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Review article

Evolution of mammalian sound localization circuits: A developmental perspective

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ABSTRACT

Localization of sound sources is a central aspect of auditory processing. A unique feature of mammals is the smooth, tonotopically organized extension of the hearing range to high frequencies (HF) above 10 kHz, which likely induced positive selection for novel mechanisms of sound localization. How this change in the auditory periphery is accompanied by changes in the central auditory system is unresolved. I will argue that the major VGlut2$^+$ excitatory projection neurons of sound localization circuits (dorsal cochlear nucleus (DCN), lateral and medial superior olive (LSO and MSO)) represent serial homologs with modifications, thus being paramorphs. This assumption is based on common embryonic origin from an Atoh1$^+$/Wnt1$^+$ cell lineage in the rhombic lip of r5, same cell birth, a fusiform cell morphology, shared genetic components such as Lhx2 and Lhx9 transcription factors, and similar projection patterns. Such a parsimonious evolutionary mechanism likely accelerated the emergence of neurons for sound localization in all three dimensions. Genetic analyses indicate that auditory nuclei in fish, birds, and mammals receive contributions from the same progenitor lineages. Anatomical and physiological differences and the independent evolution of tympanic ears in vertebrate groups, however, argue for convergent evolution of sound localization circuits in tetrapods (amphibians, reptiles, birds, and mammals). These disparate findings are discussed in the context of the genetic architecture of the developing hindbrain, which facilitates convergent evolution. Yet, it will be critical to decipher the gene regulatory networks underlying development of auditory neurons across vertebrates to explore the possibility of homologous neuronal populations.

Contents

Abbreviations: aVCN, anterior ventral cochlear nucleus; DCN, dorsal cochlear nucleus; E, embryonic; GRN, gene regulatory network; LSO, lateral superior olive; MNTB, medial nucleus of the trapezoid body; MSO, medial superior olive; P, postnatal; pVCN, posterior ventral cochlear nucleus; SOC, superior olivary complex; VCN, ventral cochlear nucleus.

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An indefinite repetition of the same part or organ is the common characteristic (as Owen has observed) of all low or little-modified forms; ... consequently it is quite probable that natural selection, during a long-continued course of modification, should have seized on a certain number of the primordially similar elements, many times repeated, and have adapted them to the most diverse purposes" (Darwin C.R., 1859).

1. Introduction

Sensory systems play a pivotal role in the exploration of the environment, in social communication, and survival. Consequently, increased sensitivity within existing senses provides broader windows to the external world. A striking example of such a process is the evolution of high frequency (HF) hearing in most mammals,[1] i.e., smooth extension of tonotopically organized hearing above 10 kHz (Fay, 1988; Grothe and Pecka, 2014; Heffner and Heffner, 2008; Manley, 2010a; Masterton et al., 1969). Most non-mammalian vertebrates do not hear significantly above this frequency range (Manley, 1971). HF hearing range in birds is limited to frequencies below 12 kHz (Dooling et al., 2000; Saunders et al., 2000) with auditory specialists, such as the barn owl, being situated at the upper limit (Gleich and Langemann, 2011; Köppl et al., 1993). Crocodiles, amphibians, and most fish do not hear above 5 kHz (Fay, 1988; Heffner and Heffner, 2008; Kenyon et al., 1998) with few conspicuous exceptions, such as some clupeiform (herring) fishes (up to 180 kHz) (Mann et al., 2001; Narins et al., 2014), some frogs (up to 34 kHz) (Feng et al., 2006; Narins et al., 2014), and pygopod (i.e. legless) geckos (up to 14 kHz) (Manley and Kraus, 2010). The extension of the mammalian hearing range into the HF region was likely positively selected for because of the benefit for sound localization (Frost and Masterton, 1994; Grothe and Pecka, 2014; Heffner and Heffner, 2008).

Comparative analyses have identified various features of mammalian ears that correlate with and enabled HF hearing (chapters 4, 5) (Manley, 2010a, 2012). In contrast, much less is known about the evolutionary trajectories of the mammalian neuronal circuits processing this information. As one important aspect of the auditory system is sound localization, the focus here is laid on neuronal circuits in the auditory brainstem that are involved in this task. Despite the fact that tetrapods (amphibians, reptiles, birds, and mammals) share a similar bauplan in the auditory brainstem, with an unusually high number of interconnected nuclei and an important role of inhibitory inputs (Fig. 1), the current view supports an independent evolution of these circuits in mammals and sauropsids (reptiles and birds) (Section 9.1) and that they represent homoplasious structures (Carr and Soares, 2002; Grothe et al., 2004; Grothe and Pecka, 2014). This likely reflects the fact that the tympanic ear evolved independently in all major tetrapod groups—the anurans, sauropsids, and mammals, as evidenced by the fossil record (Bolt and Lombard, 1985; Clack, 1997, 2002; Lombard and Bolt, 1979) and more recently by developmental genetics (Kitazawa et al., 2015) (Fig. 2).

Most models proposed so far with respect to the evolution of mammalian sound localization pathways are based on functional considerations (Carr and Soares, 2002; Christensen-Dalsgaard and Carr, 2008; Grothe et al., 2004; Grothe and Pecka, 2014). To understand the evolution of the auditory system, its development has to be analyzed as well, as changes in ontogeny underlie evolutionary changes in morphological structures (Carroll, 2008). Despite awareness of the importance of developmental information (Grothe et al., 2004), the lack of detailed data only 15 years ago precluded incorporation into previous evolutionary models. Fortunately, significant progress has been made recently in studies of the embryonic origins of auditory circuits and the gene regulatory networks (GRNs) underlying their formation (Nothwang et al., 2015; Willaredt et al., 2015b). Together with anatomical data, these studies provide novel insights into the evolutionary pathways leading to mammalian sound localization circuits.

As this review takes an evolutionary developmental perspective on the evolution of sound localization circuits, I will first outline current concepts relating to evolutionary processes in development. To understand how evolution has shaped auditory circuits, I will then provide an introduction to the acoustic cues for sound location. Then the hallmarks of the mammalian ear and the evolution of hearing in mammals will be briefly reviewed. Subsequently, anatomical and developmental data will be provided that indicate a close relationship between major therian (marsupial and placental) projection neurons of sound localization circuits. This postulated model will represent an important framework for making predictions that can be approached experimentally. Finally, the phylogenetic relationships of vertebrate sound localization circuits will be discussed.

2. Concepts in evolutionary development

2.1. Evolutionary processes operating on development

Development produces the body plans of living organisms and novel structures are the outcome of mutational alteration of preexistent developmental programs (Carroll, 2008). Evolutionary changes are thus tightly linked to developmental processes. Three intimately interwoven evolutionary processes have been proposed to lead to new forms in organisms: (1) dissociation, (2) duplication and divergence, together with (3) co-option of developmental processes (Raff, 1996). Conducive to these processes are the modular organization of biological processes (Raff, 1996) and large genotype networks (Wagner, 2011; Wagner, 2014a).

(1) Dissociation of developmental processes is required to allow the addition to, or subtraction of, features from an ontogeny to occur and this relies on the modular organization (see below)

[1] The definition of mammals is difficult in the fossil record, as the defining features evolved over different time periods and extinct mammals therefore represent mosaic forms (Manley, 2012; Vater et al., 2004). Concerning the middle ear, I will follow the criteria given for the definitive mammalian middle ear (DMME) *sensu* Allin and Hopson (1992); Luo (2011): an ectotympanic ring for the tympanic membrane, three middle ear ossicles, detachment of both the ectotympanic ring and the malleus from the mandible in the adult. Note that the DMME has likely evolved more than once (Allin and Hopson, 1992; Luo, 2011; Rich et al., 2005).

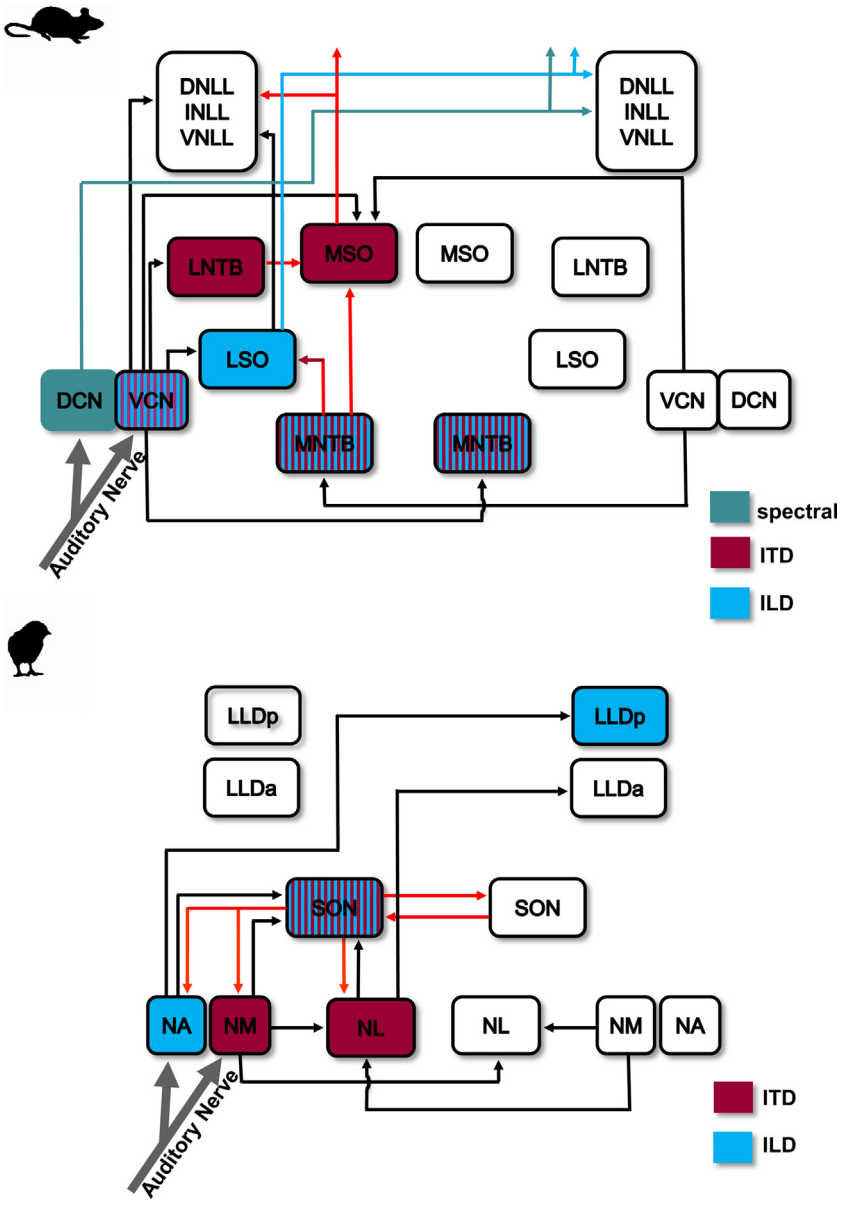


Fig. 1. Schematic depiction of sound localization circuits in mammals and birds. (A) Major sound localization circuits in the therian mammalian hindbrain. The auditory nerve bifurcates and innervates both the dorsal cochlear nucleus (DCN) and the ventral cochlear nucleus (VCN). Neurons of the DCN innervate the inferior colliculus (IC), whereas the VCN innervates multiple nuclei within the superior olivary complex (SOC) such as the lateral superior olive (LSO), the medial superior olive (MSO), and the medial nucleus of the trapezoid body (MNTB). The MNTB provides glycinergic inhibition to both the MSO and LSO. MSO and LSO neurons have major projections to the ventral, intermediate, and dorsal nucleus of the lateral lemniscus (VNLL, INLL, and DNLL, respectively) before reaching the inferior colliculus (Fig. 6). (B) Major sound localization circuits in the avian hindbrain. The auditory nerve bifurcates and innervates both the nucleus angularis (NA) and the nucleus magnocellularis (NM). Neurons of the NA project to the posterior part of the dorsal lateral lemniscus (LLDp). The NM projects to the nucleus laminaris (NL) of both sides and to the superior olivary nucleus (SON). The SON provides GABAergic feedback inhibition to the NM, NL, and the contralateral SON. Note that not all nuclei and projections in the respective auditory hindbrain sides are shown. The avian circuit for sound localization in the vertical plane is unknown.

of these processes. The best known example is neotony (Beer, 1958; Gould, 1977; Haeckel, 1866).

(2) Duplication and divergence are meristic changes, that is, alterations in numbers of a biological entity with subsequent acquisition of novel functions. This process is best visualized at the gene level by the occurrence of many paralogous genes in metazoan genomes (Andersson et al., 2015; Reams and Roth, 2015). Their subfunctionalization or neofunctionalization after duplication were suggested as a major evolutionary driving force (Conant and Wolfe, 2008; Ohno, 1970; Wagner, 2011). Other meristic traits include vertebrae, pharyngeal arches (from which the middle ear ossicles are derived), bristles, and feathers (Raff, 1996), and as will be argued below, mammalian sound localization circuits.

