

Neuronal mechanisms regulating the critical period of sensory experience-dependent song
learning

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Abstract

Neuronal circuits are intensively shaped depending on experiences received during developmental critical periods. How neuronal circuits are sculpted can even affect the later development of higher cognitive functions, such as vocal communication skills. Here, we propose songbirds that learn to sing from early auditory experiences as a model for understanding the neuronal mechanisms underlying the development of multistep vocal learning. By applying the principal concepts of neuronal mechanisms for regulating the timing of critical periods, which have been well investigated by using experience-dependent

22 mammalian cortical plasticity, we review our current understanding of the underlying neuronal
23 mechanism of the song-learning critical period.

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25 Keywords: critical period; plasticity; neuronal circuits; songbird; vocal communication; learning;
26 auditory

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1. Introduction

From our own experience, we know that experiences, particularly during developmental periods, have great impacts on our perceptual skills and even on the later learning of higher cognitive tasks, suggesting the presence of a developmental ‘critical period’ (CP) for higher cognitive functions. The concept of the CP originally derives from developmental biology, where applications of drugs to developing embryos at particular stages cause specific malformations (Stockard, 1921). Since then, the concept of a specific developmental time window during which the impact of environmental stimuli has a greater impact has been applied to multiple fields, including neuroscience, and the neuronal mechanism of plasticity during CPs and the underlying mechanism for regulating the timing of CPs have been intensively investigated, especially in experience-dependent cortical plasticity. On the other hand, Konrad Lorenz showed that goose hatchlings can imprint upon moving objects (Lorenz, 1935), followed independently by Eckhard Hess revealing the presence of a time window for imprinting to occur (Hess, 1959), suggesting the presence of CPs even in higher cognitive functions, such as learning. Although the length and timing of CPs remain under debate, CPs exist in human speech and perception and even in language acquisition (Hartshorne et al., 2018; Kuhl, 2010; Werker and Hensch, 2015). Like humans learning to speak, songbirds learn to sing from their early auditory experiences during development. By exposing juvenile birds to different tutors at different times, the presence of a song-learning period has been found for zebra finches, a widely used songbird model (Clayton, 1988; Eales, 1985; Roper and Zann, 2006). However, despite the well-defined presence of CPs in song-learning behavior in zebra finches, neuronal mechanisms that regulate the timing and

plasticity of CPs have not yet been well described. In this review, we discuss how much we can apply the concepts that we have learned from the neuronal mechanism of CPs in mammalian cortical neuronal plasticity, especially in the visual system in rodents, to the CPs of bird song learning.

2. Multiple steps of CPs

There are multiple stages in the development of speech and perception in humans, and the existence of a distinct CP for each stage has been suggested (Kuhl, 2010; Werker and Hensch, 2015). Similarly, juvenile zebra finches learn to sing in two well-orchestrated time windows, a sensory learning period during which juveniles memorize adult songs by listening and a sensorimotor learning period during which they vocally match their vocalization to memorized tutor songs by using auditory feedback (Fig. 1A). Recent studies further suggest that learning of syllable phonology and temporal sequence happen in different steps in the later sensorimotor learning period (Lipkind et al, 2013; Lipkind et al, 2017). Sensory learning starts before they begin to sing by themselves, indicating that the sensory learning period begins earlier than the sensorimotor learning period (Brainard & Doupe, 2002; Mooney 1999). Exposing juveniles to another tutor later than 60 days post-hatching (DPH) does not lead to additional song learning (Clayton, 1987; Eales, 1985), although juveniles at this age are still updating their vocalizations, indicating that the sensory learning period ends earlier than the sensorimotor learning period does. How are these two phases of CPs organized, and how are the timings regulated? Sensory deprivation (isolation) between sequential learning from two different tutors delays the end of the

sensory learning period but not of the sensorimotor learning period (Yazaki-Sugiyama and Mooney, 2004). Deafening as well as disruptions of auditory feedbacks in adults causes slow degradation of the song, suggesting that sensorimotor matching continues in adults, although new song learning does not (Lombardino and Nottebohm, 2000; Nordeen and Nordeen, 1992; Leonardo & Konishi, 1999; Fukushima & Margoliash, 2015). Despite behavioral studies suggesting distinct time windows for sensory learning and the sensorimotor learning period, whether these two steps of the CPs for song learning are regulated by distinct neuronal mechanisms has not yet been thoroughly investigated. In the following paragraphs, we will review the studies on the neuronal mechanisms underlying CPs and further discuss which stages of CPs are regulated.

