

The Songbird as a Model for the Generation and Learning of Complex Sequential Behaviors

Michale S. Fee and Constance Scharff

Abstract

Over the past four decades songbirds have become a widely used model organism for neuroscientists studying complex sequential behaviors and sensory-guided motor learning. Like human babies, young songbirds learn many of the sounds they use for communication by imitating adults. This remarkable behavior emerges as a product of genetic predispositions and specific individual experiences. Research on different aspects of this behavior has elucidated key principles that may underlie vertebrate motor learning and motor performance in general, including (1) the mechanisms by which neural circuits generate sequential behaviors, (2) the existence of specialized neuronal circuits for the generation of exploratory variability, (3) the importance of basal ganglia–forebrain circuits for learning sequentially patterned behaviors, including speech and language, and (4) the existence of genetic toolkits that may have been coopted multiple times during evolution to play a role in learned vocal communication, such as the transcription factor FoxP2 and its molecular targets. This review presents new techniques, experiments, and findings in areas where songbirds have made significant contributions toward understanding of some of the most fundamental questions in neuroscience.

Key Words: Area X; basal ganglia–forebrain circuit; songbird; transcription factor FOXP2; vocal learning; zebra finch (*Taeniopygia guttata*)

Introduction

The songbird has emerged as a tractable model system in which to pursue answers to some of the most fundamental questions in neuroscience. How does the brain generate complex behaviors? How do humans learn these behaviors by observing others? After making an error, by

what mechanism do the consequences of that error cause someone to avoid that action in the future? Similarly, how does the brain reinforce the thoughts or actions that lead to a positive outcome? These are fundamental questions in neuroscience because the ability to learn by imitation and improve future actions based on past outcomes underlies much of what humans do. Furthermore, diseases of the basal ganglia and cortical circuitry that underlie these functions have devastating motor and cognitive consequences, highlighting the importance of understanding the biophysical and circuit mechanisms that underlie the learning and generation of complex behaviors (Albin and Mink 2006; Brown et al. 2003; Everitt and Robbins 2005; Graybiel and Rauch 2000; Leckman and Riddle 2000; Müller et al. 1997; Voon et al. 2007).

One songbird in particular, the zebra finch (*Taeniopygia guttata*), has been the focus of much research because of its proclivity to sing and breed in captivity and its rapid maturation. The song of an adult male zebra finch is a stereotyped series of acoustic signals with structure and modulation over a wide range of time scales, from milliseconds to several seconds (Figure 1A). The adult zebra finch song comprises a repeated sequence of sounds, called a motif, that lasts about a second (Immelmann 1969). The motif is composed of shorter bursts of sound called syllables, which often contain sequences of simpler acoustic elements called notes (Price 1979).

The specific acoustic pattern produced by a songbird is learned in much the same way that humans acquire a number of motor skills (Thorpe 1958). In fact, vocal learning in songbirds has attracted a great deal of attention in part because of its similarity to speech learning in humans (Doupe and Kuhl 1999; Marler 1970). Song learning proceeds through a series of stages (Figure 1B), beginning with a primarily sensory phase in which the young bird listens to a tutor (usually its father) vocalize, often without producing any song-like vocalizations itself. The bird uses this period to memorize a representation of the tutor song, forming a neural “template” of the song (Konishi 1965). After the sensory learning stage, the juvenile bird enters the “sensorimotor” stage and begins to sing; over the course of a couple of months it uses auditory feedback to refine its vocalizations to match the template. The earliest babbling vocalizations, known as “subsongs,” are highly noisy, variable, and unstructured (Figure 1C) (Immelmann 1969). Within a week or so the song enters a stage known as “plastic song,” in which the

Michale S. Fee, PhD, is a professor in the Department of Brain and Cognitive Sciences and investigator in the McGovern Institute for Brain Research at Massachusetts Institute of Technology in Cambridge. Constance Scharff, PhD, is a professor and head of the Department of Animal Behavior at the Institute of Biology of Freie Universität Berlin in Germany.

Address correspondence and reprint requests to Dr. Michale S. Fee, Department of Brain and Cognitive Sciences, 46-5133 MIT, 77 Massachusetts Avenue, Cambridge, MA 02139 or email fee@mit.edu.

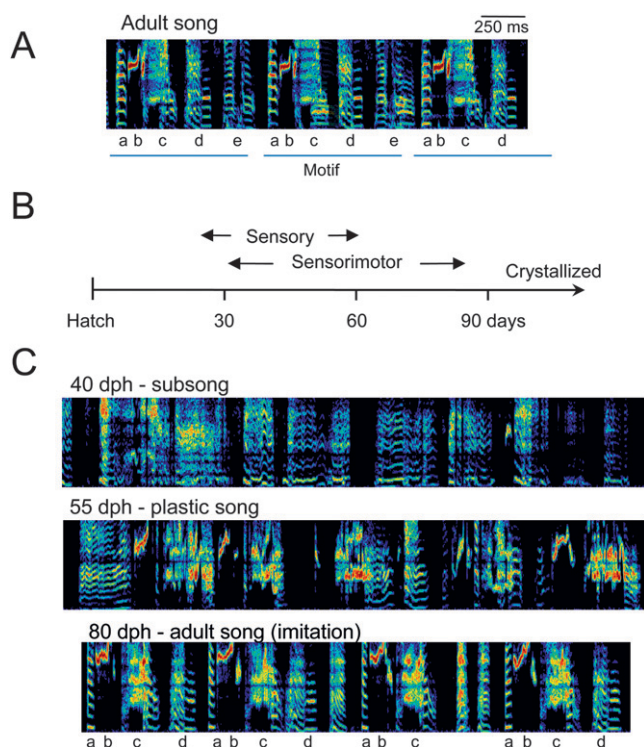


Figure 1 Description of zebra finch song and song learning. (A) Song spectrogram of an adult male single zebra finch. Letters denote syllables; a repeated sequence of syllables is called a motif. A bout of singing consists of a sequence of motifs preceded by introductory notes. (B) Timeline of song learning in zebra finches. During the sensory learning phase, the bird acquires a song “template” by listening to a tutor. During the sensorimotor phase the bird practices its song and, using auditory feedback, makes its own song match that of the tutor. (C) Song spectrograms from a juvenile zebra finch at three stages of learning. The spectrogram of this bird’s tutor is shown in panel (A). From 30 to 45 days posthatch (dph) young zebra finches sing “subsong,” which has little or no repeated acoustic structure. Older juveniles (45–80 dph) sing “plastic song,” which is variable but has some identifiable repeated structure. Adult song (>80–90 dph) has little variability and clearly identifiable syllables and motifs. This bird made a good imitation of most of the tutor syllables and sequence but failed to copy syllable “e.” Such variations in the imitation process are common.

vocalizations acquire syllables that, while still highly variable, are identifiable as repeated vocal patterns and gradually come to dominate the song as the variability decreases. At the onset of sexual maturity, the variability is substantially eliminated—a process called crystallization—and the young bird begins to produce a normal adult song, which can be a striking imitation of the tutor song (Figure 1C). Thus, the gradual reduction of song variability from early subsong to adult song, together with the gradual increase in imitation quality, is an integral aspect of vocal learning in the songbird.

While all songbird species investigated so far go through a subsong and a plastic song phase before reaching adult song, the timing and learning strategies can differ substantially (Marler 1997). In many seasonal breeders such as the

nightingale an auditory memorization phase precedes sensorimotor learning by months (Hultsch and Todt 2004), whereas in opportunistic breeders such as the zebra finch, auditory and motor learning overlap (Roper and Zann 2006). How much and when the developing “soundscape” is affected by auditory experience also varies considerably among species. Unlike children, some songbird species can develop a large repertoire of species-typical adult song elements even without hearing a tutor song, but the postmigration selection of the final song types (“action-based learning”) is based on exposure to the songs of neighboring birds (Liu and Nottebohm 2007). In other species, like the zebra finch, “innately” produced sounds are gradually shaped toward a memorized tutor song throughout development (“instruction-based learning”) (Tchernichovski et al. 2001).

Birdsong as a Model for the Generation of Complex Behavioral Sequences

The brain areas associated with song production and song learning have, to a large extent, been identified and exist in all songbird species studied (Wild 1997) (Figure 2). The muscles of the vocal organ, or syrinx, are innervated by a subset of motor neurons of the hypoglossal nucleus (the tracheosyringeal portion of the nucleus of the twelfth nerve, nXII_{ts}) (Vicario and Nottebohm 1988; Wild and Arends 1987). A primary projection to the nXII_{ts} descends from neurons in a forebrain nucleus RA¹ (robust nucleus of the arcopallium) (Nottebohm et al. 1982; Wild 1993), which is thought to be analogous to the mammalian layer V pyramidal tract neurons of motor cortex that project directly to spinal motor neurons (Karten 1991). Nucleus RA receives motor-related projections from another cortical analogue, nucleus HVC¹ (Bottjer et al. 1989; Nottebohm et al. 1976), which in turn receives direct input from several brain areas, including thalamic nucleus uvaformis (Uva) (Nottebohm et al. 1982; Williams and Vicario 1993).