(3) Preexisting structures can be co-opted for a new use. Examples include duplicated genes, wings or feathers. This process also applies to the mammalian middle-ear ossicles, as they represent transformations of pharyngeal arches that were initially gill supports, jaw supports and jaw joints (Sienknecht, 2013). Originally, auditory brainstem nuclei were also proposed to represent co-opted structures. Based on the analysis of anuran metamorphosis, it was suggested that they have their origin in the recruitment by the auditory nerve of the orphaned central pathways of the lateral-line system (Larsell,

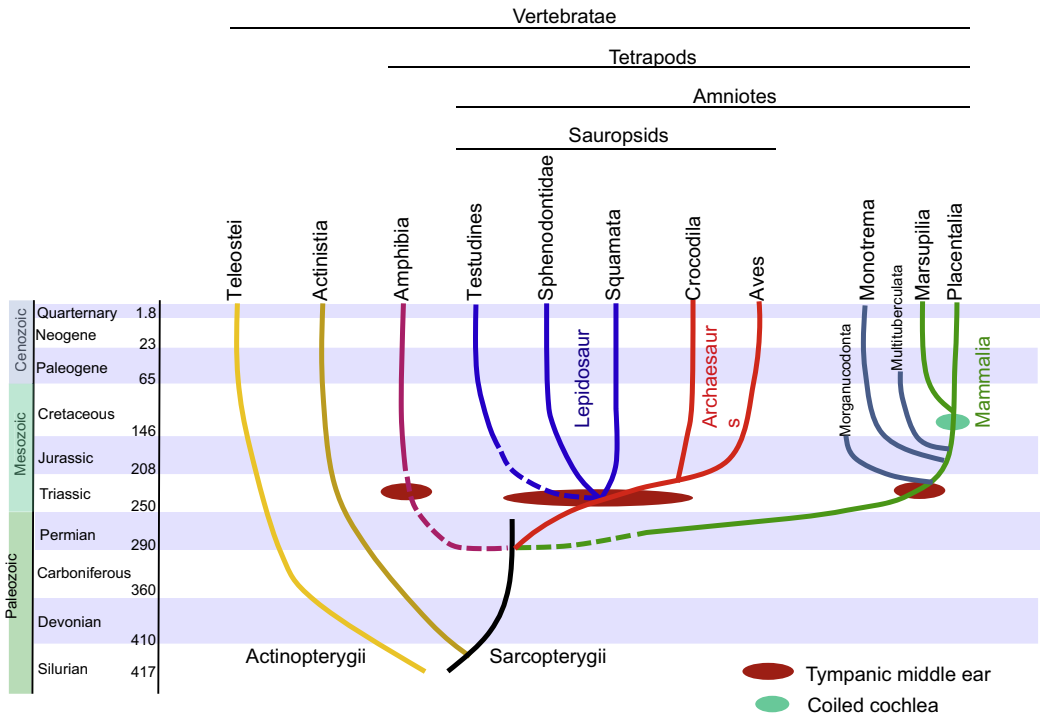


Fig. 2. Evolution of vertebrate ears. During the Triassic, tympanic middle ears capable of receiving airborne sound evolved separately among the ancestors of anura, turtles, squamates (lizards and snakes), archosaurs (birds and crocodilians) and mammals (after Grothe and Pecka, 2014; Manley, 2000, 2012).

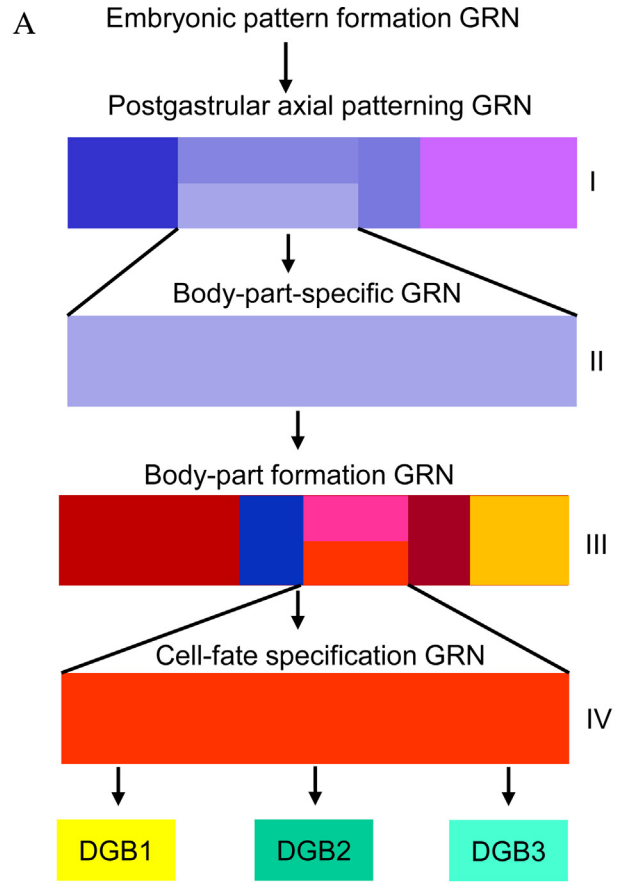
1934). This idea was later rejected, based on the simultaneous presence of the lateral line system and auditory nuclei in some frogs and bony fishes, and due to their different projection patterns (Boord and McCormick, 1984; Fritzsch, 1988; McCormick, 1999). It is currently assumed that the lateral-line sensory system has been entirely lost in amniotes (Grothe et al., 2004; Schlosser, 2012; Wullimann et al., 2011). Subsequently, a phylogenetic coincidence between the disappearance of the electroreceptive ampulla organs and the formation of the auditory dorsolatereral nucleus in anurans and tetrapods was noted, rendering co-option of the central neural pathway of electroreception by the auditory system possible (Fritzsch, 1988). However, connection patterns again do not in general agree between these pathways (McCormick, 1999). Exception are some projections such as those from the dorsal octavolateral nucleus to the torus semicircularis (the fish, amphibian and sauropsid equivalent of the inferior colliculus), which resemble the projection of the dorsal cochlear nucleus to the inferior colliculus. The dorsal octavolateral nucleus is found in all non-neopterygian fish as well as in aquatic amphibia (Montgomery et al., 1995) and receives afferent fibers from electroreceptors (Bell and Maler, 2005; Pothmann et al., 2009). Clearly, more data, such as the respective developmental pathways, need to be obtained to conclude on this proposed co-option.

An essential feature of organisms that permits any of these three evolutionary processes to occur is the modularity of developmental processes (Minelli, 2015; Peter and Davidson, 2011; Raff, 1996) (Section 2.2) (Fig. 3A). In general, modules are distinct subunits of the whole, and have a genetically discrete organization. It has become clear that most developmental processes are modular to a certain degree; that is, they are characterized by spatially restricted modules. Such developmental modules include early cell lineages, rhombomeres (r), or the imaginal discs of insects. These entities are characterized by a high density of causal links, whereas the density of links between the modules is lower (Arthur, 2014). Thus, variation within a module need not disrupt the functioning of other modules. An individual module can therefore explore its phenotypic space without necessarily affecting the entire body. This organizational principle of developmental processes is thought to enhance the evolvability of the organism (Amundson, 2005; Raff, 1996).

Another critical feature underlying evolvability is the existence of vast genotype networks (Wagner, 2011) (Fig. 3B). This term is based on the distinction between genotype and phenotype and refers to the fact that each genotype is connected by single point mutations to many genetic neighbors giving rise to the same phenotype. Consequently, genotypes of the same phenotype form large networks. Importantly, the different genetic neighborhoods of a given network contain different novel phenotypes. In most cases, a population occupies only a small part of the network. Thus, when moving through this network, a population will explore these different neighborhoods and will encounter many novel phenotypes. Such genotype networks have been shown to underlie the evolution of metabolism (Matias Rodrigues and Wagner, 2009), transcriptional regulation (Payne et al., 2014), RNAs (Schuster et al., 1994), or proteins (Ferrada and Wagner, 2010).

2.2. Gene regulatory networks

GRNs play an eminent role in setting causal links during development (Arthur, 2014; Davidson, 2006; Davidson and Erwin, 2006). They are predominantly composed of transcription factors, intercellular signaling molecules, microRNAs, and *cis*-regulatory elements, and the term gene regulatory network denotes the



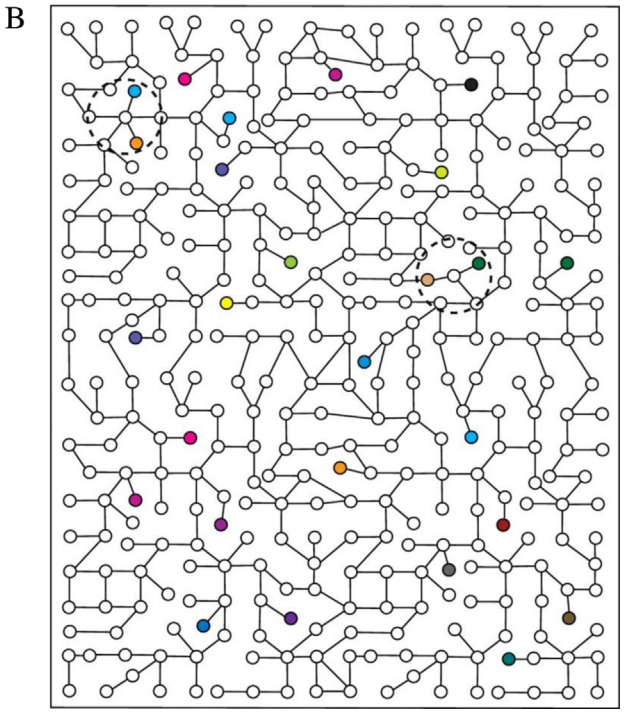


Fig. 3. Genetic concepts in evolution. (A) Schematic and simplified representation of hierarchy and modularity in developmental gene regulatory networks (GRNs). Development starts with the onset of embryogenesis at the top. The outputs of this initial (i.e. pregastrular) embryonic GRN are used to set up the GRNs, which establish a mosaic of regulatory states throughout the embryo (Box I). Within Box 1 domains, the progenitor fields for the future adult body parts are later demarcated by signals plus local regulatory spatial information. Many such progenitor fields are thus set up during postgastrular embryogenesis, and a GRN defining one of these is symbolized as Box II. Each progenitor field then becomes partitioned into subdivisions that will together constitute the body part (Box III). Each subdivision is initially defined by installation of unique GRNs producing unique regulatory states. Individual GRN sub-circuits can be re-deployed in lower hierarchies, indicated by the same color. Toward the termination of developmental processes in each region, the GRNs specifying individual cell types are set in place (Box IV). The final output are individual differentiation gene batteries (DGB1, 2, 3) in the each cell type. Modified from Peter and Davidson (2011). (B) Genotype networks. The schema represents a hypothetical set of genotypes (small open black circles) that share the same phenotype and form a genotype network; neighboring genotypes are connected by black lines and differ in single point mutations. Colored circles indicate genotypes with different phenotypes. Many different novel phenotypes can be accessed from a connected genotype network that spreads far through genotype space (Wagner, 2012). Reprinted with permission from The Royal Society.

physical and functional relationships among these components (Peter and Davidson, 2015). Their interaction allows for positive or negative influence on the expression of a target gene, thereby organizing the spatial allocation of regulatory gene expression to individual modules. This determines the developmental fate by ultimately instructing the specification of particular structures or cell types. GRNs are thus the fundamental control mechanism directing developmental processes (Peter and Davidson, 2015).

The two salient features of developmental GRNs are their hierarchical organization and their internal, modular composition (He and Deem, 2010; Peter and Davidson, 2011) (Fig. 3). Generally, the initial embryonic GRNs are followed by GRNs encoding spatial regulatory states that define the body parts and their subparts, and subsequently by GRNs for terminal functions, differentiation, and local morphogenesis (Peter and Davidson, 2011) (Fig. 3A). Thus, the inputs responsible for installation of a novel GRN depend on the prior network; i.e. the output of a given GRN at stage n provides the regulatory state instructing the next network below it at stage n + 1. The structure of GRNs is further characterized by modularity, as sub-circuits exist that are dedicated to different sub-processes. A detailed analysis of the GRN that underlies specification of a micromere cell lineage in sea urchins demonstrated the existence of separate sub-circuits consisting of small sets of genes (typically 3–8) that, together, execute a particular process (Oliveri et al., 2008; Peter and Davidson, 2015). GRNs hence operate in a modular manner. This modularity allows co-option of sub-circuits to different developmental processes. Similar cell types in different body parts serve as valuable examples.

Importantly, the regulatory states that define particular GRNs or sub-circuits are often accessible through altered expression or function of only a few genes, and sometimes even a single regulatory gene suffices. Striking examples include the formation of ectopic ommatidia by ectopic expression of the paired box transcription factor ey in *Drosophila* (see Section 9.3 for further details) (Halder et al., 1995) or the conversion of adult fibroblasts to induced pluripotent stem cells by the expression of just four transcription factors Oct4, Sox2, cMyc, and Klf4 (Takahashi and Yamanaka, 2006). This fact means that few genetic mutations may be required to alter the linkage between different GRNs or sub-circuits and their instructed modules. These mutational changes can be brought about by a variety of processes, such as single nucleotide changes in *cis*-regulatory sequences (e.g. enhancers or silencers) (Rubinstein and Souza, 2013; Wittkopp and Kalay, 2012), mobile elements containing transcription factor binding sites (Kazazian, 2004; Liang et al., 2015; Rebollo et al., 2012), or changes in the function of transcription factors (Cheatle Jarvela and Hinman, 2015; Reece-Hoyes et al., 2013). Most important are changes in *cis*-regulatory elements, as they do not perturb the established function of a given transcription factor such as its binding specificity to DNA or to other proteins and therefore do not

affect its other roles (Britten and Davidson, 1971; King and Wilson, 1975; Monod and Jacob, 1961; Wray, 2007).

Changes in *cis*-regulatory elements occur quite frequently and can result in an extensive and rapid turn-over of these sites in evolution (Wray, 2007). A comprehensive analysis of paralogous transcription factors in *Caenorhabditis elegans* revealed that the upstream regulatory regions of transcription factors are highly plastic and change much faster than the individual binding sites of transcription factors to DNA or other transcription factors (Reece-Hoyes et al., 2013). A comparison of the enhancers for the *even-skipped* gene in different fly species that are separated by between a few million to 100 million years from *Drosophila melanogaster* revealed that 70% of enhancers were altered in different Drosophilidae (Hare et al., 2008). A similar degree of evolutionary change was observed for enhancers between mouse and human (Shen et al., 2012). Importantly, for most regulatory genes, a single copy of a gain-of-function, such as an additional expression address, produces the regulatory effect (Davidson and Erwin, 2010; Ruvkun et al., 1991). This dominant action, also called haplosufficiency, as only a change to one of the two homologous chromosomes in diploid organisms is required to bring about an altered phenotype, makes such changes the basis of a powerful evolutionary process.

In conclusion, duplication, divergence and co-option of regulatory genes for new roles in the patterning of development are the most parsimonious means available for introducing changes in development, whereas invention of whole molecular assemblages is far less common. As a consequence, novel forms will arise mostly from the modification of existing modules during development. As will be laid out in the following, this likely applies to sound localization circuits as well.

