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Auditory representations and memory in birdsong learning

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Songbirds are well suited to studies of vocal processing not only because of their impressive motor abilities, but also because of their exquisite sensory system that allows them to detect subtle song variability, memorize complex songs, and monitor auditory feedback during singing. Recent experiments point to areas outside the traditional song system for being relevant to sensory functions implicated in song learning. By manipulating or suppressing activity in these areas, adult birds lose their ability to recognize the songs of their tutors and juveniles are unable to form accurate copies of tutor song. Taken together, these experiments show that the sensory mechanisms for vocal learning encompass a larger network than previously thought.

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Introduction

Learning to speak is a sensorimotor feat that involves both speech comprehension and speech production. Neurological studies in humans have suggested that comprehension and production are separately mediated by Wernicke's and Broca's brain areas, respectively [1]. However, more recent functional magnetic resonance imaging studies (fMRI) have provided correlative evidence that there are more than just these two brain areas involved, but the lack of causal evidence these techniques can yield leaves many questions about brain mechanisms for speech learning and production unanswered [2].

With regards to animal models, some bird species — unlike most mammalian contenders — have the faculty of vocal learning [3]. Many parrots and songbirds are striking vocal mimics and learn to sing similar to how human infants learn to speak. Vocal learning in children and songbirds happens during a sensitive period early in life. At the beginning, learning is primarily perceptual, which then serves to guide later vocal production [4–5]. During this process, songbirds need to hear themselves [6], and their attempts to sing gradually come to resemble those of adults. This conversion of memorized song to produced song using feedback as an error-correction mechanism has become known as the auditory template theory [6–7].

In songbirds precise manipulation of behavior and brain activity is possible, permitting researchers to address questions about sensory imprinting and vocal learning. As none of these experiments are possible in human infants because of ethical reasons, birdsong research holds much promise for the discovery of general neural principles to one of the least understood feats, speech, and language learning. We here review new insights into brain areas responsible for sensory imprinting and auditory processing in general. These recent findings put a previously underestimated set of brain areas on the map and call for new experiments to ascribe precise functions to them.

Neural circuits of song

The traditional view is that production and learning of songs are generated by the song-control system, a set of specialized brain areas. For long, this system (Figure 1) was thought to be segregated into a 'motor' pathway in which lesions in adults distort songs, and a basal-ganglia-like 'learning' pathway in which lesions in juveniles impair song learning [8–14]. One justification for this functional segregation into these two pathways is that lesions in the basal-ganglia pathway prevent song changes but do not lead to disruption of normal singing behavior [13,15], suggesting that this pathway has a necessary function for learning of songs but not for their generation. However, more recent studies have changed our interpretation of this pathway when they revealed that the juveniles' inability to learn after lesions in the basal-ganglia pathway is in fact because of a motor deficit, manifested in the suppression of subtle vocal explorations [13,16]. Such explorations are not only necessary in juveniles when they learn, but also in adults during jamming avoidance, that is, when they adapt their songs to avoid auditory feedback perturbations applied by the experimenter [17–19].

An important finding was provided in a study on subsong, a developmentally restricted form of singing in very young birds that is comparable to human babbling. It was found that subsongs are generated by exactly this basal-ganglia pathway, but not the 'motor pathway' that

