Anatomical and Synaptic Substrates for Avian Song Learning

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ABSTRACT: In songbirds, vocal learning occurs during periods of major cellular and synaptic change. This neural reorganization includes massive synaptogenesis associated with the addition of new neurons into the vocal motor pathway, as well as pruning of connections between song regions. These observations, coupled with behavioral evidence that song development requires NMDA receptor activation in specific song nuclei, suggest that experiences associated with vocal learning are encoded by activity driven, Hebbianlike processes of synaptic change akin to those implicated in many other forms of developmental plasticity and learning. In this review we discuss the hypothesis that develpmental and/or seasonal changes in NMDA receptor function and the availability of new synapses may modulate thresholds for plasticity and thereby define *sensitive* periods for vocal learning.
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***Keywords:* songbird; NMDA; learning; sensitive period**

INTRODUCTION

A great deal of research in the neurosciences concerns how the brain acquires, stores, and retrieves an organism's experience to structure behavioral change. Traditionally, these questions have been approached by studying adult animals engaged in learning (Morris, 1989; Martinez and Derrick, 1996). However, in recent years, studies of developmental plasticity also have provided insights into how experience is stored in the nervous system (Constantine-Paton et al., 1990; Knudsen and Brainard, 1995; Shatz, 1996). For instance, the ontogeny of vertebrate sensory systems reveals that early experience profoundly affects key features of nervous system organization, leaving visible signatures of synaptic change that often are more obvious than those engendered by learning in adulthood. Also, the effects of experience on developing patterns of neural organization often depend critically on the precise nature and timing of sensory stimulation, providing the experimenter a degree of control over activity-driven synaptic change that may be lacking in adult learning paradigms. These studies of early plasticity have fostered the idea that development and adult learning exist on a continuum and that in both contexts experience engages similar synaptic processes to produce neural change.

The development of song in birds occupies a central position on this continuum. On the one hand, song development clearly entails learning (Marler, 1997). In fact, songbirds normally exhibit two distinct phases of learning. During memory acquisition, birds acquire a memory of song patterns heard. This template can be stored in the nervous system for long periods before it is accessed during sensorimotor learning, the second stage in song development. At this point birds begin to produce their own songlike vocalizations, relying on auditory feedback to gradually match these utterances to the stored memories of song. In many birds, these sequential and sometimes overlapping periods of learning occur within the first several months after hatching. In zebra finches, the focus of much of the neurobiological work discussed in this review, memory acquisition roughly extends from 20 to 60 days after hatching (Immelmann, 1969; Eales, 1985, 1987). Vocal practice begins at about 35 days of age and

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culminates in the production of a stable song pattern by 80–90 days (Arnold, 1975; Immelmann, 1969). Beyond this point, auditory feedback continues to be important for maintaining adult song patterns even in some ''age-limited'' learners (Nordeen and Nordeen, 1992; Woolley and Rubel, 1996; Okanoya et al., 1991), and in open-ended learners memory acquisition and/or sensorimotor learning can reoccur in adulthood (Chaiken et al., 1994; Nottebohm and Nottebohm, 1978; Nottebohm et al., 1986).

While song development clearly entails learning, it also shares important attributes with several well-studied instances of developmentally regulated plasticity. Most birds are predisposed to acquire conspecific song (Marler, 1984, 1990), and in fact, some species will learn only from tutors with which they can interact both visually and socially (Eales, 1989; but see Adret, 1993). Such species-specific constellations of sensory cues may serve as ''gates for learning'', by diffusely affecting the motivational and attentional state of the animal in ways that promote the neural changes involved in the formation of song-related memory. This phenomenon also is characteristic of plasticity in developing sensory systems; behavioral state is crucial in determining whether a specific sensory manipulation will trigger enduring synaptic change (Singer, 1986).

Likewise, the existence of developmental and seasonal sensitive periods for song learning resembles the temporal constraints associated with experience-dependent plasticity in developing sensory systems. Although most often the timing of memory acquisition is limited to a sensitive period, recent evidence indicates that sensorimotor learning may be constrained temporally as well (Pytte and Suthers, 1996). Presumably, such sensitive periods for plasticity are defined by the time course of events that facilitate synaptic change; and in developing sensory systems, the existence of such periods has been exploited both for identifying neural processes sculpted by experience (e.g., synaptic rearrangement) and for developing hypotheses about the underlying mechanisms of synaptic change (Fox and Zahs, 1994). Similarly, we know now that sensitive periods for song learning overlap with major periods of synaptic change associated with the initial development of song-related neural pathways and the seasonal recreation of such circuits, suggesting that song learning involves factors and/or processes that are developmentally or seasonally regulated. Identifying what these events are and where they occur can help us develop hypotheses regarding the synaptic processes engaged during memory acquisition and sensorimotor learning. Useful in this regard is the fact that sensitive periods for song learning, like those for other instances of developmental plasticity, are not rigidly specified, but instead are themselves sensitive to early experience. When birds are denied the opportunity to learn conspecific song (through acoustic isolation), they often are able to learn song beyond the normal closure of the sensitive period (Immelmann, 1969; Kroodsma and Pickert, 1980; Eales, 1985, 1987). As we shall see, this ability to manipulate the timing of song learning can be a powerful tool for pinpointing those specific developmental changes that facilitate or underlie song learning.

Our goals in this review are threefold. First we will describe some of the manipulations that impair song learning in birds, briefly describing hypotheses that arise from these findings. Next we will describe the organization of song regions during learning, focusing first on synaptic and neurochemical changes within anterior forebrain regions implicated in song development, and then describing wholesale changes in neuronal addition and turnover that occur in the vocal motor pathway during learning. Finally, we will suggest further work that must be done if we are to understand how changes in synaptic chemistry and organization are related, and how such changes affect specific aspects of vocal plasticity.