3. Sound localization cues

Sound localization is one of the fundamental and most important features of hearing, as the ability of an animal to estimate the direction of the sound source is a first step in behaving appropriately in response to acoustic signals (Fay and Popper, 2000). Furthermore, it is a prerequisite for the formation of auditory objects in the presence of competing sounds, as it is a critical aspect in auditory stream segregation (Bregman, 1995). Sound segregation, the process by which acoustic components are identified as coming from one or more sound sources, and not sound localization, was recently even suggested to be the major evolutionary constraint in early mammals (Grothe and Pecka, 2014). To properly perform sound localization and sound segregation, spatial information on the horizontal and vertical directions of (azimuth and elevation) and the distance from the listener is required. In general, sound localization mechanisms for the azimuth (excluding front/back localization) depend on the comparison of the sound waves arriving at each ear and rely predominantly on two acoustic cues, interaural time differences (ITDs) and interaural level differences (ILDs) (Grothe et al., 2010; Middlebrooks, 2015; Rayleigh, 1907) (Fig. 4A and B). The mechanisms of front/back localization and the determination of elevation are different and generally depend on monaural spectral-shape cues such as peaks and notches from broadband signals that are strongly influenced by mammalian pinnae (Brown and May 2005; Grothe et al., 2010; Middlebrooks, 2015) (Fig. 4C).

ITDs reflect the difference in distance that a laterally arriving airborne sound wave must travel to reach the near and the far ear (Fig. 4A). This cue is therefore strongly dependent on the distance between the two ears and thus on the head size. As the velocity of sound in air is nominally 343 m/s, a wave will arrive 29 μs later at the far ear for each additional cm in travel distance. This amounts in humans to the requirement to detect differences of 11 μs in the arrival time of sound at both ears when resolving differences of 2° in the azimuth. Note that an action potential has a duration in the millisecond range. Small mammals, with head diameters of 2 cm, such as those living at the origin of mammalian evolution (Grothe and Pecka, 2014; Manley, 2012), experience maximal ITDs of less than 60 μs, and ~3 μs for a 10° sound source angle. Detection of these miniscule differences requires exquisite biophysical, molecular, cellular, and anatomical specializations (chapter 8) (Carr and Soares, 2002; Grothe et al., 2010; Köppl, 2012; Oertel, 2009; Trussell, 1999).

ILDs are the consequence of the shadowing effect of the head, which creates differences in the sound level at the two ears

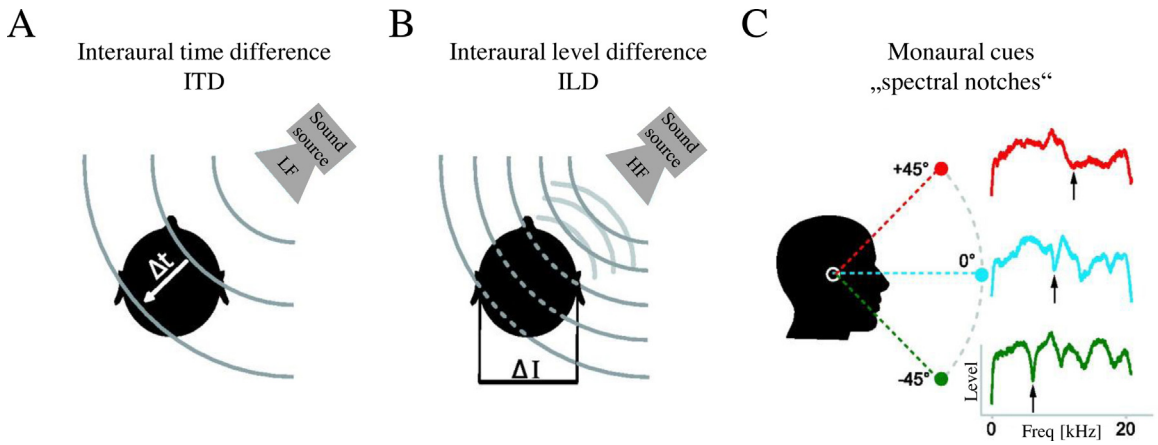


Fig. 4. Cues for sound localization. (A) Interaural time differences (ITD). For low frequencies (LF), mainly the difference in the arrival time (Δt) of a sound wave (gray lines) at the two ears is used to localize a sound source in the horizontal plane. (B) Interaural level differences (ILD). For high frequencies (HF), the shadowing effect of the head creates differences in the level of the sounds at the two ears (ΔL) that are utilized for sound localization in the horizontal plane. The shadowing effect increases for a given frequency with head size. (C) In therian mammals, sound localization in the vertical plane makes use of spectral analysis as a monaural cue. Interaction of a broadband sound primarily with the outer ear alters the effective spectrum of the sound impinging on the eardrum in a manner dependent on the location of the sound source in the vertical plane. Most prominently, the central notch (black arrows) in the effective spectrum of the sound shifts to higher frequencies when the sound source is shifted from below (−45°, green) to above the horizon (+45°, red). The spectra shown are digitally computed from 1-s white noise stimuli (cutoff frequency, 44.1 kHz) convoluted with KEMAR head-related impulse responses and averaged over 50 repetitions. Modified from Grothe et al. (2010). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(Fig. 4B). The magnitude of sound diffraction is dependent on the relative dimensions of the wavelength of the sound wave and the size and shape of the head (Brown and May, 2005; Grothe et al., 2010). Furthermore, ILDs are greatly affected by source distance (Brungart and Rabinowitz, 1999; Duda and Martens, 1998). As a crude rule of thumb, ILDs for sources further away (<1 m) become prominent for wavelengths that are shorter than the diameter of the listener's head (Christensen-Dalsgaard and Manley, 2014; Grothe and Pecka, 2014; Middlebrooks, 2015). For nearby sound sources (<10 cm), ILDs can increase significantly (Jones et al., 2013),

In mammals, the perception of source elevation is largely based on the monaural analysis of spectral cues and head-related transfer functions (HRTFs) (Brown and May, 2005; Middlebrooks, 2015) (Fig. 4C). HRTFs describe the effect that sound is not only diffracted at the head but also at the curved surfaces of the pinna and occasionally at the external ear canal. For broad-bandwidth signals, these diffractions induce subtle changes in the complex sound wave and the diffracting waves interfere with one another, changing the relative level of different frequency components. To generate prominent HRTFs, the asymmetries and convolutions of the pinna must be relatively large compared to the wavelength of the signal (Brown and May, 2005; Gardner, 1973; Shaw, 1974; Wightman and Kistler, 1989). In mammals, this pinna cue therefore relies on relatively broad-bandwidth signals and HF hearing above 10 kHz (Calford and Pettigrew, 1984; Carlile and Pettigrew, 1987; Hebrank and Wright, 1974; Heffner et al., 1995; Musicant et al., 1990). Evidence is also mounting that this influence of source direction on the acoustic signal is likewise important in distinguishing the frontal and rear hemifields of the acoustic scene and for the perception of acoustic proximity (Heffner et al., 1995; Kim et al., 2010; Wightman and Kistler, 1999). Determination of these spatial coordinates thus also benefits from HF and may have provided an additional, decisive selection pressure for HF hearing (Grothe and Pecka, 2014; Heffner et al., 1995). The importance of HRTFs in directional hearing might also explain the moveable external ears, which represents a distinct property of mammals (Carr and Edds-Walton, 2008; Christensen-Dalsgaard and Manley, 2014; Heffner and Heffner, 1992).

For reasons not yet fully understood, most early mammals were very small (in the range of centimeters), and most were likely nocturnal (Grothe and Pecka, 2014; Manley, 2012). The early evolution of HF hearing would have been of great benefit for these animals for nocturnal prey capture and predator avoidance. Furthermore, small animals more easily generate HF vocalizations, rendering HF hearing also beneficial for social communication. The reliance of directional hearing in all three coordinates on HF hearing thus presumably provided an important selection pressure in the evolution of this distinct mammalian trait (Grothe and Pecka, 2014; Heffner and Heffner, 2008; Manley, 2010a; Masterton et al., 1969).

4. Major evolutionary transformations in the mammalian ear

Anatomical and molecular changes unique to the mammalian ear have been recently covered by excellent reviews (Christensen-Dalsgaard and Manley, 2014; Manley, 2010a, 2012; Vater et al., 2004), so that only a brief outline is given here. Perhaps due to an altered diet to seeds that required crushing (Crompton, 1963; Kemp, 1982), a secondary jaw joint was selected, an event that freed up primary jaw joint bones (Maier, 1990). This released several bones, two of which, the quadrate in the upper jaw and the articular in the lower jaw, had made up the original stem amniote jaw articulation, became the malleus and incus, respectively, of the mammalian middle ear (Maier, 1990; Manley, 2010a). The third ossicle, the stapes, is derived from the hyomandibular bone (the single-ossicle columella of non-mammals). There is clear evidence that the three-ossicle structure is better suited to transmit higher-frequency sounds than the single-ossicle middle ears present in sauropsids such as archosaurs (birds and crocodilians), lepidosaurs (snakes and lizards) and anurans (frogs) (Heffner and Heffner, 2010; Manley, 2010a,b). However, HF hearing up to 32 kHz is also possible with a single bone middle ear (Gridi-Papp et al., 2008).

In the inner ear of therians, a coiled and elongated cochlea developed, allowing the representation of higher frequencies (Manley, 2012). The inner and outer hair cell types are separated by pillar cells, and the angled phalangeal processes of the outer and inner pillar cells form an arch, which constitutes the tunnel of Corti. Such a geographical landmark is specific to therian as well as monotreme ear and to the basic configuration of an organ of Corti. In addition, the bony canal wall integrated with the soft tissue: The resulting increase in stiffness of the basilar membrane presumably enabled an increased HF responsiveness by an improved impedance match between middle and inner ears at such frequencies (Manley, 2012). On the molecular level, the vertebrate prestin evolved in mammals into a highly specialized motor protein providing membrane-based electromotility to outer hair cells (Zheng et al., 2000). This electromotility causes length changes in these cells of up to 4%, at frequencies as great as 25–80 kHz (Frank et al., 1999; Gale and Ashmore, 1997) and greatly contributes to the active cochlear process (Hudspeth, 2014). Recently, it was suggested that the transformation of prestin into a motor protein might have occurred early in amniote evolution, based on the presence of a prestin-like motor in chicken (Beurg et al., 2013). It is, however, currently unclear whether this represents rather another example of convergent evolution of prestin as observed for the parallel evolution in echolocating mammals (Liu et al., 2014).

Another important feature of the mammalian ear is the absence of acoustical coupling of the two eardrums. In most non-mammalian tetrapods with a tympanic ear, both middle ears are acoustically coupled. This generates highly directional responses, because the direct and indirect (through-the-head) component of sound interact, canceling or amplifying the resulting eardrum vibrations depending on the phase difference and hence on the sound direction (Christensen-Dalsgaard, 2005; Christensen-Dalsgaard and Manley, 2014). These middle ears are therefore inherently directional. In anura and lizards, this coupling generates an effective directional difference of up to 10 dB and 35 dB, respectively (Willis et al., 2014; Christensen-Dalsgaard et al., 2011), and in geckos, directionally sensitive responses are observed in the auditory nerve, that resemble computed binaural responses from the avian nucleus laminaris or the mammalian SOC (Christensen-Dalsgaard et al., 2011). In mammals, the connections between the two ears are thin Eustachian tubes, resulting in a pure pressure receiver with no inherent directionality at the level of the middle ear (Christensen-Dalsgaard and Manley, 2014). Sound localization therefore depends completely on neuronal computation in upstream auditory centers. The decisive selection pressures for maintaining separated middle-ear spaces are not completely understood, but may involve the strong brain growth in early mammals (Manley, 2010a, 2012; Rowe, 1996), general protection of the middle ear bones from the mouth cavity, or protection from the increased respiration rate in mammals (especially small ones) (Christensen-Dalsgaard and Carr, 2008; Christensen-Dalsgaard and Manley, 2014). Indeed, persons with a permanently open Eustachian tube, a condition called *Tuba aperta*, suffer from autophony, which is an abnormally strong stimulation by respiratory noise and by their own voice (Hori et al., 2006).

Synapomorphies of the therian inner ear are the presence of primary and secondary osseous spiral laminae and a radial pattern of the cochlear nerve. The primary spiral lamina provides a more rigid support for the narrow and elongate basilar membrane and

assists routing of the cochlear nerve fibers (Dabdoub et al., 2016; Vater et al., 2004). The secondary spiral lamina is observed in the basal cochlear region and likely contributes to high-frequency hearing capabilities (Bruns, 1980; Vater et al., 2004). After signal transduction, auditory information has to be passed to the central auditory system through the spiral ganglion neurons (Rubel and Fritzsch, 2002). In theria, the cochlear nerve is arranged in a radial pattern and passes through the wall of the cochlear canal as numerous branches. In mammals, the cochlear nerve contains both type I and type II afferents. Type I neurons make up 90–95% of the cochlear nerve and receive sharply tuned inputs from inner hair cells that they send via thick myelinated axons into the brain. They likely correspond to the afferents in other tetrapods. In contrast, the residual 5% of type II ganglion neurons are considered mammalian novelties (Carr and Edds-Walton, 2008). They innervate the outer hair cells and are involved in the dynamic adjustment of hearing sensitivity and frequency selectivity (Froud et al., 2015). Furthermore, they send information on cochlear damage to the brain (Flores et al., 2015; Liu et al., 2015).

Thus, the mammalian ear shows specific traits at the external (moveable pinna), middle, and inner ear levels, and changes in both the middle ear and the inner ear contribute to the extension of the hearing range (Manley, 2012; Ruggero and Temchin, 2002; Vater et al., 2004).

5. Evolution of HF hearing in the 3 extant mammalian lineages

Mammals are a monophyletic group that arose from cynodonts, mammal-like reptiles, about 166–200 Myr ago (Luo, 2007; O'Leary et al., 2013) (Fig. 2). The first true mammals appeared in the early Jurassic and diversified into a variety of groups of which only three survived to the present day: the monotremes (egg-laying mammals), the marsupials (the young are nurtured in a pouch), and the placental mammals (Luo, 2007; O'Leary et al., 2013). The latter two groups are referred to as therian mammals.