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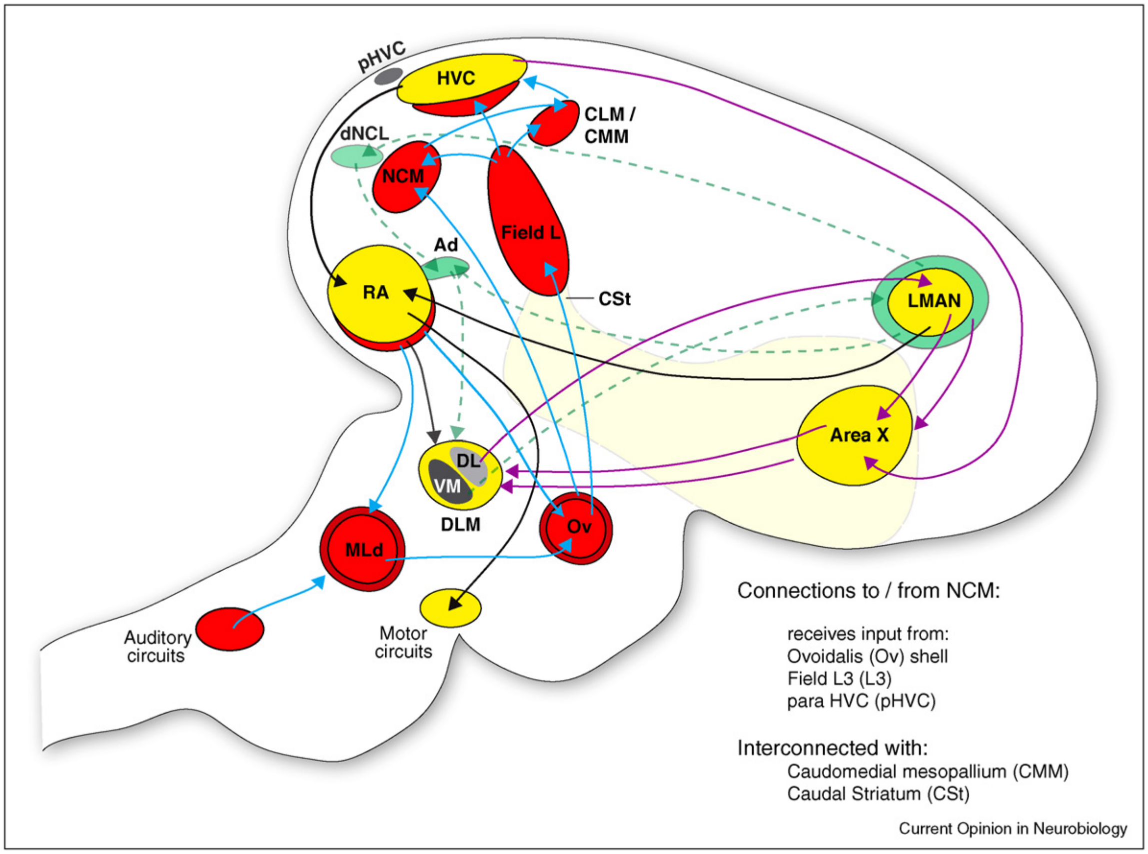
Figure 1



Current Opinion in Neurobiology

Schematic section of the songbird brain illustrating the classic song system (brain areas in yellow and connection arrows in black for the adult motor pathway and in purple for the basal-ganglia pathway). Auditory areas and areas implicated in song memorization are shown in red, connected by blue arrows. Also shown is a pathway parallel to the basal-ganglia pathway that was recently shown to be implicated in song learning, with brain areas depicted in green and connection arrows in dashed green lines. Ad: dorsal arcopallium; Area X: Area X of the striatum; CLM: caudolateral mesopallium; CMM: caudomedial mesopallium; CSt: caudal striatum; DLM: medial part of the dorsolateral thalamic nucleus; (DL: dorsolateral, VM: ventromedial); dNCL: dorsal region of the caudolateral nidopallium; Field L and HVC used as proper names; LMAN: lateral magnocellular nucleus of the anterior nidopallium; MLd: dorsal part of the lateral mesencephalic nucleus; NCM: caudomedial nidopallium; Ov: nucleus ovoidalis; pHVC: para HVC; RA: robust nucleus of the arcopallium.

generates adult songs [20•]. Hence, these more recent findings suggest that the song-control system is essentially composed of two motor pathways, one generating subsongs and variability of adult songs, and the other generating stereotyped aspects of older juveniles' and adults' songs.

Sensory and memory processes involved in song learning

It is well established that birds need to hear themselves to learn their songs [21]. Hence, the process of analyzing auditory feedback, that is, comparing it to the memorized tutor song and evaluating current motor performance, is one of the main requirements for song learning. In our opinion, any brain area relevant to this process should be considered to be part of an extended song-control system that still needs to be fully circumscribed.

How and where in the brain is auditory feedback processed and used to update the motor system? Evidence for auditory feedback processing in the traditional song-control system is scarce [22–24]. In a recent study in search of neural traces of auditory feedback from our lab, recording electrodes were placed in field L (the main thalamo-recipient zone of the auditory pallium) and in the caudolateral mesopallium (CLM). Unsurprisingly, some neurons in both field L and CLM responded to perturbations of auditory feedback. The acoustic perturbations were delivered through a loudspeaker while juvenile birds practiced their songs. More surprisingly, some neurons responded with exceeding high sensitivity to perturbations. Other neurons did not respond at all to perturbations, but their firing lead or predicted vocal onsets [25•]. This study thus revealed that sophisticated motor-related auditory processing is taking place already

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close to the sensory extreme of forebrain structures potentially involved in song learning and that all brain areas in the pathway from field L to motor areas could potentially be of crucial relevance as well.

