A Comparative View of Cerebellar Morphology and Diversity in Fishes

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Abstract Fish represent the most diverse vertebrate class. Through evolutionary time and habitat adaptations, bony and cartilaginous fishes have taken up nearly every aquatic environment of the globe imaginable. These factors have uniquely shaped brain growth, morphology, and even the appearance of functional specializations. The mature cerebellum of different fish lineages is largely reflective of these pressures, providing an unprecedented opportunity to study how this structure has become specialized and has diverged in morphology compared with other vertebrate groups. At a functional level, accumulating evidence points toward a multifaceted role of the fish cerebellum, involved in diverse processes such as movement, cognition and emotion, and sensory-motor learning. While early cerebellar development appears to be largely conserved across vertebrates, including fish, numerous features set these species apart, making them fascinating models to better understand neurodevelopment and environmental pressures. The goal of this chapter is to provide an overview of the distinctive features that characterize the cerebellar architecture of major fish lineages.

Keywords Cerebellum · Cerebelloid structures · Bony fish · Cartilaginous fish · Morphology · Neurodevelopment · Neurogenesis · Comparative

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Introduction

Fish represent the most diverse vertebrate class [39], having adapted to nearly every aquatic habitat possible and representing the most phylogenetically ancient vertebrate lineages. This makes extant fish species tremendously attractive to study the evolution of brain development and specialization. In many cases, lifestyle specializations are reflected by changes in the morphology of brain structures over ontogeny that are coupled with the environment and functional needs [40]. This is equally true of the fish cerebellum that has maintained a basic organizational plan similar to that of their land relatives [34], but this has also been modified by environmental factors as a consequence of major fish radiations. Representing basal vertebrates [7, 67], Chondrichthyes (sharks and rays) and Osteichthyes (bony fish), which additionally include Sarcopterygians (lobe-finned fish) and Actinopterygians (ray-finned fish), serve as extremely valuable models to study the evolution of cerebellar development (*see* Fig. 1). Comparative neuroanatomical investigations of the cerebellum between different major fish lineages as well as tetrapods can provide a rich understanding of the evolution of the cerebellar structure–function relationship.

   The cerebellum of fishes displays by far the most structural variation compared to any other vertebrate class [44]. With this in mind, the overarching goal of this chapter is to highlight how such diversity in structure has arisen and how the cerebellar architecture of fishes has over time deviated or been to some extent remodeled, from the fundamental vertebrate cerebellar organizational plan. This review is by no way meant to be exhaustive but rather to provide an overview, as several excellent in-depth reviews investigating cerebellar development and diversity in fishes have been previously published [34, 57, 66, 67, 72, 74, 93]. Across major groups of fishes, most of our current-day knowledge arises from in-depth studies of
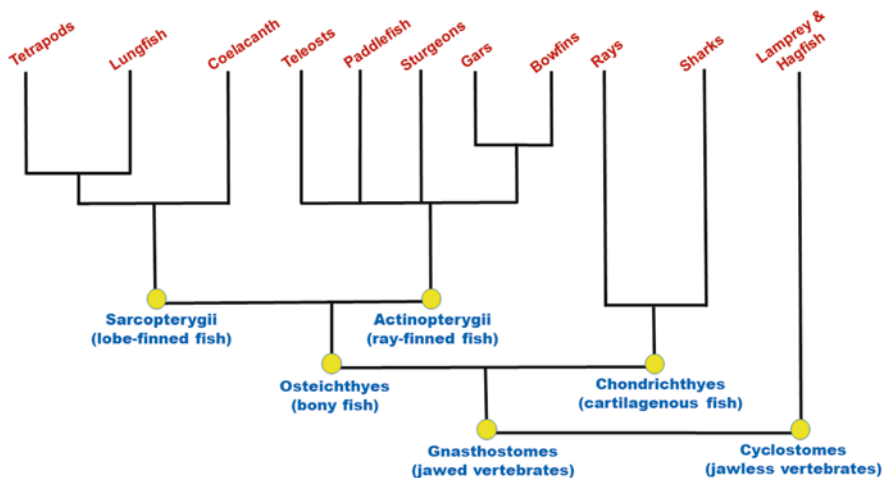

Fig. 1 Cladogram showing the relationship between major groups of fishes

the teleost cerebellum—considered to represent the foundational cytoarchitectural form of the fish cerebellum [67]. This neuroanatomical blueprint provides us with a morphological reference map as we consider deviations from this plan as a result of divergent radiations or habitat and behavioral specializations.