Monotremes, which comprises echidnas and platypus, share with therian mammals the three-ossicle middle ear; it is, however, disputed whether this is a true monophyletic trait or arose independently in monotrema and theria (Luo, 2007; Manley, 2010a; Meng and Wyss, 1995). Monotremes lack substantial pinnae, their cochlea is curved, but not coiled, and has a terminal dilation at the end (the lagena). The organ is relatively short, ~4.4 mm in length in the platypus and ~7.6 mm in the echidna (Denker, 1904; Ladhams and Pickles, 1996; Manley, 2012). Furthermore, the bony osseous spiral laminae are absent (Vater et al., 2004). The number of rows of hair cells is generally higher than in therian mammals. There are two to five irregular rows of inner hair cells throughout most regions of the cochlea, with a reduction to one irregularly spaced row at the extreme base and apex, six or seven irregular rows of outer hair cells throughout most of the cochlea duct, and three or four rows of pillar cells (Ladhams and Pickles, 1996). Despite these differences in cell number and patterning, the presence of inner and outer hair cells separated by a tunnel of Corti, as well as the presence of pillar cells and Deiter's cells, specialized supporting cells, indicate the mammalian configuration of the monotreme cochlea. This view is also supported by the shape and internal organization of the outer hair cells, with cylindrical cell bodies, one layer of laminated cisternae along the lateral wall, and the distribution of mitochondria (Vater et al., 2004). In addition, prestin is also present in monotremes and shows high sequence similarity to the therian orthologues (Okoruwa et al., 2008). This is in agreement with the presence of a cochlear amplifier in monotremes (Mills and Shepherd, 2001). Functional demonstration that the monotreme prestin acts as a motor protein and that their outer hair cells show fast motility is still lacking.

In monotremes, the bone of the cochlear duct is not integrated into the soft tissue of the cochlea (Manley, 2012) and the middle ear of the echidna (*Tachyglossus aculeatus*) is stiff, rendering it less efficient in propagating sound waves received by the tympanum (Aitkin and Johnstone, 1972). Audiograms were described as V-shaped, with best sensitivity at 5 kHz for platypus, and U-shaped with best sensitivity at 4–8 kHz for echidnas (Mills and Shepherd, 2001), with a rapid decrease in sensitivity in both frequency directions (Aitkin and Johnstone, 1972; Gates et al., 1974; Mills and Shepherd, 2001). Note, however, that the high-frequency flanks of the audiograms of monotremes extends to higher frequencies (about 16 kHz)[2] than in all non-mammalian tetrapods (Vater et al., 2004). Interestingly, monotremes show at the very base of the cochlea, where HF sound is transduced, a hair cell configuration similar to therians by having one inner hair cell and two outer hair cells (Ladhams and Pickles, 1996).

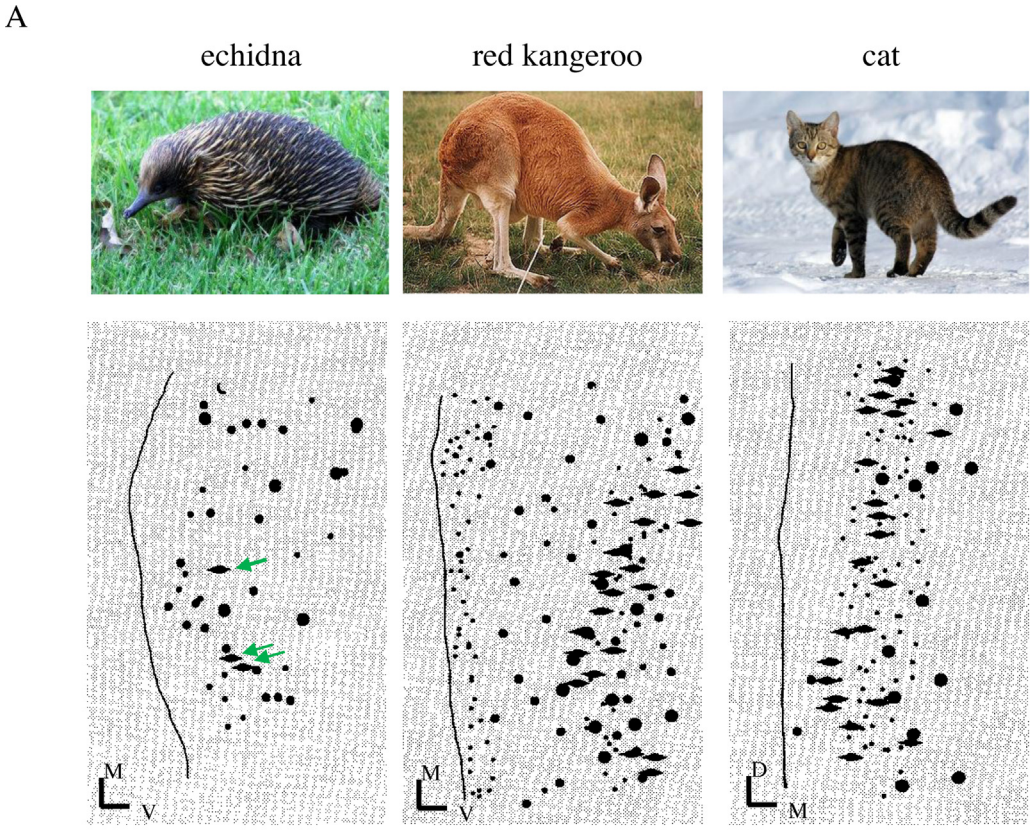
The two therian lineages split into placentals and marsupials around ~120 Myr ago in the Early Cretaceous period (Bininda-Emonds et al., 2007; Luo, 2007; Luo et al., 2011) (Fig. 2). Extant marsupial habitats are restricted to America and Australasia, with the North American opossum (*Didelphis virginiana*) being considered to represent an ancestral type compared with the Australasian marsupials such as the quoll (*Dasyurus hallucatus*) and the possum (*Trichosurus vulpecula*) (Aitkin, 1995; Mitchell et al., 2014). Opossums display a rather shallow, insensitive audiogram, with best hearing frequencies between 5 and 64 kHz (Frost and Masterton, 1994), whereas the quoll and the possum have V-shaped curves with best sensitivity centered at 8 and 18 kHz, respectively (Aitkin et al., 1994; Aitkin, 1995; Gates and Aitkin, 1982).

Placentals are the most abundant mammals and have diversified into every niche for vertebrates, including land, air, and water. This adaptation to various habitats and their large differences in size, ranging from the smallest extant mammal, the Etruscan shrew (length 2 cm) (Jurgens et al., 1996), up to the largest living animal, the blue whale (length 30 m), likely explains the significantly wider variation in hearing range, up to 150 kHz in some toothed whales, when compared to other vertebrates (Castellote et al., 2014; Heffner and Heffner, 2008; Vater and Kossl, 2011). Thus, different upper frequency limits of hearing are present in the different mammalian lineages. In monotremes, the HF is up to ~16 kHz (Mills and Shepherd, 2001), whereas marsupials have a hearing range up to 40–60 kHz (Aitkin, 1995), and placentals up to 150 kHz (Castellote et al., 2014; Heffner and Heffner, 2008; Manley, 2012; Vater and Kossl, 2011). Note, however, that only few marsupial species have been analyzed, and their upper hearing range may therefore be underestimated.

6. Neuroanatomy of mammalian sound localization circuits

In therian mammals, three major sound localization pathways exist. Monaural HRTFs associated with elevation, proximity, and front/back location are thought to be initially processed in the dorsal cochlear nucleus (DCN) (Imig et al., 2000; May, 2000; Middlebrooks, 2015; Oertel and Young, 2004; Sutherland et al., 1998; Young et al., 1992), whereas the binaural ILD and ITD cues, the basis of azimuthal sound localization, are first computed in the LSO and MSO, respectively (Brown and May, 2005; Caird and Klinke, 1983; Grothe et al., 2010; Middlebrooks, 2015) (Fig. 1A).

[2] The hearing range is usually given as the audibility at a level of 60 dB SPL (Heffner and Heffner (1990),Heffner et al. (2001)). This level also applies to the study of Mills and Shepherd.



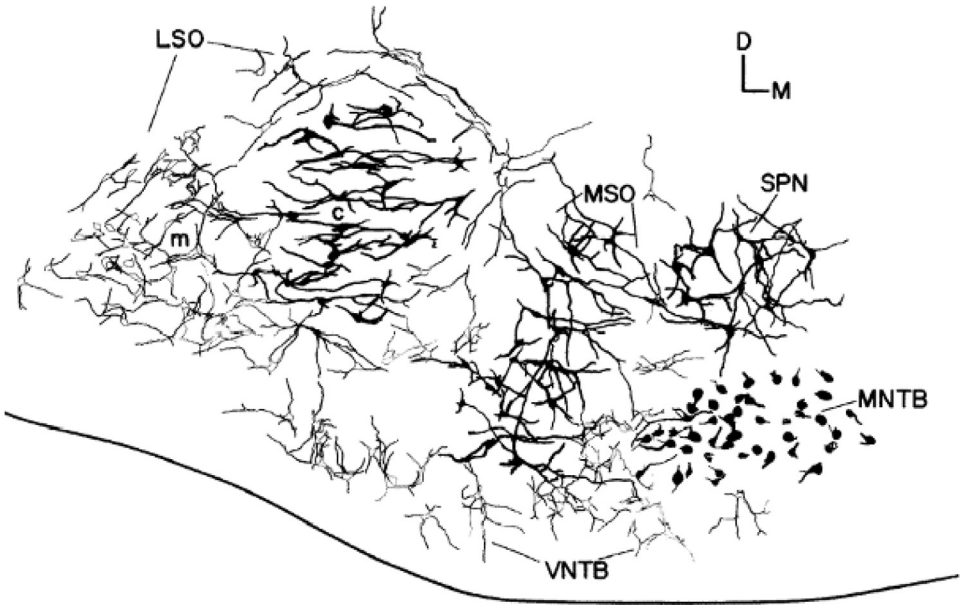


Fig. 5. Anatomical architecture of mammalian sound localization circuits. (**A**) Sketches of sections through the DCN of different mammalian lineages showing unlaminated DCN in echidna (*Tachygossus aculeatus*) and laminated DCNs from the red kangaroo (*Macropus rufus*) and the cat (*Felis catus*). Green arrows point to fusiform-type cells in the DCN of echidna. (Modified from Johnson et al. (1994). Copyright Karger, reprinted by permission). D, dorsal; M, medial; V, ventral. (B) Illustration of the cytoarchitecture of the SOC taken from Golgi-Cox impregnated brain slices of the North American opossum (*Didelphis virginiana*). Note the fusiform cell layers in the core LSO and in the MSO (From Willard and Martin (1983) Copyright Pergamon Press Lt., reprinted with permission). c, core area of the LSO; LSO, lateral superior olive; m, marginal area of the LSO; MNTB, medial nucleus of the trapezoid body; MSO, medial superior olive; SPN, superior paraolivary nucleus; VNTB, ventral nucleus of the trapezoid body. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Evolution of these sound localization pathways has mainly been discussed from a physiological point of view and has focused on sound location in the azimuth (Carr and Soares, 2002; Grothe and Pecka, 2014). However, HRTFs also strongly benefit from an extended hearing range (Heffner and Heffner, 1992). Indeed, the therian DCN with its layered structure is considered a novelty (Bell, 2002; Bell et al., 2008; Johnson et al., 1994), although it shares neuroanatomical similarities (such as a superficial molecular layer derived from granule cells and a principle cell layer with apical and ventral dendrites) with the electrosensory dorsal octavolateralis nucleus of most nonteleost fishes, the lateral line medial octavolateralis nucleus of all fishes and some amphibia, and the electrosensory lateral line lobe of electroreceptive teleost fishes (Montgomery et al., 1995) (see Section 9.3 for a non-homology-based explanation). The evolutionary trajectories of the LSO and MSO and their relationships to functionally equivalent nuclei in other vertebrates are less clear. In the following, the key anatomical properties of the mammalian circuits for sound localization are discussed, before turning to developmental data.

6.1. Anatomy of the mammalian DCN

The mammalian DCN takes variable forms, with distinct organizational principles in monotremes and therian mammals (Johnson et al., 1994). The therian DCN is subdivided into several layers (Cant, 1992; Lorente de No, 1933; Nieuwenhuys et al., 1998) (Fig. 5A). The precise number varies in different reports and between different species. A typical DCN, as defined by Lorente de No (1933) for the cat and mouse, contains 5 layers. The three outer layers are related to specific segments of the bipolar fusiform (or pyramidal) cells. The superficial or outer molecular layer contains their apical dendrites, layer 2 is made up of the somata of the fusiform cells, which form a single row intermingled with cartwheel cells and granular cells, and layer 3 contains their basal dendrites. The apical dendrites are contacted by the unmyelinated axons of the granular cells, which form parallel fibers similar to those of the cerebellar cortex (Mugnaini et al., 1980). The basal dendrites are innervated by the auditory nerve and by D-stellate cells from the ventral cochlear nucleus (VCN) (Bal and Oertel, 2000; Oertel and Young, 2004). Layer 4 of the DCN is situated deep in the pyramidal cell basal dendrites and contains a dense network of afferent and efferent fibers. Finally, layer 5 represents the deepest portion of the DCN, consisting of giant cells, as well as granular cells that separate the DCN from the VCN. In primates, a progressive reduction of the granular layers is seen, and concomitantly, the fusiform cells lose their position as a radially oriented peripheral cell layer and become localized throughout the central region of the DCN (Moore, 1980). The laminated organizational principle of the DCN also exists in the North American opossum, *Didelphis virginiana* (Willard and Martin, 1983), the australian brush tail possum *Trichosurus vulpecula* (Aitkin and Kenyon, 1981), and the red kangaroo (*Macropus rufus*) (Fig. 5A). The axons of the principal fusiform cells exit the DCN as the dorsal acoustic stria, and pass dorsally over the restiform body and through the vestibular nuclei to arch through the tegmentum to the contralateral IC (Nieuwenhuys et al., 1998).

Monotremes, by contrast, have an unlaminated DCN, which likely represents an ancestral condition (Fig. 5A) (Johnson et al., 1994). In the echidna *Tachyglossus aculeatus*, only diffusely located cells were recognized (Johnson et al., 1994). This conforms to an earlier description of the DCN in this species, which noted both its very small size compared to the VCN and the presence of only small cells (Abbie, 1934). The precise cell type(s) have not yet been described in this species. The unlayered DCN in monotremes corresponds well with the lack of pinnae in these animals (Manley, 2012).