NEURAL SITES AND PROCESSES IMPLICATED IN SONG LEARNING

Progress towards understanding the neurobiology of birdsong has been facilitated by the existence of a discrete network of brain regions that has evolved in parallel with the capacity for learned song behavior (Brenowitz, 1997). The functional organization of this system is discussed at length elsewhere in this issue (Wild, 1997; Margoliash, 1997; and Doupe and Solis, 1997), so we will only review briefly what has been learned about the function of these regions through lesion and electrophysiological studies. Figure 1 is a simplified schematic of brain regions involved in song learning and production. It is not intended to depict all of the circuits engaged during the development and adult expression of this behavior, but instead focuses on regions and pathways about which we have ontogenetic information and therefore discuss in this review (see Brenowitz et al., 1997, for a more complete overview). Currently, this system is viewed as two intimately related circuits: an anterior forebrain circuit necessary for normal song development and a descending motor pathway controlling song production. Since neurons in both of these circuits are responsive to com-

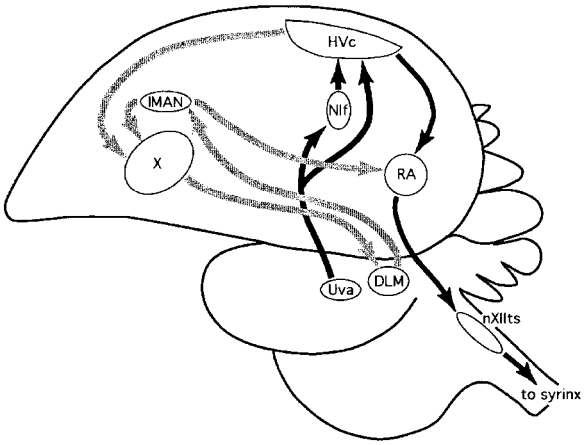

Figure 1 Avian song learning and production are controlled by a discrete system of brain regions, some of which are shown in this schematic saggital view. Regions and connections drawn in bold are involved in the motor control of song behavior. Shown in gray is the anterior forebrain pathway that indirectly connects the HVc to the RA via Area X, DLM, and lMAN. This circuit is necessary for song learning but not required for production of stable song in adult birds. DLM = medial portion of dorsolateral nucleus of the anterior thalamus; lMAN = lateral magnocellular nucleus of the anterior neostriatum; NIf = nucleus interfacialis; nXIIts = tracheosyringeal portion of hypoglossal nerve nucleus; RA = robust nucleus of the archistriatum; Uva = nucleus uvaeformis; X = Area X.

plex auditory stimuli (Katz and Gurney, 1981; McCasland and Konishi, 1981; Margoliash, 1983; Williams, 1989; Doupe and Konishi, 1991), both likely are involved in auditory-based learning. The anterior forebrain circuit includes the Area X, DLM (medial portion of the dorsolateral nucleus of the anterior thalamus), and lMAN (lateral magnocellular nucleus of the anterior neostriatum). Both the lMAN and Area X of adult birds contain neurons remarkably selective for the bird's own song pattern, and in the lMAN these complex response properties develop over the course of song development (Doupe, 1997; Doupe and Solis, 1997). In zebra finches, a sensitive period learner, lesions of these forebrain regions prevent normal song learning, while comparable damage in adult birds does not affect the production of stereotyped song patterns (Bottjer et al., 1984; Sohrabji et al., 1990; Halsema and Bottjer, 1991; Scharff and Nottebohm, 1991; Nordeen and Nordeen, 1993).

The descending motor pathway controlling song production includes the nucleus uvaeformis (Uva), nucleus interfacialis (Nlf), HVc, robust nucleus of the archistriatum (RA), and tracheosyringeal portion of the hypoglossal nucleus (nXIIts). Premotor activity occurs in these nuclei during singing (Margoliash, 1997), and damage or stimulation of this circuitry causes immediate disruptions of song behavior (Nottebohm et al., 1976; McCasland and Konishi, 1981; McCasland, 1987; Simpson and Vicario, 1990; Vicario, 1991; Vu et al., 1994; Yu and Margoliash, 1996). Importantly, this motor pathway provides several inputs to the anterior forebrain circuitry including a large projection from the HVc to Area X, and it receives output from this circuit through the lMAN-RA projection. However, because of their critical role in song production, it has been difficult to test directly how this ''motor circuit'' participates in song learning. One would expect, though, that the organization of these regions surely must be shaped by the experiences associated with sensorimotor learning and/or memory acquisition.

Aside from the lesion work cited above, there have been very few attempts to interfere directly with the neural substrates of normal song learning. In one set of studies, we demonstrated that zebra finch song learning depends on processes mediated by the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor, a receptor that has been implicated in many other forms of learning and developmental plasticity (Cotman et al., 1988; Lincoln et al., 1988; Morris, 1989; Constantine-Paton et al., 1990). Aamodt et al. (1996) reported that pharmacological blockade of NMDA receptors compromises memory acquisition. Specifically, juvenile male zebra finches exposed to a conspecific song tutor for 2 h every other day were significantly impaired in song learning if they received systemic injections of MK-801, an NMDA receptor antagonist, 30 min before tutoring sessions. Identical injections of MK-801 restricted to nontutoring days did not affect the amount of tutor song material that was successfully acquired and mimicked. Because NMDA receptor blockade interfered with learning only when it overlapped with song tutor presentation, these results indicate that the NMDA antagonist impaired learning by disrupting processes specifically associated with memory acquisition, rather than sensorimotor learning. Although in this initial study auditory brain stem evoked potentials in juveniles were unaffected by MK-801 injections, no further attempt was made to assess the perceptual, motivational, or attentional decrements resulting from NMDA receptor blockade. Also, since MK-801 was administered systemically, this work did not provide information concerning the location of NMDA receptors important for memory acquisition.

More recently, Basham et al. (1996) employed a similar paradigm, but delivered the competitive

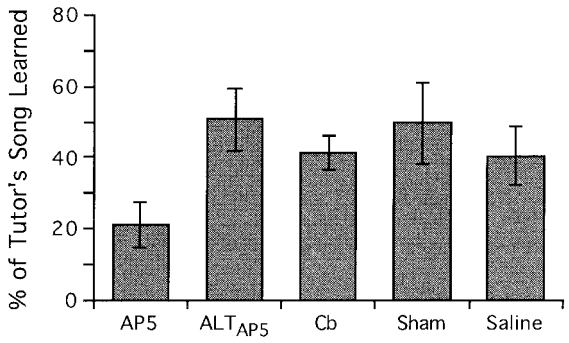

Figure 2 Percentage of the tutor's song learned by 90 days of age in five different groups of zebra finches. Groups designated AP5 and ALT$_{AP5}$ received bilateral injections of the NMDA receptor antagonist AP5 into the lMAN either just prior to tutoring or on nontutoring days, respectively. Other birds received injections of either saline into the lMAN (saline) or AP5 into the cerebellum (Cb) just prior to tutoring, or were left uninjected (Sham). (From Basham et al., *Neurobiol. Learn. Mem.* **66:** 295–304, © 1996, Academic Press, reproduced with permission.)