In an attempt to put into perspective the extensive literature on the fish cerebellum that has spanned over a century, this chapter is organized into three sections. *First*, I describe the common cerebellar developmental plan observed from studies in teleosts and how the morphology of the mature cerebellum compares to that of other vertebrates. *Second*, I will provide direct examples of how the cerebellum has diversified across major fish lineages and the role of the environment in shaping the mature cerebellum. *Finally*, this chapter comes to a close by briefly discussing the lifelong neurogenesis present in the cerebellum of many fish species, opening the door to exciting opportunities to explore the function of these cells using a combination of traditional and modern-day experimental approaches. It is my hope that by the end of this chapter readers gain a more robust comparative understanding of the cerebellar architecture of fish from development to adult.

Development of the Fish Cerebellum and Its Structural Organization

Similar to other vertebrates, fish share a highly conserved cerebellar developmental plan. Pioneering comparative work by R. Nieuwenhuys [67] has shown that the origins of the vertebrate cerebellum are commonly derived from the rostral rhombencephalon where two bilaterally symmetrical anlages (i.e., also known as embryonic domains or territories) are dorsally situated. As embryonic development proceeds, these domains fuse in the midline plane. Meanwhile, the rhomboid fossa widens and the angle between the cerebellar territories and two sides increases eventually leading to the fused halves of the cerebellar primordium producing a transverse-oriented plate-like structure [67]. In rodent models, a similar process has been described whereby the rostrocaudal axis of the cerebellar anlage undergoes a 90° rotation to then become the mediolateral axis [76]. The formation of this plate and subsequent growth are driven by early waves of neurogenesis that give rise to the different types of cerebellar neurons that will populate the mature structure. A tightly regulated sequence of progenitor activity arising from two distinct germinal zones, the ventricular zone and upper rhombic lip, are responsible for producing final neuronal subtypes (reviewed in Carletti and Rossi [13], Kaslin and Brand [34]). Comparative work across model vertebrates has revealed, however, slight deviations in the expansion of the cerebellum and the migration pattern of early progenitors [12].

Molecular and genetic characterization of cerebellar development in vertebrates shows that the initial phase of midbrain and cerebellar development commonly depends on the isthmic organizer situated at the midbrain–hindbrain boundary.

While the finer nuances of this process are beyond the scope of this chapter, excellent reviews have shown that a complex cascade of molecularly driven temporospatial events controls early cerebellar specification, including key pathways such as Fibroblast Growth Factor and Wnt, along with a host of transcriptional factors; importantly *otx* and *gbx* [34, 54, 86, 88, 91]. These in turn lead to the establishment of distinct cerebellar territories and provide cues to specify the later cytoarchitecture of the mature cerebellum. To date, this process in fishes has been best described in the zebrafish (*Danio rerio*) model, owing to the high amenability of transparent embryos and rapid development to larval stages ([33, 37, 91]; reviewed in [34]).

Of all jawed vertebrates, fish, along with birds and mammals, maintain the largest adult cerebelli and display the most pronounced structural diversity [68]. With the exception of Cyclostomes (also known as Agnathans; hagfish and lamprey), the cerebellum is characterized by a major lobe, the centrally located corpus cerebelli, and two bilateral lobes, known as the auricles (flocculus in tetrapods; also known as the vestibulocerebellum; [2]). The auricle is considered a specialized domain of the corpus primarily receiving vestibular input [34]. In fish, it is commonly known as the eminentia granularis [37]. This cerebellar architecture holds true across most fish lineages, but in many instances can be further complemented by the addition of cerebelloid structures that enhance species function, behavior, and specialization.

