

—Review—

Review Series: Frontiers of Model Animals for Neuroscience

Songbird: a unique animal model for studying the molecular basis of disorders of vocal development and communication

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Abstract: Like humans, songbirds are one of the few animal groups that learn vocalization. Vocal learning requires coordination of auditory input and vocal output using auditory feedback to guide one's own vocalizations during a specific developmental stage known as the critical period. Songbirds are good animal models for understand the neural basis of vocal learning, a complex form of imitation, because they have many parallels to humans with regard to the features of vocal behavior and neural circuits dedicated to vocal learning. In this review, we will summarize the behavioral, neural, and genetic traits of birdsong. We will also discuss how studies of birdsong can help us understand how the development of neural circuits for vocal learning and production is driven by sensory input (auditory information) and motor output (vocalization).

Key words: auditory feedback, basal ganglia-cortical circuit, deafening, motor circuit, sensorimotor learning

Introduction

Many animal species communicate by vocalization. Although the vocalizations of most animal species constitute their innate behavior, some animal groups, such as mammals (humans, cetaceans, bats, elephants, and pinnipeds) and birds (oscine songbirds, parrots, and hummingbirds) develop a complex vocal pattern through vocal learning [23, 24]. The songbird is an attractive animal model for understanding the mechanisms underlying vocal learning because non-human primates and rodents have a limited ability to modify their vocalization [39]. There are approximately 3,500 songbird species all over the world, and their birdsong shows a readily quantifiable species-specific variation, ideal to investigate the

developmental changes of acoustic and sequential song structure (Fig. 1). Some species of birds such as the zebra finch and canary are easily bred under laboratory conditions [48]. These features mean that studies of songbirds can provide excellent insights into the evolution, function, development, and mechanisms of vocal learning. Here we review vocal learning in songbirds, with particular focus on auditory input as a developmental epigenetic factor of vocal development. First, we highlight the parallels between human speech and birdsong and introduce the neural mechanisms involved in vocal production and learning. We then provide an overview of the contribution of auditory input during vocal development and maintenance.

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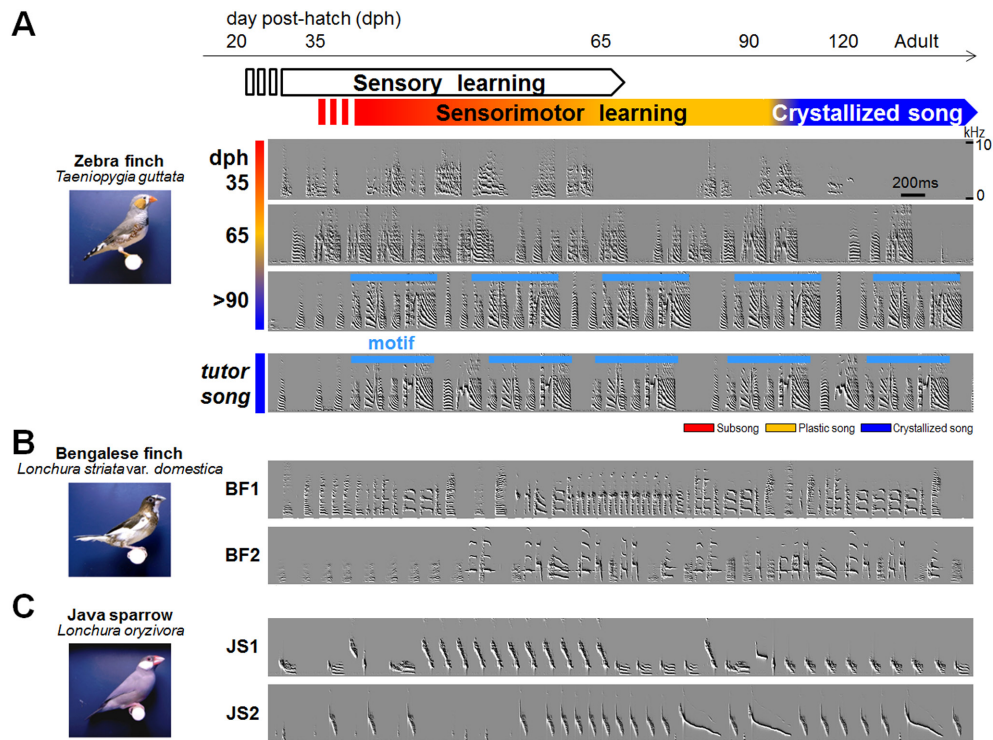


