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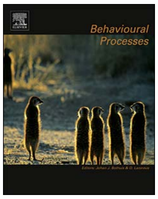

Developmental song learning as a model to understand neural mechanisms that limit and promote the ability to learn

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ABSTRACT

Songbirds famously learn their vocalizations. Some species can learn continuously, others seasonally, and still others just once. The zebra finch (*Taeniopygia guttata*) learns to sing during a single developmental “Critical Period,” a restricted phase during which a specific experience has profound and permanent effects on brain function and behavioral patterns. The zebra finch can therefore provide fundamental insight into features that promote and limit the ability to acquire complex learned behaviors. For example, what properties permit the brain to come “on-line” for learning? How does experience become encoded to prevent future learning? What features define the brain in receptive compared to closed learning states? This piece will focus on epigenomic, genomic, and molecular levels of analysis that operate on the timescales of development and complex behavioral learning. Existing data will be discussed as they relate to Critical Period learning, and strategies for future studies to more directly address these questions will be considered. Birdsong learning is a powerful model for advancing knowledge of the biological intersections of maturation and experience. Lessons from its study not only have implications for understanding developmental song learning, but also broader questions of learning potential and the enduring effects of early life experience on neural systems and behavior.

1. Introduction

1.1. Overview

Developmental song learning is a complicated process that has deep parallels with human speech acquisition (Doupe and Kuhl, 1999). The endpoint of this process is the production of a meaningful vocalization to attract mates, evaluate and maintain social relationships, and defend territories (Clayton et al., 2009). Developmental song learning requires coordinated sensory, motor, and sensorimotor functions that proceed on a backdrop of generalized neural maturation. It depends on a distributed brain network, in which each node has functional specializations but is dependent upon signals from other nodes. Studies of songbird neuroscience have made seminal contributions to a variety of fields. This review is structured to highlight how investigation into elements of developmental song learning is poised to make additional unique contributions, as we have known for decades that the ability of a juvenile zebra finch to learn song fluctuates but we do not yet know the neural mechanisms by which this occurs. Application of emerging methods and targeted behavioral paradigms to this powerful natural system can reveal fundamental principles of how learning is limited and promoted in songbirds and other systems.

1.2. What are Critical Periods?

Critical periods (CPs) are restricted developmental phases when experience has profound and persistent effects on the brain and behavioral patterns. Each CP is characterized by a specific age of onset, a particular type of stimulus that functionally modifies the underlying brain area, and a “close” that depends on that same stimulus and which reflects a switch to a state in which the stimulus no longer drives the neural organization of the brain system (Hess, 1959; Knudsen, 2004; Takesian and Hensch, 2013). The third property is important, as it distinguishes a CP from an instance of age-limited neural plasticity that is regulated by maturational events, rather than the combination of maturation and experience that defines a CP.

CPs are typically identified behaviorally, but behavioral changes reflect underlying shifts in brain plasticity. CP onset occurs when a brain region organizes sufficiently for mechanisms of plasticity to reliably encode the experience via molecular and cellular responses that support a moderate range of possible behavioral outcomes (Fig. 1). During the CP, the relevant experience activates plasticity mechanisms, remodeling the brain such that ultimately, properties of neural stability dominate those of plasticity. The outcome of experience-dependent change in a CP is a loss of plasticity such that the brain circuit is no

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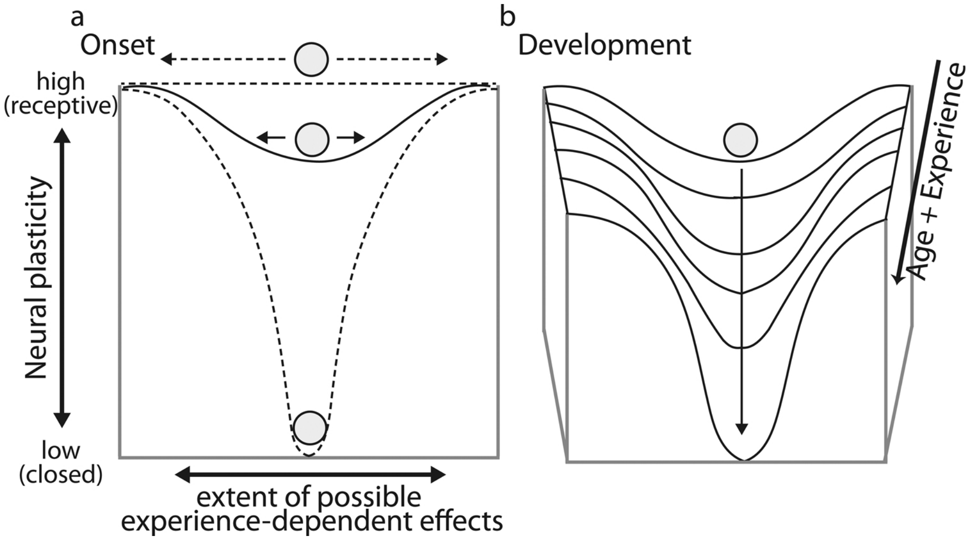

Fig. 1. Conceptual framework of neural plasticity that underlies a CP in behavior.
a: The onset of a CP is characterized by a state of generally high neural plasticity (y-axis) but with limits that restrict the possible behavioral outcomes of experience (x-axis). The result is a brain system (gray circle) that has selective receptivity to a particular stimulus that can guide behavioral patterns within a proscribed range. The balance of neural plasticity and experience-dependent behavioral change that characterizes a CP is represented by the solid, curved line. High neural plasticity without limitations leads to a neural system that can be pushed without bounds by experience (top, horizontal dashed line), resulting in a wide range of behavioral patterns that remain in flux. Alternatively, insufficient neural plasticity in a brain area prevents any influence of experience (deep curved, dashed line). These latter two plasticity states are unlikely to be found in a brain system with a CP. b: Through a process of accumulated age and experience (z-axis), a brain system regulated by a CP loses neural plasticity, reaching a closed state with a final, persistent pattern of behavior that is unmodifiable by additional experience (termination of the vertical arrow).

longer modifiable and behavior is restricted to its current pattern (Fig. 1).

Since the initial descriptions of CPs, data have emerged that some systems described as having a CP demonstrate at least temporary perturbations from stability upon later experience. The term Sensitive Period has therefore been adopted to describe this broader category of behaviors with a less extreme close to experience-dependent plasticity. Here, we will use the term CP, but acknowledge that there are conditions under which adult song plasticity can be observed (Deregnaucourt and Gahr, 2013; Funabiki and Funabiki, 2008).

