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Network dynamics underlie learning and performance of birdsong

Richard Bertram[1], Richard L Hyson[2], Amanda J Brunick[2], Diana Flores[1] and Frank Johnson[2]

Understanding the sensorimotor control of the endless variety of human speech patterns stands as one of the apex problems in neuroscience. The capacity to learn – through imitation – to rapidly sequence vocal sounds in meaningful patterns is clearly one of the most derived of human behavioral traits. Selection pressure produced an analogous capacity in numerous species of vocal-learning birds, and due to an increasing appreciation for the cognitive and computational flexibility of avian cortex and basal ganglia, a general understanding of the forebrain network that supports the learning and production of birdsong is beginning to emerge. Here, we review recent advances in experimental studies of the zebra finch (*Taeniopygia guttata*), which offer new insights into the network dynamics that support this surprising analogue of human speech learning and production.

Addresses

[1] Department of Mathematics, Program in Neuroscience, Florida State University, Tallahassee, FL 32306-4510, United States

[2] Department of Psychology, Program in Neuroscience, Florida State University, Tallahassee, FL 32306-4301, United States

Corresponding author: Johnson, Frank (johnson@psy.fsu.edu)

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Serial order in behavior – the ability to link several distinct motor gestures to produce a purposeful sequence of behavior – is perhaps best exemplified by human speech. For example, if you read this sentence aloud your vocal tract will effortlessly transition through a sequence of distinct motor configurations on a millisecond time scale. How the human brain accomplishes such feats remains largely unknown. However, by harnessing the unique behavioral and neural features of song learning by the zebra finch, several underlying principles are beginning to emerge. Notable parallels to human speech include: **1.)** a brain and vocal tract that are the result of selection pressure to hear and produce rapid sequences of vocal sounds; **2.)** a dedicated forebrain network that supports auditory processing and motor sequencing of learned vocal sounds; **3.)** the origins of adult vocal patterns are found in developmental sensitive periods for auditory learning and sensorimotor learning.