Nuclei HVC and RA are involved in the motor control of song in a hierarchical manner (Vu et al. 1994). Recordings in singing zebra finches have shown that HVC neurons that project to RA transmit an extremely sparse pattern of bursts: each RA-projecting HVC (HVC_(RA)) neuron generates a single highly stereotyped burst of approximately 6 ms duration at one specific time in the song (Figure 3A) (Hahnloser et al. 2002). During singing, RA neurons generate a complex sequence of high-frequency bursts of spikes, the pattern of which is precisely reproduced each time the bird sings its song motif (Yu and Margoliash 1996). During a motif, each RA neuron produces a fairly unique pattern of roughly 12 bursts, each lasting ~10 ms (Leonardo and Fee 2005). It is not yet known precisely how these complex sequences of bursts are related to vocal output—for example, how the

¹Abbreviations used in this article: AFP, anterior forebrain pathway; DAF, disruptive auditory feedback; DLM, medial portion of the dorsolateral thalamus; HVC, used as the proper name; LMAN, lateral magnocellular nucleus of the anterior nidopallium; RA, robust nucleus of the arcopallium

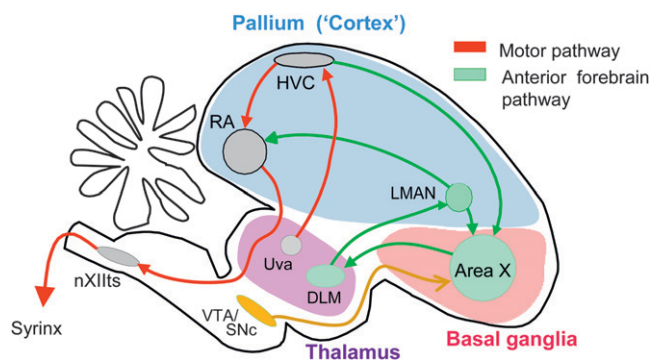


Figure 2 Avian brain nuclei related to song control. The motor pathway is necessary for song production and the anterior forebrain pathway (AFP) is necessary for song learning. In the motor pathway, the vocal organ, or syrinx, is innervated by motor neurons in the brainstem (nucleus nXIIIts). Motor neurons are innervated by a forebrain nucleus RA (analogous to descending projections from layer V of cortex; Karten 1991), which receives premotor input from nucleus HVC, which in turn receives afferents from the thalamic nucleus Uva. Nucleus RA also receives input from nucleus LMAN, the output nucleus of the AFP. The AFP is a cortical-basal ganglia loop that consists of LMAN, basal ganglia homologue Area X, and the pallido-recipient thalamic nucleus DLM. Note that RA, HVC, and LMAN are in the avian pallium, which is evolutionarily and developmentally related to mammalian cortex (Reiner et al. 2005). DLM, medial portion of the dorsolateral thalamic nucleus; LMAN, lateral magnocellular nucleus of the anterior nidopallium; nXIIIts, tracheosyringeal portion of the twelfth nerve; RA, robust nucleus of the arcopallium; Uva, nucleus uvaformis; VTA/SNc; ventral tegmental area/substantial nigra pars compacta.

telencephalic orchestration of singing interfaces with brainstem motor and respiratory circuits downstream from RA. These peripheral mechanisms are an area of active research (Riede and Goller 2010; Sturdy et al. 2003) and are part of an ongoing effort to study the convergent mechanisms that control the production of both human speech and birdsong (Jarvis 2004).

A Simple Model of Vocal Sequence Generation in Adult Birds

Based on the observations that RA-projecting HVC neurons generate a single burst of spikes during the song motif and that different neurons appear to burst at many different times in the motif, it has been hypothesized that these neurons generate a continuous sequence of activity over time (Fee et al. 2004; Kozhevnikov and Fee 2007). In other words, at each moment in the song, there is a small ensemble of HVC_(RA) neurons active at that time and only at that time (Figure 3B), and each ensemble transiently activates (for ~10 ms) a subset of RA neurons determined by the synaptic connections of HVC neurons in RA (Leonardo and Fee 2005). Further, in this model the vector of muscle activities, and thus the configuration of the vocal organ, is determined by the convergent input from RA neurons on a short time scale, of about

10 to 20 ms. The view that RA neurons may simply contribute transiently, with some effective weight, to the activity of vocal muscles is consistent with some models of cortical control of arm movement in primates (Fetz and Cheney 1980; Todorov 2000).

A number of studies suggest that the timing of the song is controlled on a millisecond-by-millisecond basis by a wave, or chain, of activity that propagates sparsely through HVC neurons. This hypothesis is supported by an analysis of timing variability during natural singing (Glaze and Troyer 2007) as well as experiments in which circuit dynamics in HVC were manipulated to observe the effect on song timing. Specifically, bilateral cooling of HVC during singing by use of a thermoelectric heat pump (a Peltier device) revealed that all aspects of song timing—duration of song syllables, interval between syllable onsets, and interval between motif onsets—are slowed by approximately 3% per degree Celsius of HVC cooling (Figure 3C) (Long and Fee 2008). In contrast, bilateral cooling in RA had no effect on song timing. Thus, in this model, song timing is controlled by propagation of activity through a chain in HVC; the generic sequential activation of this HVC chain is translated, by the HVC connections in RA, into a specific precise sequence of vocal configurations.

Birdsong as a Model for Motor Learning

In addition to its inputs from HVC, the premotor nucleus RA also receives synaptic input from nucleus LMAN¹ (lateral magnocellular nucleus of the anterior nidopallium), which, like HVC and RA, is contained within the pallium, a region of the avian brain analogous to mammalian cortex (Reiner et al. 2004b). LMAN is the output of a circuit known as the anterior forebrain pathway (AFP)¹, which includes a thalamic nucleus DLM¹ (medial portion of the dorsolateral thalamus) and a basal ganglia homologue Area X, which in turn receives input from LMAN and HVC (Figure 2) (Okuhata and Saito 1987; Reiner et al. 2004a). Synaptic inputs to RA from LMAN and HVC are glutamatergic. However, while HVC inputs are mediated by a mixture of AMPA (α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) and NMDA (N-methyl-D-aspartic acid)-type glutamate receptors (Stark et al. 1999), LMAN inputs are mediated primarily by NMDA receptors, as evidenced by their near complete blockade by AP5 (2-amino-5-phosphonopentanoic acid) (Mooney 1992; Mooney and Konishi 1991; Ölveczky et al. 2005; Stark and Perkel 1999).

Lesions or pharmacological manipulation of LMAN and Area X disrupt song learning in juveniles, but, unlike lesions to the motor pathway, have little effect on singing ability in adults (Basham et al. 1996; Bottjer et al. 1984; Scharff and Nottebohm 1991; Sohrabji et al. 1990). However, studies have shown that lesions in these two areas have strikingly different effects on song learning. Permanent bilateral lesions of LMAN result in an impoverished adult song that shows poor imitation of the tutor, a small number of abnormally