NMDA receptor antagonist AP5 intracranially to demonstrate that NMDA receptor activation within the anterior forebrain circuit is critical for normal song development. In this case, previously isolated male zebra finches were tutored every other day between 32 and 52 days of age (the peak of the sensitive period). Learning from the tutor was impaired if AP5 was infused into the lMAN bilaterally just prior to the tutoring sessions, but was not affected either by similar infusions into the cerebellum or by lMAN infusions on nontutoring days (Fig. 2). While the study did not rule out a role for other song regions in learning, it firmly implicated NMDA receptor-mediated events in or around the lMAN as crucial to normal memory acquisition. It is not known whether the AP5 infusions reduced learning by interfering with processes that specifically underlie the acquisition or storage of song related memories, or by disrupting other processes required for learning (stimulus recognition, attention, and motivation). However, an important aspect of this work was the demonstration that identical AP5 infusions into the lMAN do not diminish the ability of juvenile zebra finches to perceive differences between conspecific and heterospecific song.

Normal song development also can be disrupted by manipulating the action of gonadal androgens (Bottjer and Johnson, 1997). Castration and treatment with the antiandrogen flutamide can delay or prevent development of a stable song pattern (Nottebohm, 1969; Arnold, 1975; Kroodsma, 1986; Marler et al., 1988; Bottjer and Hewer, 1992), while treating juveniles with exogenous androgen promotes premature fixation on an impoverished song pattern (Sossinka et al., 1975; Korsia and Bottjer, 1991; Whaling et al., 1995). Although it is presumed that these effects of androgens are exerted on sensorimotor learning, this is not known for certain. Also, the site(s) at which androgens exert their effects on song development have not been identified. However, androgen-accumulating neurons are located throughout the song system (Arnold, 1980; Arnold et al., 1976), and Bottjer and Hewer (1992) reported significant decreases in the volumes of both Area X and the lMAN in juvenile male zebra finches treated with flutamide. The volumes of other song regions (HVc and RA) were not affected by this treatment, but cellular measures (e.g., dendritic extent) were not examined. It also is possible that androgens modulate neurochemical processes important for song learning, such as the development of catecholaminergic systems (Barclay and Harding, 1988, 1990) or NMDA receptor function (Weiland, 1992; Kus et al., 1995).

ONTOGENY AND PLASTICITY IN THE ANTERIOR FOREBRAIN NUCLEI

Consistent with their established role in song learning, the nuclei of the anterior forebrain circuit establish their afferent and efferent connections relatively early in development. Most HVc neurons that project to Area X are born before hatching in canaries (Alvarez-Buylla et al., 1988), and in zebra finches the axons of these neurons arrive within Area X as early as posthatch day 12 (Sohrabji, 1990). Yet during the ensuing 4–6 weeks, the number of HVc neurons that can be retrogradely labeled from Area X increases considerably in young male zebra finches (Burek et al., 1993), as does the overall volume of the HVc–Area X terminal field (unpublished observations) and overall volume of Area X itself (Bottjer et al., 1985; Nordeen and Nordeen, 1988a).

As Area X increases in volume, it adds hundreds of thousands of new neurons, and thymidine autoradiography indicates that this neuron addition reflects the production and insertion of new cells (Nordeen and Nordeen, 1988a). Most likely, the neurons added to Area X during learning contribute to the intrinsic circuitry of Area X, since they are not labeled following injections of retrograde tracer into the only known target of Area X, the DLM (Sohrabji et al., 1993). As yet, there have been no explicit tests of how this massive addition relates to the role of Area X in song development. Since the

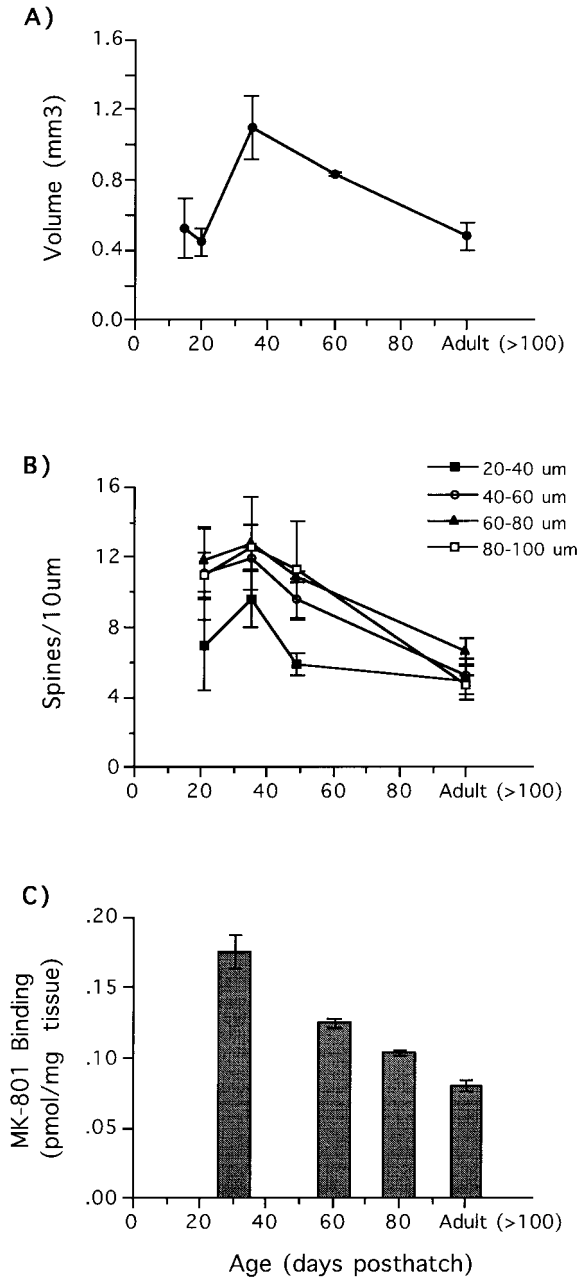

Figure 3 Developmental changes in three features of lMAN organization: (A) the overall volume of the DLM–lMAN terminal field, (B) dendritic spine density, and (C) NMDA receptor binding. The data shown in the top panel are measures of total anterograde terminal labeling over the lMAN following placement of a Dil crystal within the DLM (modified with permission from Johnson and Bottjer, 1992). Data shown in the middle panel are frequencies of dendritic spines on lMAN spiny neurons measured at four different distances from the cell soma (modified with permission from Nixdorf-Bergweiler et al., 1995).Data shown in the bottom panel are specific binding of the noncompetitive NMDA receptor antagonist, [^{3}H]MK-801. (From Aamodt et al., *J. Neurobiol.* **27:** 76–84, © 1995, John Wiley & Sons, Inc., reproduced with permission.) All data shown are means ± S.E.M.