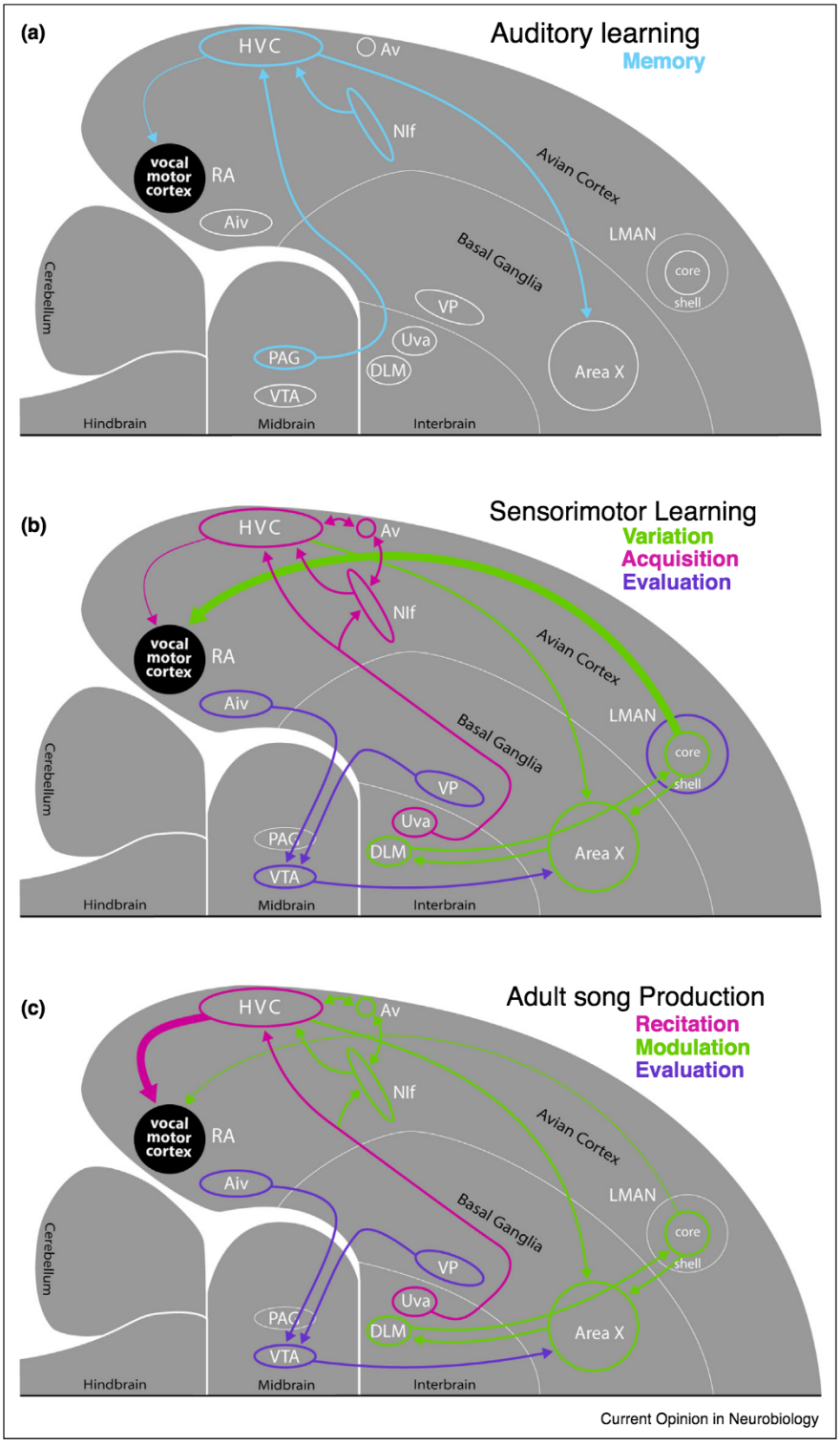
Auditory learning in a 'motor' pathway

Although only male zebra finches learn to produce song, juveniles of both sexes experience auditory learning, forming an auditory memory of the song of the adult male 'tutor' that raises them. For juvenile males, the auditory memory of tutor song serves as an internal reference – accessed via auditory feedback – to guide the sensorimotor learning of song. To understand how auditory memory is encoded, a first step is to characterize the neural loci and pathways involved in memory formation.

While much work has focused on the formation of juvenile auditory memories within higher portions of the ascending auditory stream (reviewed in Ref. [1••]), recent evidence suggests that a juvenile auditory memory of tutor song also forms within HVC, a premotor region long known to direct song production in adults (see Figure 1a, all acronyms defined in Figure 1 legend). Briefly, the formation of an auditory memory can be blocked by targeting HVC with pharmacological or optogenetic manipulations, but only when these manipulations coincide with exposure to a tutor song [2]. So too when manipulations target cortical (NIf) or dopaminergic (PAG) input to HVC [2,3], but not when manipulations target avian auditory cortex, Field L [2]. An important role for the NIf-HVC pathway is further demonstrated by 'optogenetic tutoring' of juvenile males by stimulating NIf input to HVC with patterned light [4].

Formation of an auditory memory of tutor song within HVC appears to involve both synaptic and non-synaptic plasticity. Here, note that HVC is a mosaic of at least 4 cell populations – interneurons, and distinct populations that project to Av (association cortex), RA (vocal motor cortex), and Area X (basal ganglia). Exposure to a tutor song stabilizes HVC spine turnover [5], shifts the balance of HVC inhibitory and excitatory synapses [6], and exerts intriguing effects on the intrinsic physiology of HVC neurons [7]. That is, exposure to tutor song promotes creation of transient 'juvenile-typical' intrinsic physiology in HVC neurons [8], whereas tutor deprivation results in

Figure 1



Sagittal/horizontal views of selected brain regions and pathways that underlie the learning and performance of zebra finch song. Compared to mammals, note that the avian forebrain possesses a distinct and arguably more 'flight-worthy' (weight and space efficient) organization. Avian cortex eschews lamination in favor of modularity, permitting a greater density of neurons per unit of enclosed volume [69••] and supporting cognitive and computational functions that rival or exceed those of much larger primate brains [70]. **(a)** Selected brain regions and pathways involved in the juvenile formation of an auditory memory of an adult tutor song. For clarity, ascending auditory pathways – where there is also evidence of auditory memory formation [1••] – and descending vocal-motor pathways are not shown. **(b)** During sensorimotor learning, distinct

premature adult-like phenotypes [7]. Unlike the slower-developing efferent connectivity of HVC-RA neurons, HVC-X neurons establish robust connectivity with the basal ganglia before auditory learning [9]. Given the key role of the basal ganglia in sensorimotor learning (see below), HVC-X neurons seem an attractive candidate for encoding or conveying a memory of tutor song.