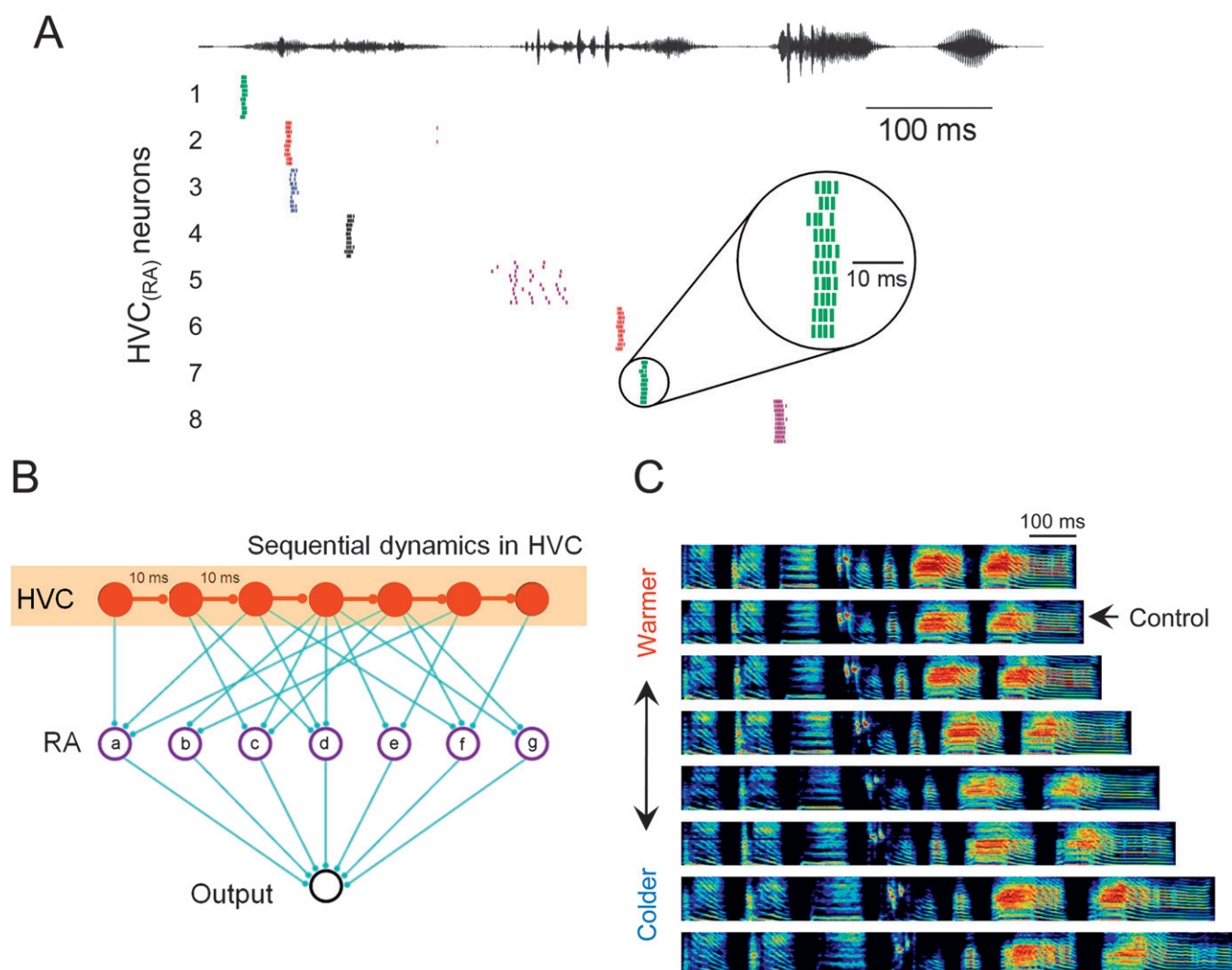


Figure 3 Mechanisms of sequence generation in the adult song motor pathway. **(A)** Spike raster plot of 8 antidromically identified RA-projecting HVC neurons recorded sequentially in a single singing zebra finch. Spikes from 10 sequential song motifs are shown for each neuron. Each neuron generates exactly one burst of ~6 ms duration during each rendition of the song motif (from Hahnloser et al. 2002). **(B)** Illustration of the hypothesis that RA-projecting HVC ($HVC_{(RA)}$) neurons burst and activate each other sequentially in groups of 100 to 200 coactive neurons. Each group of HVC neurons drives a distinct ensemble of RA neurons to burst. The neurons converge with some effective weight at the level of the motor neurons to activate syringeal muscles. **(C)** Bilateral cooling of HVC with a thermoelectric device results in a slowing of song at all time scales (subsyllabic structure, intervals between syllable onsets, and intervals between motif onsets). This result suggests that the biophysical dynamics that underlie all of these time scales may reside in HVC, and rules out the possibility that any of the time scales are autonomously controlled by dynamics outside HVC. Adapted from Long and Fee (2008).

simple syllables, and, in the juvenile song, premature crystallization (loss of variability) (Bottjer et al. 1984; Scharff and Nottebohm 1991; Sohrabji et al. 1990). Permanent lesions of Area X also result in a poor imitation of the tutor song, but in contrast to LMAN lesions, the song does not crystallize, syllable morphology remains abnormal, and the adult bird retains a large number of syllables with abnormally high sequence variability (Scharff and Nottebohm 1991).

Recent advances in understanding of avian functional neuroanatomy have revealed the extent to which Area X and its interactions with cortical-like HVC and LMAN are homologous to the mammalian basal ganglia (BG^1) and its interaction with cortex (Figure 4). Area X and the mammalian BG are

both topographically organized into cortico-striato-pallidal-thalamocortical loops that share striking similarities in their neurochemistry, cytoarchitecture, and synaptic connectivity (Alexander et al. 1986; Doupe et al. 2005; Luo and Perkel 2001). Furthermore, as shown in Figure 4, four major cell classes in the mammalian striatum are also present in Area X: (1) medium spiny neurons (MSNs) that express either enkephalin or substance P, (2) fast-spiking (FS) interneurons, (3) cholinergic tonically active neurons (TAN), and (4) low-threshold spiking (LTS) interneurons. Furthermore, these striatal neuron types share essential features of their spiking activity with their mammalian counterparts, both in vitro (Farries and Perkel 2002) and in the behaving animal (Goldberg and Fee 2010).

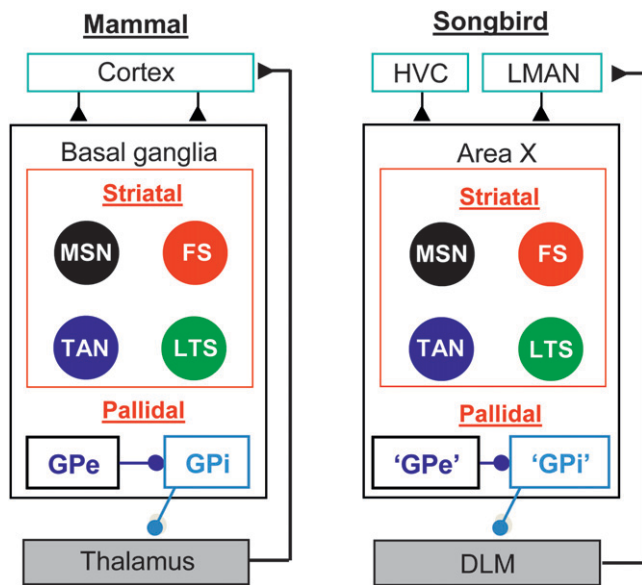


Figure 4 Comparison of mammalian and avian basal ganglia-forebrain circuitry. The avian Area X is homologous to the mammalian basal ganglia (BG) and includes striatal and pallidal cell types. The BG forms part of a highly conserved anatomical loop through several stations, from cortex to the BG (striatum and pallidum), then to thalamus and back to cortex. Similar loops are seen in the songbird: the cortical analogue nucleus LMAN projects to Area X, the pallidal components of which project to the thalamic nucleus DLM, which projects back to LMAN. Like the mammalian BG, Area X contains medium spiny neurons (MSN), fast-spiking interneurons (FS), tonically active neurons (TAN), and low-threshold spikers (LTS). Area X also contains GPi-like pallidal neurons that project to the thalamus, and GPe-like pallidal neurons that project within Area X. Note that there are some differences between Area X and mammalian BG. For example, Area X does not appear to contain, or interact with, neurons homologous to those of the mammalian subthalamic nucleus (STN; not shown), nor does Area X have a direct projection to midbrain dopaminergic areas (not shown). DLM, medial portion of the dorsolateral thalamus; GPe, external globus pallidus; GPi, internal globus pallidus; LMAN, lateral magnocellular nucleus of the anterior nidopallium.

Area X also contains two pallidal-like cell types: thalamus-projecting neurons densely innervated by the striatal-like spiny neurons (Carrillo and Doupe 2004; Farries et al. 2005b), similar to the classical “direct” pathway of the BG; and locally projecting pallidal neurons, similar to the classical “indirect” pathway. The singing-related firing patterns of these two cell classes are similar to those of neurons observed in the internal and external pallidal segments (GPi and GPe, “direct” and “indirect” pathways, respectively) of the behaving primate (Goldberg et al. 2010). This detailed structural and functional homology in such phylogenetically distinct groups as songbirds and primates hints at a highly conserved underlying BG circuit function in the vertebrate brain (Reiner 2009). Understanding the relation between songbird and mammalian BG is an important area of ongoing research (Gale and Perkel 2010a).