1.3. CP features of developmental song learning

1.3.1. General description of zebra finch song acquisition

Every male zebra finch hatches with the potential to learn to sing (females cannot sing because components of the required brain circuitry do not develop). As adults, each male sings one stereotyped and unique song. Mature song emerges after a developmental process of coordinated sensory and motor functions (Fig. 2a, b). The foundation of song learning is sensory learning, wherein the juvenile forms an auditory memory of an adult "tutor" bird's song (Fig. 2a, b). Through a process of sensorimotor error correction, the juvenile uses his memory of the tutor's song to guide his initial innate, immature vocalizations into an adult, stereotyped song structure that largely resembles that of the tutor's. The tutor is typically the juvenile male's dad, but it does not have to be. Young males who experience unrelated adults copy their songs at high, normal levels, perhaps because social interactions between juvenile and adult males increase the probability that a specific adult will serve as the tutor bird (Ahmadiantehrani and London, 2017a, 2017b; London and Clayton, 2008; Adret, 2004a, 2004b; Williams, 1990; Chen et al., 2016; Baran et al., 2017; Mann and Slater, 1995).

1.3.2. Onset and closing of enhanced sensory learning phase in zebra finches

A key feature of CPs is that there are defined ages of onset and closing for the enhanced phase of experience-dependent neural plasticity. Based on a series of behavioral experiments, the phase for tutor song memorization has been fairly well defined as ending at Posthatch day 65 (P65) (Eales, 1985, 1987; Roper and Zann, 2006; Morrison and Nottebohm, 1993; Slater et al., 1991; Böhner, 1990, 1983; Adret et al., 2012). The onset of sensory learning has been more difficult to precisely define, perhaps in part because of natural variation across individuals. However, data from a systematic study of early life tutor experience revealed that tutor experience prior to P30 does not support tutor song copying, whereas exposure starting at P30 does, suggesting that this age marks a robust onset of sensory song learning capabilities (Fig. 2 in Roper and Zann, 2006). These ages do not preclude the influence of early auditory experience in shaping tutor song learning, but indicate that a period between P30 and P65 is the typical phase for tutor song memorization (Fig. 2; Adret et al., 2012; Chen et al., 2017; Braaten, 2010). Notably, sensory song learning is restricted despite the fact that zebra finches live in colonies and adult males sing throughout the day, every day. This highlights that access to tutor experience does not determine the ability to memorize tutor song, rather that the brain undergoes shifts in the plasticity required to learn from those song experiences.

1.3.3. Stimulus and functional specificity of sensory learning, behavior, and CP closing

If a male is exposed to tutor song P30-65, he works for approximately 30 more days to refine his vocal output, but is not influenced by subsequent tutor song exposure (Fig. 2). If, however, a bird is isolated from song P30-65 (we call these birds "Isolates"), he can pattern his song based on a tutor he experiences after P65 (Fig. 2; Eales, 1985, 1987; Morrison and Nottebohm, 1993). This is strong evidence that tutor experience, not a state of maturation, is the primary factor that determines whether or not a juvenile can memorize tutor song beyond P65. Further, tutor song isolation does not alter the timecourse or frequency of song production in Isolates, or patterns of gene expression in motor control brain areas (Mori and Wada, 2015). Isolate song structure contains several abnormal features because the juvenile lacks a guide for remodeling his immature vocalizations (Fig. 2). But, unlike the sensory learning circuit which is fundamentally affected by tutor song experience, the motor program proceeds even in the absence of song exposure, seemingly by innate drive (Mori and Wada, 2015; Morrison and Nottebohm, 1993; Deregnaucourt et al., 2004).

Isolates demonstrate that we can partially separate sensory from motor components of developmental song learning, and dissociate maturational age from tutor song experience to predict the ability of a P65 male to memorize tutor song. Together, these findings indicate that it is tutor song memorization, not motor rehearsal, that is most affected by experience, supporting a line of inquiry into sensory brain areas to elucidate mechanisms of a learning CP. Additionally, they demonstrate that tutor experience between P30-65 has two major effects on developmental song learning: 1) it provides an auditory memory of the tutor's song to guide production of a meaningful song structure, and 2) it provides the signal that minimizes neural plasticity and prevents the juvenile from future tutor song memorization.