Our early understanding of the cerebellum of fishes has arisen primarily from detailed descriptions of teleost fishes [67]. Teleostei is one of four superorders of the subclass Actinopterygii that also include the superorders Palaeoniscoidei, the Chondrostei, and the Holostei. Collectively, these superorders comprise more than 30,000 fish species, although most modern-day bony fish belong to Teleostei. Thus, in many cases, deviations in the cerebellar plan across fishes are contrasted with the basic teleost morphology and structural design. As mentioned above, the teleost cerebellum shares numerous traits with other vertebrate classes, but at the gross anatomical level, obvious differences are found. Specifically, these include an absence of cerebellar nuclei and well-defined foliations, as seen in the neocerebellum of mammals [28], and the development of a rostral protrusion termed the valvula cerebelli [57], not found in a number of other vertebrates.

The cerebellum of teleost fish and the large majority of fish species is defined by three major structures: the valvula cerebelli, the corpus cerebelli, and the vestibulolateral lobe ([21, 58, 90]; *see* Fig. 2). The valvula cerebelli is the rostral-most structure of the cerebellum, a structure absent in Cyclostomes, Chondrichthii (sharks and rays), and Crossopterygii (ceolacanth; [45]). The valvula projects rostrally as a pouch-like structure [67] into the midbrain ventricle below the superficially located optic tectum. Across species, the valvula cerebelli is variable both in size and shape and in some species can also include a lateral domain [21]. Extreme examples of this variation are illustrated by the extraordinary expansion of the valvula cerebelli in Mormyridae where it has hypertrophied to become a superficial structure that covers the entire surface area of the brain (*further described in section* "Morphological Diversity of the Fish Cerebellum"; [22, 78, 80, 82]). Studies show that the valvula cerebelli receives much of its primary input from the tertiary lateral line system, the tractus mesencephalon-cerebellaris posterior [67]. In Mormyrid fish, this tertiary
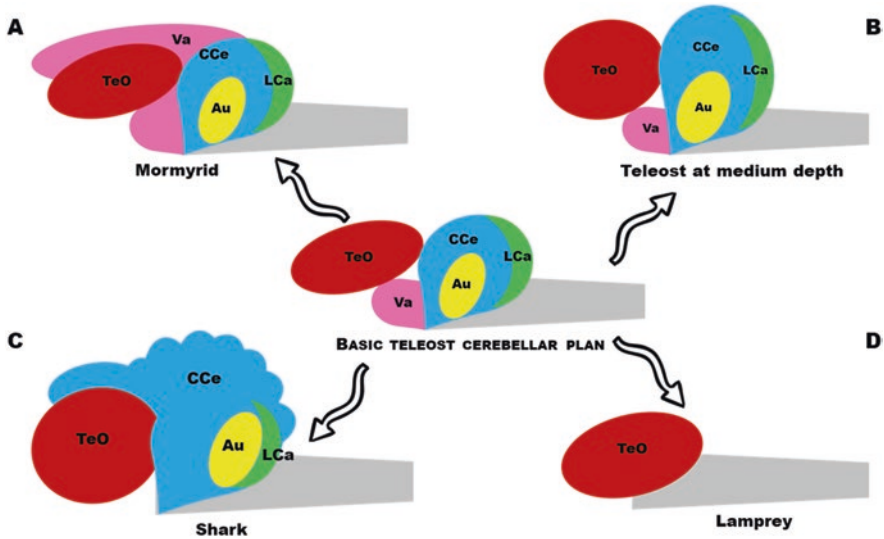
Fig. 2 Schematic representation of differences in cerebellar morphology in reference to the basic teleost cerebellar architectural plan (center). (**a**) Mormyrids display an extreme enlargement of the valvula cerebelli that projects over top of the optic tectum. (**b**) Teleosts specialized to a medium depth in the water column show an enlarged cerebellum and optic tectum. (**c**) Sharks demonstrate an increased degree of foliation of the corpus cerebelli, with this structure projecting over the optic tectum. A valvula cerebelli is absent. (**d**) Lamprey (jawless vertebrate) lacks a true cerebellum. In (**a–d**), precerebellar and cerebelloid structures are not shown; gray indicates a simplified view of the medulla oblongata and spinal cord. *TeO* optic tectum, *Va* valvula cerebelli, *CCe* corpus cerebelli, *Au* auricles (eminentia granularis in teleosts), *LCa* caudal lobe of the cerebellum

input is defined by electrosensory projections arising from the lateral toral nucleus of the midbrain [60]. However, evidence for direct lateral line input from the anterior lateral nerve has also been reported [89].

