that it is not [Nieuwenhuys et al., 1997]. Although most anatomists conclude that a cerebellum is present in lampreys, this cerebellum is small and difficult to distinguish [M.A. Pombal, personal communication], as it is made up of a few scattered cells in the rhombic lip that are embedded among commissural fibers and what may be parallel fibers. However, the MON with its overlying cerebellar crest is clear in Pacific hagfish (Eptatretidae) and in lampreys. The DON with its cerebellar crest is also clear in lampreys. Thus, these cerebellum-like structures, the MON and DON, probably evolved as early as, or even earlier than, the cerebellum itself.

The traditional view that the cerebellum is an organ of motor control may be only partially correct. Paulin [1993] has suggested that the cerebellum might be better viewed as a sensory processor that analyzes and processes sensory

information for subsequent use by the motor system. Several lines of evidence suggest a sensory role. First, the regions of the cerebellum that are relatively enlarged in different animals are those that receive input from the most highly developed senses in those animals. The enlarged regions of the cerebellum in echolocating bats and cetaceans, for example, are those that receive auditory input. Second, the lack of a sharp border between the granule cell masses of some cerebellum-like structures that are clearly sensory and the granule cell layer of the cerebellum is also consistent with a sensory role for the cerebellum. Thus, the eminentia granularis of teleosts, the lateral granule mass of elasmobranchs, and the granule cells of DCN all merge with the granule layers of the different cerebellums. Finally, embryology suggests a sensory role for the cerebellum as the cerebellum is derived from the sensory (alar) plate of the neural tube. Emphasis on the role of the cerebellum as a sensory processor, analyzing such input for subsequent use by the motor system, makes it possible to group the cerebellum with the other cerebellum-like structures, all of which are clearly sensory.

The most obvious difference between the histology of the cerebellum and that of the other cerebellum-like structures is the climbing fiber input to cerebellar Purkinje cells. Each Purkinje cell receives input from a single climbing fiber that makes a very large number of synaptic contacts on the same cell. Such climbing fibers have been observed morphologically in most vertebrate groups, including elasmobranchs [Alvarez-Otero et al., 1993], teleosts [Meek and Nieuwenhuys, 1991], birds [Cajal, 1952], amphibians [Sotelo, 1969], reptiles [Hillman, 1969], and mammals [Cajal, 1952]. Physiologically, a single action potential in the climbing fiber evokes a large, all-or-none, excitatory postsynaptic potential (EPSP) in the Purkinje cell that in turn evokes postsynaptic spikes. Such climbing fiber responses have been observed in all vertebrates in which Purkinje cells have been recorded, including teleosts [Kotchabhakdi, 1976; V.Z. Han, personal communication], amphibians [Nacimientos, 1969], reptiles [Llinas and Nicholson, 1969], and mammals [Eccles et al., 1967]. Such strong synaptic input from a single presynaptic fiber has not been observed either morphologically or physiologically in any cerebellum-like structure other than the cerebellum.

Climbing fibers terminate on the smooth branches of Purkinje cells, not on the spiny branchlets where parallel fibers terminate. The smooth branches extend throughout the molecular layer in mammals, but in all other vertebrate classes the smooth dendrites are confined to a deep-

er portion of the molecular layer. Thus, the climbing fibers terminate on the smooth, proximal portions of Purkinje cell dendrites in non-mammals (as illustrated by gray arrows in fig. 3).

Climbing fiber input is considered here as analogous, at least, to the sensory input to deep layers in the other cerebellum-like structures. Climbing fibers arise from the inferior olive at the base of the brain. But cells of the inferior olive are derived from the alar plate (like the cerebellum) and migrate to their ventral location during development. Different parts of the inferior olive receive input from different sensory systems, and climbing fibers to different parts of the cerebellum respond with great sensitivity and specificity to sensory stimuli, including visual [Maekawa and Simpson, 1972], auditory [Mortimer, 1975], vestibular [Precht et al., 1976; Barmack and Shojaiku, 1992], and somatosensory [Robertson, 1985] stimuli.