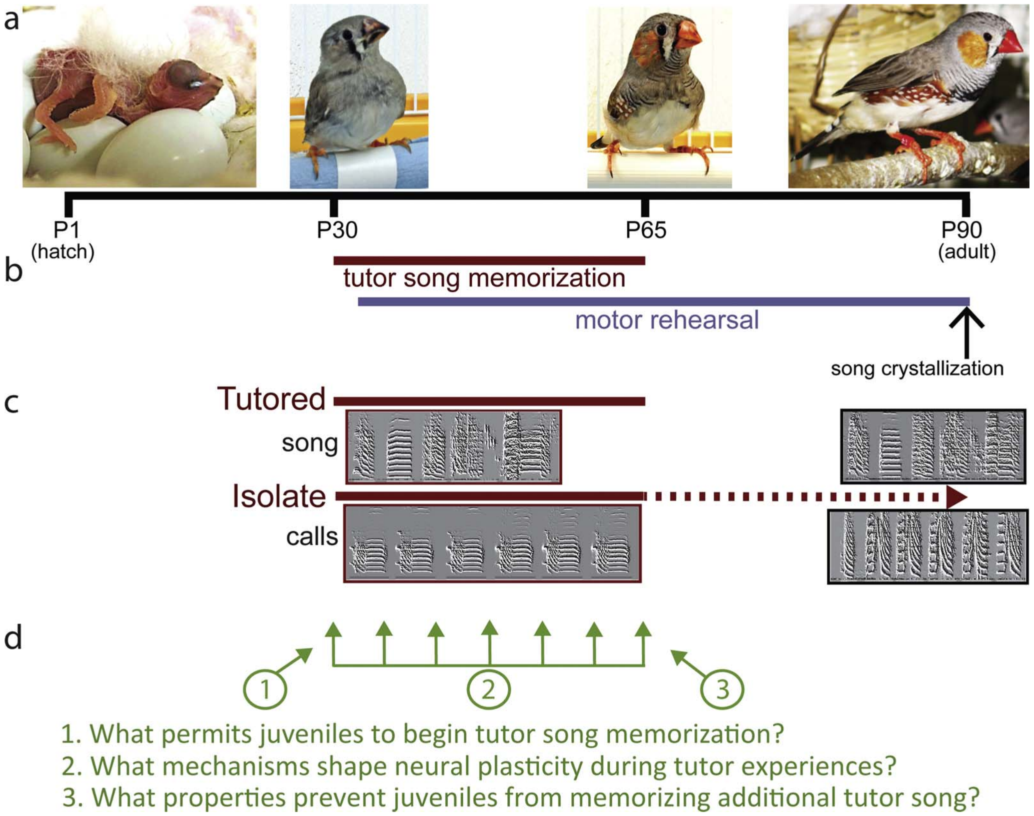

Fig. 2. Timeline of Posthatch development with major events and questions for song learning.
a: The process of song learning occurs during Posthatch development, a life phase with dramatic alterations. The timeline begins at P1, the day of hatch. P90 birds are sexually mature and therefore considered adults. P30 and P65 are key ages for onset and closing of the CP for tutor song memorization. Images of males at each key age are above timeline to show maturational progress. b: Developmental song learning requires coordination of sensory (tutor song memorization; red bar and font) and motor (blue bar and font) learning. Normally, tutor song memorization proceeds from P30-65, and the motor rehearsal phase, which utilizes the memory of tutor song to guide the juvenile's emerging song structure, begins ~P35 and proceeds until adulthood. Around P90, each male sings one stereotyped, or "crystallized" song. **c:** Males who experience a tutor ("Tutored") P30-65 sing high fidelity copies of the tutor's song, reflecting in large part the juvenile's ability to memorize the tutor's song. In contrast, males who not experience tutor song P30-65 ("Isolate") have an extended phase during which, if they are subsequently exposed to song, can memorize and produce a faithful copy (red dotted arrow). Isolate birds still "sing", reflecting some innate and experience-independent control over the motor system. Isolate birds do not need to be raised in acoustic isolation to have an extended period for tutor song memorization; exposure to females, who also display social behaviors and produce trains of calls that share many acoustic features with song, is not sufficient experience to close the CP at P65. Sonograms bounded by red P30-65 represent either a tutor's song (Tutored) or set of female calls (Isolate). Sonograms bounded by black at P90 show a high fidelity copy of the tutor song (Tutored) or abnormal song produced by a female-reared Isolate. **d:** The combination of a behaviorally-definable age of onset (1) and close (3) of a learning phase, and the reliance of closing on a specific experience (tutor song; 2), indicates that tutor song memorization is a valuable system in which to identify neural mechanisms that define the three main questions of a CP.

Isolates also reveal an intriguing feature of the stimuli that regulates experience-dependent plasticity. In some CPs, the animal needs to be completely deprived of the stimulus modality to extend plasticity. For example, for a CP that organizes mouse primary visual cortex, it is necessary to seal the eyes from all light to maintain experience-dependent plasticity (Hensch, 2005). In contrast, it is not necessary to deprive juvenile male zebra finches of all sound to extend the age for tutor song memorization. Raising juvenile males with females extends the age at which tutor song memorization can occur (Fig. 2; Eales, 1985, 1987; Morrison and Nottebohm, 1993). Females produce calls that share many of the species-specific acoustic features of song syllables and are oftentimes rapidly repeated in short bursts that can have similar durations and overall element number to song bouts (Fig. 2). We do not yet understand how a bird isolated from hearing song can distinguish a series of calls from a song bout. Existing data do not point to a simple factor; it is possible that it is a combination of social, multisensory processing, and innate processes are involved (Adret et al., 2012; Dooling and Prior, 2017; Chen et al., 2016, 2017; Adret, 2004a, 2004b; Araki et al., 2016; Menyhart et al., 2015; Deregnaucourt et al., 2013). This feature, however, does demonstrate that the CP for tutor song memorization is not dependent on acoustic stimulus per se, rather a complex, integrated experience that distinguishes it as a learning CP.

1.4. Three major research questions of a CP

The restricted phase during which tutor song memorization normally occurs, and the ability to manipulate the closing of this learning ability by controlling tutor song exposure represents a uniquely powerful opportunity to discover factors that limit and promote the ability to learn. As they pertain to tutor song memorization, three research questions of CPs can be defined (Fig. 2):

1. What factors contribute to the onset of stimulus-specific neural plasticity such that the CP for tutor song memorization can begin?
2. How are tutor experiences encoded, and how do factors required for learning correspond to those that contribute to CP closing?
3. What are the neural properties that prevent additional tutor song memorization despite continued exposure to adult songs after CP closing?

1.5. Age, experience, and brain area are core dimensions for CP investigations

It will be challenging to answer these three questions. Like investigation into all CPs, understanding tutor song memorization requires careful consideration of both age- and experience-dependent processes. Age may be particularly important for CP onset; experience is required to shape the affected brain circuit and pattern learned behavior, and CP closing depends on it. The complexity of the tutor song experience that regulates CP plasticity creates additional mechanistic considerations; it is not obvious that neural processes for this CP would be the same as those regulated by sensory deprivation. Further, the relationship between the process of learning (i.e. tutor song memorization) and the state of being capable of learning (i.e. the processes that restrict tutor song memorization to one period in spite of continuous exposure to song) is incompletely understood; each could depend on distinct mechanisms. Additionally, understanding the mechanisms of age and experience requires consideration of the specialization and interconnectedness of the brain areas required for developmental song learning.