Fig. 1. Song learning and species differences in song pattern. (A) Examples of song development in a zebra finch. The zebra finch is known as a closed-ended learner, meaning that once a stable species-specific song pattern “motif” is developed, the song structure remains unchanged throughout life [8, 22, 74]. This stereotypy of crystallized song enables precise quantification of the similarities and differences in vocal development and song patterns between experiments, allowing for examination of genetic and epigenetic factors that contribute to the acquisition and maintenance of complex vocal patterns. (B, C) Examples of adult song patterns of two Bengalese finches (B) and two Java sparrows (C).

Human Speech and Birdsong

Although birds and mammals diverged from a common ancestor approximately three hundred million years ago [25], birdsong broadly possesses three behavioral traits similar to that of human speech [7].

First, sensory and sensorimotor learning is crucial for the development of both the birdsong and human speech [7]. Sensory learning is the initial phase. Animals listen to and memorize conspecific adult vocalization as their template (Fig. 1A). The sensorimotor learning follows, and animals start vocalizing, gradually matching their vocalization to the memorized template (Fig. 1A). At the early stage of sensorimotor learning, fledgling juvenile songbirds produce unstructured sounds. These sounds are referred to as subsong. The subsong is similar to the babbling vocalization of human infants [4]. Juveniles compare these sounds with the memorized template and achieve vocal imitation through a process of trial-and-error vocal-

izations using auditory feedback (Fig. 1A). Thus, this reliance on tutor experience and auditory feedback means that birds raised in complete social and acoustic isolation will develop abnormal song (Figs. 2B and C) [33, 40].

Second, learned vocalizations consist of a complex motor sequence, quantifiable at the phonological and syntactical levels in both songbirds and humans. Although the human speech and birdsong share common features and their vocal patterns are defined as ordered strings of sounds, they are different in a critical character. Human speech has the flexible capacity to convey meaning associated with distinct sound (phonology) and word (syntax) order, while songbirds use their songs for territorial advertisement and for mate attraction, just conveying the information about the individual identity of the bird to receivers [42].

Third, vocal learning occurs within a critical period, usually at the early developmental stage before adulthood. Both songbirds and humans are unable to learn