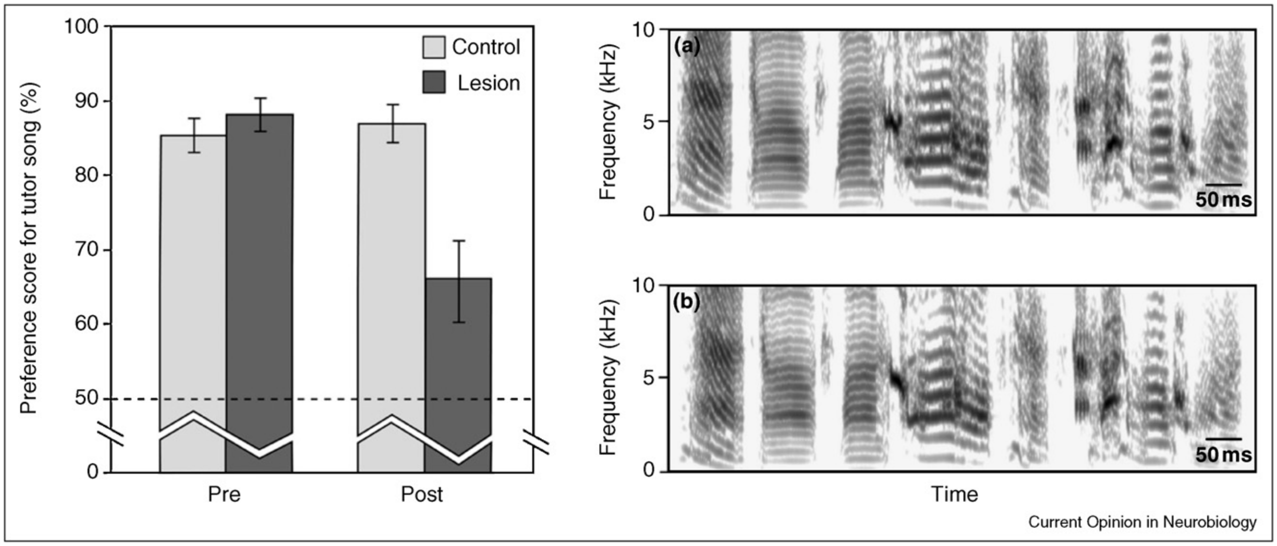
Indeed, a couple of recent studies have shown that a higher auditory brain region outside the classical song-control system has a function specific to the memorization and recognition of tutor song. In very young birds, London and Clayton have transiently suppressed protein synthesis in major parts of the auditory lobule including the caudomedial mesopallium (CMM) and the caudomedial nidopallium (NCM) during controlled tutoring sessions and found that birds produce poor copies of tutor song on maturation [26••]. This deficit in song imitation was not because of transient deafening by drug infusion, as adult birds subjected to the same treatment performed well in a difficult song-discrimination task. The London and Clayton findings suggest that the formation of a sensory memory of tutor song requires a conserved molecular pathway in CMM and NCM. Further experiments will be necessary to verify that the observed deficit is specifically related to impaired template learning and not also to disrupted sensorimotor integration. Such a possibility could be addressed by subjecting a group of juvenile birds to the same treatment in between tutoring sessions rather than during tutoring sessions. Given the observed deficits specific to tutor-song memorization, is the auditory lobule the main locus in which a template of tutor song is stored? And, does it hold the hypothetical tutor-song memory for extended periods of time, or is the memory only stored for a brief time and soon thereafter consolidated elsewhere in the song system?