The inferior olive is certainly much more than a sensory relay. This additional complexity is indicated by the large projections to the inferior olive from the cerebral cortex, the large projections from inhibitory neurons of the cerebellar nuclei [Fredette and Mugnaini, 1991], the intrinsic rhythmicity of the inferior olive [Llinas and Yarom, 1986], and the gating of climbing fiber responses to sensory input by motor command signals [Gellman et al., 1985; Lidieth and Apps, 1990]. Nevertheless, it is clear that climbing fibers in many parts of the cerebellum convey precise sensory information to the smooth dendrites of Purkinje cells.

Granule cells of the cerebellum receive input from a rich variety of sources, including motor command related signals, sensory signals from many different modalities, and signals from different regions of the cerebral cortex relayed through the pons. These signals are conveyed by parallel fibers to Purkinje cells where they can be used to predict the input conveyed by climbing fibers to the proximal dendrites (see below, 'Possible Similarity of Function for Cerebellum-Like Structures').

Additional Anatomical Similarities

The previous section emphasized the anatomical features that are shared by all of the different cerebellum-like structures. These included a molecular layer with parallel fibers that course in the same direction and Purkinje-like cells that receive the parallel fiber input on the spines of their apical dendrites and sensory input on their basilar dendrites or on the proximal portion of their apical dendrites. Additional similarities are also present which may

be shared by only a subset of the different cerebellum-like structures or have not yet been looked for in all of the structures. These include similar cell types, proteins, and connections.

Cell types within the granule cell masses that give rise to the parallel fibers appear to be very similar in several of the cerebellum-like structures. Granule cells in the cerebellum [Cajal, 1952], in the DCN [Kane, 1974], in the eminentia granularis [where the parallel fibers of ELL and MON arise; Bell, unpublished observations in the mormyrid] all have the classic granule cell shape of a small round cell bodies with 3 to 6 thin dendrites extending out radially and terminating in claw-like postsynaptic structures. Large, GABAergic Golgi cells are similarly distributed throughout the granule layer in all these structures. An unusual and only recently identified cell, the unipolar brush cell, is also present in the cerebellum [Floris et al., 1994], DCN [Floris et al., 1994], and eminentia granularis [Bell, unpublished observations], but is not present in structures that are not cerebellum-like. Finally, GABAergic stellate cells are present in the molecular layer of most cerebellum-like structures [Montgomery et al., 1995] (fig. 3).

Immunocytochemistry and in situ hybridization show that the same or similar genes are expressed in different cerebellum-like structures. This has been especially studied with regard to the cerebellum and the DCN, where antibodies to many proteins stain both Purkinje cells and DCN cartwheel cells [Berrebi et al., 1990]. Unipolar brush cells in both structures [Floris et al., 1994] and in the eminentia granularis of mormyrids [Bell, unpublished observations] stain with antibodies to calbindin, calretinin, and metabotropic glutamate receptors 1 and 2/3. Immunocytochemistry shows that the dendrites of Purkinje cells [Maeda et al., 1990], DCN cartwheel cells [Ryugo et al., 1995] and Purkinje-like cells of the teleost optic tectum marginal layer [Berman et al., 1995; Bell, unpublished observations] express high levels of 1,4,5-phosphate (IP3) receptors, but that the dendrites of Purkinje-like cells of the ELL do not [Berman et al., 1995]. The NR1 subunit of the NMDA receptor is present in Purkinje-like cells of the teleost ELL [Berman et al., 2001], the teleost MON [Bell, unpublished observations], the teleost optic tectum [Bell, unpublished observations], and the DCN [Petralia et al., 1996], but cerebellar Purkinje cells do not show such staining.

The external connections of some of the different types of cerebellum-like structures can be quite similar. Several of the cerebellum-like structures that receive sensory input from octavolateral receptors (eighth nerve, lateral

line, or electroreceptor end organs) project bilaterally to mesencephalic nuclei via the lateral lemniscus. Such structures include the DON, MON, ELL, and DCN. In contrast, the cerebellum, parts of which receive primary afferent input from the eighth nerve, has a quite different pattern of projection. The similar afferent connections, from the retina and the torus longitudinalis, of the RLN and the optic tectum marginal layer have already been mentioned.