Just as Area X is necessary for vocal learning in the songbird, the mammalian BG is involved in motor control and learning (Graybiel 1994). Impairments of BG function affect serial processing and sequential behaviors, including speech and language, and are seen in Parkinson’s disease, schizophrenia, obsessive-compulsive disorder, Huntington’s, Tourette’s, and the tardive syndromes (Brown et al. 2003; Müller et al. 1997). Since Area X and the mammalian BG circuit share design features and functional significance, the neural mechanisms of song learning are likely to be directly relevant to both the mammalian BG and human disease (Doupe et al. 2005).

Hypotheses for the Role of the AFP in Learning

The importance of the AFP in vocal plasticity in the songbird has led to a number of hypotheses about the specific role this circuit plays in learning (Troyer and Bottjer 2001). These hypotheses have focused on three major functions that are thought to be necessary for song learning: (1) the comparison of auditory feedback during singing with the memory of the tutor song, (2) the generation of motor variability that allows the young bird to learn by exploring vocal space, and (3) the computation of an error signal or instructive signal that is transmitted to the motor pathway to drive learning.

Auditory Comparison

One of the most influential models of the AFP is that this circuit is involved in the comparison between auditory feedback during singing and the memorized tutor song, or template (Troyer and Bottjer 2001). The strongest evidence in favor of this AFP comparison hypothesis is that neurons throughout the AFP exhibit auditory responses in anesthetized, sleeping, and awake birds (Dave and Margoliash 2000; Hessler and Doupe 1999; Katz and Gurney 1981; Margoliash 1986; McCasland and Konishi 1981). Auditory responses in Area X and LMAN probably arise via the projection to Area X from HVC (Doupe 1997; Prather et al. 2008, 2009; Theunissen and Doupe 1998), which in turn receives auditory inputs from several auditory centers (Coleman and Mooney 2004; Coleman et al. 2007; Fortune and Margoliash 1995).

Although this idea remains influential, there is some evidence against it. If the AFP is involved in evaluating song to determine vocal errors, it might be expected that AFP neurons would be auditory responsive *during singing*. This hypothesis has been examined by comparing the song-related neural activity and activity-dependent gene expression in LMAN and HVC in normal and deafened birds (Hessler and Doupe 1999; Jarvis and Nottebohm 1997; Kimpo and Doupe 1997) and examining the responses of these areas to the playback of disruptive auditory feedback (DAF¹) during singing (Kozhevnikov and Fee 2007; Leonardo 2004; Prather et al. 2008). Although the disruption of auditory feedback in many of these experiments was sufficient to induce slow degradation of song structure over the course of days or

weeks, there was no evidence of auditory sensitivity in HVC or in the AFP during singing. A recent study reported auditory sensitivity to DAF during singing in HVC in Bengalese finches (*Lonchura striata domestica*; Sakata et al. 2008). However, in these experiments the DAF stimulus was of sufficient intensity to induce acute motor effects on song temporal structure. Thus the observed auditory responses could be related to fast auditory-motor interactions (Sakata and Brainard 2006; Yamada and Okanoya 2003) rather than to error signals subserving vocal learning.

Of course, an alternative possibility is that the auditory processing related to song template storage and comparison may occur in the extensive network of auditory regions in the songbird forebrain (Mello et al. 2004). This view is gaining support from a number of directions. Recent experiments have demonstrated that pharmacological blockade of protein synthesis in some forebrain auditory areas during tutor exposure leads to a poor imitation of the tutor song (London and Clayton 2008). More recent research has used immediate early gene expression to show a selective response in these brain areas to tutor song (Gobes et al. 2010). Finally, single-unit recordings in singing zebra finches have revealed the existence of auditory forebrain neurons that do not have simple auditory responses but instead show strong premotor-related activity and responses to DAF only during singing (Keller and Hahnloser 2009). These neurons exhibit a degree of auditory-motor convergence that might be expected in circuits carrying out online template-comparison.

Altogether, these studies suggest that the auditory forebrain, rather than the AFP, may play the central role in song template storage and performance evaluation.

Vocal Exploration in Juvenile Songbirds

The reinforcement learning (RL) model of basal ganglia function (Sutton and Barto 1998) proposes a learning strategy reminiscent of a trial-and-error search (Doya and Sejnowski 1995, 1998). In this model, an animal experiments with its motor repertoire and receives sensory-driven evaluative feedback that reinforces action sequences that improve output. The combination of randomness and selection can result in extremely sophisticated behaviors and has been successfully used to engineer motor control in robots and to model BG-dependent sequence learning in primates (Beiser and Houk 1998; Contreras-Vidal and Schultz 1999; Gutnisky and Zanutto 2004; Suri and Schultz 1998, 1999).

The fact that songbirds require auditory feedback during all stages of song learning to properly master their songs by imitation is well established (Konishi 1965) and is consistent with the RL view of vocal learning. Likewise, trial-to-trial variability during the sensorimotor phase may reflect implementation of the second requirement of RL, vocal “exploration” (Doya and Sejnowski 1995), which allows the bird to sample a variety of outputs, increasing the chance of producing template-matched vocalizations. Indeed, studies have shown that an artificially imposed association between natural

song variations and vocal error drives plastic changes in song in both adult and juvenile birds (Andalman and Fee 2009; Tumer and Brainard 2007).

The first explicit suggestion that the AFP drives vocal exploration came from early modeling work (Doya and Sejnowski 1995) and was based on studies of the effects of LMAN and Area X lesions on song and song learning (Scharff and Nottebohm 1991). Since then, a number of studies have fairly firmly established that the AFP, in particular nucleus LMAN, contributes to the generation of vocal variability in all stages of vocal development. Lesion and gene expression studies have shown that LMAN is involved in the acoustic and even behavioral variability of adult birds (Kao et al. 2005; Liu and Nottebohm 2005); bilateral lesions or inactivation of LMAN in juvenile birds largely abolish variability during learning (Figure 5) (Ölveczky et al. 2005; Scharff and Nottebohm 1991). Furthermore, the inactivation of NMDA-type glutamate receptors in RA largely eliminates song variability, suggesting that LMAN generates variability by driving RA neurons via glutamatergic synaptic input (Ölveczky et al. 2005).

Based on a number of observations, LMAN also appears to play an active premotor role in generating subsong vocalizations in young juvenile zebra finches (Aronov et al. 2008). Complete bilateral lesions of HVC have little effect on these early vocalizations, whereas bilateral lesions or inactivation of LMAN in the subsong stage render the birds unable to sing. In addition, single-unit recordings of RA-projecting LMAN neurons in singing juvenile birds reveal that most of these neurons exhibit a strong premotor correlation with subsong acoustic structure, producing a significant increase in spike rate 10 to 50 ms before the onsets or offsets of subsong syllables. These findings, together with the observation that LMAN stimulation can produce immediate perturbations of vocal output (Kao et al. 2005), suggest that LMAN, not HVC, plays a predominant premotor role in the generation of exploratory babbling (Aronov et al. 2008).

Thus we have a view in which the AFP plays an essential role in vocal exploration throughout the ontogeny of song learning. Early in the subsong stage, the vocalizations are dominated by the LMAN input to RA, whereas HVC inputs appear to have little effect on vocal output. During the plastic song stage, HVC begins to contribute significantly, such that HVC and LMAN inputs play a more balanced role. In this stage, HVC produces some repeated or structured vocal elements, while LMAN still contributes to the generation of variability. Finally, in the adult zebra finch, the stereotyped input from HVC predominates while the noisy input from LMAN is greatly diminished, resulting in highly stereotyped sequences. However, LMAN continues to contribute variability in adult birds, which may be important for the maintenance of adult song or for ethological reasons (Kao et al. 2005; Liu et al. 2005). This model suggests a gradual transfer, throughout development, of the premotor control of singing from the AFP to the classical (HVC → RA) motor pathway. It seems likely that this process can be reversed and repeated in birds for which song variability is seasonal, such as canaries (*Serinus canaria*), whose song is highly stereotyped