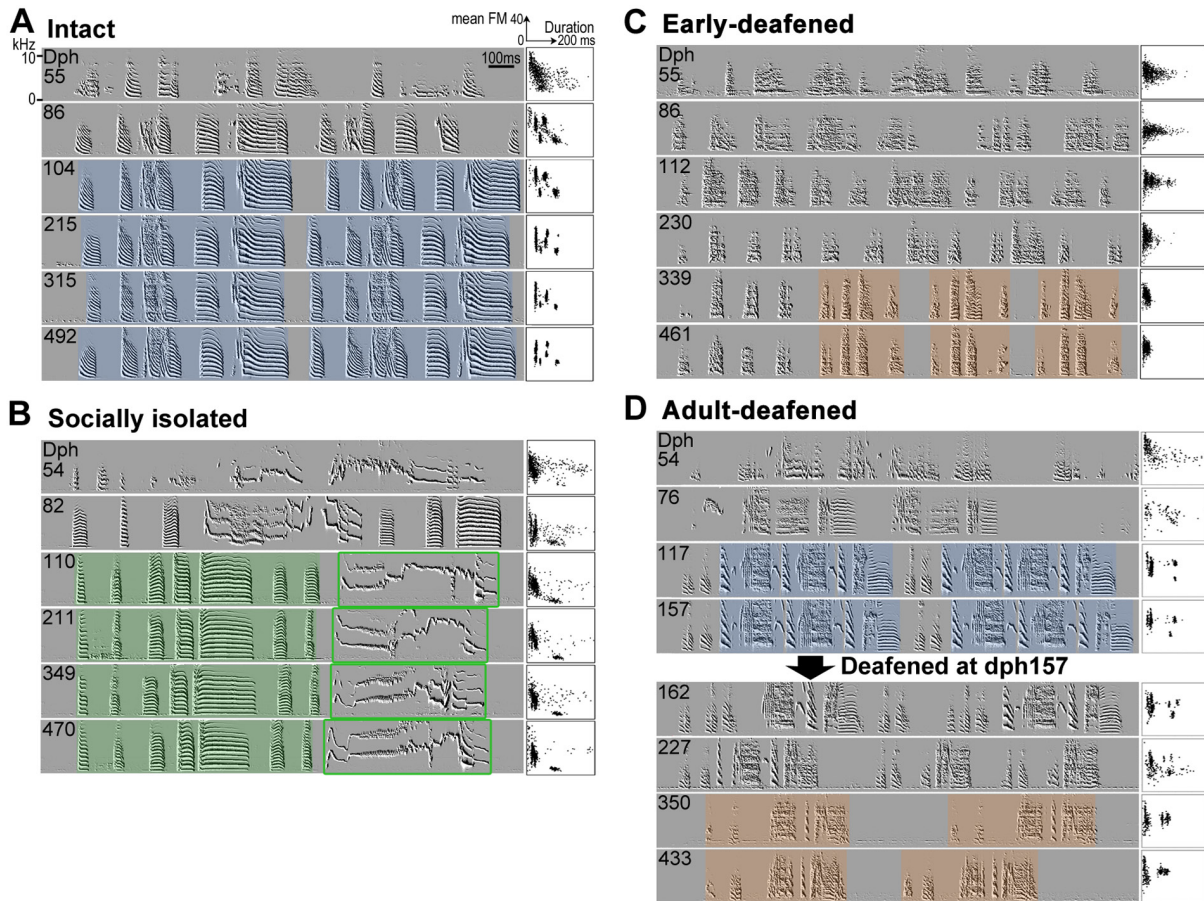


Fig. 2. Examples of song development and syllable scatter plots [duration versus mean frequency modulation (FM)] in an intact, a socially isolated, an early-deafened, and an adult-deafened bird. (A, B) Colored portions (blue and green) highlight stable song motifs. The intact and socially isolated birds exhibited song stability around dph 110. The crystallized song pattern of the socially isolated bird is similar to that of the intact (normal) bird, except for a prolonged and variable syllable (green bracket). (C) Orange shading highlights stable song motifs. (D) Song before and after adult deafening. Blue shading indicates crystallized motifs, which developed at dph 100–150.

vocalization equally well throughout their life. Although it is critical that humans and birds are provided with appropriate auditory and social conditions during the critical period to achieve vocal learning, they are different with regard to the following point: humans are able to learn new words and languages throughout their life. Some species of songbirds categorized as closed-ended vocal learners, e.g., the zebra finch and Bengalese finch, which are commonly used in research, are unable to learn new songs at the adult stage, while others categorized as open-ended vocal learners, e.g., the canary, have the ability to imitate new sounds to some extent as adults. Neurogenesis in the adult avian brain was first reported in canaries [14]. This neurogenesis allows for replacement of old neurons with new ones and results in a sea-

sonal fluctuation in the neuron number that correlates with the capacity of song plasticity [30].

As outlined above, birdsong shares numerous behavioral traits with human speech. In contrast, with regard to their vocal organs and respiratory systems, there are subtle differences in the functional morphology [56]. Birds generate sound using an organ named the syrinx, which is part of the respiratory system, whereas humans generate sound using the larynx, which contains the vocal folds. However, the basic mechanism underlying sound generation in birds shows strong analogies to the human source-filter mechanism. In both the cases, vocalizations are generated by airflow-induced oscillation of the vocal folds in the human larynx and elements in the wall of the syrinx, followed by filtering and tuning

of sound by the upper airway. To generate vocal sounds, the components of the peripheral vocal system, such as respiration organs, vocal organs and vocal tract structures require to be precisely coordinated through the neural control of a number of different muscles [65]. The following text elaborates on the neural substrates involved in vocal development and how they contribute to this process.