Do female zebra finches also form auditory memories in HVC? Although they do not sing, psychophysical evidence indicates that juvenile female zebra finches form an auditory memory of tutor song [10,11]. Despite evidence that HVC plays a role in song perception in females of other songbird species [12,13], HVC in female zebra finches has received modest experimental attention as it was initially believed to be vestigial, lacking male-typical network connectivity. However, we recently demonstrated that female zebra finches possess a fully networked HVC [14] and preliminary data show that female HVC neurons have intrinsic physiological properties that are quite similar to those of males. For example, HVC-X neurons respond to depolarizing current with tonic spiking, while HVC-RA neurons typically respond with one or a few spikes (Figure 2). These similarities suggest a conserved function between sexes and, since the females do not sing, one possibility is that HVC may also be a site of auditory memory formation in female zebra finches. These findings, however, say nothing about the local synaptic connectivity of female HVC neurons, or the behavioral function of the female network, which could be quite different from that of males [15,16].

Sensorimotor learning – distinct neural pathways for variation, acquisition, and evaluation of song

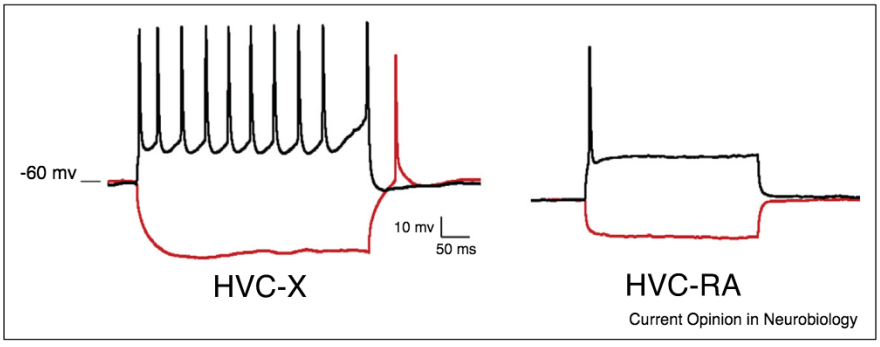
Three behavioral stages characterize sensorimotor learning in males – subsong, plastic song, and crystallized adult song. Figure 1b shows the configuration of the network at the onset of juvenile subsong, when the activity of vocal motor cortex (RA) is dominated by input from the Anterior Forebrain Pathway (AFP, green). AFP premotor activity, conveyed to RA from $LMAN^{core}$, results in rambling vocal sequences that resemble infant babbling [17]. By driving the vocal organ throughout its dynamic range, subsong may act as a calibration step, allowing the juvenile bird to form associations between different vocal gestures and different sounds. Recent work suggests that the unpatterned acoustic structure of subsong is regulated by Area X of the avian basal ganglia [18,19], where activity is modulated by descending input from HVC and LMAN and ascending dopaminergic input from the midbrain. Note that ablation of either LMAN or Area X in juveniles disrupts sensorimotor learning [20,21].

Rudiments of the tutor song first appear during plastic song, often beginning with repetitions of a single syllable [22]. Plastic song reflects the growing influence of a second premotor pathway (magenta in Figure 1b) that culminates in HVC input to vocal motor cortex. Multiple sources of afferent input to HVC, organized in a fascinating orthogonal topography [23], influence the motor acquisition of song by HVC. Among these inputs to HVC, thalamic input (Uva) drives HVC premotor activity [24•] and ablation evidence shows the importance of NIf [25,26], Av [27], and MMAN [28] for sensorimotor learning (for clarity MMAN input to HVC not shown in Figure 1). As sensorimotor learning unfolds, vocal output is shaped by the combined activity of the two premotor inputs to RA – HVC and LMAN [29]. However, as HVC influence grows, due in part to the addition of HVC-RA neurons via neurogenesis [30], $LMAN^{core}$ influence on vocal motor cortex diminishes, but does not completely extinguish, as crystallized adult song is achieved (compare Figure 1b and c and see Ref. [31]).