The central portion of the cerebellum consists of the corpus cerebelli, the only portion of the cerebellum visible at the external brain surface of most teleosts [57]. It is considered a tubular structure projecting either rostrally or caudally in different teleost species and is connected to the rhombencephalon by a short stalk, the peduncle [74]. This structure is functionally distinct from the caudal lobe, or vestibulolateral lobe, as its afferent input is not related to the acousticolateral system. In the zebrafish, a species that has been studied in considerable detail with regard to cerebellar development [34, 36, 37], the cerebellar corpus includes only a single folia and reveals the stereotypical anterior extension, the valvula cerebelli [34].

The caudal-most structure of the cerebellum is known as the vestibulolateral lobe [57, 74], considered homologous to the tetrapod vestibulocerebellum. The vestibulolateral lobe of fishes is composed of the eminentia granularis and caudal lobe. For many years, there has been debate as to whether the eminentia granularis in teleosts is equivalent to the auricles of tetrapods [27] or whether the auricles and the granular eminences are truly different structures [75]. Most recently, the former

hypothesis has been supported that this structure is homologous to the auricle of other vertebrates [90]. The vestibulolateral lobe is currently understood to have a strong connection with the central lateral line sensory region.

Histologically, the teleostean cerebellar cortex demonstrates much less organized lamination compared to the more rigid trilaminar cortex of tetropods [57]. The mammalian cerebellum is characterized by three layers that form the cerebellar cortex, including the outer molecular layer with few resident neuronal somas, a monolayer of conspicuous Purkinje cells, and a deep granular layer consisting of a large proportion of small granule cells (reviewed in [18]). This well-defined laminar organization has generally been shown to carry over to nonmammalian vertebrates with the exception of fish and Cyclostomes [44]. These characteristic zones of the cerebellar cortex and their respective cell types are considerably more variable across fish species [57, 74]. To this end, Purkinje cells can be found in the molecular layer, while granule cells can be observed lateral to the Purkinje cell layer. Notably, in teleosts, basket cells are absent [93]; therefore, inhibitory feedback loops are only created by Golgi and stellate cells. In addition, eurydendroid cells appear to further replace deep cerebellar nuclei of other vertebrates [26, 31]. In terms of branching, the dendritic tree of Purkinje cells in fishes is more complex than in amphibians and reptiles, but never as extensive as demonstrated in mammals [74]. In teleosts, the proximal, smooth part of the dendritic tree, which contains the receptive surface for climbing fibers, does not penetrate the molecular layer as seen in mammals. This has been best shown in mormyrid teleosts but is thought to be common across teleost species.

A final trait that sets teleosts apart from many of their land-dwelling relatives is the presence of additional precerebellar and cerebelloid structures. Precerebellar nuclei are neuronal nuclei that extend most of their projections to the cerebellum and therefore are intimately associated with the cerebellum. These structures appear to be unique to fishes. Examination of precerebellar structures in zebrafish shows the existence of two precerebellar nuclei, the nucleus valvula lateralis, and the nucleus paracommissuralis (reviewed in [34]). Specifically, the nucleus valvula lateralis is found in the tegmentum of the midbrain beneath the cerebellar corpus, with its main efferent target being granule cells in the corpus cerebelli and valvulae cerebelli. Conversely, the nucleus paracommissuralis is located in the midbrain and receives input from telencephalon while sending major output to the cerebellum and torus longitudinalis [11, 84].

Unlike precerebellar structures, cerebelloid structures are defined by having a similar architecture and organization as the cerebellum (i.e., cerebellar-like) but are spatially separate [55]. To date, a number of cerebelloid structures have been identified in aquatic vertebrates, largely fishes, including structures such as the medial (i.e., MON; processes lateral line input) and dorsal (i.e., DON; processes input from electroreceptors) octavolateral nucleus, and electrosensory lobes in advanced bony fishes possessing an electrosensory system [4]. However, across all mammals, with the exception of monotremes, the dorsal cochlear nucleus is also considered a cerebelloid structure [4]. Similar to the classic role of the cerebellum in processing sensory–motor input [10], the cerebelloid structures of fishes also process sensory