Possible Similarity of Function for Cerebellum-Like Structures

The ELL of mormyrid fish, the ELL of gymnotid fish, and the DON of elasmobranch fish have all been shown to act as adaptive sensory processors [Bell, 1982; Bodznick, 1993; Bastian, 1995]. Each of these structures can generate a negative image of predicted electrosensory input patterns after a period of association between predictive signals conveyed by parallel fibers and a consistent pattern of electrosensory input to the deeper layers. Addition of the negative image of predicted input to the actual input removes or minimizes predicted features of the sensory inflow. Such removal allows novel sensory features to stand out and makes better use of the information processing and storage capacity of the brain. Adaptive sensory processing in these structures has been reviewed elsewhere [Bell et al., 1997a; Bell, 2001] and is described only briefly here.

The electric organ discharge (EOD) of mormyrid electric fish affects the ELL in two distinct ways – via primary afferent fibers from electroreceptors excited by the EOD and via an electric organ corollary discharge (EOCD) signal associated with the motor command that evokes the EOD. The two signals can be separated by giving curare to the fish. Curare blocks the EOD itself but the EOD motor command continues to be emitted spontaneously ('fictive discharging'). The effect of the electric organ corollary discharge (EOCD) on Purkinje-like cells of ELL is transformed by a few minutes of pairing with an electrosensory stimulus to the receptive field of the cell (fig. 4A). Such pairing results in an EOCD response that was not present before the pairing and which is a negative image of the previously paired sensory response. Similar experiments show that the negative image is specific to the polarity of the paired sensory response (excitation vs. inhibition) and to its timing relative to the EOD motor command. The EOCD-evoked negative image is also specific to the spatial pattern of the paired sensory response as the sensory

stimulus must affect the cell, that is, be within the cell's receptive field, in order to be effective [Bell, 1982].

Similar negative image formation occurs in the ELL of gymnotid electric fish after pairing electrosensory stimuli with tail bending [Bastian, 1995] (fig. 4B), and in the DON of elasmobranch fish after pairing electrosensory stimuli with respiratory ventilation [Bodznick, 1993] (fig. 4C). Negative images in the gymnotid ELL and in the elasmobranch DON are specific to the polarity, the timing, and the spatial distribution of the sensory response, as in the mormyrid ELL. The canceling of a predicted sensory response by the addition of a negative image of that response is shown particularly clearly in figure 4C, where coupling to the ventilatory rhythm reduces a large initial response ('0 min') to almost nothing ('25 min').

A variety of different predictive signals can be used to evoke negative images in the gymnotid ELL and the elasmobranch DON. Thus, both proprioceptive signals from the trunk and whole body electrosensory signals can evoke negative images of electrosensory responses with which they have been paired in the gymnotid ELL [Bastian, 1999]. Similarly, proprioceptive signals, corollary discharge signals, and whole body electrosensory signals are all effective as predictive signals in the elasmobranch DON [Bodznick et al., 1999].

Plasticity has been demonstrated at synapses between parallel fibers and Purkinje-like cells in the ELL of mormyrids [Bell et al., 1997b], the ELL of gymnotids [Bastian, 1999], and the DON of elasmobranchs [Bodznick et al., 1999]. Both depression and potentiation of synaptic strength are present. Several lines of evidence [Bell et al., 1997a] as well as modeling studies [Nelson and Paulin, 1995; Roberts and Bell, 2000] strongly suggest that plasticity at this synapse is responsible for the negative images of predicted sensory responses.