Neural Substrates of Vocal Learning and Production

In vertebrates such as mammals and birds, the central nervous system is divided into five basic regions: the hindbrain, the midbrain, the thalamus, the cerebellum, and the cerebrum. Across vertebrate species, there is similar structural organization throughout most of these five brain regions, except the cerebrum. In birds, the cerebrum is organized into large cell clusters; on the other hand, in mammals, the cerebrum is divided into subcortical nuclei, such as the basal ganglia, and the cerebral cortex, which consists of six main layers. However, recent studies have indicated that the avian striatal and pallidal domains are well conserved in relation to their counterparts in the cerebrum of mammals (Fig. 3) [25, 26]. Both humans and songbirds have specific brain regions involved in vocal learning and production. Humans have a specialized circuit that forms a network of brain areas (including Broca's area and temporal areas) devoted to speech perception and production. Syntax-related networks are reported to exist in the opercular/triangular parts of left inferior frontal gyrus and the left lateral premotor cortex [29]. In addition, the basal ganglia are considered to be involved in prosodic modulation and language acquisition [1, 12]. Several studies have indicated that compared with the native language the basal ganglia showed different activity during speech production and syntactic processing of a second language [11, 31]. The basal ganglia are engaged in language learning in adults. The identity and function of the neural networks contributing to vocalization have been particularly well studied in songbirds through a variety of neurophysiological and molecular biology methods.

The brain areas associated with song learning and production, the song nuclei, are organized into two major circuits: the posterior vocal motor circuit and the anterior basal ganglia–forebrain circuit (Figs. 3A and C). The vocal motor circuit is involved in the generation of

vocal patterns through a hierarchical process of regulation of syllable sequence and acoustic features [17, 73]. Furthermore, the premotor HVC nucleus is the only song system nucleus that receives direct projections from auditory areas [5], and it has a crucial role in encoding the experience of the tutor song [58]. Mirror neurons have been reported in HVC of some songbirds [13, 53] such as the swamp sparrow and Bengalese finches. These neurons display a precise form of vocal–auditory mirroring in analogy to the motor–visual ones found in human and nonhuman primate cortical motor areas. This form of sensorimotor correspondence is considered to be important for vocal learning and communication [44]. In contrast, the basal ganglia–forebrain circuit in both humans and songbirds is involved in motor and cognitive processes, such as control of vocal movements and reinforcement-based learning. In songbirds, this circuit plays a crucial role in song learning by supporting vocal exploration with direct premotor bias in response to the vocal experience [3, 6, 27, 61], and it also maintains learned vocalizations using auditory feedback. Variability in the sequence and structure of syllables is reduced by the presence of a female [27]. Physiological studies have indicated that this context-dependent change in song variability is accompanied by changes in singing-related neural activity within cortical nucleus LMAN [27, 60]. A recent study also revealed that the basal ganglia nucleus Area X is essential for singing-related patterned burst firing of LMAN, which is critical for vocal plasticity and adjustment in response to auditory feedback [32]. Together, these two premotor circuits are believed to produce vocalizations at different stages of song development. The poorly structured subsong, akin to human babbling, is driven primarily by the basal ganglia–forebrain circuit, whereas the adult song is highly stereotyped and is driven primarily by the motor circuit. Transferring control of song from the basal ganglia–forebrain circuit to the motor circuit is crucial for regulating vocal plasticity and stabilization [9].

Human speech and birdsong result from the development of specialized brain regions for vocal learning and production, which develop through interaction between genetic and environmental factors. However, little is known about the genetic mechanisms underlying vocal development. Overcoming this problem requires an appropriate model system whose genomic information has been well understood and in which genetic manipulation can be performed. For example, *FoxP2*, a Forkhead box