signals, receive input from the periphery to the deep layers, and parallel fiber input to the molecular layer. Two cerebelloid structures are observed in fishes, including the cerebellar crest and torus longitudinalis. The cerebellar crest is a layer of parallel fibers that cover the lateral line primary sensory brain stem region, originating from a bilateral mass of granule cells caudal to the cerebellar lobe termed the granular eminence [44, 67]. Likewise, the torus longitudinalis is a paired ridge of granule cells located along the medial boundary of the tectum that projects parallel fibers to the surface of the midbrain tectum in the marginal layer [55, 57]. The torus receives input from the valvula cerebelli and is present exclusively in actinopterygian fishes. Both the cerebellar crest cells and torus longitudinalis are defined by unidirectional parallel fibers [57].

Zebrafish provide an excellent example of how in some fish species, the definition of cerebelloid structures can be extended to include a collection of associated structures forming a functional unit or system [34]. In this species, two cerebelloid systems are present. First, in the hindbrain, the medial octavolateral nucleus, along with the eminentia granularis, and the cerebellar crest (crista cerebellaris) are considered to form a cerebelloid system. Here, Purkinje-like cells in the medial octavolateral nucleus extend their apical dendrites to the molecular layer of the cerebellar crest. The cerebellar crest is a molecular fiber layer continuous with the most caudal aspect of the corpus cerebelli. Second, the torus longitudinalis coupled with the midbrain optic tectum forms a second cerebelloid system in zebrafish. Interestingly, in this context, the fiber-rich superficial marginal layer in the optic tectum has been suggested to act as the molecular layer—with the marginal layer receiving parallel fibers from the torus longitudinalis. It is currently hypothesized that the circuit formed between the torus longitudinalis and optic tectum aids in regulating and predicting visuomotor response given that granule cells in the torus longitudinalis respond to visual stimuli as well as to stimuli that evoke eye movements [24, 73]. A more detailed discussion of cerebelloid structures and their proposed function in anamniotes and mammals can be found in work by Bell [4], Bell et al. [5], and Devor [16].

Morphological Diversity of the Fish Cerebellum

Across jawed vertebrates, marked variation in the developed cerebellum exists as a consequence of evolutionary lineages and habitat adaptations. A best example of this is seen by the spectrum of cerebellar size and foliation across amniotes (reptiles, birds, mammals) and anamniotes (fish, amphibians). Only birds and mammals demonstrate the extensive foliation seen at the gross anatomical level, which drastically enlarges the cerebellum of these animals. Rather, fish display considerably developed cerebellums, albeit non-foliated, whereas this structure is much smaller in amphibians and reptiles [57]. However, an incredible feat unique to fish is the impressive level of cerebellar diversity that has been shaped by both evolution and environment. Comparative studies relating fish brain growth with neuroecological

specializations illustrate the impressive "evolutionary plasticity" of brain structures and their ability to become optimized in accordance with the behavioral requirements of the species. In other instances, evolutionary time leading to lineage divergence is likely the mechanism at play that drives cerebellar remodeling. By surveying the morphological variation of the cerebellum across representative fish models and lineages (*see* Fig. 2), new clues regarding how these structural adaptations have come about and their functional role can be explored.

The first true cerebellum of jawed vertebrates is thought to have arisen in cartilaginous fishes [93]. Interestingly, the developmental form of the cerebellum of sharks and rays mirrors that of adult Cyclostomes—characterized by a simple plate-like structure. Notably, only recently has it been confirmed that Agnathans do not possess a traditional cerebellum, but instead cerebelloid structures, including the DON and the MON [93]. As cerebellar development progresses in cartilaginous fishes, a more elaborate cerebellum can be observed. Bilaterally, a rostrolaterally directed lengthening and outpocketing of the caudolateral parts of the cerebellar territory give rise to the paired auricles. At the same time, a dorsally directed evagination of the rostromedial parts of the cerebellar plate forms the corpus cerebelli [67]. The dorsally situated, unpaired, corpus cerebelli ventrally encloses the large ventricular cavity. Meanwhile, the dorsal aspect extends rostrally over the roof of the midbrain and caudally over the lower lip, a band of nervous tissue laterally continuous with the upper leaf of the auricles [67].