All of the cerebellum-like structures are characterized by parallel fibers conveying signals that can predict sensory input to the deeper layers and by Purkinje-like cells that receive both parallel fiber and sensory inputs. Thus, the results obtained in mormyrids, gymnotids and elasmobranchs suggest the hypothesis that similar adaptive processing might occur in other cerebellum-like structures. In the dorsal cochlear nucleus, for example, parallel fibers conveying information about movements of the pinna or of the head could elicit negative images of the expected changes in auditory input, a possibility that is supported by the recent discovery of associative synaptic plasticity at parallel fiber synapses in the dorsal cochlear nucleus [Fujino and Oertel, 2002]. The creation of negative images of predicted inputs and the removal of predictable

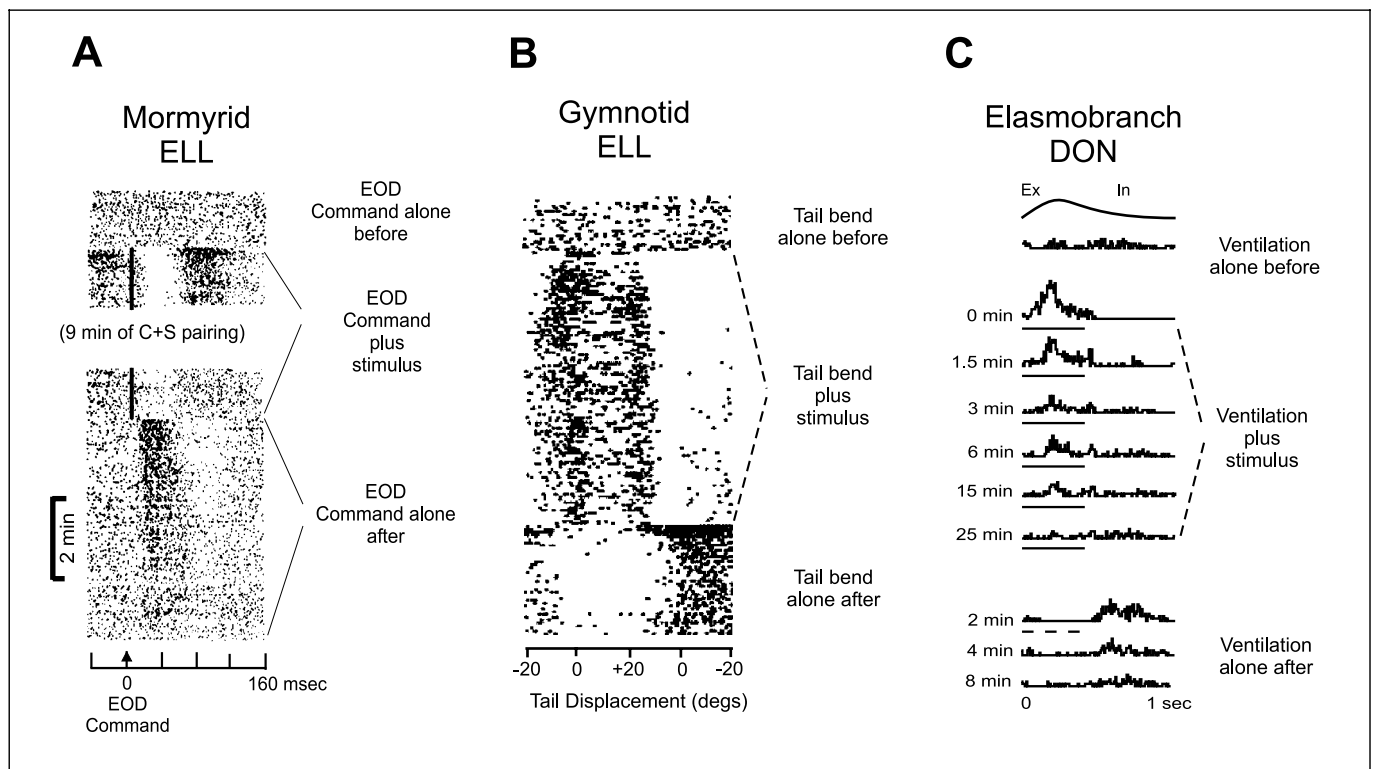


Fig. 4. Formation of negative images of predicted sensory responses in three different cerebellum-like structures. **A** Raster display of the responses of a cell in the mormyrid ELL. Each dot represents an action potential. The EOD motor command occurs at time 0. The command initially has no effect 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 cycle of movement. 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, revealing 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 opposite to the previously paired sensory response [from Bodznick, 1993].

features would be useful in many systems, and selection for the ability to carry out such processing could have contributed to the evolution of cerebellum-like structures in different systems.