A longstanding question is how the juvenile zebra finch brain evaluates and shapes vocal output toward a facsimile of the tutor song. Although two distinct premotor pathways control vocal output during sensorimotor learning [29], recent data suggest that only one – the AFP – is targeted by brain regions that evaluate the developing song pattern (purple in Figure 1b). In this regard, AFP function in zebra finches supports the broad consensus that midbrain dopaminergic input to the mammalian basal ganglia is critical for goal-directed learning. To summarize work across multiple laboratories, dopaminergic (VTA) input to Area X of the avian basal ganglia, possibly acting on D1 receptors located on Area X interneurons, influences that ability of auditory feedback to guide adaptive changes in vocal output [32,33,34,35,36,37]. Further evidence of mammal-bird homology comes in the form of basal ganglia expression of members of the FoxP family, transcription factors essential for human speech development [38]. Area X expression of FoxP genes also influences zebra finch sensorimotor learning [39••,40••].

brain regions and pathways drive juvenile vocal variation and exploration, vocal acquisition of a facsimile of the tutor song, and feedback-based evaluation. **(c)** Adult recitation of song requires a small subset of the brain regions and pathways necessary to learn song. Interestingly, many of the regions and pathways involved in juvenile sensorimotor learning retain the ability to evaluate and modulate the fine spectral-temporal structure of adult song (see text for additional details). Brain Region Acronyms: **Aiv** – ventral intermediate Arcopallium; **Area X** – Area X of the avian basal ganglia; **Av** – nucleus Avalanche; **DLM** – Dorsal Lateral nucleus of the Medial thalamus; **HVC** – acronym is name; **LMAN** – Lateral Magnocellular nucleus of the Anterior Nidopallium; **MMAN** – Medial Magnocellular nucleus of the Anterior Nidopallium; **NIf** – Nucleus Interfacialis; **PAG** – Periaqueductal Gray; **RA** – Robust nucleus of the Arcopallium; **Uva** – nucleus Uvaeformis, **VP** – Ventral Pallidum; **VTA** – Ventral Tegmental Area.

Figure 2



Physiological phenotypes of HVC projection neurons in adult female zebra finches. HVC projection neurons in adult males have distinct physiological phenotypes [7,8] and this is true for adult female HVC neurons as well. Those projecting to Area X (identified by prior injection of a retrograde tracer) tend to show multiple spikes in response to depolarizing current injection and a subtle 'sag' in response to hyperpolarizing current injection. They also tend to have a depolarization after release from hyperpolarizing current that sometimes results in a rebound action potential. Putative RA-projecting cells, contrastingly, often show a limited number of action potentials in response to depolarizing currents and no sag or rebound in response to hyperpolarizing currents.

Two regions, Aiv and VP, appear to control performance-based dopamine release in Area X via opposing glutaminergic and GABAergic inputs to VTA, respectively [41••,42••]. Juvenile ablation of either region disrupts sensorimotor learning [42••,43,44]. Interestingly, it appears that the integrated activity of Aiv and VP may 'guardrail' (constrain and shape) AFP premotor activity in the direction of the target song. That is, the pitch of a syllable will be moved away from an 'error' or toward a 'correct' production depending on whether the Aiv or VP input to VTA is activated [41••,42••]. It should be noted that these conclusions are based on studies of adult birds and it remains to be seen whether the circuits needed for adult birds to shift the pitch of a previously learned syllable are the only ones used for developmental learning of song. For example, a third region, $LMAN^{shell}$, which surrounds $LMAN^{core}$, shows differential auditory responses to tutor song versus a juvenile bird's own developing song that gradually dissipate as song is learned, potentially reflecting an ongoing consolidation of progress made toward a facsimile of the tutor song [45].

Although important questions remain – such as how HVC acquires the song [46] when performance-based feedback appears to be directed toward Area X – studies of zebra finch sensorimotor learning have already revealed the deep conservation of basal ganglia function across vertebrate species. In demonstrating the conserved function of the FoxP family of transcription factors in human and zebra finch vocal development [39••,40••] and by fulfilling predictions of actor-critic models of mammalian basal ganglia function [41••,42••] this work marks an important step toward a general understanding of vertebrate brain function.