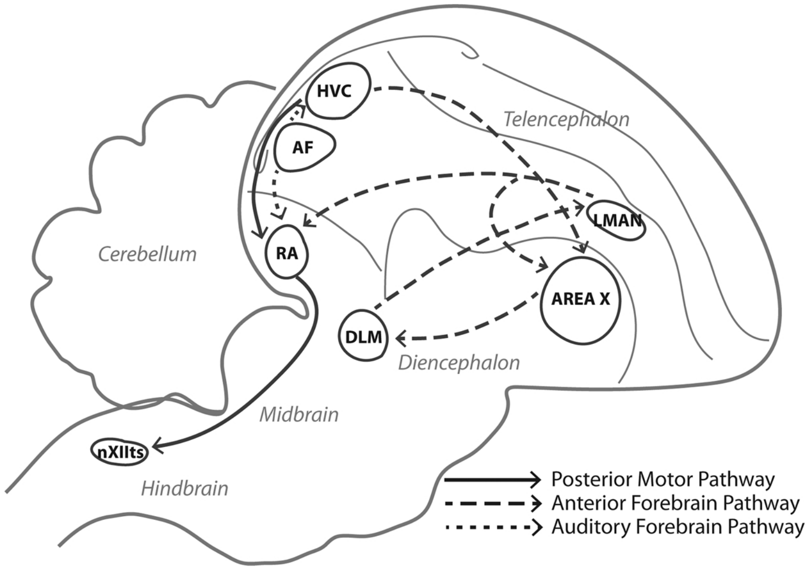

Fig. 3. Developmental song learning requires coordinated function across specialized but interconnected brain regions.
Three major modules of the song circuit are depicted in this cartoon of a sagittal section of an adult male zebra finch brain (dorsal is up, rostral is right); circles represent large brain regions within the circuit. The auditory pathway (dotted lines) provides information from the auditory forebrain complex (AF) to HVC and RA via projections to their adjacent processing regions HVC-shelf and RA-cup (not shown). HVC and RA are the two telencephalic nodes in the posterior motor pathway (solid lines), which is essential for song production. The sensorimotor AFP (dashed lines) is crucial for plasticity and stability of motor output, especially as juveniles acquire song. HVC is a component of both the AFP and posterior motor pathway.

Developmental song learning requires a distributed neural circuit (Fig. 3). The circuit is sometimes described in modules. One, the anterior forebrain pathway (AFP), includes the lateral magnocellular nucleus of the anterior nidopallium (LMAN) and Area X, which insert flexibility or stability into the motor system and have greater effect on song structure during sensorimotor error correction and song acquisition compared to stereotyped adult song production (Bottjer et al., 1984; Scharff and Nottebohm, 1991; Aronov et al., 2008; Doupe and Solis, 1997). In a second module, the posterior motor pathway, HVC (proper name) and the robust nucleus of the arcopallium (RA) drive vocal motor output, especially in adults (Nottebohm et al., 1976). HVC is a hub region within the entire circuit, projecting to both RA and Area X, and receiving auditory information. The auditory forebrain, containing a region of primary auditory cortex (Field L), and two regions with higher-order processing capabilities, the caudomedial nidopallium (NCM) and caudomedial mesopallium (CMM), was not included in the original description of the song circuit but has emerged as an integral element for sensory song learning (Mello et al., 2004; Dugas-Ford et al., 2012; Wang et al., 2010; London and Clayton, 2008; Yanagihara and Yazaki-Sugiyama, 2016; Nottebohm and Arnold, 1976; Ahmadiantehrani and London, 2017a, 2017b; Phan et al., 2006; Gobes et al., 2010). The regions of the auditory forebrain are highly interconnected, and they project to HVC and RA in the posterior pathway (via adjacent processing regions HVC-shelf and RA-cup), providing an anatomical pathway for auditory information to become integrated with the motor output of the system (Fig. 3; Bauer et al., 2008; Vates et al., 1996; Theunissen et al., 2004).

As sensory learning is most obviously regulated by the combination of maturational stage and tutor song experience, it is reasonable to predict that signatures of the CP for tutor song memorization are located in dedicated higher-order auditory processing areas such as NCM and CMM. But because this auditory information must reach other components of the circuit such as HVC and the AFP for guided motor rehearsal, it is plausible that signatures of CP experience are observable in those loci, too. It is important to also consider that an area outside of the song circuit may be instrumental in creating the representation of song as a distinct, complex stimulus, and that this region controls the CP for tutor song memorization.

1.6. *Why study genomes?*

The transitions between different plasticity states across the CP manifest at the cell and circuit levels but they are controlled at the genomic level because the genome largely determines the structure and function of the brain. It contains the code for receptors and transporters, enzymes, cytoskeletal and structural proteins, organelles, noncoding RNAs, transcription factors, and molecular cascade proteins, i.e. the components that support a cell's identity, plus its ability to survive, grow, communicate, and change (Fig. 4; Clayton, 2000). Investigation at molecular genomic levels have led to crucial discoveries about brain development and experience-dependent synaptic plasticity including learning and memory (Tully, 1996; Lee and Silva, 2009; Kandel, 2012; Sacktor, 2011; Pearson et al., 2005; Varjosalo and Taipale, 2008). Further, gene manipulations provided some of the first insights into mechanisms that control neural plasticity for CPs in other systems (Hensch et al., 1998).

The songbird research community has a legacy of discovery based on molecular and genomic investigation. These studies have demonstrated how differential regulation of genes can contribute to neural organization, function and behavior (Clayton, 2007, 2013; Mello and Clayton, 2015; Warren et al., 2010). Genetic analysis of unmanipulated zebra finches and cross-species finch hybrids reveal that some features of song can be directly influenced by genetics, but also suggest that some of the effect of genetics may be on the ability to learn itself (Forstmeier et al., 2009; Mets and Brainard, 2015; Woodgate et al., 2014). To understand a CP in tutor song memorization, it is necessary to capture how genomic responses to tutor experiences dynamically intersect with the maturational genetic program to govern neural plasticity.

1.7. *Perspective of the paper*

In this piece, we will consider developmental song learning from the perspective of the three major questions of CP outlined above. We will review what readouts of molecular and genomic function have already taught us, and propose strategies that can be used for future avenues of investigation. The review is not intended to be comprehensive; thorough treatments of the song system, recent updates on the state of avian genomes and genomic function, the history and dominant theory of CP mechanisms, and the parallels between developmental song learning and human speech acquisition have been written (Mello and Clayton, 2015; Knudsen, 2004; Doupe and Kuhl, 1999; Bottjer and Arnold, 1997; Bolhuis and Moorman, 2015; London, 2013; Gobes et al., 2017). The goal here is to present a reformulation of songbird data in the conceptual framework of a CP for learning. Zebra finches will be the focus because we understand their behavioral and neural features of developmental song learning better than most species.