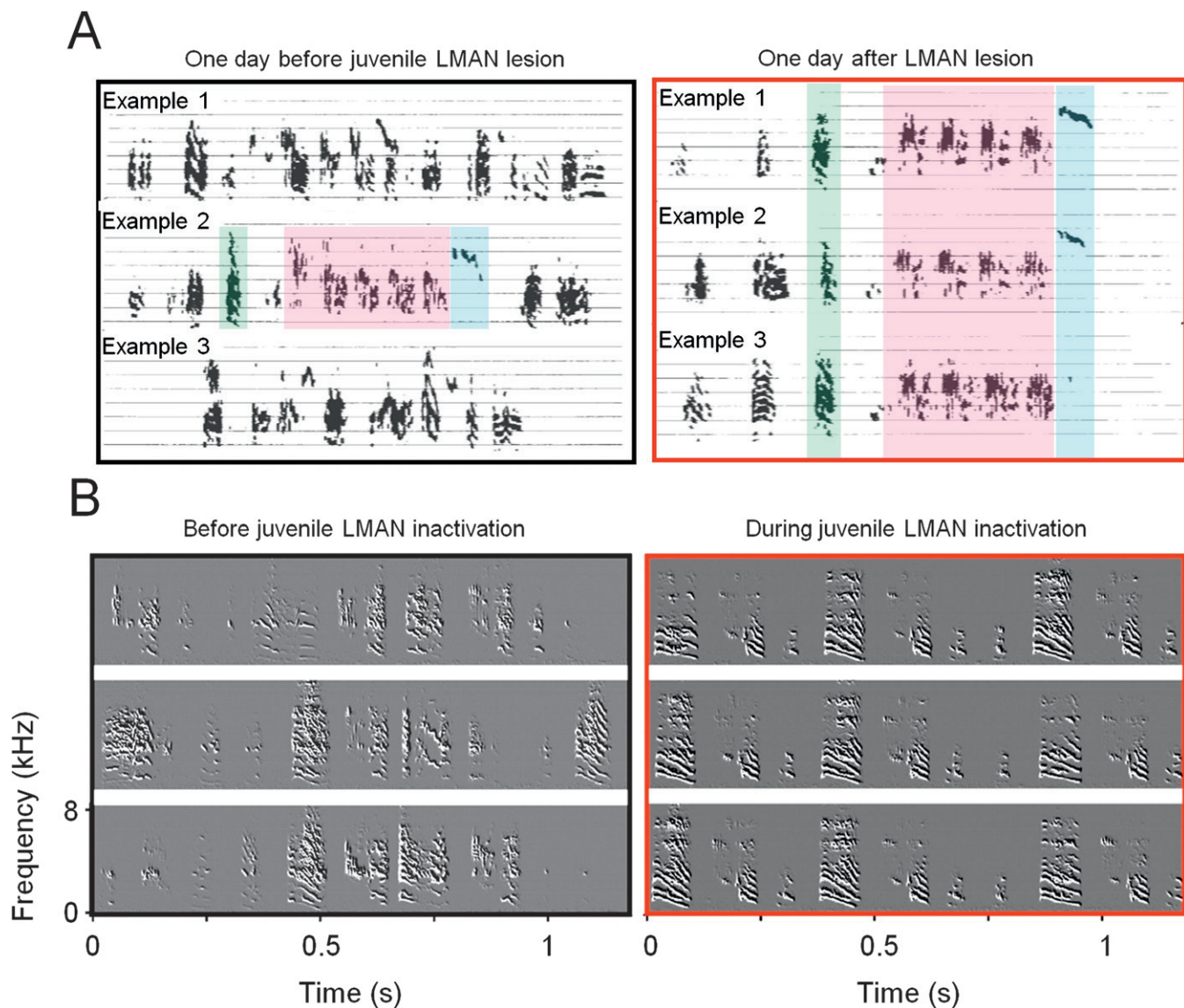


Figure 5 Effect of LMAN (lateral magnocellular nucleus of the anterior nidopallium) lesions on song variability. Elimination of LMAN significantly reduces vocal exploration, making the otherwise variable song of the juvenile zebra finch highly stereotyped. **(A)** Spectrograms of the songs of a juvenile zebra finch (42 days posthatch, dph) immediately before (left) and 1 day after (right) bilateral electrolytic lesion of LMAN (Scharff and Nottebohm 1991). Colored boxes indicate individual identifiable syllables. **(B)** Spectral derivatives of the songs of a juvenile zebra finch (57 dph) immediately before and after injection of tetrodotoxin (TTX) in LMAN (Ölveczky et al. 2005). In contrast to the normally large variability in sequence and the acoustic structure of plastic song syllables (left panels in A and B), a reduction of sequence and acoustic variability was manifest both 1 day after electrolytic lesion and immediately after TTX infusions (right panels in A and B), revealing a highly stereotyped song produced by the motor pathway. Spectral derivatives based on the method of Tchernichovski et al. (2000).

during the mating season and more variable the rest of the year (Nottebohm et al. 1990).

A number of questions arise regarding the mechanisms by which the AFP generates variability in vocal output. For example, how does the activity in LMAN modulate the firing patterns in nucleus RA, leading to vocal variability? What causes the developmental reduction of variability? Which are the AFP nuclei involved in generating variability? Does the variability in LMAN firing patterns arise from circuitry intrinsic to LMAN, or is it driven by afferent inputs? In the latter case, variability could arise within the

circuitry of DLM or Area X, or could involve the entire LMAN → Area X → DLM loop. Localization of the circuitry that generates variability will make it possible to study models of the biophysics and circuit dynamics that lead to random or chaotic firing patterns in neural circuits (van Vreeswijk and Sompolinsky 1996).

The existence of a specialized circuit in the brain that generates variability is a fascinating aspect of the song system and may have broad implications for understanding the origin of variability in neuronal firing patterns, the origin of behavioral variability that underlies learning, and the

variability inherent in higher cognitive processes such as play and creativity.

Error-Related Signaling

The reinforcement learning framework of vocal learning requires that variability in the motor output be accompanied by a mechanism that evaluates the vocal performance and produces plastic changes in the vocal output (Sutton and Schultz 1998). In fact, one of the earliest hypotheses for the function of the AFP is that it may provide an instructive signal that drives plasticity in the motor pathway (Bottjer et al. 1984). While it has been long known that lesions of the AFP produce severe deficits in vocal learning (Bottjer et al. 1984; Brainard and Doupe 2000; Scharff and Nottebohm 1991; Sohrabji et al. 1990), conclusive evidence for error-related signals in the AFP has been elusive.

The ability to experimentally manipulate the dynamics of vocal learning has enabled several advances in the study of vocal learning in songbirds. Because song learning normally occurs slowly, it can be difficult to correlate small daily changes in the song with electrophysiological recordings or experimental manipulations of the neural circuitry that are typically done on a time scale of hours. Two broad approaches that have been useful to study vocal learning involve the rapid induction of a song template (Tchernichovski et al. 2001) and the presentation of DAF (Leonardo and Konishi 1999). More recently, several laboratories have developed the use of conditionally presented DAF to induce motor-dependent vocal “errors” in real time during singing. If the presence of these “errors” is conditional on one vocal parameter (say, the pitch of a harmonic stack), the bird rapidly learns to alter the pitch of that syllable to avoid the feedback “error” (Andalman and Fee 2009; Tumer and Brainard 2007). Learned vocal changes in the presence of conditional auditory feedback can be rapid, such that the bird nearly completely avoids the feedback error within several hours of singing (Figure 6). Interestingly, the induced pitch changes were specific to the targeted song syllable and did not generalize to other syllables (Tumer and Brainard 2007), suggesting a strong temporal specificity to the learning process.

Conditional auditory feedback was recently used to directly address the question of whether LMAN in juvenile zebra finches does indeed produce a direct premotor contribution to the vocal output that biases the song away from vocal errors (Andalman and Fee 2009). The approach in these experiments was to transiently inactivate LMAN at the end of several hours of feedback-driven learning and look for evidence of “regression,” or “unlearning.” If learned changes in song are due to plasticity in the motor pathway, then LMAN inactivation would reduce variability but would not produce any immediate regression. In contrast, if LMAN makes a direct premotor contribution to vocal output that biases the output in the learned direction, then LMAN inactivation should result in a regression of the learned changes. The experiments showed that LMAN inactivation at the end of a day of learning pro-

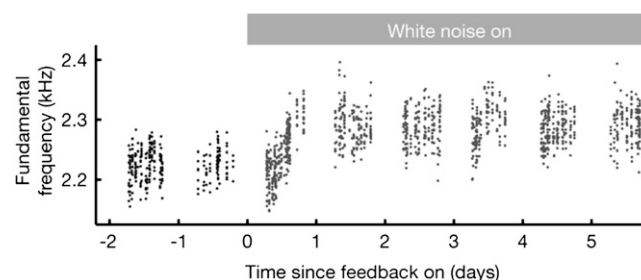


Figure 6 Rapid learning (within 1 day) of pitch changes resulting from playback of noise bursts during a song syllable. The playback of the noise is contingent on the pitch of the syllable: the noise burst is played only during syllable renditions whose pitch falls below the mean pitch of the syllable. The pitch of the syllable shifts upward such that, by the end of the day, few syllables receive noise bursts. Image reproduced with permission from Tumer and Brainard (2007).

duced an immediate regression of the day’s learned changes in song pitch, suggesting a substantial contribution of AFP-driven bias to vocal learning (Figure 7). The presence of AFP bias is further suggested by small but significant correlations in the motif-aligned firing pattern of LMAN neurons (Kao et al. 2008; Leonardo 2004; Ölveczky et al. 2005).