A partial answer comes from a recent experiment by Gobes and Bolhuis, who have performed irreversible NCM lesions in adults, with the goal of exploring the involvement of NCM in tutor song recognition. They found that bilateral neurotoxic lesions to the NCM of adult male zebra finches strongly reduce tutor-song preference (Figure 2, left) in a simple behavioral test, but do not affect the males' song production or their ability to discriminate calls (Figure 2, right) [27••]. If we view a reduction in tutor-song preference as being equal to a loss of song memory or access thereto, these findings suggest that the NCM performs an essential role not only in the formation of a tutor-song memory, but also in the representation and recall of that memory throughout a bird's life. In summary, the London and Clayton and Gobes and Bolhuis studies for the first time established the necessity of NCM/CMM in song learning. How can we reconcile their findings on specific involvement of NCM/CMM in tutor-song memorization with the broader literature on song representations?

Molecular responses in NCM correlate with song-learning performance

NCM and CMM are higher auditory and association areas that are sometimes viewed as being analogous to Wernicke's area in humans [10,28]. NCM is extensively connected with other areas in the nidopallium (L2a, L3, and possibly also pHVC) as well as distinct areas in the mesopallium (CMM), in the thalamus (Ov shell), and possibly in the striatum (CSt) [29–32]. All of these areas project to NCM, but only the connections to CMM and CSt are reciprocal/bidirectional (Figure 1). Besides the reciprocal connection to NCM, CMM also

Figure 2



NCM lesions in adult birds have no effect on singing but on song perception. Left: mean preference for tutor song is reduced in NCM-lesioned birds. 'Pre' and 'post' refer to preference tests before and after the lesion, and 'control' to birds injected with vehicle. The error bars indicate the SEM. Right: song is unchanged after neurotoxic lesions in NCM of adult zebra finches (**(a)** before and **(b)** after the lesion). Reproduced with permission from [27].

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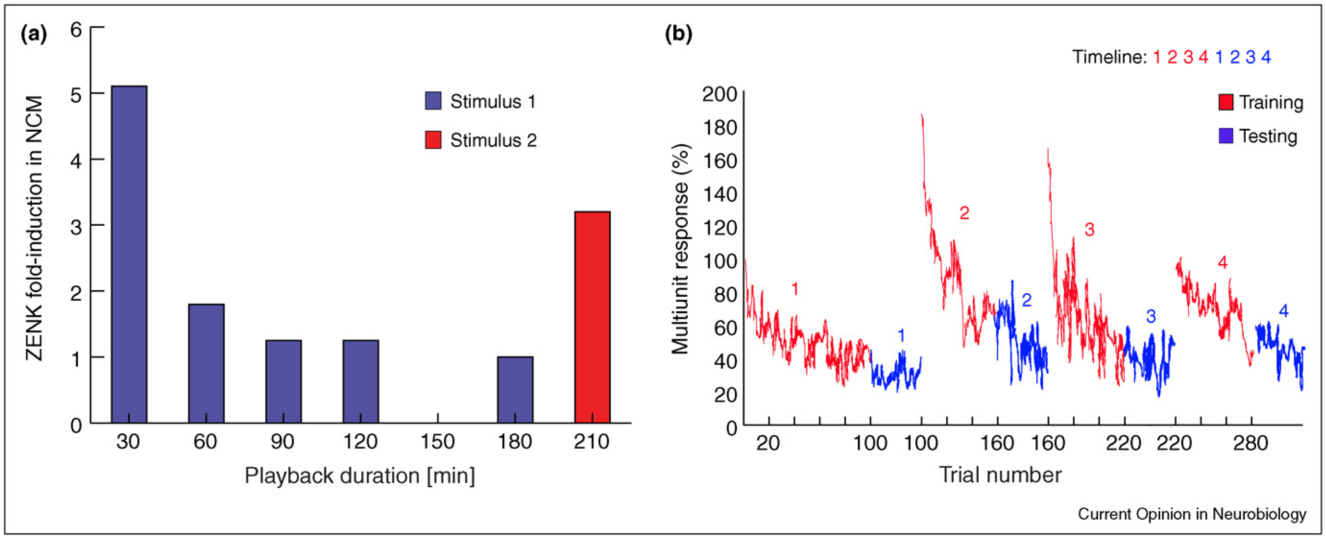
Figure 3



NCM responses habituate during repeated stimulus playback. **(a)** ZENK expression is strong after 30 min exposure to a particular song (Stimulus 1, leftmost blue bar). Longer exposures yield lower ZENK expression (blue bars). Presenting a novel stimulus (Stimulus 2) for 30 min after three hours playback of Stimulus 1 elicits a strong ZENK response (red bar), comparable to the 30-min playback response to Stimulus 1. Figure adapted from [39]. **(b)** Multiunit activity at a single recording site adapts during repeated presentation of each of the four stimuli (red, 1–4). When the four stimuli are presented again (blue, 1–4), the adaptation continues where it previously stopped, demonstrating a stimulus-specific memory of adaptation state. The presentation order of the stimuli is shown as a timeline on top. The playback duration of each trial is 2.5 s, including a 0.5 s silence interval preceding stimulus onsets. Figure adapted from [51].

shares a reciprocal connection with CLM [29] and receives a projection from the Ov shell [29,33,34].