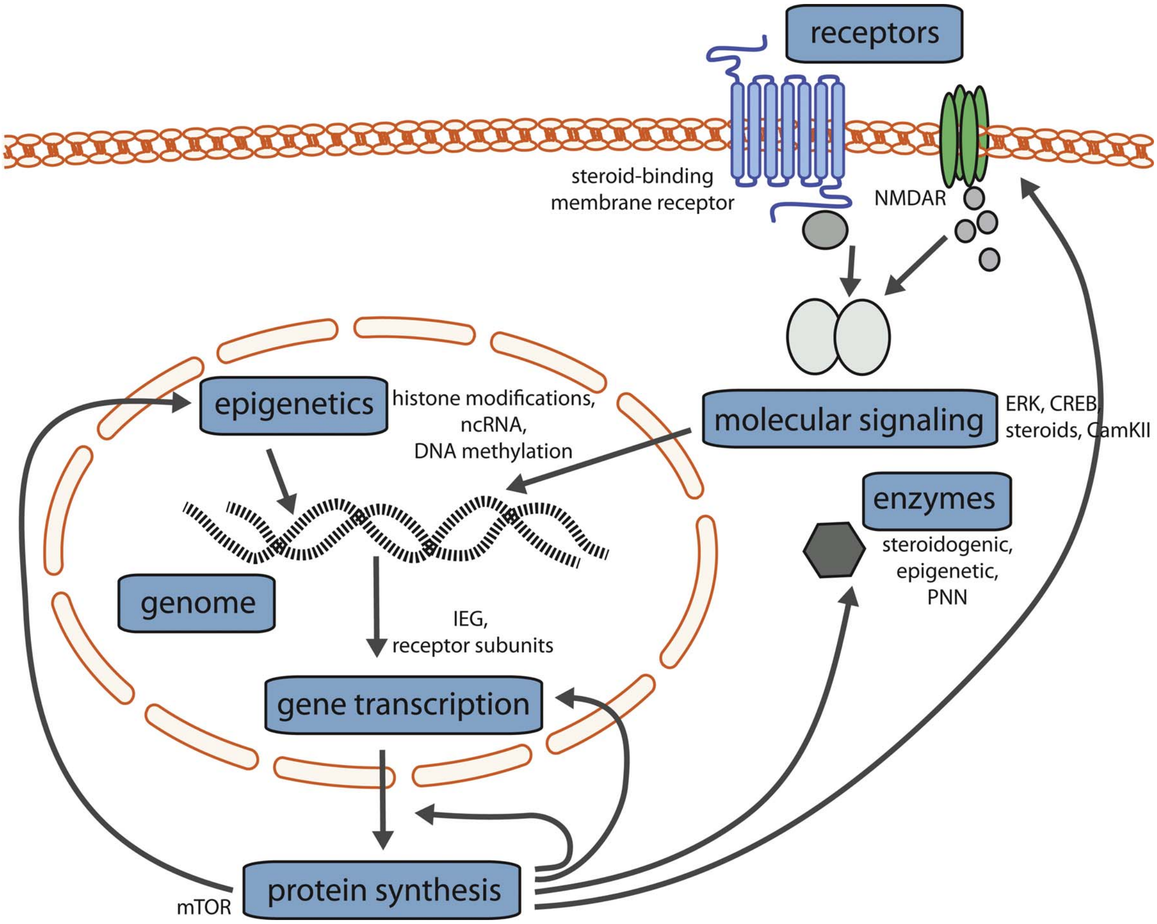

Fig. 4. The genome encodes cellular components that change with age and respond to experience to modify neural plasticity.
Regulated genomic function determines cellular function. Genomes encode for nearly all of the cellular components required for its structure and function, and cell activity feeds back to the genome in a dynamic cycle of regulation. Understanding readouts surrounding the genome therefore provide insight into the neural plasticity postulated to change as the ability to memorize tutor song fluctuates. Examples of the cell components from the text are included adjacent to their category.

2. Question 1: What is required for the onset of the CP for tutor song memorization?

2.1. Context

The onset of a CP represents a switch in brain function to a state that is receptive to a specific experience. As such, the onset depends on the maturational program whereby the cell populations, complement of molecular factors, and genomic state compatible with experience-dependent plasticity are organized. In some ways, understanding mechanisms gating the onset of the learning phase is the hardest CP question to answer because there are likely individual differences in the exact timing, and we do not yet have a reliable behavioral measure for the onset of learning ability (Alibali and Goldin-Meadow, 1993). The expectation is that onset is characterized by a suite of genes or molecular cascades that become responsive to hearing song at that time, but not before, in brain areas controlled by a CP for tutor song memorization.

2.2. Immediate early genes (IEGs)

For example, immediate early genes (IEG) can be expressed within minutes because their transcription is regulated by proteins activated on millisecond timescales (Loebrich and Nedivi, 2009). IEG transcription depends on the cell spiking, but is more selective, representing a specific molecular response to cell activity (Mayford and Reijmers, 2016; Kimpo and Doupe, 1997). In adult zebra finches, playbacks of novel conspecific song induce robust IEG expression exclusively in NCM and CMM, but not field L, of the auditory forebrain (Mello et al., 1992). In juveniles, the magnitude of the response to hearing song is attenuated. For the IEG ZENK (*zif268, egr-1, ngfi-a, krox24*), this occurs because its basal mRNA levels are already at high levels that are indistinguishable from adult song-induced levels (Jin and Clayton, 1997). Notably, unstimulated ZENK levels peak in males at P30, the first age at which tutor song experience is significantly represented in mature song structure (Roper and Zann, 2006; Jin and Clayton, 1997). P30 ZENK basal levels are significantly higher than at P20 and qualitatively distinct from levels at P40 (Jin and Clayton, 1997). Interestingly, at the protein level, comparison of ZENK and another IEG, FOS, revealed that females, who likely memorize their dad's song but cannot sing, have different molecular responses to novel conspecific playbacks at P30 than males (Bailey and Wade, 2003; Braaten et al., 2006; Riebel, 2000). Neurophysiological responses to novel conspecific playbacks are equivalent in male P20 and P30 NCM, raising the possibility that molecular and genomic responses provide signaling specificity that manifests as the onset of tutor song memorization (Stripling et al., 2001).

2.3. mTOR molecular signaling

Molecular signaling cascades involved in learning would also be predicted to become responsive to song experience at P30. Perhaps the clearest evidence of molecular signaling coming "on-line" at the onset of the CP is from a recent study of the mechanistic Target of Rapamycin (mTOR) molecular signaling cascade in juvenile zebra finches. mTOR protein complexes are well-suited to signal CP onset because they integrate signals from multiple receptor types to sense a complex cellular environment. mTOR then modulates synaptic function, in part by regulating protein translation, which can have widespread effects on cellular plasticity (Shimobayashi and Hall, 2014; Hoeffer and Klann, 2010). In NCM and CMM, mTOR activation after hearing song playbacks is regulated by age, sex, and prior song experience (Ahmadiantehrani and London, 2017a, 2017b). P30 males, but not P23 males or females at P23 or P30, show high levels of mTOR activation after hearing song playbacks, and males isolated from hearing song P23-30 show enhanced mTOR responses compared to normally-reared P30 males. The results of this playback experiment provide molecular support for a functional shift in the auditory forebrain in days prior to P30. Activation of mTOR is behaviorally-relevant; mTOR signaling is also required in the auditory forebrain during tutor experiences for tutor song copying to occur (Ahmadiantehrani and London, 2017a, 2017b). Interestingly, the Extracellular signal Regulated Kinase (ERK) cascade is also required in the auditory forebrain during tutor song memorization (London and Clayton, 2008). ERK activation is required for ZENK transcription, and ERK and mTOR cascades crosstalk (Cheng and Clayton, 2004; London and Clayton, 2008; Mendoza et al., 2011). The mTOR cascade may therefore be a valuable mechanism to gain insight into neural properties that support CP onset.