developmental increase in Area X volume and neuron number occurs normally in zebra finches that have been deafened prior to song learning (Burek et al., 1991), it seems unlikely that the growth of this region is a signature of learning. On the other hand, the plasticity afforded by the insertion of new cells and the elaboration of afferent terminals within Area X may foster learning. In zebra finches, the addition of new neurons to this region is much greater in young males than in either young females (who do not normally sing) or adult males beyond the sensitive learning period (Nordeen and Nordeen, 1988a; Sohrabji, 1990). Also, in male swamp sparrows, the net addition of Area X neurons is closely associated with the peak period of memory acquisition, whereas the total number of these neurons does not change significantly during later sensorimotor learning (Nordeen et al., 1989).

Area X also exhibits some interesting neurochemical changes during the period of song learning. Catecholamine (CA) histofluorescence in Area X of male zebra finches increases between 35 days and adulthood, as does immunoreactivity for tyrosine hydroxylase, the rate-limiting enzyme in CA biosynthesis (Soha et al., 1996). In fact, developmental changes in both CA and cholinergic systems occur throughout the song system, including the lMAN, RA, and HVc, perhaps reflecting the maturation of widely projecting, ascending systems originating within the brain stem (Sakaguchi and Saito, 1989, 1991; Soha et al., 1996). Little is known about the source of these projections, except in the case of Area X where catecholamine histofluorescence reflects innervation from the brain stem nucleus AVT (Lewis et al., 1981). These neurochemical changes are interesting in that acetylcholine and CAs play an important role in modulating the ability of sensory experience to promote synaptic and behavioral change in other cases of developmental plasticity and early learning (Kasamatsu and Pettigrew, 1976; Bear and Singer, 1986; Sullivan et al., 1989, 1994; Dalmaz et al., 1993; Rangel and Leon, 1995). The CA innervation of song regions may exert similar regulation over song learning, but as yet there have been no reports of increases or decreases in the propensity for learning following manipulations of the CA system.

It is not known when the projection from Area X to the DLM first develops; however, it seems likely that this pathway is in place by the onset of memory acquisition. Injections of tracer into the DLM label a sparse population of very large Area X neurons as early as 15 days after hatching in male zebra finches (Sohrabji, 1990; Johnson and Bottjer, 1992). This pathway has not been studied in young

birds using anterograde tracers, however, and there have been no attempts to describe how this projection changes over the course of learning. The DLM itself decreases in volume by about 25% between 20 and 50 days after hatching, although the number of DLM neurons remains stable during this time (Johnson and Bottjer, 1992).

Some of the most well-studied anatomical changes associated with song learning involve the lMAN and its afferent innervation from the DLM. As shown in Figure 3(a), anterograde labeling of this DLM–lMAN pathway in young male zebra finches reveals that the terminal field of DLM afferents to the lMAN expands nearly threefold between 20 and 35 days after hatching (Johnson and Bottjer, 1992). At its peak, the volume occupied by these terminals extends well beyond the population of magnocellular neurons that define the lMAN in Nissl-stained material. Over the next several weeks, this initially exuberant DLM projection recedes to a volume just slightly larger than that defined by the Nissl-stained boundaries of the lMAN. Although the functional significance of this terminal retraction is not known, it may have important implications for the segregation of song-related circuitry within the anterior neostriatum. The DLM–lMAN–RA pathway in adult male zebra finches is topographically organized: The dorsal/lateral portion of the DLM projects to the magnocellular core of the lMAN, which in turn projects to the RA; while the ventral/medial DLM projects to the parvicellular shell of the lMAN, which projects to the archistriatum just lateral to the RA (Johnson et al., 1995; Bottjer and Johnson, 1997). As the DLM terminals retract developmentally, the Nissl-defined boundaries of the lMAN also recede (Bottjer and Arnold, 1986; Bottjer and Sengelaub, 1989; Burek et al., 1991). While this decrease in lMAN volume does not result in a loss of RA-projecting lMAN neurons (Nordeen et al., 1992), other neurons may be lost from the lMAN, either producing or resulting from the reorganization of DLM afferents.

It is not yet known if the pruning of DLM afferents in the lMAN is influenced by auditory experiences associated with song learning, but this regression of afferent innervation is accompanied by dendritic changes in the lMAN that are experience-dependent. As shown in Figure 3(b), the density of dendritic spines on lMAN spiny neurons decreases between 35 and 55 days of age in male zebra finches (Nixdorf-Bergweiler et al., 1995). Importantly, early isolation from conspecific song delays or prevents this developmental decline in spine density (Wallhäusser-Franke et al., 1995). To date, this is the only song system measure that has been shown to be influenced by auditory deprivation, and the findings strongly implicate synaptic change within the lMAN as a substrate for song learning. However, it is not clear how to interpret these dendritic changes, since isolation from conspecific song both prevents learning and extends the sensitive period for learning (Immelmann, 1969; Kroodsma and Pickert, 1980; Eales, 1985, 1987). One interpretation is that experience-dependent decreases in spine density (and regression of thalamic afferents, perhaps) reflect the acquisition and storage of song material per se. On the other hand these dendritic changes may reflect experience-dependent maturational changes that influence the threshold for learning (e.g., the development of intrinsic inhibitory circuits) but do not directly participate in the encoding of song-related memories.

Correlated with these changes in synaptic organization within the lMAN are striking changes in the expression of NMDA receptors within this region. Aamodt et al. (1992, 1995) showed that binding of the selective NMDA receptor antagonist MK-801 decreases steadily in male zebra finches between 30 days and adulthood [Fig. 3(c)], a period encompassing both memory acquisition and sensorimotor learning. This decline in overall lMAN NMDA receptor binding reflects both a twofold decrease in receptor density and a dramatic increase in the affinity of MK-801 for NMDA receptors within this region (Aamodt et al., 1995). More recently, we have learned that the decrease in NMDA receptor number within the lMAN reflects developmentally regulated gene transcription. *In situ* hybridization indicates that the expression of mRNA for the R(one) subunit of the NMDA receptor decreases within the lMAN of male zebra finches between 30 days after hatching and adulthood (Basham et al., 1997).