NCM and CMM are implicated in the neural representation of songs, as revealed by gene expression [35,36], with the most prominent gene an immediate-early gene encoding a transcriptional regulator (ZENK; also known as zif-268, egr-1, NGFI-A, or Krox-24). ZENK is involved in memory consolidation [37] and is induced in NCM after playback of conspecific songs, but much less so after playback of heterospecific songs and not at all after playback of tone bursts [36]. ZENK induction was also found in adjacent areas of the auditory forebrain including CMM [32]. ZENK expression in NCM is contingent on hearing, because singing alone does not induce high ZENK levels in deafened birds [38]. In NCM, repeated playbacks of one song induces increased ZENK mRNA levels for the first 30 min, but then levels decline back to baseline levels despite continued stimulation with the same song [32,39]. Hence, if a song is perceived as 'novel' it induces a ZENK response; after the song has been entrained it no longer induces ZENK (Figure 3a). Playback of single syllables elicits ZENK expression in distinct subregions of NCM, but responses to paired stimuli can be nonlinear, that is, habituation to individual stimuli does not elicit habituated responses when these stimuli are presented in pairs [40]. In juvenile NCM, ZENK expression induced by song playback depends on social environment and is not seen in birds raised in isolation [41•]. ZENK expression elicited by playback of tutor song in NCM and CMM is not higher than expression elicited by playback of BOS or novel song [42], suggesting that the song representations in these areas are not biased toward the tutor song. However, ZENK expression to tutor song in NCM positively and significantly correlates with the number of song elements shared with the tutor [43•], suggesting in combination with the London and Clayton study that the NCM ZENK response constrains the ability of birds to imitate a song. No similar correlation between number of tutor-song elements copied and ZENK or FOS (the protein product of the immediate-early gene c-fos) expression was found in CM [42,44].

Note that in females, a representational bias for tutor song has been found. Comparing the ZENK response to playback of tutor song and novel song, tutor song elicited significantly more expression in CMM but not in NCM [45]. Furthermore, in non-songbirds, ZENK expression to conspecific and heterospecific vocalizations revealed increased response to conspecific vocalizations only in CMM but not in NCM [46]. Hence, these experiments show that also non-learners exhibit species-specific sensory processing in NCM and CMM, but that the relative roles of CMM and NCM appear diverse across species and sexes.

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NCM spike response habituation corroborates ZENK studies

Electrophysiology has shown that NCM neural responses in awake and head-restrained birds are very broadly tuned [47,48], as neurons respond to conspecific and heterospecific songs, to artificial stimuli such as white noise and pips, but not to pure tones. However, there is no marked response preference for conspecific songs over conspecific songs played back in reverse, and over heterospecific songs [49]. Broad NCM tuning is already present in very young birds before they start to sing [49]. With the exception of anecdotal evidence [7], we are unaware of any study that found NCM response selectivity to tutor song based on response strength, a standard method to establish stimulus preference in songbirds [50].

One of the reasons response selectivity is not simple to characterize in NCM is the dramatic response habituation found there. In awake birds, electrophysiological responses in caudal NCM habituate to repeated presentation of the same song stimulus, in reminiscence of the ZENK findings. Habituation of responses is mainly because of a response decrease between the first and second song presentation [51], but requires sufficient numbers of playbacks typically in excess of 100 [48]. Habituation to conspecific calls and songs outlasts habituation to other complex stimuli [52] and is most pronounced in adults [49]. Thus, habituation rate constitutes a neural activity read out that reveals NCM preference for conspecific song but contrasts with spike-frequency that yields no preference [48]. Most interestingly, the extent of immediate habituation induced by a particular novel song is not diminished when other conspecific songs are presented in alternation (Figure 3b), suggesting that NCM is specialized for remembering the calls and songs of many individual conspecifics [53•]. The emergent picture from these studies is that the rate of NCM response habituation reflects whether a given stimulus is novel or familiar; the rate is high for novel stimuli and low for familiar stimuli.