6.2. Anatomy of the mammalian SOC

Similar to the DCN, the mammalian SOC underwent important histoarchitectonical changes during evolution. The therian SOC comprises the LSO and MSO, the MNTB, and several *peri*-olivary nuclei (Fig. 5B) (Schwartz, 1992). The placental LSO consists of several cell populations, with fusiform (or bipolar) cells being the predominant cell type in the cat (Cant, 1984), gerbil (Helfert and Schwartz, 1987), guinea pig (Schofield and Cant, 1991) and rat (Rietzel and Friauf, 1998). Up to six additional cell types have been described, including multipolar, unipolar, bushy and marginal cells (Helfert and Schwartz, 1986; Rietzel and Friauf, 1998). In many species, the LSO is convoluted, giving rise to an S-shaped form in cats and rats or a U-shaped form in mice and guinea pigs. In a comparative analysis of monotremes and marsupials, Ziehen (1904) noted the first tendencies to convolution of the LSO in the marsupial *Perameles obesula*. In placentals, excitatory input to the LSO is provided mainly by spherical bushy cells of the ipsilateral anterior ventral cochlear nucleus (aVCN), with a minor contribution of globular bushy cells of the same side, whereas inhibitory input comes from the ipsilateral MNTB and the lateral nucleus of the trapezoid body (Fig. 6A) (Thompson and Schofield, 2000). Principal cells of the LSO make three different projections to the central nucleus of the IC: a major, crossed glutamatergic projection, a minor, uncrossed glutamatergic projection, and an uncrossed glycinergic projection (Saint Marie et al., 1989) (Fig. 6B). In addition, neurons of the LSO project to the dorsal nucleus of the lateral lemniscus of both sides (Shneiderman et al., 1999; Siveke et al., 2006). The projection neurons do not differ in size, shape, or location of their somata in the cat LSO (Saint Marie et al., 1989). The only difference is that uncrossed glutamatergic projection neurons originate from the LF limb of the LSO (lateral side) and the crossed ones from the HF limb (medial side) (Glendenning and Masterton, 1983; Loftus et al., 2010).

In marsupials such as the opossum *Didelphis virginiana*, a bipartite LSO has been described, with a centrally-located core and a marginal area surrounding the core laterally, dorsally, and ventrally (Fig. 6B) (Willard and Martin, 1983). Notable is that principal neurons in the core have a fusiform shape and form a stack, closely resembling the MSO neurons in shape and in orientation of the dendrites (Fig. 5B). Two thirds of these cells project to the contralateral IC, whereas the remainder project to the ipsilateral IC (Willard and Martin, 1984) (Fig. 6B). In addition, in IC, injected horseradish peroxidase bilaterally labels the marginal zone. On the ipsilateral side, the labeled cells form a ring surrounding the core, whereas contralateral labeled neurons form a narrow band in its ventrolateral area (Willard and Martin, 1984).

The MSO consists of a sheet of fusiform cells with their dendrites pointing medially and laterally. These dendrites are contacted by excitatory projections from spherical bushy cells of the ipsilateral and contralateral aVCN (Grothe and Pecka, 2014; Nieuwenhuys et al., 1998). In addition, the neurons receive inhibitory inputs from globular bushy cells of both aVCNs via the ipsilateral lateral nucleus of the trapezoid body and the MNTB (Fig. 6A) (Couchman et al., 2010; Grothe and Pecka, 2014; Grothe and Sanes, 1993). MSO neurons make excitatory projections to the ipsilateral central nucleus of the IC (Cant, 2013; Loftus et al., 2010; Oliver, 2000). In addition, the MSO establishes a strong projection to the ipsilateral dorsal nucleus of the lateral lemniscus and a minor projection to the contralateral side (Siveke et al., 2006). Finally, local collateral projections from the MSO target the neighboring superior paraolivary nucleus (Kuwabara and Zook, 1999).

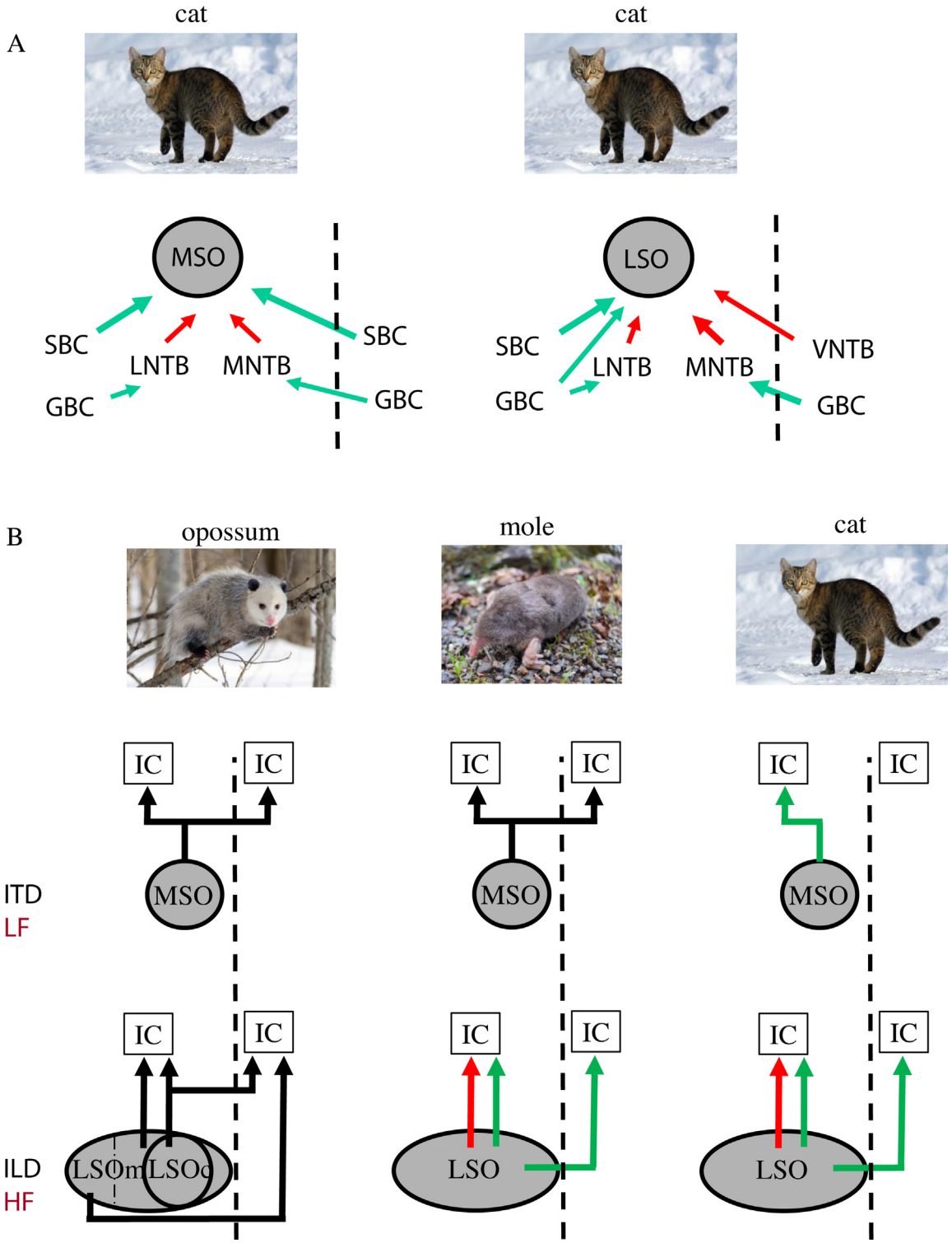


Fig. 6. Projection pattern of hindbrain sound localization circuits. (A) Schematic illustrating the innervation pattern of the placental-therian LSO and MSO. Red, glycinergic projection; green, glutamatergic projection. (B) Schematic illustrating the pattern of the crossed and uncrossed projections from the MSO and LSO to the IC in the North American opossum (*Didelphis virginiana*) after Willard and Martin (1983), the Japanese mole (*Mogera wogura*) after Kudo et al. (1990a), and the cat (*Felis catus*) after Glendenning and Masterton (1983). Note that only major projections are depicted and that the color code in the mole is extrapolated from data in the cat. LSOc, core area of the lateral superior olive; GBC, globular bushy cell; LNTB, lateral nucleus of the trapezoid body; LSOm, marginal area of the lateral superior olive; MNTB, medial superior olive; MSO, medial superior olive; SBC; spherical bushy cell; VNTB, ventral nucleus of the trapezoid body. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

A third important nucleus within the sound localization circuits of the SOC is the MNTB (Fig. 1A). This nucleus is located within the fiber tracts composing the trapezoid body and consists mainly of large, rounded principal neurons. In addition, stellate and elongate neurons are present (Schwartz, 1992). The principal cells are innervated by axon terminals from globular bushy cells within the contralateral aVCN. Note, however, that Harrison and Irving (1964) observed degeneration of synaptic endings in the anterior half of

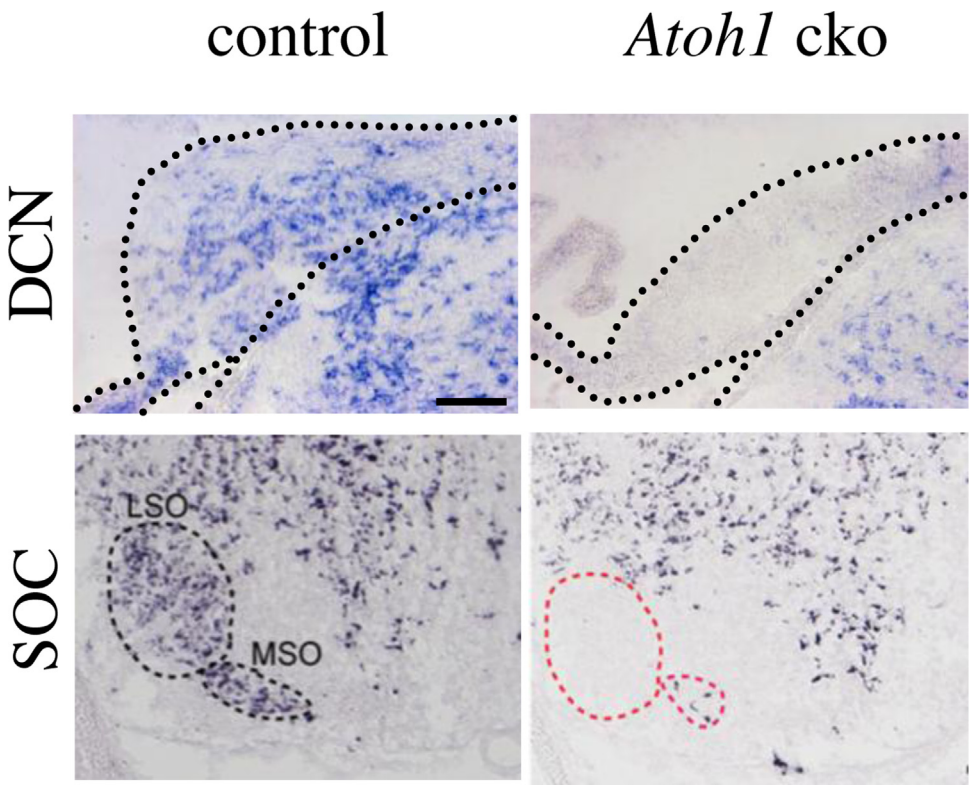


Fig. 7. VGlut2$^+$ neurons in sound localization circuits are derived from an Atoh1$^+$ cell lineage. RNA *in situ* hybridization of transverse section of the cochlear nucleus complex at E18.5 reveals the absence of VGut2$^+$ neurons in the presumptive DCN, and the MSO and LSO of mice lacking Atoh1 (Atoh1 conditional knockouts). Data modified from Fujiyama et al. (2009) for the DCN and Maricich et al. (2009) for the MSO and LSO.

the MNTB after destruction of the aVCN and degeneration in the posterior half of the MNTB after destruction of the posterior ventral cochlear nucleus (VCN). The cellular origin of the latter projections is unknown, as is the relationship of this dual input to the dual origin of MNTB neurons that are derived from r3 and r5 (Maricich et al., 2009). MNTB neurons make inhibitory glycinergic projections to various nuclei, including the binaural LSO and MSO and the monaural superior paraolivary nucleus and the nuclei of the lateral lemniscus (Grothe, 2003; Kandler and Friauf, 1993; Kulesza and Grothe, 2015; Schwartz, 1992) (Fig. 6A). The MNTB thus serves as an important relay nucleus providing synaptic inhibition to various auditory nuclei (Fig. 6A).

The superior olive of monotremes has been described in several anatomical studies. In a comparative monograph on the central nervous system of platypus and echidna, Kölliker [1901] noted "I have detected the superior olive . . . .in both monotreme species, poorly developed in *Ornithorhynchus*, whereas it was of considerable size and well developed in *Echidna* . . . ."[3]; According to that study, the superior olive of *Ornithorhynchus* consists of rounded cells of 14–20 μm diameter, which form a medial and a lateral limb. Input is provided by fibers of the trapezoid body of the same and the contralateral side, whereas projections leave from the dorsal end (Kölliker, 1901). Hines (1929) assigned a more medially-located population to the superior olive, based on its direct connectivity to the contralateral superior olive. However, such direct connectivity is not present in the placental SOC (Glendenning and Masterton, 1983), weakening Hines' interpretation. The relatively poor development likely makes the precise assignment of this nucleus in *Ornithorhynchus* difficult and further anatomical studies, including tracer injection into the IC or expression analyses of molecular markers, are required to settle the issue. Of note is the fact that both reports agree on the absence of an MNTB (Hines, 1929; Kölliker, 1901). This corresponds to a poorly developed trapezoid body, with few auditory fibers (Hines, 1929; Kölliker, 1901; Ziehen, 1897). Whether the poorly developed auditory system represents an ancestral condition or an adaptation to the amphibious life style of *Ornithorhynchus* is unknown.