The cerebellum itself might carry out a similar type of adaptive processing [Bell et al., 1997a; Devor, 2000]. Plastic change has been demonstrated at the parallel fiber to Purkinje cell synapse following the pairing of parallel fiber and climbing fiber inputs [Ito, 1984, 2001]. Moreover, parallel fibers in many regions of the cerebellum convey signals that could be used to predict the climbing fiber inputs to the same cerebellar region. Climbing fibers

are commonly viewed as signaling an undesirable condition, such as an error in motor performance. If synaptic plasticity results in parallel fiber activity eliciting a negative image of expected climbing fiber input, and if the Purkinje cells are connected to the rest of the brain so that a pause in their activity opposes whatever it was that evoked the climbing fiber input, then the cerebellum would serve to minimize the undesirable conditions signaled by climbing fibers. The described process is only a restatement of Ito's theory of motor learning [Ito, 1984], but it places the cerebellum within the framework of the other cerebellum-like structures.

The concept of homology is of central importance for understanding the evolutionary origins of similarities among different structures in different taxa. The concept has been used in various ways, but will be used here in the sense of historical or phylogenetic homology [Bolker and Raff, 1996; Futuyma, 1998; Butler and Saidel, 2000]. In this usage, a character is considered homologous across different taxa if the taxa have inherited the character from a common ancestor that also had the character. Such homology requires a congruence between the distribution of the character in the different taxa and their phylogeny, as determined by analysis of all the other characters and the fossil record. If the presumed common ancestor of two taxa with a similar character did not have the character, then the character is not homologous. There must also be a continuity of information. If the character is present in two different taxa and also in their common ancestor, but disappeared and then reappeared during the evolution of one of the taxa, then the character is not homologous.

The cerebellums of different vertebrates are clearly homologous according to this phylogenetic definition. All vertebrates from lampreys to mammals have a cerebellum, and parsimony therefore implies that the cerebellum was present in the common ancestor. Thus, the similarity among vertebrate cerebellums is best explained by homology. In addition, similarity of the same cerebellum-like structure across different taxa can, in most cases, also be best explained by homology. This is true for the MONs of aquatic vertebrates and myxinooids, the DONs of many electroreceptive aquatic vertebrates, the marginal layer of the optic tectum of ray finned fish, and the DCN of marsupial and eutherian mammals. In each case, the phylogeny indicates that the group that possesses the cerebellum-like structure had a common ancestor, and that similarity of the structure across different taxa can be explained by evolution from that common ancestor.

The similarities among ELLs of different electroreceptive teleosts or among the RLNs of different bony fish cannot be explained by homology, however. The osteoglossid and euteleost taxa with ELLs are widely separated from each other in phylogeny and the many sister groups of taxa with ELLs do not have ELLs. Parsimony therefore indicates that the common ancestor of osteoglossid and euteleost cohorts did not have an ELL either. Moreover, the ancestor of teleosts is presumed to have been a holostean fish and holosteans do not have an ELL. The different taxa with RLNs are also widely separated from each other in phylogeny and most of their sister groups do not

have the nucleus. Parsimony therefore indicates that the common ancestor of taxa with an RLN did not have the structure.

Similarities among the different types of cerebellum-like structures also cannot be explained by homology. There is 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. Indeed, there is no evidence for an ancestral structure from which even two of the presently existing cerebellum-like structures evolved.

How then can we explain the similarities among the different cerebellum-like structures? Structural similarities that are not due to homology are referred to as examples of 'homoplasy'. Homoplasy is considered to have three possible origins: *parallel evolution*, in which two structures evolved independently but in a similar manner under similar selective pressure from the same ancestral structure; *evolutionary reversal*, in which a structure that is present in the common ancestor of two taxa disappeared and then reappeared in one or both taxa; and *convergence*, in which two structures evolve toward similarity via independent evolutionary paths because of similar selective pressure [Futuyma, 1998].