The neuroanatomical and neurochemical changes that occur in the lMAN during learning, coupled with the observation that song learning relies on NMDA receptor activation, fit a pattern that has been articulated most clearly in studies of activity-dependent change within the developing vertebrate visual system. In this case, key patterns of neural organization (e.g., the topographic mapping and ocular segregation of inputs) have been ascribed to a competitive, activity-driven rearrangement of synapses mediated by Hebbian-like processes of synaptic change (Constantine-Paton et al., 1990; Shatz, 1996). The synaptic strengthening (or weakening) that arises from patterned input is mediated by activation of NMDA receptors, which detect coincident pre- and postsynaptic activity by being both ligand- and voltage-gated. Thus, competing afferent fibers

that convey correlated activity are mutually reinforcing and engage NMDA receptor-coupled processes that produce changes in synaptic strength.

Consistent with this view, the timing of sensitive periods for plasticity within the visual system has been linked to developmental changes in the functional characteristics of NMDA receptors. In the visual cortex, NMDA receptor density declines as the segregation of ocular dominance columns becomes resistant to manipulations of visual input (Bode-Greuel and Singer, 1989; Gordon et al., 1991). Furthermore, developmentally regulated plasticity in the visual system is associated with maturational changes in NMDA receptor physiology that may affect the stringency of coincidence detection (Tsumoto et al., 1987; Fox et al., 1989; Carmignoto and Vicini, 1992; Hestrin, 1992). As in song learning, the sensitive period for visual cortical plasticity is prolonged in the absence of suitable stimulation (Cynader and Mitchell, 1980; Cynader, 1983; Mower, 1991), and although manipulations that prolong the sensitive period do not retard the developmental reduction in overall NMDA receptor binding (Bode-Greuel and Singer, 1989; Gordon et al., 1991), they do delay maturational changes in NMDA receptor physiology (Carmignoto and Vicini, 1992; Fox et al., 1991, 1992).

We speculate that developmental regulation of NMDA receptors within the lMAN may affect the capacity for song learning, and we have investigated this hypothesis by determining if developmental changes exhibited by these NMDA receptors are affected by manipulations that delay or accelerate closure of the critical song learning period. Reminiscent of findings in the visual system, extending the sensitive period in zebra finches either through deafening or isolation from conspecific song does not prevent the developmental decrease in overall MK-801 binding within the lMAN (Aamodt et al., 1995). Although this result indicates that developmental regulation of NMDA receptor density within the lMAN does not necessarily define the sensitive period, it is still possible that the decrease in receptor level reduces the capacity for learning, since late learners do not reproduce tutor songs as proficiently as do birds exposed to song earlier (unpublished observations). Also, it may be that developmental changes in the physiology (rather than density) of NMDA receptors are more relevant to the capacity for experience-dependent neural plasticity. Recall that as the density of NMDA receptors declines within the lMAN during song learning, their affinity for MK-801 increases (Aamodt et al., 1995). This pharmacological change may reflect alterations in the subunit composition of the receptor (Chazot et al., 1994; Laurie and Seeburg, 1994; Priestley et al., 1995), which likely influence physiological properties of the receptor such as the duration of ionic currents and voltage sensitivity (Monyer et al., 1992, 1994; Ishii et al., 1993). Perhaps as in mammalian systems (Wenzel et al., 1997), there is developmental regulation of NMDA receptor subunit composition in the song system. If so, extension of the sensitive period may prove to delay maturational changes in NMDA receptor structure, thereby influencing its channel properties and affecting the threshold for initiating synaptic change.

CREATING AND RECREATING VOCAL PATHWAYS DURING LEARNING

Avian song learning is expressed as a change in vocal behavior, and therefore, auditory experience must ultimately structure motor or premotor pathways for song. However, establishing whether motor pathways are affected directly during memory acquisition or sensorimotor learning has been difficult because damaging them immediately disrupts (or prevents) subsequent song production (Nottebohm et al., 1976; Simpson and Vicario, 1990). Thus, while it is safe to assume that some portion(s) of the motor circuitry is shaped by auditory experience at least during vocal practice, we do not yet know where these modifications occur. Furthermore, because the ontogeny of the motor system has not been characterized fully, we are far from having a comprehensive view of how the maturation of motor circuitry might affect vocal learning.

Nonetheless, several features of the HVc and the RA suggest that these regions could play pivotal roles in song learning, and a great deal of correlational yet converging evidence suggests that neural change in the HVc–RA portion of the motor pathway may be significant for learning. Both the HVc and the RA are linked directly to the anterior forebrain circuit, and therefore are positioned well to participate in song learning. The HVc is a primary site through which auditory information is conveyed to the song system, and appears to be necessary for auditory responsiveness within the descending vocal motor pathway (Doupe and Konishi, 1991; Vicario and Yohay, 1993; Williams, 1989). The RA is uniquely positioned at the confluence of descending motor (and auditory) projections from the HVc and the output of the anterior forebrain circuit. Also, since the RA is the primary target of the lMAN, a region that has been implicated directly in memory acquisition (Basham et al., 1996), and indirectly in sensorimotor learning (Bottjer et al.,

1984; Scharff and Nottebohm, 1991), it seems likely that motor circuitry within the RA is shaped by the activity of the anterior forebrain loop during learning. Most important, as detailed below, there is robust neuronal growth and synaptic reorganization within the HVc and the RA during both song development in juvenile songbirds and seasonal modification of songs in adult canaries.

As young male zebra finches are memorizing song material and beginning to rehearse song, the HVc increases significantly both in volume and neuron number (Bottjer et al., 1985; Bottjer et al., 1986; Nordeen and Nordeen, 1988). Similar growth occurs in young canaries that are learning song in their first year of life (Nottebohm et al., 1986). Thymidine autoradiography has confirmed that the addition of HVc neurons in juvenile zebra finches and canaries reflects protracted birth and incorporation of new neurons (Alvarez-Buylla et al., 1988; Nordeen and Nordeen, 1988b). Furthermore, in both species, the majority of these new HVc neurons eventually innervate the RA. Because they contribute to the motor pathway, we can be reasonably confident that these new projection neurons participate in song behavior and their insertion and differentiation therefore may contribute to neural plasticity important for song learning. Interneurons also are added to the HVc during song development, but we do not yet know if this cohort of neurons is involved in song behavior, perception, or both. Given recent evidence that intrinsic circuitry within the HVc is involved in premotor programming (Vu et al., 1994; Yu and Margoliash, 1996), their addition may well contribute to the development of song behavior.