In *Echidna*, the superior olive is larger than in *Ornithorhynchus*, with rounded cells of 20–25 μm diameter (Kölliker, 1901). Similar to *Ornithorhynchus*, it comprises medial and lateral regions, with the lateral part being larger (Abbie, 1934; Fuse, 1926; Kölliker, 1901). The cells receive substantial input from the cochlear nucleus complex. Only a few cells were observed intermingled within the fibers of the trapezoid body and were suggested to represent the homolog of the therian MNTB (Abbie, 1934; Kölliker, 1901). Also, a more recent study of the echidna nervous system noted only a small MNTB, which was positive for the marker Calbindin 28k (Ashwell, 2013; Friauf, 1993). Thus in the azimuthal sound localization circuits of monotremes, these anatomical data suggest a poorly developed MNTB. However, final clarification awaits re-analysis of the auditory brainstem of monotremes using additional molecular markers such as VGlut1 (Blaesse et al., 2005), Bassoon or Piccolo (Dondzillo et al., 2010) for the calyceal terminals, or tracing studies. Furthermore, an immunohistochemical investigation identified the transcription factors En1, Sox2, and FoxP1 as part of the GRN of this nucleus, making them also valuable molecular markers (Marrs et al., 2013). Recently, a developmental microarray study of the mouse MNTB was reported that also should provide rich information on the molecular repertoire of this nucleus (Kolson et al., 2015).

[3] Translation by the author.

Taken together, the anatomical data reveal that both the laminated DCN and the SOC, with its high number of nuclei (>6), are apomorphic characters of therian mammals. These anatomical structures are thus associated with the emergence of HF hearing in mammals. It is still not known when exactly mammalian HF hearing emerged. The effective hearing range in monotremes extents to ~16 kHz (Aitkin and Johnstone, 1972; Ashwell, 2013; Gates et al., 1974; Mills and Shepherd, 2001). It is therefore unclear whether they can capitalize on HF-based ILDs for sound localization in the far field.

Unfortunately, no data are available on the acuity of sound localization in monotremes. It is therefore unknown how much they use HRTFs or binaural cues for sound localization or simply rely, for instance, on lateralization. On the whole, hearing likely does not play an important role in these animals, as they vocalize little and there is no evidence that they use sound for prey detection (Ashwell, 2013). This is supported by the fact that the entire auditory system up to the cortex is poorly developed (Ashwell, 2013). Ziehen, in a comparative macroscopic study of the central nervous system of mammalia, noted, for instance, a poorly developed inferior colliculus and medial geniculate body in both *Echidna hysterix* and *Ornithorhynchus paradoxus*, as compared to marsupials and most placentals (Ziehen, 1897).

7. Principal projection neurons of sound localization circuits represent serial homologs

The principal projection neurons in the DCN, LSO and MSO are fusiform cells (aka spindle-shaped). In marsupials, all three cell populations are arranged in a single-layered stack (Fig. 5). This cytoarchitecture is also present in the placental DCN and MSO. Only the placental LSO deviates from this organization, with fusiform cells more randomly distributed in the nuclear domain. Both DCN and MSO fusiform neurons express the vesicular glutamate transporter 2 (VGlut2$^+$) (Ito et al., 2011; Maricich et al., 2009) (Fig. 7). In the LSO, two types of fusiform cells are present, one being VGlut2$^+$ (Fig. 7) and the other expressing the vesicular inhibitory amino acid transporter VIAAT (VIAAT$^+$) (Ito et al., 2011). Noticeably, the VGlut2$^+$ cells in all three nuclei share not only cell morphology and neurotransmitter phenotype, but also a common embryonic origin. Cell fate mapping in the mouse using Cre-driver lines revealed that all three populations originate from an Atoh1$^+$/Wnt1$^+$ cell lineage in the rhombic lip of r5 (Farago et al., 2006; Maricich et al., 2009; Nothwang et al., 2015; Rose et al., 2009) (Fig. 7). This region likely corresponds to the A1 microzone of the closed neural tube (Kohl et al., 2012; Puelles, 2013) (Fig. 8A). Accordingly, ablation of *Atoh1* in transgenic mice results in loss of these neurons (Fujiyama et al., 2009; Maricich et al., 2009) (Fig. 7). This is in contrast to many other cell types in the DCN (Farago et al., 2006; Fujiyama et al., 2009) and all other cell populations in the SOC (Maricich et al., 2009; Rose et al., 2009). In the DCN, inhibitory neurons such as cartwheel, Golgi, stellate, and tuberculoventral cells are derived from a Ptf1a$^+$/Wnt1$^+$ lineage (Fujiyama et al., 2009) (Fig. 8A). The remaining afferent neurons of the SOC are also mainly derived from a non-lip region of r5 (i.e. outside the hindbrain A-type region A1-A4 (Puelles, 2013)), but their precise origin is still unknown. Analysis of a *Ptf1a$^+$:Cre*-driver mouse line demonstrated that this transcription factor lineage does not contribute to the SOC (Ebbers et al., 2016). There is, in addition, a contribution of r3 to the MNTB (Maricich et al., 2009). All three fusiform cell populations also express the LIM homeobox transcription factors Lhx2 and Lhx9 in an Atoh1-dependent manner (Rose et al., 2009). These homeobox transcription factors play a central role in the formation of correct axonal projection patterns (Chedotal, 2014; Kohl et al., 2012, 2015) and in the expression of a glutamatergic neurotransmitter phenotype (Kohl et al., 2015).

In addition to their common embryonic origin, VGlut2$^+$ projection neurons of the DCN, LSO, and MSO are born at the same time in various species: in rats at E12-13 (Altman and Bayer, 1980; Kudo et al., 1996, 2000), in mice at E10 (Pierce, 1973; Rose et al., 2009), and in rabbit at E12 (Oblinger and Das, 1981). In the marsupial *Dasyurus hallucatus*, available data indicate a birth date of principal DCN neurons between days 5–7 of pouch young, similar to LSO neurons (Aitkin et al., 1991). MSO neurons are presumably born a few days earlier, as they were not labeled by tracer injection after day 3 (Aitkin et al., 1991). All three populations in placentals also receive excitation at their dendrites and glycinergic inputs at the soma, and, at least during development, GABAergic input (Grothe and Pecka, 2014; Oertel and Young, 2004). Thus, despite some differences in the timing of the expression and the localization of the receptors, they possess the genetic program to express these distinct postsynaptic neurotransmitter receptors. Taken together, the major excitatory projection neurons of therian sound localization circuits in the brainstem share many important characteristics: cell morphology, neurotransmitter phenotype, columnar organization, embryonic origin, and cell birth. A close relationship between the LSO and MSO, based on shared functional features, was also recently emphasized in a model of the evolution of sound localization circuits (Grothe and Pecka, 2014). Both nuclei also share a very similar input pattern, with excitatory input from ipsilateral spherical bushy cells and inhibitory input from the MNTB and the lateral nucleus of the trapezoid body of the same side (Fig. 6A). Furthermore, they display a similar gene expression pattern as revealed by RNA *in situ* hybridization (Ehmann et al., 2013).

The commonalities between DCN, LSO, and MSO fusiform cells suggest that they represent serial homologs. This term was coined by Owen (1848) to account for repeated elements that correspond with one another within an organism, an observation already made earlier by (Vicq-d'Azyr, 1774) for the skeleton and by Goethe (1790) for various parts of plants. Serially repeated structures are frequently observed, as they likely represent the most parsimonious means of generating additional structures in relatively short evolutionary time spans (Raff, 1996) (chapter 2). This would have allowed to rapidly capitalizing on the extended hearing range. A likely scenario for the generation of these three serial homologies comprises a delayed cell cycle exit of neuronal precursors to enlarge the cell pool (Charvet et al., 2011; Finlay et al., 2001) and subsequent changes in *cis*-regulatory elements in neuronal subpopulations resulting in the recruitment and loss of different transcription factors altering GRNs and thus cell fate (Section 2.2). Examples in sea urchin and cell fate decisions (Section 2.2) demonstrate that only few transcription factors have to undergo changes in expression to change GRN sub-circuits during development, and this can happen in evolutionarily short time periods due to changes in *cis*-regulatory elements (Section 2.2). A recent genotype network analysis of binding sites of 108 mouse transcription factors suggested that any binding site sequence is only one point mutation away from a binding site of another transcription factor (Payne and Wagner, 2014). This enables rapid evolution of GRNs. In humans, for instance, most recent estimates indicate 10–100 mutations per genome per generation (Kong et al., 2012).

The widespread presence of serial homologs was already noted by Darwin (1859). They have also previously been described in the auditory system. The middle ear ossicles of tetrapods are derived from viscerocranial pharyngeal arches. These structures are segmentally-repeated skeletal elements that originally supported the gills (Sienknecht, 2013). Serial homologs can be distinguished into paramorph and homomorph characters (Riedl, 1978; Wagner,

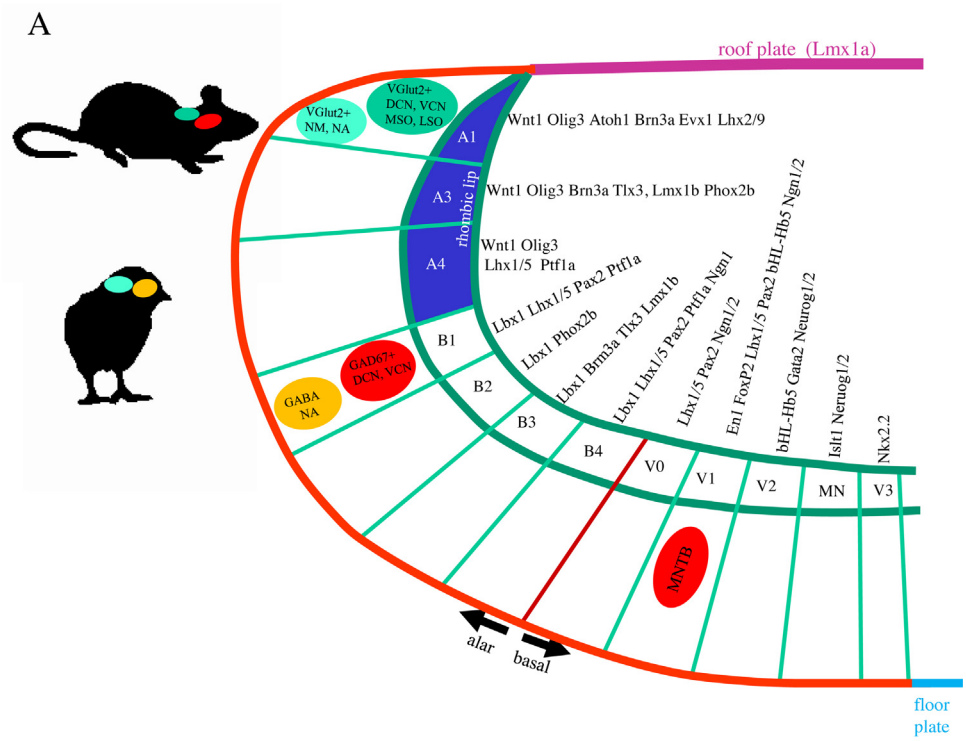


Fig. 8. Schematic patterns of dorsoventral microzones and their genetic architecture. (A) Schematic transverse section through the developing hindbrain at the r3-r5 level showing class A, B, and V neurons and their contributions to auditory structures. The contribution of A1 progenitors to VGut2$^+$ neurons and Ptfa1$^+$ B1 progenitors to inhibitory neurons in the auditory hindbrain is based on MNTB neurons are derived from an EN1$^+$ lineage (Jalabi et al., 2013). Note that A2 is not depicted, as it is only present caudally of r6 (see (B)); this microzone would also express *Ngn1* and *Ptfa1*. The operational definition of A1-A4 Wnt1$^+$ microzones as rhombic lip is based on (Farago et al., 2006; Puelles, 2013) and expression data for microzones are mainly taken from (Alaynick et al., 2011; Gray, 2008; Kohl et al., 2012). NA; nucleus angularis; NM, nucleus magnocellularis. Modified from (Puelles, 2013). (B) Presence of microzones across different rhombomeres and properties of derived neurons. Data taken from (Gray, 2008). The presence of V1 along the rhombomeres is based on *En1* expression (Davis et al., 1991). Comm, commissural projections; GABA/Gly, GABAergic/glycinergic; Glu, glutamatergic; SC, spinal cord.

2014b). Paramorph characters are individualized morphological duplicates, such as the anterior and posterior paired appendages in vertebrates (Minelli, 2002), whereas homomorphs are non-individualized repeat units such as red blood cells (Wagner, 2014b). As the fusiform cells of the DCN, LSO, and MSO show clear signs of individuality, such as functional specializations and distinct innervation patterns, they represent paramorphs.

An interesting individualization of the three cell populations during evolution occurred with respect to their projections (Fig. 6B). All three types of principal cells project, among other nuclei, to the central nucleus of the IC (see 6.1 and 6.2 for details). However, there are notable differences. The placental fusiform cells of the DCN and the majority of the LSO cell population project to the contralateral IC with the LSO projection joining the dorsal acoustic stria that originates from the DCN (Glendenning and Masterton, 1983). In contrast, the MSO cells project by large to the ipsilateral IC (cat: Glendenning and Masterton, 1983; Henkel and Spangler, 1983; rat: Riemann and Reuss, 1998; gerbil: Nordeen et al., 1983). Furthermore, LSO neurons project bilaterally into the dorsal nucleus of the lateral lemniscus, whereas MSO neurons

project predominantly to the ipsilateral dorsal nucleus of the lateral lemniscus with only 11% of labeled MSO neurons after retrograde labeling from the contralateral dorsal nucleus of the lateral lemniscus (Siveke et al., 2006). Recently, it was shown that bushy cells of the aVCN require Robo3 for midline crossing (Di Bonito et al., 2013b; Renier et al., 2010). If this protein is also essential for contralateral projections from the DCN and LSO, it should be down-regulated in the majority of MSO neurons. Interestingly, phylogenetic analyses reveals the potential of LSO and MSO neurons to form both crossed and uncrossed projections (Kudo et al., 1990b, 1990a) (Fig. 6B). In the opossum, some LSO cells from the core, as well as MSO cells, send axon collaterals to both sides (Willard and Martin, 1984). This potential is also present in placentals, as a subpopulation of VGlut2$^+$ LSO neurons also project to the ipsilateral IC (Glendenning and Masterton, 1983). In the japanese mole (*Mogera wogura*), an ancestral placental, projection of the LSO is largely restricted to the contralateral IC, whereas MSO neurons project bilaterally (Kudo et al., 1990b, 1990a).