3. Neuronal mechanism of CPs in bird song learning

A few decades ago, Hubel and Wiesel found that closing one eye of kittens, but not of adult cats, causes the loss of visual responsiveness of neurons in the primary visual cortex to stimulations to the deprived eyes (ocular dominance (OD) plasticity) (Hubel and Wiesel, 1970; Wiesel and Hubel, 1963) and suggested that cortical neuronal circuits are shaped depending on sensory experiences from the environment. Since then, the mechanisms by which neuronal circuits modify their structures and functions, as well as the underlying neuronal mechanisms regulating the timing, opening and closing of CPs, have been intensively investigated using OD plasticity. A series of studies have suggested some principles for regulating the timing of the CP (Hensch, 2004). In higher cognitive behaviors,

such as imprinting, bird song learning and human speech development, while the presence of CPs is obvious based on behavior, the neuronal mechanism that regulates the timing and plasticity during the CP has not yet been well described. Here, we will consider whether each of the principles suggested from OD plasticity in mammals can also be applied to CPs in zebra finch song learning.

1) Activity-dependent regulation of CP timing

The onset timing of CP of OD plasticity is determined by sensory experiences (Hensch, 2004). Dark rearing as well as TTX injection into the retina delays the onset of the CP of OD plasticity (Chapman et al., 1986; Mower, 1991; Mower et al., 1985). On the other hand, earlier onset of the CP of OD plasticity by increasing GABA activity in the earlier developmental stages does not lengthen the duration of the CP (Fagiolini and Hensch, 2000), suggesting that sensory experience triggers the onset of the CP and once it's open the duration of the CP is determined. Similarly, in zebra finch song learning, sensory deprivation in the form of isolation from father's songs during the sensory learning period allows juvenile zebra finches to learn from tutors to which they are exposed beyond the normal CP (> 60 DPH), while it delays little the end of the sensorimotor learning period (Eales, 1987; Morrison and Nottebohm, 1993). Auditory isolation during a particular period also delays NMDA current development in the song nucleus LMAN (Livingston et al., 2000), where song motor plasticity is regulated (Kao et al., 2005; Ölveczky et al., 2005). As observed in mammalian OD plasticity, the timing of CPs in zebra finch song learning has been suggested to be regulated by auditory experiences. Series of experiments in which juveniles are exposed to tutors at different ages and for different durations suggest that auditory

experiences of father's songs regulate both the beginning and the duration of CPs (Eales, 1987, 1985; Roper and Zann, 2006; Yazaki-Sugiyama and Mooney, 2004). However, as all the studies analyzed the data by the extent of song learning, which includes factors of both sensory and sensorimotor learning, the precise periods of sensory and sensorimotor learning are not yet clear.

2) Regulation of CPs by inhibitory signaling

In mice in which neurons have poor GABA release (GAD 65 KO), monocular deprivation even during the normal CP does not cause OD plasticity, and injection of the GABA_A receptor modulator diazepam restores OD plasticity at any age (Fagiolini and Hensch, 2000). Although there are several subtypes of GABA-positive interneurons in the mammalian neocortex, the emergence of a particular cell type, large basket parvalbumin (PV)-expressing interneurons, shows a close correspondence with the onset of the OD CP (del Río et al., 1994). The acceleration of PV neuron development by BDNF causes precocious OD CP (Huang et al., 1999). Moreover, deletion of sensory inputs delays the maturation of perisomatic GABAergic inputs, which normally come from PV neurons (Cellerino et al., 1992; Chattopadhyaya et al., 2004). Transplantation of immature PV neurons into primary sensory areas can restore plasticity after the end of the CP (Tang et al., 2014). In addition to regulating the timing of CPs, inhibitory neurons show a unique plasticity pattern in response to sensory deprivation and are suggested to control cortical network plasticity (Yazaki-Sugiyama et al., 2009a). Even beyond the primary visual cortex, auditory deprivation delays GABA current maturation in the primary auditory cortex of gerbils (Takesian et al., 2012). Together, these findings suggest that maturation of GABA inhibitory signaling triggers CP onset. Although GABA