At least in zebra finches, this addition of new HVc–RA projection neurons not only entails synaptogenesis within the HVc but is also associated with synaptic rearrangement within the RA. While the lMAN innervates the RA as early as 15 days after hatching in this species, the anatomical connection between the HVc and RA is sparse prior to 30 days of age (Mooney, 1992; Mooney and Rao, 1994). At approximately 35 days after hatching, there is a massive invasion of the RA by HVc axons (Konishi and Akutagawa, 1985), and over the ensuing few weeks the density and number of HVc synapses in the RA increase dramatically while the density of synapses derived from the lMAN decreases (Herrmann and Arnold, 1991). The volume of the RA doubles in size during this same period as neurons both grow larger and decrease in density (Bottjer et al., 1985, 1986; Nordeen and Nordeen, 1988a).

The hypothesis that neuron addition to the vocal motor pathway provides a unique opportunity for auditory input to shape the organization of the vocal motor circuitry is supported by a variety of correlational data that consistently link vocal learning to periods of heightened HVc neuron addition. First, the production and incorporation of new HVc neurons in male zebra finches is much greater during the sensitive period than later in life (Nordeen and Nordeen, 1988b). Also, in this species the incorporation of new neurons is significantly greater in young males than in young females (who never sing), and in both juvenile females and adult males very few of the HVc neurons that are produced contribute to the HVc–RA pathway. Second, vocal plasticity and HVc neuron addition also correlate in birds capable of modifying their songs in adulthood. In particular, seasonal periods of vocal plasticity in adult canaries coincide with seasonal peaks in the incorporation of HVc–RA vocal motor neurons (Alvarez-Buylla and Kirn, 1997). Birds incorporate far more new HVc neurons during nonbreeding periods when new song syllables are added to the vocal repertoire than during the spring breeding season when songs are stable (Alvarez-Buylla et al., 1990; Kirn et al., 1994). Moreover, the addition of new RA-projecting HVc neurons specifically is four or five times greater in the fall than in the spring to early summer. It is worth noting that this neuronal addition is accompanied by the loss of other HVc–RA projection neurons (Kirn and Nottebohm, 1993). Thus, neurons that form this portion of the motor pathway for song behavior are replaced in adult canaries, and the rate of this neuronal replacement varies on a seasonal cycle that is synchronized to seasonal changes in vocal stability.

While these correlational data suggest that progressive events within the HVc–RA pathway sustain and temporally restrict song learning, it is difficult at this point to relate neuron addition to specific phases of vocal learning. In zebra finches, memory acquisition and sensorimotor learning overlap, and the timing of memory acquisition in young canaries has not been defined precisely. Also, changes in song behavior in adult canaries could reflect solely the rehearsal and incorporation of song material that was memorized during the first year of life. For these reasons, we studied the development of song regions in swamp sparrows, a species in which memory acquisition ends long before the onset of sensorimotor learning (Marler and Peters, 1988; Marler et al., 1987). At least in this species, HVc neuron number and HVc and RA volume increase specifically during the period of memory acquisition. Sensorimotor learning is not associated with any further changes in these anatomical measures (Nordeen et al., 1989).

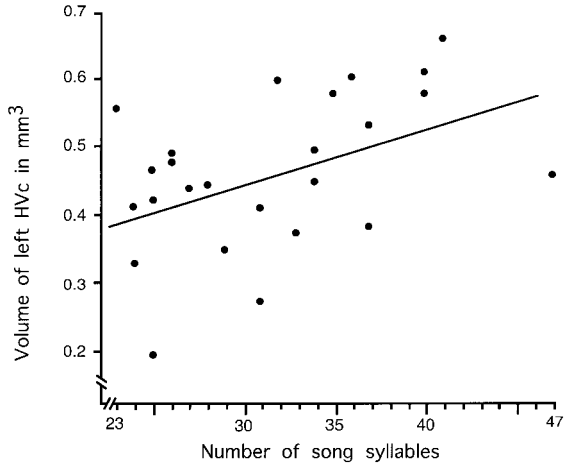

Figure 4 Relationship between the overall volume of the left HVc in adult canaries and the number of different syllable types in the song repertoire. Reprinted from Nottebohm, F., Kasparian, S., and Pandazis, C. Brain space for a learned task. (1981). *Brain Res.* **213,** pp. 99–109, with kind permission of Elsevier Science–NL, Sara Burgerhartstraat 25, 1055 KV Amsterdam, The Netherlands.

Other research suggests that the extent of neural growth in the motor pathway constrains how much song material is learned. Among individuals of a given species, the HVc and RA exhibit remarkable variation in neuron number and overall volume. Nottebohm first noted that adult canaries with large HVcs and RAs tend to produce a larger repertoire of song syllables than do those with smaller HVcs and RAs (Fig. 4), and he speculated that the size of the HVc might set limits on how much song material can be learned and/or produced (Nottebohm et al., 1981). A similar correlation between brain space and song behavior has been seen in several other species, as well as across related species of songbirds (Brenowitz et al., 1993; Brenowitz and Arnold, 1986; Canady et al., 1984; DeVoogd et al., 1993; Kroodsma and Canady, 1985). Importantly, this relationship is regionally specific: although there is a tremendous amount of individual variation in the size of several other song nuclei, these differences do not correlate significantly with repertoire size.

Although one interpretation of this correlation is that HVc growth and song learning are regulated independently (e.g., by gonadal hormones) (Bottjer and Johnson, 1997; Arnold, 1997), several studies have been aimed at establishing causality within this brain–behavior relationship. Given that early experience clearly influences the growth and differentiation of mammalian (Diamond et al., 1972; Greenough, 1987; Weiler et al., 1995) and avian (Clayton, 1995) brain regions in other contexts, it had been speculated that variation in the amount of song material encountered during learning might produce individual differences in the number of neurons retained in song control regions (e.g., the HVc). However, direct tests of this hypothesis do not support it. Early deafening does not compromise the development of HVc volume, neuron number, or neuron size in male zebra finches despite the fact that this manipulation precludes both memory acquisition and sensorimotor learning and results in highly abnormal song behavior (Burek et al., 1991). Also, in marsh wrens, the number of syllables heard during song development affects final repertoire size without influencing the number of HVc or RA neurons (Brenowitz et al., 1995). Thus, individual differences in the opportunity to learn song material do not regulate the growth of the HVc, and therefore cannot account for the positive relationship between the size of this song region and repertoire size.