A further intriguing variation concerns the migration of these neurons. Whereas VGlut2$^+$ DCN neurons remain in the alar plate, the MSO and LSO neurons migrate after birth to the ventral part of the basal plate. This difference might be related to the different innervation patterns. Whereas VGlut2$^+$ DCN neurons receive major input from the ipsilateral auditory nerve (Oertel and Young, 2004), especially the VGlut2$^+$ neurons of the MSO and to a minor extent those of the LSO (Fig. 6B) receive inputs from the contralateral side (Thompson and Schofield, 2000). This is also true for other important nuclei of the SOC such as the MNTB and the superior paraolivary nucleus (Thompson and Schofield, 2000). Importantly, axonal crossing of the midline occurs at the floor plate, which spans the width of the neural tube at its ventral midline (His, 1888) (Fig. 8A). Its ependymal cells provide a variety of attractive and inhibitory guidance cues, that selectively influence the growth of different populations of axons (Chedotal, 2014; Colamarino and Tessier-Lavigne, 1995). The migration of the SOC to the ventral area of the hindbrain might have facilitated their innervation. It is worth noting that projections from the ventral cochlear nucleus cross the midline and enter the vicinity of the presumptive contralateral MNTB at E14.5, whereas the MNTB becomes only discernible in this region at E17 (Hoffpauir et al., 2010; Howell et al., 2007). Thus the MNTB neurons have to arrive at the ventral hindbrain to make synapses with the commissural neurons of the ventral cochlear nucleus.

8. Evolution of sound localization circuits in mammals

A major discussion concerning sound localization circuits revolves around their order of appearance. The major issue is whether ITD (MSO) or ILD (LSO) processing sound localization circuits were present at the origin of mammals[4] or whether both evolved in parallel (Christensen-Dalsgaard and Carr, 2008; Grothe and Pecka, 2014; Manley, 1972; Masterton et al., 1969; Rosowski and Graybeal, 1991).

The ITD-first scenario hypothesizes pretympanic tetrapod ancestors that probably sensed LF sounds (<2 kHz) by vibration of the skull. At these frequencies, bone conduction is most efficient (Christensen-Dalsgaard and Manley, 2014). Directionality of hearing is provided by sensitivity to skull vibration direction, assisted by subsequent binaural processing in the brain. It is then assumed that early tympanic ears in non-mammals acted as pressure gradient receivers. This ear displays best directional sensitivity at frequencies between 2 and 4 kHz, as the phase difference of sound reaching the external and internal surface of the eardrum is the arrival time difference divided by the cycle time. This feature renders phase difference minimal at LF, as an arrival time difference of 100 μs produces a phase difference of 10° at 1 kHz, but only 1° at 100 Hz (Christensen-Dalsgaard and Carr, 2008). At LF, the phase difference between sound on the internal and external side will be minimal, resulting in reduced eardrum movements. Frequencies far below 2 kHz (<400 Hz) will therefore rely on the LF pathways of the pretympanic ancestors. This LF pathway is proposed to then evolve into the ITD pathway, thereby representing the ancestral pathway. In this scenario, the ITD pathway would have co-opted preexisting neuronal structures, whereas the ILD pathway would represent a novelty, emerging with the tympanic ear (Christensen-Dalsgaard and Carr, 2008).

The second scenario assumes that both the ILD and ITD pathway represent novelties in mammals, with the ILD pathway having originated first (Grothe and Pecka, 2014). This hypothesis is based on several observations. All mammals possess a three-ossicle middle ear (no intermediate one-ossicle or two-ossicle middle ear were observed so far in the fossil record), which was conducive to the evolution of hearing above 10 kHz. Due to their small size, early mammals experienced only tiny ITDs (<50 μs), the computation of which requires highly sophisticated and specialized neuronal circuits. Specializations include on the molecular level fast AMPA receptors (Geiger et al., 1995; Raman et al., 1994) and potassium channels including K_v1 and K_v3 (Johnston et al., 2010; Li et al., 2001; Oertel, 2009; Parameshwaran et al., 2001) to ensure temporally precise, ultrafast, and high frequency neurotransmission (Golding, 2012). On the cellular levels, large presynaptic terminals such as the calyces and the endbulbs of Held are hallmarks of sound localization circuits (Borst and van Soria Hoeve, 2012; Gersdorff and Borst, 2002; Grothe et al., 2010; Manis et al., 2012). In contrast, ILDs are large in the near field and at HF. Furthermore, the operational principle of the LSO with its requirement of high temporal acuity and phase locking (Joris and Yin, 1995; Tollin and Yin, 2005) represents an excellent preadaptation for ITD detection in larger animals (Grothe and Pecka, 2014). It is worth noting that the placental LSO harbors LF-processing neurons that are sensitive to ITDs (Finlayson and Caspary, 1991; Joris and Yin, 1995; Tollin and Yin, 2002). Finally, the early mammal *Morganucodon* was assumed to have HF hearing, based on detailed comparative analysis of its three-ossicle middle ear (Rosowski, 1992).

With respect to this debate, some observations lend support to the "ITD first" scenario. i) The ears of both the monotremes and the multituberculata, an extinct mammalian lineage, represent a condition likely not supporting well HF hearing (Manley, 2012; Meng and Wyss, 1995; Vater et al., 2004). The cochlea of multituberculata was short (<6.5 mm), contained a lagena macula and was uncoiled, and the ossicles were robust (Manley, 2012; Vater et al., 2004). The similarity of the ears of these two lineages argues also against a secondary reduction of the auditory system in monotremes (Manley, 2010b). ii) About 100 Mio years passed between the emergence of the three-ossicle middle ear (~230 Mio years ago) and changes in the inner ear such as coiling (~125 Mio years ago) that correlate with HF hearing (Fig. 2). The assumption of HF hearing in *Morganucodon* (Rosowski, 1992) likely ignored the requirement of appropriate changes in the inner ear for HF hearing (Manley, 2012; Ruggero and Temchin, 2002; Vater et al., 2004) and that the malleus was still firmly attached to the dentary (Meng et al., 2011). Furthermore, the skulls studied initially had been distorted during fossilization (Hurum, 1998). *Morganucodon* therefore experienced ILDs mainly in the near field (>10 cm). This would likely limit the use of ILDs to parent-child relationships at close range, whereas other important functions of sound

[4] Note that the evolution of mammalian directional hearing is not explicitly addressed by Christensen-Dalsgaard and Carr in their 2008 paper, but the general ideas put forward by the authors should also hold true for mammals.

localization such as mate search and prey/predator detection would not significantly benefit. iii) Concerning sound localization circuits proper, both Kölliker (1901) and Abbie (1934) described fibers of the contralateral trapezoid body arriving directly in the superior olive of monotremes, similar to the situation in the therian MSO. However, it is unclear whether this observation holds true for both limbs of the monotreme superior olive. iv) Monotremes likely lack a prominent MNTB, which is required for the subtraction mechanism in the LSO (but note the general poor development of the auditory system in these species).

A solution to this conundrum might come from the identification of specific genetic markers for the therian LSO and MSO and their subsequent analysis in monotrema. This would provide evidence for the presence of an LSO, MSO, or both in monotremes. Furthermore, comparative analysis of the GRN underlying formation of the LSO and MSO will inform our understanding of the developmental evolution of these neuronal populations. Large scale transcriptome data of the SOC with transcription factors enriched in the SOC compared to the entire brain have recently been reported (Ehmann et al., 2013). Together with the high-resolution spatiotemporal gene expression atlas of the developing mouse (Thompson et al., 2014), they might provide important insights into the genetic programs of the MSO and LSO. In addition, a *VGlut2:Cre* driver mouse line is available (Vong et al., 2011) that, crossed with a fluorescence protein reporter mouse line, will allow in depth characterization of the developing MSO and LSO neurons by RNAseq profiling and related systems approaches (Junker and van Oudenaarden, 2014; Shapiro et al., 2013). The assembly of GRNs from these data will be highly informative concerning their evolutionary trajectory and relationships.

9. Phylogenetic trajectory of sound localization circuits

9.1. Shared and distinct features of mature mammalian and avian sound localization circuits

Important insight into the evolution of mammalian sound localization circuits will also come from the clarification of their phylogenetic relationship to the corresponding circuits in other vertebrate groups. All vertebrates share a large number of auditory nuclei in their brainstem (Carr and Code, 2000; Glendenning and Masterton, 1998; Grothe et al., 2004). This resulted in the concept of homologous auditory brainstem nuclei. This idea was supported by similarity in the structural and physiological properties of the afferent innervation of the mammalian cochlear nucleus complex and the avian nucleus angularis and nucleus magnocellularis (Ryugo and Parks, 2003) and shared cellular and molecular features. These include fusiform cell type (Carr et al., 2001; Hausler et al., 1999), giant synapses in alligator lizards, turtles, birds and mammals (Ryugo, 2014), as well as large neurons, AMPA receptors with very fast kinetics and very rapid desensitization, and a specific repertoire of low and high threshold K^+ channels in central auditory nuclei of both birds and mammals (Carr and Soares, 2002). However, the independent evolution of tetrapod tympanic ears (Fig. 2) and important differences in sound localization circuits between birds and mammals (Fig. 1) argue for convergent or parallel evolution of most or even all parts of the auditory brainstem (Grothe et al., 2004). A clear example of important circuit variation can be seen in the superior olive. In mammals, this is a complex structure composed of several nuclei (superior olivary complex) (Schwartz, 1992) processing various acoustic features that are key elements in sound localization (Grothe et al., 2010) (Fig. 1). In birds, this center consists of the single superior olivary nucleus that provides GABAergic feedback inhibition to several other auditory nuclei (Carr and Code, 2000; Lachica et al., 1994) (Fig. 1). Furthermore, ILDs are computed in the lateral superior olive (LSO) in mammals, but this structure has no equivalent in birds, where this cue is first processed in the posterior part of the dorsal lateral lemniscus (Manley et al., 1988; Mogdans and Knudsen, 1994; Ohmori, 2014) (Fig. 1). Moreover, other mammalian auditory nuclei, such as the posterior ventral cochlear nucleus (pVCN) have no anatomical equivalent in birds (Grothe et al., 2004; Grothe and Pecka, 2014) (Fig. 1). Finally, the DCN of mammals and the nucleus angularis of birds also show striking differences in connection patterns (Grothe et al., 2004). It is even currently unclear where most birds compute cues for vertical sound localization, even though birds (that lack pinnae) likely experience cues to do so (Schnyder et al., 2014).

On the physiological level, a notable difference is observed between the mammalian MSO and the nucleus laminaris, its avian counterpart. Both are involved in azimuthal sound localization, but the MSO receives phasic glycinergic input that causes hyperpolarization (Grothe and Sanes, 1993, 1994), whereas the nucleus laminaris receives tonic GABAergic inhibition that causes depolarization (Hyson et al., 1995; Monsivais et al., 2000). Current evidence indicates that the nucleus laminaris processes ITDs according to the Jeffress model with the use of delay lines (Jeffress, 1948), whereas in mammals, they might be computed from the overall discharge rate within the broadly tuned MSO (Lesica et al., 2010). Important insight into the precise evolutionary relationships between mammalian and avian sound localization circuits might result from a comparative analysis of the underlying GRNs.

9.2. Similar developmental programs for sound localization circuits

Recently, progress has been made with respect to the genetic origin of chicken auditory nuclei. A *Cre* driver line, expressing the recombinase under an *Atoh1* enhancer element, labels neurons that project to the torus semicircularis and to the nucleus laminaris, two avian auditory structures (Kohl et al., 2012). These $Atoh1^+$ neurons therefore likely reside in the nucleus angularis and nucleus magnocellularis (Fig. 1). Like their mammalian counterparts (Fujiyama et al., 2009; Kohl et al., 2015), these projection neurons are $VGlut2^+$ (Kohl et al., 2015). This genetic similarity between avian and mammalian auditory hindbrain nuclei extends to inhibitory neurons. The $Ptfa1^+$ lineage, which contributes GABAergic neurons to the mammalian DCN (Fujiyama et al., 2009), was recently demonstrated to do the same for the chicken nucleus angularis (Kohl et al., 2015). It will be interesting to see whether other transcription factors associated with mammalian auditory brainstem structures, such as Neurod1 in the dorsal cochlear nucleus (Fritzsch et al., 2006), or MafB in the LSO and MSO (Marrs et al., 2013), are expressed in auditory nuclei of other vertebrate lineages.

The shared genetic lineage of mammalian and avian sound localization circuits stands to some extent in contrast to the established differences in rhombomeric origins. The mammalian aVCN and its avian counterpart NM derive from r2-r3 and r5-r8, respectively (Cramer et al., 2000; Farago et al., 2006), and their rhombomeric origins thus do not overlap. Other nuclei thought to be functionally equivalent, such as the MSO (r5) and NL (r5 and r6) show only partial overlap in their rhombomeric origin. Only the avian superior nucleus and the mammalian SOC with the exception of the MNTB (partially originating in r3) are both derived from r5 (Cramer et al., 2000; Willaredt et al., 2015a). Thus, development data also reveal both shared and distinct features, similar to the adult system.

Interestingly, in several groups of other tetrapod groups, sound localization circuits also contain fusiform cells (anura: (Jacoby and Rubinson, 1984; Templin and Simmons, 2005); caiman (Leake, 1974); lizard: (Szpir et al., 1995). This may also be the case in bony fish (McCormick, 2011; McCormick and Hernandez, 1996)). Thus

fusiform cells might have been evolved multiple times independently, as their bipolar morphology was likely to be under positive selection pressure. Their shape facilitates the formation of isofrequency bands, an important organizational principle in the central auditory pathway. Nevertheless, recent forward genetic experiments in fish reveal a closer genetic link to mammalian auditory nuclei than might have been assumed.