What is the role of AFP bias in the long-term changes in the motor pathway that underlie song learning? By updating each day the pitch threshold for which noise is played back, it is possible to produce several sequential days of learning in which learned pitch changes accumulated from day to day (Tumer and Brainard 2007). LMAN inactivation experiments demonstrated that these accumulated changes were not entirely due to AFP-driven bias but that plasticity in the motor pathway also contributed significantly. Furthermore, the amount of AFP bias exhibited on one day was highly predictive of the amount of plasticity in the motor pathway the next day (Andalman and Fee 2009). This finding is consistent with the hypothesis that biased variability from LMAN can actively drive plasticity in the motor pathway (Kao et al. 2005; Ölveczky et al. 2005; Troyer and Doupe 2000). Of course, plasticity in the motor pathway could also be shaped by a neuromodulator-based reinforcement signal transmitted directly to RA (Fiete et al. 2007).

Even if AFP bias did not constitute an instructive signal to RA that drives plasticity, LMAN-generated variability could serve another interesting function during learning: it could produce a more efficient exploration of motor space by generating more fluctuations in directions that produce a better outcome. Strategies that use prior information to direct future sampling (exploration) are common in numerical optimization and search algorithms, such as the conjugate gradient and Newton-Raphson methods (Shewchuk 1994). In this sense, the AFP implements a smarter search strategy with biased variability than would be possible with unbiased variability.

How does LMAN variability become biased in response to vocal experience? Area X is ideally situated to monitor the vocal fluctuations driven by LMAN and reinforce those that

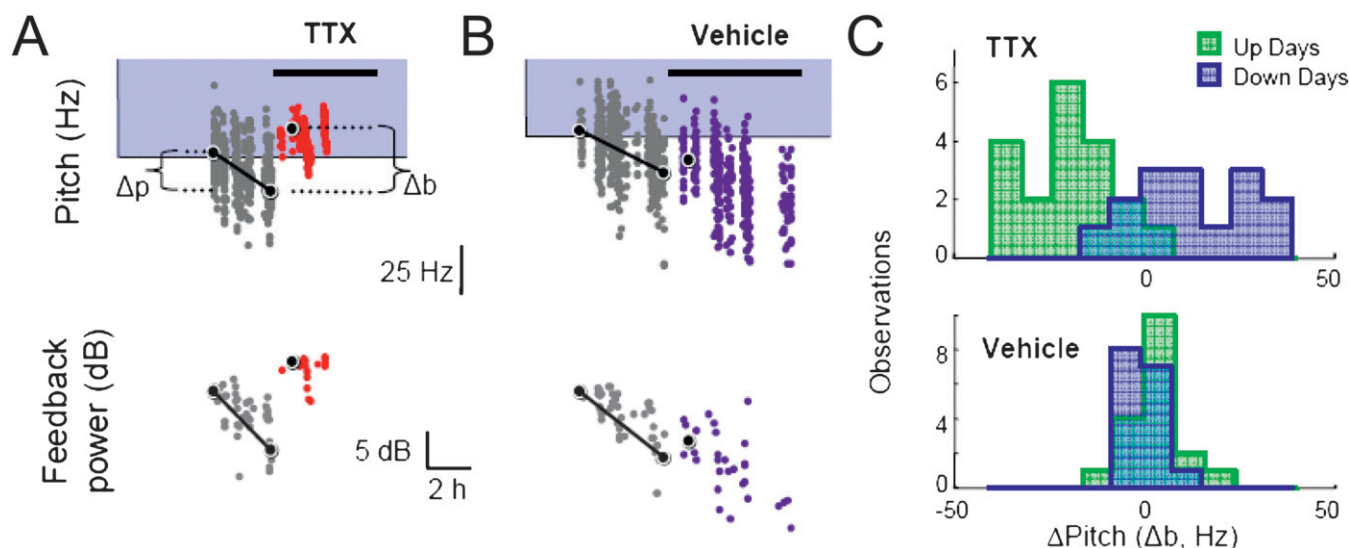


Figure 7 LMAN (lateral magnocellular nucleus of the anterior nidopallium) inactivation reveals a premotor contribution of the anterior forebrain pathway to vocal learning. **(A)** Average pitch of each rendition of a syllable targeted with conditional auditory feedback for 4 hours (top panel, grey dots). On the day shown, the disruptive feedback was targeted to syllable renditions with a higher-than-average pitch, causing the pitch to move gradually downward. As the pitch decreased, so did the amount of disruptive feedback (bottom panel). After the infusion of tetrodotoxin (TTX) into LMAN (red dots), syllable pitch reverted to a higher pitch and feedback power (in decibels, dB) increased. Δp , total learned change in pitch; Δb , regression of pitch after infusion. **(B)** Same as for panel A but for days of vehicle infusion instead of TTX. Black dots indicate the mean pitch in the morning, before and after infusion. **(C)** Histogram of pitch changes from pre- to postdrug infusion shows significant pitch change after TTX infusion (top panel) but not vehicle infusion (bottom panel). “Up days” indicates results from days on which the pitch was pushed downward, as in (A); “down days” indicates results from days on which the pitch was pushed upward. Note that pitch regression during LMAN inactivation is opposite the direction of ongoing learning, suggesting that LMAN makes a direct premotor contribution to learned changes in song. Image reproduced with permission from Andalman and Fee (2009).

lead to a better outcome. Area X receives collaterals of the LMAN axons that project to RA (Vates et al. 1997) and thus can directly “observe” the variability signal transmitted to RA. Area X also receives a strong dopaminergic projection from the midbrain (Figure 2) (Gale et al. 2008; Person et al. 2008), which in mammals has been shown to carry reward information (Schultz 2002), and receives an efference copy of timing signals from HVC (Hessler 1999; Kozhevnikov and Fee 2007), which could confer temporal specificity to the learning process. It is thus possible that medium spiny neurons in Area X could function to correlate the fluctuations of LMAN activity, at a particular time in the song, with a dopaminergic reward signal. Through its projection to DLM, Area X could then reinforce the patterns of LMAN activity that lead to a better-than-expected match to the memorized template. This model is speculative, but is consistent with some views of mammalian BG function (Graybiel 2008) and presents an interesting framework within which to examine the function of the AFP.

These experiments raise many questions crucial to a further understanding of the role of this BG-forebrain circuit in vocal learning: What are the dynamics of the relation between vocal “error” and (1) the generation of AFP bias on a finer time scale than these early experiments have examined and (2) plasticity in the motor pathway? What is the relation between AFP bias and changes in spiking patterns in LMAN? Do these changes occur during sleep, as some recent experiments suggest (Shank and Margoliash 2009)? Do neuromodulatory

inputs to Area X, RA, or other song control nuclei carry error- or performance-related signals? If so, how and where are these signals computed from auditory feedback? The ability to experimentally manipulate auditory feedback to drive rapid plastic changes in these brain areas introduces an unprecedented opportunity to study the detailed circuit mechanisms that underlie motor learning in cortical and basal ganglia circuits.

Genetic Contributions to Learning in Birdsong and Human Speech

Babies, be they human or songbird, learn to communicate with sounds as a result of specific experience—the language environment they are born into in the case of humans, or the particular song a tutor sings to the young songbird. But not everything can be imitated. What can be learned depends on learning capacity and is also subject to a number of constraints: the nature of the auditory filters that decide what is worth imitating; the “instrument” (the larynx in humans and the syrinx in birds), whose physical and physiological properties affect what sounds it can produce; and the interplay between breathing and singing. These factors, as well as the learning faculty itself, depend on the activity of genes. While there has been much progress zooming in on the neural mechanisms of song learning in birds, the role of genes has only recently come into focus.

Four avenues of inquiry into the contribution of genes to song learning have been pursued. The first approach hypothesizes that brain regions involved in song control and song learning are characterized by different transcriptional activity than other regions. The second approach is based on differential gene expression in song control regions as a result of singing or listening to song. Screening by a variety of methods for these differences has indeed turned up a number of promising candidate genes that are differentially regulated (Li et al. 2007; Lovell et al. 2008; Wada et al. 2004). The third line of research in songbirds has explored candidate genes from other animal systems, particularly genes involved in learning and memory and, more recently, human language. The fourth line of investigation involves analysis of behavioral variability in singing or song learning within a species for associations with genetic variability. The success of this fourth type of study depends on two ingredients: well-defined behavioral trait differences in the animals under investigation, and a good coverage of genetic markers; the latter has greatly improved with the recently sequenced zebra finch genome (Warren et al. 2010). In another songbird, the great tit (*Parus major*), quantitative genetic approaches have found a link between particular variants in a dopamine receptor gene (DRD4) and a fitness-related trait, boldness in exploratory behavior (Fidler et al. 2007; Korsten et al. 2010).