An alternative hypothesis is that naturally occurring variations in HVc neuron addition limit how much song material can be learned. While this has not been tested directly, circumstantial evidence remains consistent with this view. Among a group of marsh wrens that were tutored with a large sample of song types, the volume of the RA correlated positively with the number of song types produced, and a similar although weaker brain–behavior relationship was evident for the HVc (Brenowitz et al., 1995). Also, among a group of young male zebra finches that were raised together with two adult tutors, individual differences in the number of HVc neurons correlated significantly with the number of song syllables accurately copied from the tutors (Ward et al., 1996). Since we know that learning *per se* does not regulate the development of HVc neuron number, these data suggest that HVc neuron number influences how much song material can be accurately reproduced.

The lack of a significant correlation between HVc volume and repertoire size in some other species has challenged the idea that the size of this song nucleus constrains song learning (Bernard et al., 1996; Brenowitz et al., 1991; Kirn et al., 1989). It may be that the lack of correlation between HVc volume and repertoire size in some species may reflect how repertoire size was quantified (Brenowitz, 1997). However, these studies also have not distinguished learned from unlearned syllables. Perhaps the number of neuronal components in the HVc does not limit how many different syllables can be produced, but rather limits how much song material can be learned (i.e., accurately stored during memory acquisition, or reproduced as a function of sensorimotor learning). Further controlled studies will

be needed to determine if there are significant species differences in the degree to which total repertoire size reflects the amount of conspecific song accurately copied.

One way that song could be influenced by both the timing and extent of HVc–RA neuron addition is if the associated synaptogenesis provides a unique opportunity for auditory experience to selectively stabilize neural connections and thereby shape the organization of the vocal motor circuitry. Although both the HVc and the RA contain NMDA receptors which could function as components in Hebbian synapses (Aamodt et al., 1992; Ball, 1994; Mooney, 1992; Mooney and Konishi, 1991; Sakaguchi et al., 1992), there is no direct evidence that auditory experiences associated with song learning affect synaptic organization within either of these regions. However, in adult birds, HVc neurons exhibit a preference not only for conspecific song elements, but for a bird's own song pattern (Margoliash, 1983, 1986, 1997). Such auditory selectivity, even for familiar songs, is not evident in young birds that have been tutored but are not yet singing, and thus appears to be established by the process of sensorimotor learning (Volman, 1993; Doupe and Solis, 1997).

Until recently the assertion that auditory experience shapes the connections of new neurons incorporated into the vocal motor pathway presented a paradox. For many years, it was thought that the stereotyped song patterns achieved in age-limited learners do not require continuing auditory or proprioceptive feedback (Bottjer and Arnold, 1984; Konishi, 1965; Price, 1979). Thus, the concept of a central motor program emerged that predicted song execution by a relatively static neural system. However, our studies of neurogenesis in the song system were at odds with this notion because they indicated that adult male zebra finches continue to add, albeit at a very gradual pace, new HVc–RA projection neurons. If the integration of these new neurons into existing circuitry is shaped normally by auditory experience, then how could adult song remain stable in the absence of auditory feedback given the continual insertion of new neuronal elements? This paradox fueled a reinvestigation of the role of audition in the maintenance of stereotyped song and led to the discovery that adult zebra finch song deteriorates gradually if auditory feedback is removed in adulthood (Nordeen and Nordeen, 1992). Although few changes in song were evident within 6 to 8 weeks after deafening, by 16 weeks many preoperative syllables were no longer evident, new syllables were produced, and the temporal structure of song had been modified. Also, in Bengalese finches, another age-limited learner, the temporal structure of song is reorganized rapidly upon removal of auditory feedback, and the morphology of song syllables also deteriorates (Okanoya and Yamaguchi, 1997; Woolley and Rubel, 1997). These more recent findings are consistent with the view that neuronal incorporation in the vocal motor pathway imparts plasticity, and ''crystallized'' adult song patterns normally remain stable in the face of continued neuron addition within this pathway because new synapses are ''tutored'' by auditory feedback from the bird's currently produced, stereotyped song.

FUTURE DIRECTIONS

One working hypothesis that emerges from the findings discussed above is that during memory acquisition, song-related memories are encoded by anterior forebrain circuitry via an NMDA receptor-dependent sculpting of initially exuberant synaptic connections. Furthermore, the threshold for such learning may be constrained by developmental and/or seasonal changes in NMDA receptor function and the availability of naive circuitry. Studies of experience-dependent change in other developing neural systems support these notions and can serve to guide further research to develop these ideas. For instance, while the observation that NMDA receptor antagonists impair memory acquisition suggests that these receptors promote synaptic changes that underlie the acquisition and storage of song-related memories, this notion is fraught with the same problems that have plagued investigations of NMDA receptor function during developmental periods of plasticity in sensory systems and in adult learning. Specifically, more work is needed to rule out generalized effects of NMDA receptor blockade that could interfere with learning. Our demonstration that AP5 infusions into the anterior forebrain impair memory acquisition without affecting performance in a simple discrimination task is an important first step, but other learning paradigms must be employed that can evaluate deficits in perception, motivation, or attention more precisely.

Similarly, we need to probe further the role of NMDA receptors in information processing within the DLM–lMAN pathway. Although stimulation of DLM afferents evokes a significant synaptic response in the lMAN even when NMDA receptors are blocked (R. Mooney, personal communication), studies that combine behavioral pharmacology with electrophysiology are needed to establish that AP5 disrupts learning by interfering with processes specific to synaptic plasticity, rather than by sup-

pressing activity generally within the anterior forebrain circuit. It also will be important to assess whether song learning is affected by manipulations that influence downstream biochemical processes implicated in NMDA receptor-mediated plasticity (e.g., kinase activation). Such studies could increase our confidence that AP5's disruption of song learning involves processes specific to neural plasticity rather than information processing.