inhibitory signals have been reported to shape auditory response properties of zebra finch brain, as in the mammalian higher auditory cortex, development of GABA inhibitory signal has not yet been well studied. While the number of GABAergic neurons in the song motor nucleus, RA, peaks near the end of the sensory learning period in males, which sing, it does not in females, which do not sing (Sakaguchi, 1996). Furthermore, recent study showed developmental implementation of local inhibitory signals for auditory responsiveness in sensory-motor integration area, HVC (Vallentin et al, 2016). On the other hand, the numbers of PV neurons are reported to be stable in most of the nuclei of the song system, HVC, RA and LMAN, and instead decrease in Area X during development. On the other hand, social isolation, which delays the end of the sensory learning CP, prevents the maturation of PV neurons (Balmer et al., 2009). The immunoreactivity for BDNF proteins increases over the song learning period in the song control nucleus only in male zebra finches, while the development of PV neurons has not been examined (Tang and Wade, 2013). We previously reported that acceleration of GABA inhibitory function in the zebra finch juvenile brain during early developmental stages by diazepam injection disrupts song learning (Yazaki-Sugiyama et al., 2009b), suggesting that maturation of GABA inhibitory currents triggers the CP of bird song learning. However, the location of the inhibitory system has not yet been identified.

3) Molecular markers of the end of a CP

While maturation of GABA inhibitory function has been suggested to trigger the onset of CPs, some molecular markers seem to stop neuronal plasticity in the juvenile period. Among several molecular brakes reported, NgR (gene for the nogo-66 receptor) (McGee et al.,

2005; Stephany et al., 2014), the acetylcholine receptor linker LYNX1 (Morishita et al., 2010), and perineuronal nets (PNNs) are the most prominent markers, which act as anatomical brakes on neuronal plasticity. Maturation of PV neurons triggers the onset of the CP and controls OD plasticity in V1 (Cellerino et al., 1992). PNNs enwrap PV neurons during development, in an activity-dependent manner (Sugiyama et al., 2008), and they function to maintain the ionic concentrations in neurons (Härtig et al., 1999). PNNs are thought to anatomically stabilize the neuronal circuit connection, and removing PNNs in adults restores the OD shift after monocular deprivation (Pizzorusso et al., 2002). Sensory deprivation, such as dark rearing, which delays the onset of the CP, delays the emergence of PNNs surrounding PV neurons. In zebra finch song learning, the emergence of PV neurons is not correlated with song learning during development. However, PNN enwrapment of PV neurons in HVC and Area X begins during the sensory and sensorimotor learning periods, and sensory deprivation (isolation) delays PNN development (Balmer et al., 2009). Interestingly, PNN formation in the song nucleus is much more limited in bird species that retain vocal plasticity in adulthood (Cornez et al., 2017).

4. Brain areas for neuronal plasticity during song-learning CPs

The existence of CPs in zebra finch song learning is well accepted based on their behavior, and neuronal mechanisms for regulating CPs have been investigated. However, the type of neuronal plasticity that occurs and the areas in the zebra finch brain that show plasticity during sensory and sensorimotor learning have not been identified. As described in previous paragraphs, there have been reports about various areas of the zebra finch brain, especially components of the song system, in relation to molecular markers for

ending CPs and to the maturation of inhibitory neurons triggering the onset of CPs, but none of these has been completely described. Recently, we examined the zebra finch brain region in which neuronal plasticity is observed during the sensory learning period when a memory of tutor song is formed through auditory experiences. A number of studies have suggested that tutor song memories can be mapped to the caudomedial nidopallium (NCM), a region homologous to the mammalian higher auditory cortex. The expression level of an immediate early gene, ZENK, is higher in the NCM of birds exposed to tutor songs than in birds exposed to novel songs (Bolhuis et al., 2000; Gobes et al., 2010; Terpstra, 2004). NCM neurons decrease neuronal auditory responsiveness along with repeated song stimulation (habituation), and the rate of habituation is slower for tutor song repetition than for novel conspecific song repetition (Phan et al., 2006). Furthermore, blocking extracellular-signal-regulated kinase activity in the NCM in juvenile zebra finches prevents song learning (London and Clayton, 2008). Recently, we performed chronic recording of neuronal activity from the NCM of juvenile zebra finches over song learning. We identified two neuronal subsets, broader spiking (BS) and narrower spiking (NS) neurons, which were distinct in spike shapes and firing rates. Among them, a specific subset of BS neurons in the tutored juveniles showed highly selective auditory responses to the experienced tutor's songs, while these neurons were barely found in isolated pre-tutored juveniles and in isolated age-matched control juveniles (Fig. 2). Moreover, we found that the selectivity of auditory responsiveness decreases with the blockade of local GABA inhibitory functions within the NCM (Yanagihara and Yazaki-Sugiyama, 2016). The NCM is suggested to be a place where neuronal circuits are shaped for sensory song learning.