In many species of cartilaginous fishes, considerable variation exists in the size and degree of foliation (i.e., wall infolding) of the corpus cerebelli (reviewed in [92]). The presence of varying degrees of cerebellar foliation in chondrichthyans is a feature rarely seen in most populations of teleosts. Early comparative studies of sharks and rays of different sizes have revealed that transverse grooves of different depths can be conspicuously detected on the surface of the corpus as a result of foliation [85]. Smaller species display a very shallow groove, while in larger bodied species deeper grooves and additional sulci subdivide the corpus into multiple lobes. Across vertebrate taxa, increased foliation is thought to accommodate an increase in cerebellar surface area [79]. This in turn allows for an increase in Purkinje cell numbers, thereby enhancing cerebellar processing capacity and facilitating the complexity of cerebellar-dependent functions and behaviors [32, 81, 87]. Histologically, the chondrichthyan cerebellum demonstrates walls with four distinct cell layers: the fiber zone, the granular layer, the layer of Purkinje cells, and finally the molecular layer [67]. Chondrichthyes further feature two cerebelloid structures, including the DON and the MON that join bilateral auricles at the hindbrain [66].

The most primitive bony fishes, namely the Sarcopterygians, further provide an excellent example of how cerebellar diversity closely aligns with major fish radiations. Sarcopterygians are only represented by the sole surviving Crossopterygian, the coelacanth (*Latimeria*), and six extant species of lungfishes worldwide. Studies of *Latimeria* show that its cerebellum can be seen as a well-developed, dome-shaped structure [93], defined by a dorsal evagination of the corpus cerebelli and very large auricles [61, 62]. The impressive size of the auricles is proposed to have developed in conjunction with the highly differentiated lateral line system in this species. The

lateral line system is a sensory system present along the body wall of most fish species composed of thousands of neuromast cells that function to sense hydrodynamic input regarding relative movements between the body and the surrounding aquatic environment [9, 64]. Within the corpus, distinct molecular, Purkinje, and granular cell layers are well organized, a feature uncommon across most modern-day teleosts. Purkinje cells, however, show less laminar organization in the lateral auricles.

Compared to most other groups of fish, the cerebellum of lungfishes is relatively small and has been considered to be more closely related to that of amphibians [93]. The African lungfish (*Protopterus*) is defined by larger paired auricles that overhang the lateral sides of the midbrain, but only a modest sized corpus cerebelli. By contrast, the Australian lungfish *(Neoceratodus)* features smaller auricles but a larger corpus cerebelli, compared to its African relative [29]. However, in both species of dipnoan, a reasonable degree of lamination can be observed representing the three characteristic cerebellar layers: the molecular, the Purkinje, and the granular [67]. Both the coelacanth and lungfish lack an anterior protruding valvula cerebelli, characteristic of teleosts.

Sampling across fish species provides valuable insight regarding the intersection between brain growth, habitat specialization, and structural diversity. Within the wild, studies have shown that the species environment can impose selection pressure on specific regions of the brain, and some excellent examples come from structural modifications of the cerebellum. Some of the best-studied species demonstrating this evolutionary adaptation come from populations of African cichlids [94]. However, in some extreme cases, unprecedented enlargements of the cerebellum have also been observed in distinct groups of fishes as they take on new sensory processing modalities. Most notably, this attribute belongs to electric fishes, such as gymnotiformes and mormyrids, where the cerebellum has largely outgrown the rest of the brain. The role of the environment in shaping structure-specific brain morphology and the behavior processes of fishes has received considerable attention over the years. For example, in both bony and cartilaginous fishes, relative enlargement of the cerebellum has been associated with locomotor behaviors, habitat complexity, swimming speed and agility for prey capture, proprioception, and the acquisition of sensory input [30, 92]. Conversely, the presence of a small cerebellum appears to be a predictor of lower activity levels and a close association with the substrate in fishes [71].