Another important issue concerns how NMDA receptor activation during memory acquisition translates into changes that encode the acquired template. One important step will be to learn if and how the striking anatomical changes observed in the lMAN are related to NMDA receptor function. The most parsimonious hypothesis is that conspecific song promotes patterned changes in lMAN dendritic spines and DLM afferents via processes that require NMDA receptor activation. This notion clearly predicts that such anatomical changes would be prevented in birds receiving AP5 infusions during memory acquisition. Of course, understanding the functional significance of such activity-dependent synaptic patterning will require further elaboration of how the lMAN and its afferents are organized and how this organization develops. The lMAN is organized topographically with respect to its projection to the RA (Johnson et al., 1995), and over the course of learning, lMAN neurons develop very specific auditory response properties, becoming tuned to characteristics of the bird's own song (Doupe, 1997; Doupe and Solis, 1997). Are these properties of lMAN neurons defined by the organization of DLM afferents, and do they depend on NMDA receptor-dependent synaptic rearrangement during memory acquisition? It will also be important to identify the biochemical cascades that lead to permanent change in synaptic organization and function within the lMAN. For example, we would predict that exposure to conspecific song during memory acquisition triggers biochemical changes in the anterior forebrain similar to those associated with NMDA receptor-mediated synaptic change in other systems (e.g., calcium-dependent activation of protein kinases) (Nicoll and Malenka, 1995).

Continuing to explore the biology of sensitive periods for avian song learning should aid us in identifying neural substrates for this behavior. The timing of such periods undoubtedly is dictated by the cooccurrence of many developmental (or seasonal) events, but the fact that NMDA receptor populations in the song system exhibit changes that correlate with periods of plasticity is intriguing and consistent with other studies of developmental plasticity (e.g., the mammalian visual and auditory systems). However, we need to understand how the pharmacological changes observed relate to NMDA receptor function, and thus how they may alter the propensity for song learning. In the mammalian visual cortex, developmental changes in NMDA receptor affinity have been linked to changes in the subunit composition of these receptors. Furthermore, developmental changes in the expression of particular subunits have been correlated with changes in the ion channel kinetics of the receptor, a change that could influence the threshold for Hebbian-like processes that underlie experience-dependent change. Recent studies in our lab reveal a developmental decline in the expression of NMDA receptor subunits within the lMAN (Basham et al., 1997), but developmental studies of channel function are needed to evaluate the functional consequences of this change. Finally, comparative studies offer another powerful way to test the relationship between NMDA receptor expression and the capacity for vocal learning. Such studies may reveal that particular isoforms of the NMDA receptor within the lMAN are prerequisite to song learning no matter when such learning occurs.

Another notion highlighted in this review is that vocal learning may be limited by the extent of ongoing synaptogenesis and synaptic rearrangement within the motor pathway. That is, the synaptic plasticity afforded by this neuronal addition may be a necessary (although perhaps not sufficient) substrate through which auditory experience can shape vocal motor patterns. The tremendous species diversity in the timing of vocal plasticity offers a powerful natural experiment by which to evaluate this hypothesis. So far, studies of song development in zebra finches and canaries as well as seasonal vocal plasticity in adult canaries attest to the significance of HVc neuron addition during song learning, but this comparative approach needs to be extended to other species. Also, direct manipulations of HVc neuron addition are needed to determine how the timing and/or rate of this developmental process affects the propensity for song learning. In species where songs are learned in discrete time windows relatively late in development, it may be possible to attenuate or facilitate HVc neuronal incorporation without producing grossly abnormal brain development. Finally, we need to determine directly if the synaptic connections made by new HVc neurons are in fact influenced by auditory experience during learning. There have not yet been any studies designed to evaluate whether early isolation from conspecific song, or even deafening, alters develop-

mental patterns of axonal arborization within the vocal motor pathway.

While song learning may be constrained temporally by when HVc neuron addition occurs, the capacity for learning may be limited by the actual number of neurons incorporated into this region. Although this hypothesis has been addressed only by correlational studies, it finds support from comparisons across species of songbirds as well as among individuals within three unrelated species of songbirds (marsh wrens, canaries, and zebra finches). Thus, songbirds offer an extraordinary opportunity to test the possibility that individual differences in learning capacity relate to naturally occurring differences in brain space. To understand this relationship better, we need to determine the behavioral consequences of manipulating HVc neuron number. Toward this aim, it will be important to establish the mechanisms responsible for the tremendous individual variability in HVc neuron number. It is possible that hormones play a significant role. In both canary and zebra finch eggs, yolk concentrations of testosterone vary greatly; and in canaries, these levels increase with the order of laying and are positively correlated with later aggressive behavior (Schwabl, 1993). Also, estradiol (a metabolite of testosterone) can promote the incorporation of HVc neurons in young female zebra finches (Nordeen and Nordeen, 1989), and individual differences in estradiol have been linked to song-learning propensity in sparrows (Marler et al., 1987). If individual differences in early hormonal titers do contribute significantly to naturally occurring variation in HVc neuron number, this could provide an avenue through which to test the relationship between HVc neuron number and learning propensity. Alternatively, neurotrophic molecules may prove useful tools for manipulating neuron number (Craig et al., 1996; Johnson et al., 1997; Kirschenbaum and Goldman, 1995).

Song learning is a complex, multistaged process, and it is likely that its timing is dictated by the interaction of many different neural substrates. Because ours is only one of several reviews in this issue that concern the biology of song learning, we have focused our attention largely on two candidate mechanisms: NMDA receptor-dependent synaptic rearrangement within the anterior forebrain pathway and the insertion of new neuronal elements into the vocal motor pathway. The evidence correlating these events with periods of vocal plasticity is strong, but we need to resist becoming myopic in our perception of how song learning may be facilitated and constrained. There are dramatic changes in the catecholaminergic innervation of song nuclei that also coincide with periods of learning and these changes may reflect an important role for these neurotransmitters in promoting synaptic change (Sakaguchi and Saito, 1989; Soha et al., 1996). Also, maturational changes in inhibitory circuitry, which have yet to be characterized, may serve to constrain song learning as seems to be the case in other instances of developmental plasticity (Kirkwood and Bear, 1994). We already know that hormones influence both song behavior and its neural substrate (Bottjer and Johnson, 1997), and so we need to understand more about how hormones interact with the anatomical correlates of song learning. Also, continuing to investigate how structural and synaptic proteins change their expression developmentally within the song system will help to further define conditions that promote plasticity and help reveal the cellular mechanisms that encode song-related memories (Clayton, 1997). As we continue to catalog individual events associated with avian song development, it will be important to investigate which of these events are reflections of learning and which are maturational processes that establish conditions that foster learning. Likewise, we need to establish how these ontogenetic events relate to one another. Many may represent independently regulated processes that together conspire to foster plasticity, while others may represent causally related events in cascades that lead to permanent change in neural organization and function.

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