When NCM response habituation was evaluated for tutor song, it was found that a familiarity index reflecting the strength of this habituation was high in birds that performed good imitations of tutor song and low in birds that performed poor imitations. Hence, response habituation in NCM is a neural correlate of song-imitation accuracy [54], and agrees with an earlier study that found tutor-song induced ZENK expression levels in NCM to positively correlate with the number of song elements shared with the tutor [43•]. In essence, these findings reveal that we can tell how much a bird has learned from its father without comparing the songs but by simply inspecting NCM responses to the father's song. Thus, NCM contains not just a sensory 'novelty' code, but also a tutor-song code that is neither purely sensory nor motor in its nature.

Is there a brain area with a true sensory code for tutor song, that is, in which neural responses are selective to tutor song? [55]. Selectivity to tutor song over other song stimuli has been observed in multiunit activity in HVC of awake juvenile birds [56]. It is currently not clear whether this selectivity emerges do-novo in HVC or is already present upstream of HVC. In anesthetized birds, neurons in the caudal mesopallium (CM) and in field L respond selectively to conspecific songs (CON) over most natural and artificial sounds tested [50]. In field L this selectivity emerges during development, whereas in CLM it is already present in very young birds [55]. In addition, CMM neurons are weakly selective for the bird's own song (BOS) over CON [57]. However, no electrophysiological evidence has been found for tutor-song selectivity in field L and the CLM. CMM cells have also been shown to specifically hold auditory memories of learned songs other than the BOS. In European Starlings that underwent song-discrimination training using go/no-go or two-forced choice paradigms, Gentner and Margoliash have shown that CMM cells respond more to familiar than to unfamiliar songs [58•], revealing a plastic neural representation of songs in CMM.

Given these findings, it will be important to examine electrophysiological responses to tutor song in CMM and NCM using standard selectivity measures such as the d' measure [59,60]. Effects of response habituation will have to be taken into consideration when quantifying selectivity. Irrespective of whether tutor-song selectivity will be found, the connections between CMM and NCM raise the question how a relatively simple 'respond to most familiar' neural code in CMM is translated into a more complicated 'habituate to most familiar' neural code in NCM. Possibly involved could be inhibitory connections from CMM to NCM [61] and some form of synaptic depression or spike-frequency adaptation. Also, if a tutor-song memory in NCM is used for song learning, then we need to better understand how the habituation code in NCM is combined with auditory feedback to be transformed into updated motor instructions. Hypothetical mechanisms could be evaluated using computational models.

Conclusions

The necessity of NCM for tutor-song memorization and recognition is now established. The observations from ZENK expression and electrophysiology studies agree well with each other, as both reveal a 'novelty' code in NCM that reflects the bird's past sensory experience. However, ZENK is one of many immediate-early genes and presence or lack of correlation with electrophysiology should not be over-interpreted, as other genes and gene products may be similarly informative.

In our view, rather than to systematically scrutinize all these genes, it will be more important to gain more

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insights into NCM and CM neural activity in freely behaving and singing birds. This is of particular importance because recently yet another pathway has been shown to be necessary for song learning (Figure 1) [62•]. More refined experiments are now needed to narrow down the functions of these various pathways and brain areas. One reason for this need is that lesion or inactivation studies may reveal necessity for song memorization, but by themselves are weak indicators of the actual function of a brain area. To store and retrieve the tutor memory may require activity in a large network. For example, the template could be stored in CMM, but retrieved via NCM. In this view, NCM lesions would suppress memory recognition simply because access to the memory is broken. It would be interesting to test whether NCM contains neurons that are sensitive to differences between the developing BOS and the tutor song. The existence of such neurons is speculative, but conceivable because of categorical auditory responses found in the premotor brain area HVC [63•]. If categorical responses to the tutor song relative to the BOS were to be found, this would constitute a significant finding, because it would allow birds to detect small differences between the current BOS and the template and so explain the remarkable accuracy with which birds can imitate their tutors. Electrophysiological recordings could also provide insights into when tutor-song memories are processed and retrieved from memory. For example, memories could be consolidated during sleep and retrieved after the bird sang or while it sings [56,64–66].

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