We limit our review to the second line of research and highlight studies in songbirds that address the role of one candidate gene, *FoxP2*, which is relevant for human speech and language. Findings on other, learning-related or song-system-specific genes are summarized in a comprehensive recent review (White 2009).

FoxP2, a Transcription Factor Relevant for Human Speech and Birdsong

The forkhead box (FOX) protein FOXP2² has captured the imagination of scientists and laymen alike because it was the first gene causally related to a fairly specific speech and language phenotype, developmental verbal dyspraxia (DVD), alternatively called childhood apraxia of speech, CAS; for definition, see American Speech-Language-Hearing Association, www.asha.org (Lai et al. 2001). DVD's core symptoms are inaccurate and incomplete pronunciation of words, difficulties with repeating multisyllable nonsense words, and impaired receptive speech (Simms 2007). In addition, *FOXP2* belongs to a group of genes for which multiple studies have found clear evidence for positive selection in the human lineage (Enard et al. 2002; Yu et al. 2009). Given that language may have uniquely human features, it is tempting to speculate that understanding *FOXP2* may illuminate how speech and language work mechanistically and how they evolved.

²Following nomenclature proposed by Kaestner and colleagues (2000). Uppercase (FOXP2) and lowercase (FoxP2) refer to human and nonhuman transcription factors, respectively; the terms in italics (*FOXP2* and *FoxP2*) refer to the respective genes or RNA transcripts.

The link between the transcription factor FOXP2 and language was first recognized in the large three-generation KE family, whose members are disproportionately affected by language impairments: about half of the members of this family have autosomally dominantly inherited *FOXP2* point mutations, and similar speech and language phenotypes exist in unrelated individuals with other *FOXP2* mutations (Lai et al. 2001; MacDermot et al. 2005). Since the discovery of *FOXP2* mutations in the KE family, in vitro and in vivo studies, including different animal studies, have made considerable progress in addressing the molecular, neural, and evolutionary function of FoxP2 in different systems.

FoxP2 research has followed three main directions. First, refining the speech phenotype and identifying neural structural and functional correlates in persons with *FOXP2* mutations; second, analyzing evolutionary changes in the *FoxP2* sequence across the animal kingdom and in particular the hominid lineage; and third, using animal and cell culture models to gain insight into the mechanism of its molecular, cellular, and behavioral function. We highlight recent findings in songbirds that relate to the language phenotype in humans (for reviews of FoxP2 research in other animal and in vitro model systems, sequence evolution, and analysis of the human phenotypes, see Fisher and Scharff 2009; Vargha-Khadem et al. 2005; Vernes and Fisher 2009; White et al. 2006).

FoxP2 During Brain Development

FoxP2 belongs to the large forkhead box transcription factor family of genes that is remarkably conserved across the animal kingdom and is implicated in many diseases and developmental processes of many tissues (Hannenhalli and Kaestner 2009). Consistent with a developmental role of other Fox proteins, FoxP2 is expressed in regions of the vertebrate embryo in which inductive signals organize adjacent proliferation of neural progenitors and subsequent migration (Scharff and Haesler 2005), a feature that persists in adult avian but not mammalian neurogenic zones (Rocheffort et al. 2007). Structural and functional brain imaging of humans with *FOXP2* mutations shows subtle volume differences and striking activation differences during language tasks, particularly in corticocerebellar and corticostriatal circuits. These findings are consistent with a role for FOXP2 in early brain development and with the possibility that reduced FOXP2 levels affect later ongoing processing of language, causing activity-driven structural changes in established neural circuits. Indeed, FoxP2 continues to be expressed in adult brain circuits of various vertebrates and is thus a candidate for involvement in postdevelopmental circuit function.

FoxP2 in Postnatal Brain Function

Research in songbirds has determined that FoxP2 plays a role in established neural circuits, particularly those relevant for auditory-guided vocal motor learning (Haesler et al.

2004). In juvenile zebra finches, FoxP2 expression levels are 10-20% higher during the phase of vocal sensorimotor learning than before or after. Likewise, FoxP2 levels are elevated in Area X in a strain of adult canaries that incorporate new song elements into their repertoire in late summer and fall, the end of the breeding season. Thus, changes in FoxP2 expression in Area X coincide with those in vocal plasticity (Haesler et al. 2004). In addition, in both juvenile and adult zebra finches, FoxP2 expression levels vary with prior singing activity (Teramitsu and White 2006; Teramitsu et al. 2010). Interestingly, levels of FoxP2 protein in the medial, but not lateral, geniculate nucleus also change after auditory stimulation in mice (Hornig et al. 2009), emphasizing that neural activity can regulate the expression of FoxP2 in specific subsets of neurons in different species.

To address a possible causal relationship between FoxP2 expression and vocal learning, FoxP2 levels were experimentally reduced using lentivirus-mediated RNA interference in Area X of juvenile zebra finches throughout the sensorimotor song learning phase (Figure 8). The FoxP2 knockdown birds copied tutor songs only partially, imitating some elements but omitting others, imitating less accurately, and producing song elements more variably during each rendition (Haesler et al. 2007). Zebra finches with knocked-down FoxP2 in Area X remain able to generate a normal range of sounds. Interestingly, mice with reduced or absent FoxP2 are also able to produce the entire repertoire of ultrasonic distress and isolation calls (Gaub et al. 2010). Together, these data suggest that the sensorimotor integration necessary for the imitative learning of sounds is more likely to be affected by altered FoxP2 levels than the motor production itself. This song phenotype of FoxP2 knockdown zebra finches strikingly echoes the incomplete and inaccurate renditions of words and highly variable pronunciation in humans with a mutated *FOXP2* gene. FoxP2 levels were not manipulated during embryonic development in these experiments, but only when song control brain circuits were already largely assembled, suggesting that a reduction of FoxP2 affects postnatal function independently from effects on early nervous system development.

In Area X, FoxP2 is expressed in spiny neurons that mirror many features of mammalian striatal medium spiny neurons, except that in songbirds they continue to be added throughout adult life. Spiny neurons in Area X are innervated by glutamatergic HVC neurons (Farries et al. 2005a), which fire sparsely during singing (Kozhevnikov and Fee 2007) and in response to auditory stimuli in swamp sparrows (*Melospiza georgiana*; Prather et al. 2008). It has recently been shown that, during singing, putative medium spiny neurons recorded in juvenile zebra finches fire sparsely, like HVC neurons (Goldberg and Fee 2010). The HVC-to-Area X projection onto the spiny neurons is modulated presynaptically by midbrain dopaminergic input (Ding and Perkel 2002). Because nigral dopamine acts on many behavioral systems, including reward learning, the integration of pallial and dopaminergic signals in FoxP2-expressing spiny neurons may be essential for fine-tuning song motor output to

match the tutor song model. This notion is consistent with recent neuroanatomical and functional findings in adult male zebra finches (Gale and Perkel 2010b). Modulation of FoxP2 expression might up- or downregulate neural plasticity-relevant genes that in turn could affect motor learning via structural and functional changes of the spiny neurons. Indeed, recent data show that spiny neurons in Area X of adult male zebra finches have significantly fewer spines after undergoing lentivirally mediated FoxP2 knockdown (Schulz et al. 2010). Altered synaptic plasticity and impaired motor learning in mice carrying either the human *FOXP2* sequence or mutation are consistent with this interpretation (Enard et al. 2009; Groszer et al. 2008).

These studies illustrate the use of animal models to identify the organizational level of language at which a particular gene is required. A *FOXP2* deficit manifests itself in imperfect execution of the orofacial gestures that produce speech sounds (Vargha-Khadem et al. 2005); this effect could in principle be due to improper cranial motor neuron function, but studies instead point to cortical-BG circuits, which are more centrally involved in initiating and sequencing vocal gestures.