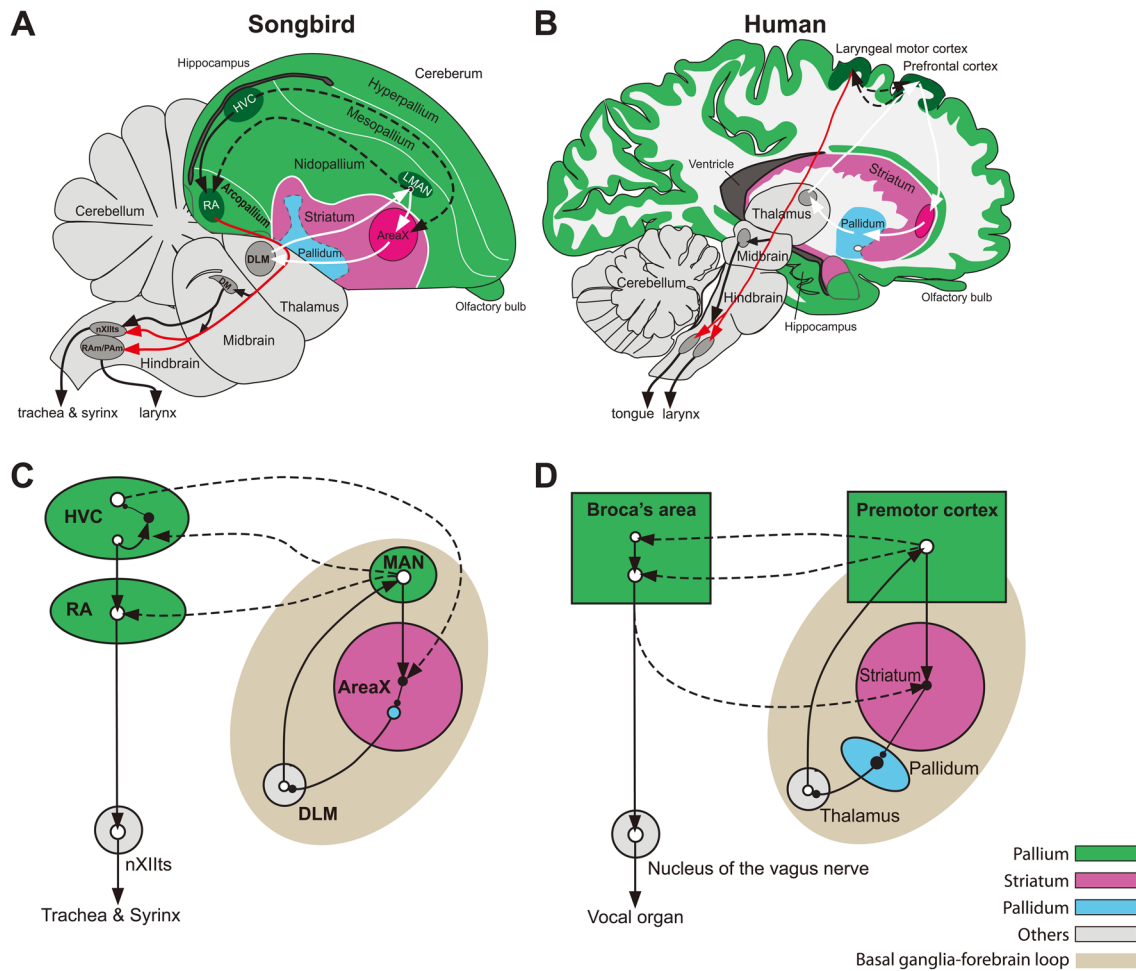


Fig. 3. Schematic diagrams of the brain areas involved in vocal learning and production. (modified from Horita and Wada, 2011 [20], and Pfenning *et al.*, 2014 [50]). (A, B) Upper drawings illustrate a brain section from a male zebra finch (A) and a human (B). Solid black arrows denote connections within the posterior vocal motor circuit (from HVC to RA to brainstem motor nuclei). White arrows denote connections within the basal ganglia–forebrain circuit. Dashed black arrows denote connections between the two circuits. Red arrows show the direct connections found only in vocal learners, which project from vocal motor cortex regions to brain stem vocal motor neurons. (C, D) Lower drawings illustrate comparative and simplified connectivity of anterior and posterior vocal circuits in a songbird (C) and a human (D). DLM: dorsal lateral medial nucleus of the thalamus, DM: dorsal medial nucleus of the midbrain, HVC: a vocal nucleus (no acronym), LMAN: lateral MAN, MAN: magnocellular nucleus of the anterior nidopallium, nXIIts: twelfth nucleus, tracheosyringeal part, RA: robust nucleus of the arcopallium, Ram/Pam: nucleus retroambiguus/parambiguus.