2.4. Excitatory/Inhibitory balance

The balance of excitatory and inhibitory signaling is a general feature of maturation and CP neural plasticity in other systems. Experience-dependent plasticity in a CP for primary visual cortex function can be (re-)opened with manipulations of GAD65, an enzyme which produces the inhibitory neurotransmitter GABA, and GABA-ergic neurons that express parvalbumin, a calcium-binding protein (Hensch et al., 1998; Davis et al., 2015). Although it has not been directly tested in the context of tutor song memorization CP onset, inhibition may be a key property guiding developmental song learning (Luo and Perkel, 1999; Spiro et al., 1999; Grisham and Arnold, 1994; Thode et al., 2008; Wild et al., 2001). Recently, inhibitory signaling in HVC was demonstrated to stabilize syllables across the developmental song learning process, showing how changes in inhibitory balance can significantly affect song behavior (Vallentin et al., 2016). It is possible that age- and experience-dependent alterations in parvalbumin and GAD65 cells also occur in the auditory forebrain across the CP for tutor song memorization, permitting a receptive state for sensory learning.

3. Question 2: How does tutor experience diminish neural plasticity required for later learning?

3.1. Consideration of learning, and the ability to learn

The search for mechanistic understanding for how a juvenile male memorizes his tutor's song has understandably garnered a lot of attention (Adret, 2004a, 2004b; Nordeen, 1997; Nordeen and Nordeen, 2004). However, to understand the CP for tutor song memorization, the central question is slightly different: how is the tutor experience encoded in such a way as to prevent future song learning?

It is possible that the ability to learn is diminished by the same processes required for tutor song memorization, but it is also possible that these mechanisms are divergent. For example, juveniles require very little tutor experience to faithfully copy the tutor's song but we do not yet know if that level of experience is sufficient to close the CP (Deshpande et al., 2014; London and Clayton, 2008; Tchernichovski et al., 1999; Ahmadiantehrani and London, 2017a, 2017b; Böhner, 1990). Further, while existing evidence suggests a direct effect of tutor song experience on regulating plasticity in higher-order auditory processing areas, their projections could transmit those experience-dependent influences to HVC, and additional downstream AFP areas integral to controlling plasticity during song acquisition. Published studies do not yet incorporate the possible relationships between tutor song memorization and the a priori receptiveness to learning, but some reveal brain areas and molecular processes that show transient and, in some cases, persistent, effects of tutor experience. These results can provide jumping-off points for disambiguating the processes required to learn from an experience from those that are required to be able to learn.

3.2. Experience-dependent mechanisms in the auditory forebrain

Properties of the auditory forebrain are affected by tutor experience. Gene expression studies and in vivo neurophysiology indicated that NCM in particular may be integral for tutor song memorization (Bailey and Wade, 2003, 2005; Gobes et al., 2010; Jin and Clayton, 1997; London et al., 2009a, 2009b; Phan et al., 2006; Yanagihara and Yazaki-Sugiyama, 2016). There are also large shifts in basal and song-induced profiles of auditory forebrain gene expression across the CP, which may be driven by tutor experience (Bailey and Wade, 2003, 2005; Jin and Clayton, 1997; London et al., 2009a, 2009b; Maul et al., 2010; Tomaszycki et al., 2006). A similar profile was not found in the posterior motor pathway and AFP (Mori and Wada, 2015). In vivo functional tests of ERK and mTOR have demonstrated that molecular signaling in the auditory forebrain during tutor experiences is needed for song copying (Ahmadiantehrani and London, 2017a, 2017b; London and Clayton, 2008). Additionally, traces of tutor experience persist in the auditory forebrain, as revealed by song playback experiments and the structural organization of lateralized function (Gobes et al., 2010; Phan et al., 2006; Chirathivat et al., 2015; Moorman et al., 2012). These data are consistent with evidence that tutor song experience affects sensory song learning, suggesting NCM and CMM are informative areas in which to investigate mechanisms of CP neural plasticity.

3.3. Learning mechanisms in the Anterior Forebrain Pathway

Perhaps reflective of the distributed nature of sensory information throughout the song circuit, tutor experience also activates molecular processes integral to learning and memory in HVC and Area X. In normally-tutored juveniles, a kinase required for long term memory, Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), is phosphorylated in Area X after tutor experiences (Singh et al., 2005; Hell, 2014; Sweatt, 2016; Coultrap and Bayer, 2012). Area X has properties of the mammalian basal ganglia, and no known direct sensory functions, yet CaMKII was activated even in juveniles who did not sing during the tutor sessions (Gale and Perkel, 2010; Doupe et al., 2005; Person et al., 2008). Additionally, a transcription factor central to learning and memory, cAMP Response Element Binding Protein (CREB), is activated by song playbacks in HVC (Sakaguchi et al., 1999). Interestingly, activated CREB (pCREB) was detected solely in HVC cells that project to Area X, not those that terminate in the premotor nucleus RA. This experiment was performed in adult zebra finches, but a role of pCREB in developmental song learning was demonstrated with the use of transgenics (Abe et al., 2015). Birds expressing a mutated gene that prevented CREB phosphorylation copied less of their tutor's song than controls and transgenics expressing the constitutively active form of CREB. These birds have both endogenous and mutated CREB, and both genes were transcribed widely throughout the brain, but pharmacological inhibition of pCREB in Area X presents compelling data that pCREB disruption in Area X causes song deficits. Interestingly, CREB transgenics also showed deficits in an associative learning paradigm that used auditory stimuli as the conditioned stimulus (Abe et al., 2015). It is not surprising that HVC and Area X would be sensitive to auditory information given their position downstream of the auditory system and their role in sensorimotor learning, but additional experiments will be needed to specifically parse tutor song memorization from sensorimotor functions in these studies, and tie them to CP alterations in neural plasticity.