The independent radiations of African cichlids by far provide one of the most accessible, natural experimental datasets as to how habitat stratification impinges upon brain morphology. In all three East African Great Lakes, feeding strategy and microhabitat utilization have been shown to correlate strongly with individual brain structures [30]. Focusing on cerebellar size, it was reported that this structure was considerably enlarged in populations living at medium depths in the water column. This demonstrated that cerebellar morphology was more influenced by microhabitat use rather than feeding type, at least in this population [40]. By contrast, studies of the Antarctic icefish (Notothenoidae; [17]), a perciform relative of cichlids, revealed that the eminentia granularis and crista cerebellaris functionally involved in sensing olfaction and acoustic-lateralis input demonstrated most variability in morphology

across the 32 species examined. These two studies highlight that these related yet isolated populations can display disparate morphological adaptations to their unique environment in order to presumably increase fitness.

This section would not be complete without mention of the extreme cerebellar adaptation in electric-sensing fishes, including Mormyriformes, Gymnotiformes, Siluriformes, and Xenomystinae [93]. These groups are defined by and are unique among ray-finned fishes as having evolved electroreception. Best studied is the gigantocerebellum of the mormyrid. From an evolutionary standpoint, passive electrosensing using ampullary electroreceptors arose first in osteoglossomorph fishes, permitting the detection of external bioelectric fields [14]. Mormyroids became the first species to evolve electric organs and tuberous electroreceptors, allowing for functional electrolocation and communication [80]. Impressively, the cerebellum of mormyrids accounts for nearly 1% to the total body weight of these fishes [59], largely due to the outgrowth of the anterior valvula cerebelli, completely covering the dorsal aspect of the brain [57].

While one might expect extreme differences in the cerebellar neuroanatomical blueprint of mormyrid fishes, with the exception of its conspicuously larger valvula cerebelli compared with other teleosts, it generally follows the same morphological organization [57]. A clear valvula, corpus, and caudal lobe can be observed, but unlike other teleosts, additional subdivisions are present. As reviewed by Meek [57], the valvula includes the valvula strictiori sensu, but also the lobus transitorius and lobe C_1. Of particular note, the corpus cerebelli is distinguished by three additional lobes: C_2 and C_3 directed rostrally, and C_4 directed caudally. Finally, the caudal lobe is differentiated into both the anterior part (connecting to the mechanosensory lateral line lobe) and the posterior part (connecting to the electrosensory lateral line lobe) [6]. Extrinsic connections of mormyrid cerebellum are in line with that of other teleostean cerebella, showing well-defined eurydendroid or giant cells that project to premotor regions [56, 69, 70], along with a highly differentiated precerebellar nucleus lateralis valvulae.

Neurogenesis and Lifelong Cerebellar Development in Fishes

The majority of this chapter has focused on the variation in the adult cerebellar form that accompanies major groups of cartilaginous and bony fishes. In the last 20 years, however, studies of teleost fishes, in particular, have illustrated that cerebellar growth can persist into later life stages as species age. To date, this has not been observed in sharks and rays, although few studies have been performed in these groups. This capacity is made possible as a result of the process of adult neurogenesis, whereby resident neural stem cells in domains of the postnatal brain known as "stem cell niches" continue to generate newborn neurons [95]. Nevertheless, even in mainstream teleost fish models like the zebrafish, it would appear that the degree of brain-wide structural growth and neural stem cell activity shows a sharp decline in older fish [19, 51], suggesting that continuous growth may not be indefinite.

Comparing the relationship between neural stem cell activity and brain growth with aging in the cerebellum of relatively short-lived (e.g., zebrafish ~3 years) and long-lived species such as the sturgeon (~50–80 years) would provide exciting new insight in this field.

Adult neurogenesis is considerably more limited across the mature neuro-axis of the brain in amniotes, but of the small sampling of bony fishes thus far appears to be a highly conserved, widespread trait [23, 46, 97]. In representative teleosts, such as the zebrafish, greater than 16 major domains show constitutively active neural stem cell proliferation that functions to generate de novo neurons [1, 25, 47]. However, upwards of 100 neurogenic sites can be detected [95, 98]. This is in stark contrast to the two main adult neural stem cell niches found in mammals, limited to the subventricular zone of the forebrain and subgranular zone of the hippocampus [63]. In teleosts, although a large number of these stem cell niches border the brain ventricles, exceptions to this rule exist, such as in the cerebellum where throughout life neuro-epithelial-like stem and progenitor cells proliferate at the upper rhombic lip [34]. Importantly, this high neurogenic capacity displayed by zebrafish is mirrored by an equally impressive neuro-regenerative capacity, including the cerebellum [3, 35, 38, 41, 43, 50–52]. Conclusive evidence for ongoing adult cerebellar neurogenesis has been demonstrated not only in the zebrafish, but the goldfish (*Carassius auratus*; [15]), cichlids (*Astatotilapia burtoni*; [53]), killifish (*Nothobranhius furzeri*; [83]), medaka (*Oryzias latipes*; [42]), and electric brown ghost knifefish (*Apteronotus leptorhynchus*; [96]). In mammals, evidence for spontaneous adult neurogenesis in the cerebellum of rabbits has been documented, though this appears to be exclusive to lagamorphs [20].