family gene that encodes a transcription factor, has been reported as the gene underlying a human developmental language impairment caused by structural abnormalities in the striatum, cerebellum, and cortex [35, 69]. Similarly, in songbirds, *FoxP2* is expressed strongly in the striatum and is regulated during vocal development [15, 66]. Knockdown of *FoxP2* in the songbird striatum impairs song learning, decreases spine density of striatal spiny neurons, and disrupts the control of vocal variability by interfering with dopamine-dependent modula-

tion [16, 62]. Other genes relevant to speech and other human language disorders have been reported to be differentially expressed in the song nuclei of songbirds [18], and investigation and manipulation of these genes has become possible following the sequencing of the zebra finch genome [72] and through use of transgenesis and viral transfection [2, 16, 43]. In addition, targeting of viral vectors to specific brain regions using microinjections can be used to regulate gene expression with temporal and spatial precision in order to analyze the func-

tion of genes, cells, and circuits [57, 58, 68].

In addition to these genetic contributors, developmental factors that influence epigenetics, such as social interaction [34] and nutrition [47], are also important in the development of vocalization and the brain regions that support it. Dysfunction of motor and auditory ability causes speech disorders, such as aphasia and stuttering. Aphasia usually results from a stroke, brain tumor, or head injury. Studies of vocal deficits by lesions to song nuclei provide us with an animal model of aphasia. For instance, an adult zebra finch becomes unable to produce a learned vocal pattern after HVC lesions [4, 63, 67]. Stuttering is the most common disorder of speech motor control in young children who are developing speech [52]. The incidence of stuttering is higher in males than in females. Stuttering is resolved by adulthood in nearly 80% of children with developmental stuttering. Twin studies have reported substantial genetic and epigenetic effects on stuttering [10, 55]. However, the neurobiological basis of this disorder is poorly understood despite recent progress in uncovering its genetic roots. From a comparative point of view, song syllable repetitions of the zebra finch resemble part-word repetitions, a common feature of stuttering [18]. Song syllable repetitions can be induced by delays or disruptions in auditory feedback during vocalization [19, 36], similar to those that can occur in humans [21]. Furthermore, auditory input is crucial for the acquisition of birdsong and human speech and can influence epigenetic factors contributing to sensorimotor learning [33, 59].

Audition for Vocal Learning and Maintenance

Audition provides important information for vocal learning, both for learning templates and for evaluation of one's own vocal output. Auditory feedback also plays an important role in maintaining stable vocal output in adulthood [19, 36, 38, 46].

When songbirds are deprived of auditory input before the sensory learning phase of song, they do not develop normal songs (Fig. 2C) [33], similar to individuals with hearing loss that have difficulty developing normal speech patterns. However, audition-deprived songbirds can still develop a certain degree of species-specific song [41, 54] and crystallize vocal patterns, though they are noisy and amorphous (Fig. 2C) [45]. In motor circuit

nuclei, developmental gene expression is found to be conserved in an age-dependent manner even in deafened birds [45], indicating audition-independent robustness of gene expression dynamics during vocal development in the song system. Although auditory information is crucial for song development, auditory input is not the main driver of developmental gene expression dynamics in motor circuit nuclei.