No single gene can elucidate whether there is a human-specific genetic toolkit that enables language development. In fact, FoxP1, another protein of the *FoxP* gene family, dimerizes with FoxP2 (Li et al. 2004) and is strongly expressed in many song control nuclei (Haesler et al. 2004; Teramitsu et al. 2004), findings that suggest *FOXP1* may also play a role in human speech. In fact, a recent case report of a child with a deletion of *FOXP1* and severe speech delay confirmed this prediction (Carr et al. 2010). Likewise, sequence variants in the *CNTNAP2* gene, which is regulated by *FOXP2*, were shown to also segregate with language abnormalities (Vernes et al. 2008). Interestingly, *Cntnap2* in songbirds shows differential expression in several song control nuclei, including Area X, LMAN, and RA (Panaitof et al. 2010).

Investigating the role of genes operating at the different levels of organ systems and neural circuits underlying language learning and production in humans and songbirds will advance efforts to understand how vocal communication works. Which evolutionary twists and turns led to vocal learning in distantly related species? How did the extra ingredients necessary for human language become instantiated biologically? One approach to the latter question is the comparison of genes and their function between nonhuman and human primates. In fact, of the approximately 23,000 human genes, the 50 to 100 that are unique to humans (Stahl and Wainszelbaum 2009) are unlikely to be solely responsible for those differences. Attention has therefore turned to orthologous genes, including *FOXP2*, that show signs of positive selection in the human lineage.

Geschwind and colleagues recently showed that in human cell lines, target genes are regulated differently by the human version of *FOXP2* than by the chimp version, and that chimp brains express some of those target genes at different levels than human brains (Konopka et al. 2009). These data suggest that quantitative as well as qualitative changes in the molecular cascade controlled by transcription factors

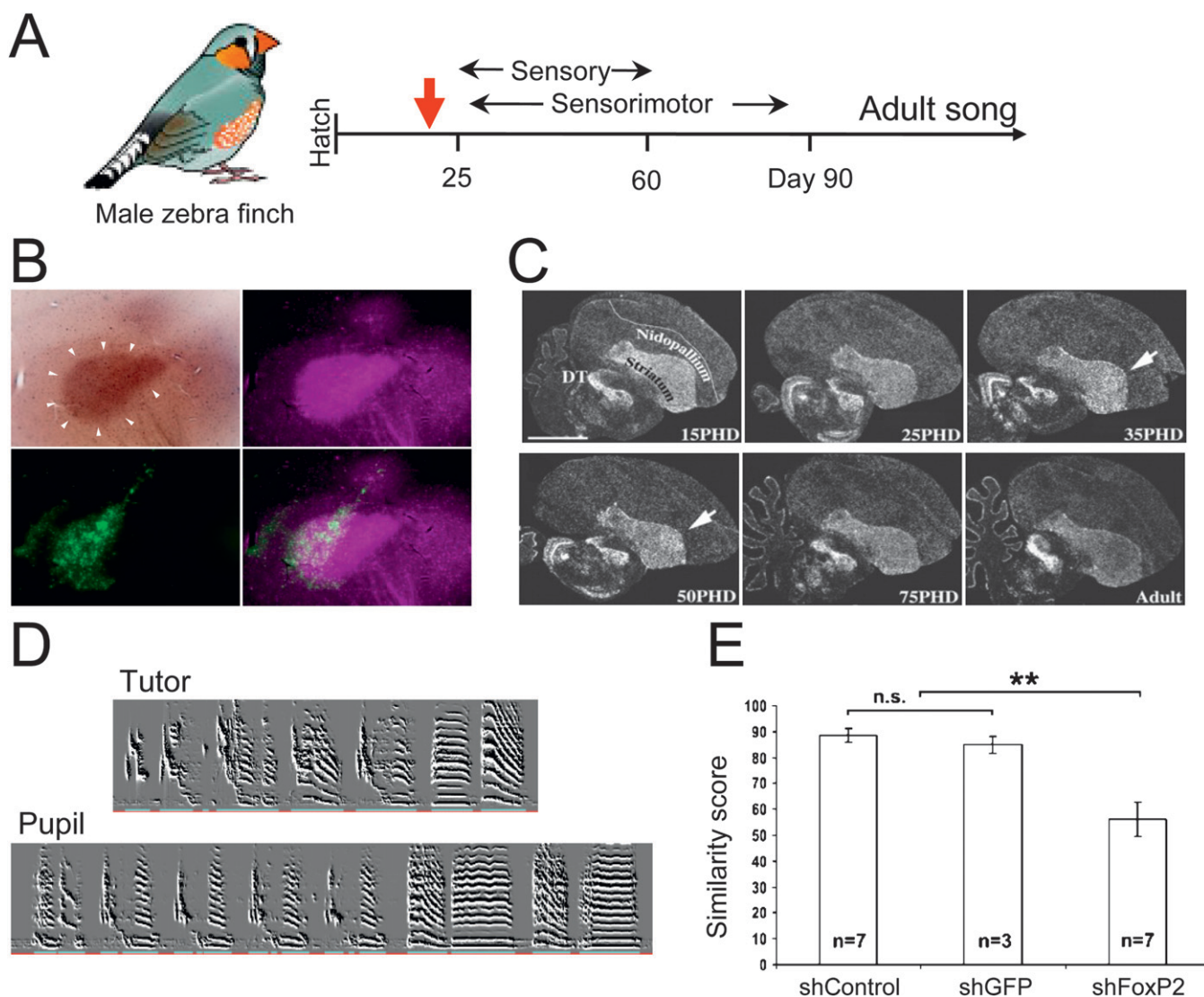


Figure 8 Summary of gene knockdown study of the role of the FoxP2 transcription factor in Area X during song learning. (A) Developmental time course of songbird vocal learning. Red arrow indicates time at which juvenile male zebra finches received bilateral injections into Area X with lentivirus carrying a short hairpin RNA (shRNA) interference construct. (B) The extent of the viral infection is made visible through virally mediated green fluorescent protein (GFP) expression, covering part of Area X (bottom left panel). (C) FoxP2 messenger RNA in Area X is dynamically regulated during development; Area X expresses more FoxP2 than the surrounding striatum at 35 and 50 posthatch days (phd) (arrows), when song learning occurs most rapidly. DT, dorsal thalamus. (D) Spectrograms of a tutor (top) and of an adult pupil (bottom) that received knockdown of FoxP2 in Area X as a juvenile. Note incomplete and inaccurate song imitation. (E) Quantification of similarity with tutor song of control pupils and pupils with FoxP2 knockdown. Control experiments were carried out with nontargeting shRNA sequences (shControl) and shRNA sequences targeting GFP (shGFP). n.s., not significant. Images in (B) and (D) reproduced with permission from Haesler et al. (2007). Image in (C) reproduced with permission from Haesler et al. (2004).

such as FoxP2 could be a source (but also a byproduct) of evolutionary changes leading from the common ancestor to chimps in one lineage and humans in another.

FoxP2 constitutes an example of a gene that both is relevant for human language and can be studied in the songbird model system. Other genes relevant for singing in songbirds (White 2009) may be relevant for human cognitive function, including language, as is true of a rho guanine nucleotide exchange factor—its expression in zebra finch Area X is regulated by singing (Wada et al. 2006) and it is associated with mental retardation in humans (Kalscheuer et al. 2009).

The recent completion of the sequencing of the zebra finch genome (Warren et al. 2010) and associated studies will greatly enhance the power of such comparative approaches.

Summary

Studies in the songbird have yielded a wealth of information about how complex sequential behaviors are generated and learned by neural circuits. Song production involves a small set of discrete nuclei whose functions are beginning to be

understood. Nucleus HVC appears to act as a clock or timer that generates a precise sequence of bursts of spikes. This sequence is subsequently routed or transformed by nucleus RA to generate an appropriate pattern of downstream motor neuron activation. Vocal learning in the songbird, which involves the programming of the HVC sequence and the downstream connections, involves a highly conserved basal ganglia–forebrain circuit (Bentivoglio 2003), which shares many essential features with mammalian BG circuits—cell types, intrinsic connectivity, interaction with thalamic and cortical circuitry, dopaminergic innervation, and molecular signatures.

One of the unique features of the LMAN/Area X/DLM pathway in songbird BG-forebrain circuitry is that its function appears to be restricted to song learning and adult song plasticity, thus affording unprecedented access to the specific BG circuitry involved in a particular learning behavior. Taking advantage of this specificity, it has been possible to develop new tools, including molecular genetic methods, to manipulate learning and monitor neural activity in parts of the circuit. Using these tools, a number of laboratories are working to identify the role of the cortical, basal ganglia, and thalamic components of this circuit and to test hypotheses about how they act together to enable vocal learning. Understanding how this circuit generates, evaluates, and corrects motor actions may shed light on motor and cognitive learning in other species (including humans), as well as elucidate the fundamental principles of vertebrate brain function.

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