None of these explanations are really satisfactory as explanations of the similarities among cerebellum-like structures. *Parallel evolution* could have played a role in a few cases perhaps. Thus, it is possible that the DCN evolved from part of the cerebellum of an ancestral mammal by invasion of auditory nerve fibers, or that the ELLs of electroreceptive teleosts evolved from the MONs of ancestral non-electroreceptive teleosts by invasion of electroreceptor afferents into part of the MON. But there is no evidence for these scenarios, such as the existence of intermediate forms in which the cerebellum and the DCN, or the MON and the ELL, are not structurally distinct. More generally, the lack of plausible common ancestors for the different types of cerebellum-like structures, as described previously, also argues against parallel evolution as an explanation of the similarities among these structures. *Evolutionary reversal* might be invoked to explain the ELLs of teleosts as a reappearance of the electroreceptive DON that is present in more basal vertebrates. However, such a hypothesis is rather empty in the absence of more information or a mechanism, and could not, in any case, explain the similarities among other cerebellum-like structures.

Convergence resulting from similar selective pressures could have played a role in the evolution of cerebellum-like structures. This possibility was suggested in the pre-

ceding section where cerebellum-like structures were shown to be capable of removing predictable features from the sensory inflow, such a role being of great value for any sensory system in any organism. Although cerebellum-like structures might be well suited to this task, they are not uniquely suited. Other, quite different, neural structures, such as the cerebral cortex, can probably carry out similar types of processing [Singer, 1995]. In addition, it is difficult to imagine how all the striking similarities in these structures could have arisen through completely independent evolutionary processes. Something more than convergence seems to be needed to explain the similarities.

That something more is probably a shared genetic-developmental program present in all craniates that once activated can lead to the generation of a cerebellum-like structure. The many similarities in circuitry, cell morphology, immunocytochemistry, and connectivity suggest the presence of such a shared genetic program, and findings from experimental embryology support the possibility. For example, ectopic cerebellum-like structures will 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]. Finally, different independent mutations in mice that cause Purkinje cell degeneration also cause degeneration of cartwheel cells in the DCN [Berrebi et al., 1990].

All of the cerebellum-like structures are derived embryologically from the somatosensory portion of the alar plate, and it is possible that the genetic program leading to the development of cerebellum-like structures can only be activated within that portion of the embryo. It is likely too, that cerebellum-like structures that are very similar, such as the DON and the MON or the cerebellum and the DCN, share more of their genetic-developmental machinery than do structures which are rather different, such as the cerebellum and the RLN.

Developmental expression of a similar set of genes in different brain regions, or in different taxa with no common ancestor that also expresses those genes, might be described as convergence in developmental gene expression [Wray, 2002]. Such convergence in gene expression would appear to explain the convergence in histological organization shown by the different cerebellum-like structures. More generally, 'syngeny' is a useful term that has been introduced to describe similarities of structure

which are due to a shared genetic-developmental program, whether phylogenetic homology is present or not [Butler and Saidel, 2000]. Syngeny can be used to describe structures in the same organism, such as the forelimb and hindlimb, that are similar and that share some of the same genetic machinery during development but which are not homologous. The ELLs of electroreceptive teleosts, the RLNs of various bony fish, and the different types of cerebellum-like structures are other examples of structures that appear to be syngenous but not homologous. The cerebellums of different vertebrates, however, are examples of structures which are both syngenous and homologous.

In conclusion, the similarities among the different types of cerebellum-like structures can be best explained by convergence rather than by homology or parallel evolution – convergence as constrained by the available genetic-developmental programs and by the requirements for a certain type of information processing.

Acknowledgments

A sincere thank you to all the people who provided information and comments during the writing of this paper: David Bodznick, Christopher Braun, Catherine Carr, Bernd Fritsch, Richard Hawkes, Catherine McCormick, Johannes Meek, Enrico Mugnaini and William Saidel. Thanks too to Heather Eisthen, Kiisa Nishikawa, and Karger Publishers for a fine symposium on convergence and for inviting me to participate. This work was supported by grants from the National Institute of Mental Health (MH49792 and MH60996).

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