In adult humans and songbirds, disruption of auditory feedback causes gradual deterioration in learned vocalization (Fig. 2D) [19, 46, 71], and the rate of deterioration depends on age [38]. When deprived of auditory feedback, deterioration of vocal patterns is much more severe at a younger age, and deterioration takes longer at an older age. Delays or disruptions in auditory feedback during vocalization result in stuttering, deletions, and distortion of syllables [19, 36]. Furthermore, birds exhibit the capacity to adjust pitch according to perceived errors in vocal production [64], and the speed and extent of vocal error correction decreases markedly with age [28]. The vocal variability necessary for audition-dependent song plasticity is generated by the basal ganglia–forebrain circuit [3, 27, 49]. However, expression of the molecular markers of neural activity-dependent gene induction [dual specificity phosphatase 1 (*Dusp1*), *c-fos*, and *Arc*] is similar throughout development in the nuclei of the basal ganglia–forebrain circuit [45]. This suggests that molecular signaling cascades are consistently regulated regardless of age in the basal ganglia–forebrain circuit related to vocal learning and maintenance. Therefore, during vocal learning, inherited genetic programs contribute to vocal development and auditory-dependent vocal plasticity, which are directly or indirectly regulated by age or activation of vocalization (motor)-dependent epigenetic factors.

Conclusions and Future Directions

Vocal learning is an ability shared by both songbirds and humans. It is a complex form of sensorimotor learning that requires coordination of sensory input and motor output to guide one's own vocalization. Complex learned vocalization is shaped by both genetic and environmental factors during development.

Hearing impairment and developmental disabilities lead to deficits in acquired vocal patterns and maintenance during vocal development, including speech disorders, such as aphasias, and stuttering. Songbirds that

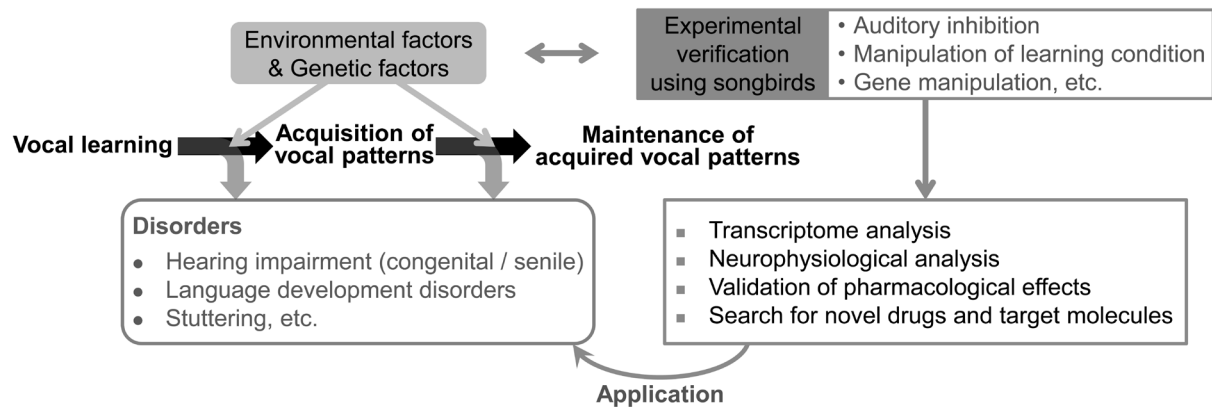


Fig. 4. A schematic highlighting the use of songbirds as a research model for disorders of vocal development and communication.

have had auditory input disrupted are useful animal models for understanding how hearing impairment affects the development of brain regions for vocal learning and production (Fig. 4).

As we have described, audition-independent robustness of gene expression is present in the songbird motor circuit, which indicates that volitional vocalization itself may have a crucial influence on epigenetic factors that activate the genetic programs necessary for regulating vocal plasticity and development of vocal patterns. In fact, a large set of neural plasticity-related genes are regulated by singing in song nuclei [37, 51, 70]. Although variability in the accuracy of syllable/word structures in human children and adults with hearing impairments has been observed, little is known about the neural basis of the variability. Language outcomes may vary by the overall hearing level, age of onset of hearing loss, and therapeutic interventions, such as hearing aids or cochlear implants. In addition, vocal development may rely not only on how good one's hearing is but also how much vocalization they produce. This suggests that interventions, such as hearing aids or cochlear implant, performed at an early stage of word production may have a more positive effect on language development in children with congenital hearing impairment.

Studies on birdsong using behavioral manipulation and genetic and neurophysiological tools have shed light on the specialized neural networks that underlie vocal learning. Further research is needed to understand how auditory input, motor activity, and aging affect the development of brain areas involved in vocal learning and production.

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