An outstanding question that remains in the field of teleost adult neurogenesis is why neurogenesis persists beyond embryonic or early developmental stages. In many fish species, structure-specific neurogenesis can be linked to the mode of growth. Most, but not all, teleost fishes are governed by indeterminate growth [65]; thus, the body, including the central nervous system, continues to add more cells as the species enlarges. This has been demonstrated in species of goldfish for many years. In the brown ghost knifefish, governed by indeterminate growth and considered a model of negligible senescence, 75% of all mitotically active cells in the mature brain are located in the cerebellum [96]. In this species, proliferative activity is seen in narrow stripes at the midline of the corpus cerebelli and valvula cerebelli, their neuroanatomical boundaries, and in the eminentia granularis. Similarly, in the zebrafish, the cerebellum proportionally grows more than other major brain structures over the juvenile stage (30–90 days post-fertilization), while the body of the cerebellum housing granule cells demonstrates remarkable growth throughout life [34].

Interestingly, recent studies in the zebrafish have illustrated that this species is characterized by determinate rather than indeterminate growth [8]. This is more reflective of growth limitations seen in amniotes. Nevertheless, this raises the question of why constitutive proliferation is necessary in structures such as the cerebellum throughout life. In-depth studies by Kaslin and colleagues [34, 36, 37] have shown that proliferative activity of stem and progenitor populations of the

cerebellum decline following juvenile development (up to 3 months), but in adulthood those derived from the upper rhombic lip continue to produce granule cells. To this end, following the juvenile stage, no Purkinje or eurydendroid cells are newly generated. This diminished degree of post-embryonic neurogenesis in the cerebellum aligns with a near plateau in zebrafish growth as compared to its close relative, the Giant Danio [8]. It also raises the possibility that these newly generated cells merely aid in maintaining homeostasis by replacing those that undergo cell death. It remains to be seen in models of determinate or indeterminate growth whether these adult stem and progenitor populations of the cerebellum are capable of characteristic responses to environmental input, such as sensory or motor stimuli, that have been shown in other stem cell niches of the adult zebrafish brain [48, 49].

Closing Remarks

The primary goal of this chapter has been to provide a general survey of the diversity of the fish cerebellum and how this structure contrasts many of the features seen in other vertebrate classes. While embryonic development of the fish cerebellum appears highly conserved with its land relatives, the appearance of new cerebellar structures, such as the valvula cerebelli, in addition to precerebellar and cerebelloid structures, highlights important phylogenetic differences across jawed vertebrates. Even across the small sampling of fishes discussed in this chapter, the manner by which the interplay between evolutionary time, lineage divergence, and habitat specialization orchestrate the morphology of the mature fish cerebellum is evident. What is more, in the adult cerebellum of teleosts, the existence of ongoing cell proliferation and neurogenesis raises exciting questions regarding cerebellar function, plasticity, and lifelong structural maintenance.

Moving forward, taking advantage of newer, more tractable laboratory models to study cerebellar ontogeny will unlock yet another level of understanding regarding this structure from a developmental and genetic perspective. For example, the tiny transparent *Danionella translucida*, no more than ~15 mm in adult size, has emerged as an exciting new model in the neurosciences [77]. With many of the same features as the zebrafish, but offering a smaller adult size, the opportunity to perform live *in vivo* imaging of cerebellar growth from fertilization to maturity has arrived. Blending traditional neuroanatomical methods along with new cutting-edge models and molecular tools to study cerebellar development, diversity, and plasticity across fish models offers an exciting future to advance the field of cerebellar neurodevelopment.

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