In another nucleus of the AFP, LMAN, a functional test of the molecular determinants of tutor song memorization focused on N-methyl-D-aspartate receptors (NMDAR), the major excitatory receptor in the brain which is fundamental to learning (Park et al., 2014; Sweatt, 2016). NMDAR are composed of several subunits. The NR2 subunits, of which there are several types, modulate the kinetics of current flow (Paoletti et al., 2013). In LMAN, the levels of the NR2B subunit were significantly higher in P40 and P60 isolates compared to tutored controls (Singh et al., 2005). Receptors with NR2B subunits have longer current decay times, a property typically associated with learning (Kash and Winder, 2007; Shipton and Paulsen, 2014; Glasgow et al., 2015). It was therefore hypothesized that tutor experience was affecting NR subunit composition, which could alter subsequent ability to encode tutor experience. However, despite finding that birds whose NMDAR were blocked during tutor sessions copied song significantly less well than controls, "slow" NR2B-containing receptor types were later shown not to be required for song learning (Livingston et al., 2000; Basham et al., 1996). However, effects of early song isolation do leave a trace in LMAN; numbers of dendritic spines are higher in Isolates than tutored males; the overabundance of synapses may maintain too much, or disordered, signaling in the AFP that contributes to long-term disrupted song patterns (Wallhausser-Franke et al., 1995).

3.4. *Steroid hormones*

Steroids are intriguing mechanisms for controlling the neural plasticity of song learning. Steroids are small molecule hormones derived from cholesterol through a series of enzymatic reactions. Steroids signal via intracellular receptors that function as transcription factors to regulate expression of suites of genes. Some steroids also bind to membrane receptors, setting off intracellular molecular signaling cascades. Steroids therefore represent a diverse set of factors that can modify neural organization and function (London et al., 2009a, 2009b).

In developing zebra finches, the estrogenic steroid estradiol is the most powerful known masculinizing agent for the posterior motor pathway and AFP (Grisham and Arnold, 1995). Behaviorally, systemic administration of the androgen testosterone P20-40 affects song similarity scores while preserving number of song repetitions sung in rapid succession, a finding which could be interpreted as a greater effect on sensory song learning than the motivation for motor song production (Korsia and Bottjer, 1991). The enzymes required to synthesize androgens and estrogens are expressed in the developing brain, including in auditory forebrain and the traditional song control circuit (London et al., 2003, 2006; London and Schlinger 2007; Jacobs et al., 1999; Perlman and Arnold, 2003). This allows for specific steroid milieus to be synthesized for a particular brain area at specific times, especially because some enzymes can be rapidly activated based on experience (London et al., 2009a, 2009b; Chao et al., 2015; Charlier et al., 2015). Steroids are known to control multiple aspects of neural plasticity such as neuronal and glial survival, dendritic arborization, cell firing properties, and transcription of factors that contribute to cellular plasticity, and could therefore be strong candidates for regulating processes by which tutor experience minimizes neural plasticity such that song experience after P65 does not alter behavior (Woolley, 2007; Carver and Reddy, 2013; Leonard and Winsauer, 2011; McEwen et al., 2015; Melcangi et al., 2014).

3.5. *Summary*

Additional work is needed to reconcile findings from different molecular factors and brain regions to draw an integrated view of how and where a CP for tutor song memorization is encoded. Existing studies do provide evidence that tutor experience influences synaptic properties, molecular signaling, and transcriptional regulation – all key elements for the type of neural plasticity that would be remodeled to close the learning CP. Additional studies that incorporate direct tests of tutor song copying from tutors presented after the normal CP close will advance mechanistic insight into how tutor experience both provides a memory to guide a juvenile's emerging song structure and creates a state of low neural plasticity that prevents tutor song memorization beyond P65.

4. Question 3: What are the neural properties that prevent additional tutor song memorization after CP closing?

4.1. *Age-matched males with differing abilities to learn*

Experience, not age, closes a CP. The enduring effect of tutor experience on learning potential suggests experience-dependent mechanisms alter fundamental properties of a brain area, rendering it unreceptive to additional experiences. Comparing age-matched males who have experienced a tutor to those who have not may therefore elucidate the mechanisms underlying the loss of neural plasticity required for tutor song memorization in tutored birds, and the extension of learning ability in Isolates.

4.2. *Epigenetic mechanisms*

Epigenetic mechanisms may be particularly informative for understanding how accumulated tutor experience can extinguish the ability to learn from a tutor after P65. Epigenetic mechanisms are activated by experience and are relatively stable within a cell and across cell lineage generations (Akbarian et al., 2013; Kouzarides, 2007; Allis and Jenuwein, 2016; Li et al., 2007). They alter the function of the genome, largely by regulating transcription, without altering the genomic sequence. There are several types of epigenetic processes including non-coding RNAs (ncRNA), DNA methylation, and histone modifications, all of which can coordinate transcriptional regulation across sets of genes (Fig. 4). This is important, as it is likely that CP closing requires modulation of multiple components of underlying neural plasticity. Measures of ncRNA, DNA methylation, and histone modifications have been published in zebra finches, although not yet in the context of tutor song memorization (Gunaratne et al., 2011; Steyaert et al., 2016; Whitney et al., 2014; Warren et al., 2010).

However, epigenetic mechanisms direct brain development and modulate learning, holding promise that they could underlie the experience-dependent loss of plasticity at the end of a cognitive CP (Matheos and Wood, 2014; Bale, 2015). For example, future experiments designed to measure the epigenome within the auditory forebrain could reveal what genes are differentially epigenetically modified depending on prior tutor experience. From these data, it would be possible to identify and then test mechanisms that close or extend the CP for tutor song memorization. Alterations in auditory input do not significantly alter gene expression within AFP or posterior motor modules of the song circuit, leaving the auditory forebrain as a possible locus for mechanisms that define CP closing (Mori and Wada, 2015). One hypothesis is that tutor experiences leads to an accumulation of repressive epigenetic mechanisms. This would limit the magnitude and complexity of possible transcriptional responses to subsequent experience. New transcription and translation is required for the neural plasticity underlying learning and memory, thus epigenetic repression could create a state of low neural plasticity precluding behavioral change (Kandel, 2012).