In fish, sound stimulates the otolith endorgans (Fay, 1984; Ladich and Popper, 2004; McCormick, 1999), and their inputs are processed in a number of different nuclei. Among them, the descending and the anterior octaval nuclei are distinguished by the fact that both of them include a region that has an ascending projection to the auditory midbrain. The auditory region in each nucleus is therefore thought to be an ancestral, first order, auditory "nucleus" (McCormick, 2011). Lineage tracing in zebrafish revealed a contribution of the Atoh1$^+$ lineage to the descending and the anterior octaval nuclei and/or a contribution to the nucleus medialis, processing mainly information from the lateral line system (Sassa et al., 2007). A precise assignment to either the two auditory nuclei or the lateral line nucleus could not be made, as the genetic marker was not maintained in the adult fish (Sassa et al., 2007). Identical to the situation in mammals, the zebrafish Atoh1a is required for neuronal expression of Lhx2 and Lhx9 (Sassa et al., 2007). Thus, in all vertebrates analyzed so far, an Atoh1$^+$ cell lineage contributes to auditory neurons. For a better assessment of the meaning of this similarity, the organization of the developing hindbrain provides important clues.

9.3. Conserved organizational principles in the developing vertebrate hindbrain

On the molecular level, the developing hindbrain is most frequently associated with the nested expression of Hox genes along the rostro-caudal axis (Tümpel et al., 2009). This Hox code functions as an important vectorial patterning device to allow or prevent deployment of GRNs that program the development of given morphological structures (Peter and Davidson, 2015; Tümpel et al., 2009). However, both the alar and basal plate of the embryonic hindbrain subdivide dorsoventrally into evolutionarily-conserved parallel microzones with different molecular profiles (Fig. 8B) (Kohl et al., 2012; Puelles, 2013). The developing hindbrain can therefore also be understood as a tagma, a term used to describe a set of adjacent segments (e.g. rhombomeres) with shared characteristics despite being partly different (Prokop and Technau, 1994; Puelles et al., 2013; Puelles, 2013). This organizational principle confers a certain generic identity that makes progenitors competent for certain neuronal cell types and cytoarchitectures across rhombomere boundaries (Fig. 8B). Inhibitory neurons, for instance, usually derive from B1, B4, V0, or V1, whereas excitatory neurons whose axons have to cross the midline are born in A1-A3 or B4 (Fig. 8B).

This organization of the hindbrain imposes severe constraints on developmental processes. An instructive example for this stereotypic patterning is provided by the cerebellum, which originates from r1. Its formation requires specification by the isthmic organizer, which is localized at the hind-midbrain transition and controls anterior hindbrain and midbrain regionalization (Fahrion et al., 2013; Martínez, 2001; Puelles, 2013). Grafts of the isthmic organizer to various rhombomeric regions resulted in the development of cerebellum-like structures. Induction requires fibroblast growth factor 8, which is secreted from the isthmic organizer and whose presence is restricted to r1 (Heikinheimo et al., 1994). Accordingly, ectopic FGF8 expression also induces cerebellum-like structures (Martinez et al., 1999). This competence likely underlies the recurrence of so-called cerebellum-like structures, such as the dorsal and medial octavolateral nuclei, the marginal layer of the optic tectum in the brain, or the DCN (Bell, 2002). The latter, with its internal organization of granule cells, the axons of which form parallel fibers, projection neurons that send their dendrites into the parallel fiber layer, and the presence of inhibitory neurons, closely resembles the cerebellar cortex (Oertel and Young, 2004). Of note, the secondary octaval population, which is part of the ascending auditory pathway in bony fishes (Osteichthyes) is, in some teleost species, also a cerebellum-like structure (McCormick, 1999; McCormick and Hernandez, 1996). The secondary octaval population contains one to three regions, ventral, intermediate, and dorsal. Both the dorsal and ventral regions are made up of fusiform cells (McCormick, 1999). In certain teleosts (modern bony fishes), which possess ventral and dorsal fusiform cells, the cells in the dorsal region extend their dorsal dendrite into the cerebellar crest, which consists of a molecular layer of parallel fibers, whereas their ventral dendrites constitute a neuropil ventral to the fusiform somata. Interestingly, basal bony fish, such as *Amiiformes* (bowfin), apparently possess only the ventral fusiform cells (McCormick, 1999). This again illustrates the competence of the hindbrain to repeatedly generate certain neuronal populations, due to the modular organization of developmental processes that can readily be co-opted (chapter 2). It will be interesting in the future to study the underlying genetic mechanisms of this co-option and whether they involve changes in *cis*-regulatory sequences of key regulatory genes such as fibroblast growth factors to initiate these novel modules.

The concept of the developing hindbrain as a tagma bears several important implications for the auditory brainstem. First, it might help to explain why vertebrate auditory neurons can be derived from different rhombomeres albeit sharing the same transcription factor lineage such as Atoh1. These shared lineages are expected to facilitate convergent evolution, as they are likely part of conserved GRN modules to drive development of lineage-specific cellular and molecular properties such as the expression of certain potassium channels. Rhombomere-specific expression patterns of other transcription factors, signaling molecules, and cell adhesion molecules (Tümpel et al., 2009) might then confer differences such as dissimilar morphology, projections, biophysical properties, etc. onto mammalian and avian sound localization circuits (Glover, 2000; Straka and Baker, 2013). Yet, some populations of the shared transcription factor lineages might even be derived from corresponding rhombomeres as suggested by the overlapping rhombomeric origin of several mammalian and avian auditory nuclei. These populations might thus represent true homologs. Different properties across tetrapods will then reflect individualization, as observed for the mammalian serial homologs. It will therefore become important to analyze in greater detail the origin and the properties of the different neuronal populations within vertebrate auditory nuclei.

Valuable insight might also come from so-called character identity networks (Wagner, 1989, 2014b). Character identity networks act downstream of the initial GRN that triggers the development of a given character and have recently been proposed as a useful criterion for homology (Wagner, 1989, 2014b). An illustrative example is the investigation of the suggested monophyletic origin of the metazoan eye (Gehring and Ikeo, 1999). This proposal was mainly based on the discovery that the transcription factor ey, which is required for eye formation in *Drosophila* (Quiring et al., 1994), is an ortholog of Pax6, which is required for eye formation in mammals (Hill et al., 1991; Ton et al., 1991). Strikingly, ectopic expression of *ey* or of its homolog *Pax6* caused development of well-formed ectopic ommatidia, with the full complement of different types of cells and structures, at different positions in *Drosophila*, such as legs, antennae, and wings (Halder et al., 1995). Subsequent studies identified other regulatory genes such as *toy*,

eya, *so* and *dac*, the products of which interact with each other and are involved in the GRN specifying the development of the eye in the fly. Again, genes belonging to the same families are expressed in the developing eyes of vertebrates, and mutations in some of them also cause eye defects (Donner and Maas, 2004; Silver and Rebay, 2005). These data indicate an apparently conserved developmental program between the insect and vertebrate eye, hence supporting the notion that vertebrate eyes and insect eyes are homologous, despite their deep morphological dissimilarities (Gehring, 1996). However, later detailed analyses of the GRNs in fly and mouse revealed striking differences. Only few of the regulatory relationships of the genes beyond *ey/Pax6* itself are conserved between *Drosophila* and vertebrates. The mouse *Eya* genes are not downstream of *Pax6* as they are in *Drosophila*, and mutations in them do not affect eye formation. Similarly, the mouse homologs of *dac* are not required for eye morphogenesis (Davis et al., 2001, 2006) and the genetic feedback linkages by which *dac* maintains expression of *ey* and *so* in *Drosophila* are missing in the mouse (Donner and Maas, 2004; Friedrich, 2006). Thus transcription factors encoded by the same gene families are involved in eye development in vertebrates and insects, but the details of their causal links, i.e. their molecular and functional interactions, are very different. It is hence more likely that these GRNs were assembled independently during the evolution of eyes in different metazoan lineages and that metazoan eyes have in fact evolved more than once (Davidson, 2006; Wagner, 2014b; Wake et al., 2011). Thus character identity networks are not only important in understanding developmental processes, but also represent a useful tool to settle open issues concerning homologous and non-homologous structures.

Second, the tagmatic organization of the hindbrain might explain the phenomenon that rather homogeneous auditory nuclei with few different cell types, such as the mammalian MNTB can originate from more than one rhombomere (MNTB: r3 and r5 (Maricich et al., 2009)). The different rhombomeric origin might nevertheless suggest a so far unidentified heterogeneity in this nucleus. In the vestibular system, different rhombomeres contribute different functional classes to multirhombomeric nuclei (Di Bonito et al., 2013a; Kasumacic et al., 2015), and a similar observation has been made when correlating segmental origin and circuits between spinal cord and the brain (Pivetta et al., 2014). It will therefore be interesting to investigate whether the r3 and r5 derived MNTB neurons correspond to the previously reported two subgroups of the MNTB with respect to their input (Harrison and Irving, 1964). Equally important will be the dissection of the contribution of the different rhombomeres to avian auditory nuclei. As mentioned before, these nuclei show a multirhombomeric origin, in contrast to the mammalian nuclei (Cramer et al., 2000; Willaredt et al., 2015a). It will therefore be very informative to identify the cellular contribution of each rhombomere to the respective nucleus in order to compare their morphology, biophysical properties, and connections. For instance, in the nucleus laminaris, the segmental border between r5 and r6 coincides with the laminar and globular organization of the cell population, respectively (Marin and Puelles, 1995). Such approaches might provide new insights into their function, as illustrated for the vestibular system (Glover, 2000).

Third, as the transcriptional code is highly conserved within the embryonic microzones, which often extend to the spinal cord (Fig. 8B), data from other cell types of a given microzone can be used to guide research in the auditory field. Renshaw cells in the spinal cord provide an interesting example. Similar to MNTB neurons, these cells constitute a glycinergic interneuron cell type (Curtis et al., 1976). Both MNTB and Renshaw cells are derived from an $En1^{+}$ cell lineage (Renshaw cells: Sapir et al., 2004; MNTB: Jalabi et al., 2013) and express Calbindin D28k (Renshaw cell: Carr et al., 1998; MNTB Friauf, 1993). Dissection of the GRN underlying Renshaw cell specialization revealed participation of the Onecut homeobox 1 and 2 transcription factors (Stam et al., 2012). A genome-wide microarray study of the developing SOC at P0, P4, P16, and P25 identified expression of both Onecut transcriptions factors in the perinatal SOC, with a strong decline after P4 (Ehmann et al., 2013). It is noteworthy that the Onecut homeobox 1 transcription factor was among the ten transcriptions factors being significantly more highly expressed in the SOC at P4 compared to the entire brain (Ehmann et al., 2013). It will therefore be interesting to study the expression and function of these two transcription factors in the MNTB in more detail. In general, the well-studied spinal cord, with plentiful information on the sequential genetic steps involved in generating precursors and postmitotic subclasses of neurons from the different microzones (Alaynick et al., 2011; Dasen and Jessell, 2009; Goulding, 2009), provides an inspiring blueprint to investigate equivalent steps in auditory neurons.

Important information will also be gained, however, by studying evolutionary changes in components of earlier-operating GRNs such as the Hox code in the developing hindbrain. Hox transcription factors act like switches to deploy or prevent deployment of GRN sub-circuits that then set up the regulatory states required for morphogenesis of given structures. The precise position and spatial extent of a given *Hox* gene expression domain varies between different vertebrate groups. In mice, *Hoxb2* is strongly expressed in r3 to r5 and is required in the specification of the r4-derived pVCN by imposing an r4-specific identity during auditory development (Di Bonito et al., 2013b). Lack of *Hoxb2* causes an expanded expression domain of the transcription factor Atoh7 in the mouse ventral cochlear nucleus. Since Atoh7 is a marker of glutamatergic neurons of the aVCN, this result indicates that the pVCN has acquired aVCN features. Interestingly, comparative *in situ* hybridization revealed low expression of *Hoxb2* in the chicken hindbrain (Tümpel et al., 2002). This molecular difference between birds and mammals might thus contribute to the absence of a pVCN-like structure in the avian auditory brainstem. It might therefore be interesting to overexpress *Hoxb2* in the developing chicken hindbrain and analyze its consequences for auditory brainstem structures. A similar approach was previously used to study the role of Hoxd1 in species-specific features of nociceptor circuits that differ in their axonal projection pattern between mouse and chicken (Guo et al., 2011). *Hoxd1* shows a mammalian-specific expression in this circuit and its ectopic expression in chicken induced the development of mammalian-like features of nociceptive neuronal circuits (Guo et al., 2011).

It may also be rewarding to compare in more detail the GRNs between lampreys and mammals. Lampreys display a regulatory network in the hindbrain comprising a Hox code and transcription factors such as Krox20 and MafB, which thus resemble those operating in jawed vertebrates (Parker et al., 2014), including the mammalian auditory brainstem (Willaredt et al., 2015a). Lampreys furthermore already have an octavolateral system with electroreception and a lateral line (Bodznick and Northcutt, 1981). Yet they lack cochlear nuclei and do not respond to sounds. Changes in GRNs between lampreys and tetrapods might therefore be informative concerning the evolution of the auditory system (Straka et al., 2014). The rhombic lip of lamprey, for instance, does not express Pax6, which is expressed in jawed vertebrates (Murakami et al., 2005).

10. Conclusion

Genetic and physiological evidence indicate that major projection neurons of mammalian circuits for sound localization represent serial homologs. This parsimonious evolutionary mechanism might have accelerated the emergence of neuronal

populations that elucidate the localization of sound sources in all three dimensions. It is abundantly clear that mechanistically, the formation of biological structures is the outcome of progressive, spatial regulatory state patterning controlled by specific GRNs and that rewiring these regulatory circuitries will introduce changes during evolution. Therefore, further investigations into these GRNs are required to precisely determine the order of the emergence of these serial homologs. Comparative analysis of these GRNs will also provide important insights into the evolutionary relationship of sound localization circuits across vertebrate groups. Analyses in fish, chicken and mammals already provided intriguing insights into conserved as well as divergent processes in generating vertebrate auditory neurons. Furthermore, they clearly demonstrate the feasibility of tackling the evolution of central auditory brainstem structures on a molecular and developmental level across different vertebrate species. This will allow the study of evolutionary processes in the auditory system on different time scales. Birds and mammals diverged about 300 million years ago (Erwin et al., 2011), whereas monotrema and theria split roughly 190 million years ago (Phillips et al., 2009). Finally, the house mouse and the gerbil, which are important models for HF and LF hearing eutherian animals, respectively, diverged only 21 million years ago (Steppan et al., 2004). The auditory system thus represents an attractive and valuable model in the field of evolutionary developmental biology.

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