Adult song – a small portion of the forebrain network required to learn song is needed to recite it

The adult songs of male zebra finches contain 3–5 spectrally distinct syllables produced in a serial order. Songs are produced several hundred times per day in a variety of social settings, the most salient being female-directed singing for the purpose of courtship. One of the fascinating aspects of adult song is that only a small portion of the forebrain sensorimotor network needed to learn the song pattern is required to recite it (magenta in Figure 1c). Remarkably, recent work suggests that this extends to the cell populations that comprise HVC itself. HVC-X neurons, essential for juvenile song learning, can be selectively ablated in adult birds without affecting recitation of song [47,48]. This is not to say that the other portions of the network (green and purple in Figure 1c) have no effect on adult vocal production, but these effects are fine spectral-temporal modulations of the vocal pattern, brought about by operant means (as in Refs. [27,32,41••,42••]) or by presentation of a female zebra finch (as in Ref. [49]). In the case of NIf and Av, note that these sources of HVC afferent input, critical for the juvenile acquisition of song (Figure 1b), retain a modulatory role during the recitation of adult song (Figure 1c).

Interestingly, the vocal influence of the AFP (green in Figure 1c) can also be 'awakened' under the condition of adult deafness. As in adult human speech, auditory feedback is required for maintenance of the adult song. In zebra finches, this occurs because auditory feedback maintains the functional dominance of HVC over LMAN in the control of vocal motor cortex (reviewed in Ref. [31]). Deafness results in the increasing influence of variable premotor input from LMAN, impairing the

ability to recite the learned song in a structured manner [50] even as HVC premotor activity remains largely unchanged [51•].

Given the limited forebrain architecture needed to recite adult song – for clarity Figure 1 does not show the descending pathways from vocal motor cortex nor ascending pathways to Uva – theories for the neural circuitry that encodes adult song have focused on HVC, where chains of interconnected HVC-RA neurons, so-called 'synfire' chains, are thought to control the timing and serial ordering of song syllables. Recent anatomical work helps constrain these theories, showing a highly modular HVC architecture, with individual modules defined by isolated patterns of extrinsic and intrinsic connectivity [23,52]. However, some HVC neurons show expansive intrinsic axon collaterals that could coordinate activity across individual modules [52]. Because HVC-X neurons are not needed to recite the adult song [47,48], attention has focused on elucidating the connectivity between HVC-RA neurons, revealing extensive connectivity among HVC-RA neurons via synaptic connections at distal dendrites, supporting the plausibility of HVC-RA synfire chains [53]. Such chains could provide syllable timing control housed entirely within HVC [54], or they could be supplemented by ascending timing input from Uva [55,56•]. Evidence that cooling HVC lengthens song syllables more than the gaps between syllables [57] motivated a model in which HVC chains code for syllables and gaps separately [58]. In addition, recent data showing independent learning of syllable phonology and syllable sequence [59], different vocal deficits following partial ablations of medial versus lateral HVC [60], and distinct populations of HVC-RA neurons that respond at characteristic moments before, during, and after song [61] support a functional heterogeneity across multiple HVC-RA chains [58].

Not all circuit models assume HVC-RA synfire chains, however. One model suggests that HVC-RA activity is propagated via functional syllable units, which do not require direct HVC-RA to HVC-RA coupling [62]. Another suggests that each HVC-RA neuron excites the next through a brainstem loop [56•], and yet another proposes that HVC projection neurons code only for vocal-gesture trajectory extrema and are not the basis of song timing [63]. These last two models are hard to reconcile with data showing that the population of HVC-RA neurons is continuously active throughout the song [64•,65•].

A different question, how stereotyped syllable production can persist in the face of variable premotor firing patterns [66,67], was recently addressed through neural network simulations [68]. This study demonstrated that firing variability increases the ability of the neural system to adjust to intrinsic perturbations such as HVC neuron death and replacement as well as environmental perturbations, with only minimal reduction in the accuracy of the system's output. One intriguing possibility is that the variable premotor activity of the AFP, necessary for song learning but not for song recitation, may play a long-term role in song homeostasis in the adult.

Conflict of interest statement

Nothing declared.

CRediT authorship contribution statement

Richard Bertram: Conceptualization, Writing - original draft. **Richard L Hyson:** Conceptualization, Writing - original draft, Validation. **Amanda J Brunick:** Writing - review & editing. **Diana Flores:** Writing - review & editing, Investigation. **Frank Johnson:** Conceptualization, Writing - original draft.

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