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205 5. Closing remarks

206 Despite the well-accepted behavioral concept of CPs in zebra finch song learning, the
207 underlying neuronal machinery remains to be explored. Here, we reviewed the studies on
208 CP in zebra finch song learning and assessed whether what we have learned from the CPs
209 of experience-dependent mammalian cortical plasticity could be applied to those of zebra
210 finch song learning. Some studies on zebra finch song learning showed clear parallels in the
211 relationship between the emergence of molecular markers for CP closure and the end of
212 song learning. However, no study has yet investigated the causality, such as testing
213 whether removing molecular brakes allows the extension of the song-learning CP. Neuronal
214 mechanisms regulating CPs have been studied intensively in mammalian experience-
215 dependent cortical plasticity. As with human speech acquisition, zebra finch learns to sing
216 in multiple steps (Brainard & Doupe, 2002; Mooney, 1999). Other studies also suggest that
217 learning of syllable phonology and sequence take place in different steps (Lipkind et al,
218 2013; Lipkind et al, 2017). The new concepts of independent regulation of each CP in zebra
219 finch song learning might shed light on the neuronal mechanism of CPs for higher cognitive
220 function, which involves separate CPs for multiple steps. Recent studies have shown that
221 adult birds can memorize and discriminate songs of their associates via certain tasks
222 (Comins and Gentner, 2013; Kriengwatana et al., 2016). The zebra finches which were
223 prevented from auditory feedbacks with loud white noise exposure retain motor plasticity
224 in the adult period (Funabiki & Konishi, 2003). Further, other studies have shown that adult
225 birds retain limited motor plasticity and can shift their pitch in response to aversive

learning (Ali et al., 2013; Andalman and Fee, 2009; Tumer and Brainard, 2007; Xiao et al., 2018). These findings suggest that zebra finch song learning can be further used to evaluate the effects of early auditory experiences on song perception or motor skills. The application of recently developed technologies to the songbird model would also accelerate the understanding the causal relations between suggested neuronal mechanisms and bird song learning and the understanding of how early life would impact higher cognitive functions.

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Figure legends

Fig. 1: Timeline of zebra finch song learning and the song system in the zebra finch brain.

A: Zebra finches learn to sing during the developmental critical period, which consists of a sensory learning period and a sensorimotor learning period. Some studies suggested the regulation of critical period with auditory experiences and the maturation of inhibitory signal.

B: Brain areas that are necessary for song learning and productions are identified as the 'song system'. HVC, at the apex of the song system, receives inputs from auditory pathways. HVC receives inputs from an auditory pathway which consists of the brain areas equivalent to (eq) the mammalian auditory cortex.

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249 **Fig. 2:** Neuronal plasticity in the zebra finch higher auditory cortex during sensory song learning.

250 Top: Timelines of chronic electrophysiology recording over the song-learning period. Inset:

251 Chronic electrophysiological recording from the NCM neurons identified two types of neurons,

252 broader-spiking (BS) and narrower-spiking (NS) neurons, which can be distinguished by their

253 spike shapes. Middle: Pie charts for the percentage of the BS neurons that show selective

254 auditory responses to tutor's song or bird's own song, recorded before (left) and after (right)

255 song learning. Bottom: Mean firing rate (FR) curves (10 ms, smoothed with a Gaussian kernel)

256 and time-aligned spectrogram for each auditory stimulus of representative BS neurons

257 recorded before (left) and after (right) song learning.

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