4.3. *Perineuronal nets*

Perineuronal nets (PNNs) regulate CP plasticity in mammalian primary visual cortex (Berardi et al., 2004; Hensch, 2005; Ye and Miao, 2013). PNNs are composed of several different proteins that can differ across brain areas, but which are largely made up of proteins with glycosaminoglycan side chains such as chondroitin sulfate proteoglycans. PNNs are part of the extracellular matrix located outside of cells, where they function to stabilize synaptic connections, and therefore affect neural plasticity directly (Sorg et al., 2016; Wlodarczyk et al., 2011). PNNs also affect other possible mechanisms of neural plasticity, notably inhibitory parvalbumin cells (e.g. Yamada et al., 2015). PNNs can regulate adult learning, though sometimes are necessary for learning and othertimes hinder it, highlighting the need for investigation into their role in each neural system (e.g. Kinden Lensjø et al., 2016; Banerjee et al., 2017; Sorg et al., 2016).

In zebra finches, there are some indications that PNNs may regulate neural plasticity for song. Sex differences in PNN have been reported in nuclei of the posterior motor pathway and AFP, and the distribution of PNN proteins becomes more intensely and specifically organized around cells in adult males compared to P33 males (Meyer et al., 2013; Cornez et al., 2015; Balmer et al., 2009). Complete developmental isolation (sound and social isolation) altered the proportion of parvalbumin cells surrounded by PNN observed in adulthood, seemingly by altering the parvalbumin population (Balmer et al., 2009). When PNNs were enzymatically degraded, however, song plasticity did not reemerge, indicating that PNNs are not sufficient to gate neural plasticity (Balmer et al., 2009). Further, while PNNs were reported in primary auditory area Field L, they are absent in adult NCM and CMM; there are currently no reports of juvenile patterns (Cornez et al., 2015). It therefore remains possible that PNN have a role in limiting neural plasticity at the end of the CP for tutor song memorization, perhaps in coordination with other cellular processes. Alternatively, PNNs may be one example of how a CP in a primary sensory area differs mechanistically from a CP for learning.

5. Strategies moving forward

For now, we have tantalizing clues for how to understand developmental song learning in the context of a CP for learning. To build on the foundational molecular, genomic, and epigenomic work, behavioral paradigms that explicitly test the ability to learn during and after the typical CP need to be established, and additional emerging methodological strategies that target different levels of analysis can be employed.

5.1. Genetic manipulation

Genetic manipulations in the form of transgenic animals have been instrumental in other systems to test the influence of a particular gene and its related functional partners on brain function and behavior (Agate et al., 2009; Scheenen et al., 2009; Huss et al., 2015; Picciotto and Wickman, 1998). Indeed, two recent zebra finch transgenics demonstrate gene effects on developmental song learning (Liu et al., 2015; Abe et al., 2012).

For use in developmental song learning studies, especially to examine CP mechanisms, two factors of gene manipulation are important: temporal control and neuroanatomical specificity. The current transgenics are not designed to control these dimensions, but the first issue is solvable by creation of conditional constructs that have transgene transcription induced by an exogenous molecule. Currently, the most tractable genetic solution to the second issue is to deliver gene manipulation constructs to individual birds, either via viral vectors or with electroporation in hatchlings (Ahmadiantehrani and London, 2017a, 2017b; Haesler et al., 2007; Heston and White, 2015). Viruses carrying transgenes can be injected directly into a brain area of interest. Viral infection rates are lower and less predictable in songbirds than in lab rodents but generation of high titer viruses for more effective infections is in continual progress, and this strategy has been successfully employed to show, for example, a causal role for FoxP2 in AFP function (Haesler et al., 2007; Heston and White, 2015). Electroporation has > 95% success rate and constructs can be neuroanatomically targeted with placement of the electrode paddles (Ahmadiantehrani and London, 2017a, 2017b; Chen et al., 2014). Viral vectors and electroporation are strategies to deliver transgenes; their cargo can include conditional constructs, thus creating both temporal and neuroanatomical control. For example, it has become possible to decrease transcription of enzymes that add repressive modifications to histones starting P30 and test if its disruption is sufficient to prevent CP closing. Of course, non-genetic pharmacological agents that disrupt molecular genomic processes also provide temporal control and can be neuroanatomically localized via infusion placement, and can be used in complement with genetic strategies.

5.2. fMRI

Although informative in many ways, one of the constraints of molecular genomic work is the inability to obtain repeated measures within the same individual. Neurophysiology is compatible with acquisition of repeated measures, but has other limitations for understanding underlying mechanisms governing CP learning, such as the timescale of the phase for tutor song memorization. Functional Magnetic Resonance Imaging (fMRI) is non-invasive and could be used in complement with molecular and genomic measures and manipulations. fMRI provides meaningful signal in songbirds (Louder et al., 2016; Van Ruijssevelt et al., 2013; Voss et al., 2007). fMRI can be used to identify regions of cellular activity in response to a particular task performed in the magnet, or to measure resting state signals to create functional connectivity maps associated with alterations in cognitive function (Miŝic et al., 2016; Román et al.,2017). For example, it is possible to adapt methods from human studies to define whole-brain functional connectivity maps across the CP in birds with and without tutor experience, in males and females, and in genetically modified birds. Results would elucidate how neural networks develop based on sex, age, and experience. They would also provide insight into whether or not a region outside of the song circuit may be involved in integrating components of the tutor experience to regulate CP closing. Data from genetically manipulated birds would inform on molecular and cellular contributions to brain network functionality. Lastly, fMRI measures can be analyzed with respect to the individual's song to provide individualized brain-behavior relationships.

5.3. Comparative studies

Nature provides the substrate for good experiments – there is a diversity in learning strategies represented across different bird species. Comparative experiments have already proven fruitful for recognizing key features of CP learning and genomic function (Murphy et al., 2017; Warren et al., 2010; Clayton et al., 2009; Louder et al., 2016). Investigation of candidate mechanisms for CP neural plasticity in seasonal learners, open learners, and in parasite species who hatch in the nest of another species but who must learn a conspecific song, will provide strong tests of generalizability and reveal additional mechanisms specific to these systems of learning. Questions include: Do the same factors that direct CP learning in juvenile zebra finches underlie these alterations in seasonal plasticity? Might species-specific patterns of IEG expression predict phases of neural and behavioral plasticity? Do PNNs dissolve and reform according to learning ability? The expectation is that with systematic cross-species examinations, it would be possible to identify conserved mechanisms that promote and limit the ability to learn.

6. Conclusion

We have known for decades that male zebra finches have a limited developmental window in which to acquire song despite constant exposure to singing birds. Features of this learning system meet criteria for a sensory learning CP. We are now in a position to leverage the advantages of the system to make unique novel contributions about neural mechanisms that limit and promote the ability to learn. Discoveries made in this system can be applied to other songbird species and models of learning to advance understanding of learning potential.

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