Seasonal plasticity in the adult brain

Anthony D. Tramontin and Eliot A. Brenowitz

Seasonal plasticity of structure and function is a fundamental feature of nervous systems in a wide variety of animals that occupy seasonal environments. Excellent examples of seasonal brain changes are found in the avian song control system, which has become a leading model of morphological and functional plasticity in the adult CNS. The volumes of entire brain regions that control song increase dramatically in anticipation of the breeding season. These volumetric changes are induced primarily by vernal increases in circulating sex steroids and are accompanied by increases in neuronal size, number and spacing. In several species, these structural changes in the song control circuitry are associated with seasonal changes in song production and learning. Songbirds provide important insights into the mechanisms and behavioral consequences of plasticity in the adult brain.

The Anatomy of the adult vertebrate brain was once believed to remain relatively static throughout an individual’s lifespan (age-related neuron loss not withstanding). In the early 1960s, however, two reports suggested the need to revise this widely held view. In 1962, Joseph Altman observed neuron proliferation in the adult rodent brain and in 1964, Edward Bennett and coworkers reported that environmental enrichment produced a subtle but significant increase in cortical mass in adult rodents. These studies suggested that anatomical plasticity persists in the brain long after early ontogeny: Almost two decades later, Fernando Nottebohm confirmed this hypothesis by demonstrating dramatic seasonal morphological changes of entire brain regions that control song behavior in canaries (Serinus canarius). Nottebohm’s discovery stimulated much research describing seasonal changes in the nervous systems of a wide variety of adult animals. Seasonal plasticity of structure and function is now known to be a common feature of the brains of many species, particularly seasonal breeders (Table 1). These animals provide...
Abbreviations: AH, anterior hypothalamus; GnRH, gonadotropin-releasing hormone; MBH, mediobasal hypothalamus; POA, pre-optic area.

powerful models within which to study naturally occurring plasticity in the adult brain. No animal, however, has provided as much insight on this topic as songbirds.

The volumes of song control nuclei change seasonally

Song is a learned behavior used by birds to attract mates and to defend breeding territories\(^5\). In oscine passerines (songbirds), song behavior is controlled by a network of discrete interconnected brain regions or nuclei (Fig. 1). Song behavior and the brain regions that control it are seasonally plastic in every species of seasonally breeding adult songbird that has been systematically studied\(^6\)-\(^9\). The entire volumes of several song nuclei, including the neostriatal region HVc (sometimes referred to as the ‘high vocal center’), the robust nucleus of the archistriatum (RA) and area X of the parolfactory lobe, are considerably larger during the spring breeding season than during autumn and winter in wild birds (Fig. 1, Table 2). In the most extreme example, the volume of HVc in spotted towhees (Pipilo maculatus) nearly triples between the non-breeding and breeding seasons (Fig. 2). This naturally occurring plasticity in the songbird brain is perhaps the most pronounced observed in any adult vertebrate. One should note, however, that not all of the song nuclei exhibit seasonal volumetric changes. For example, these changes have not been observed in the lateral portion of the magnocellular nucleus of the anterior neostriatum (IMAN)\(^3,37,39,51\). Day length is the primary environmental cue that stimulates seasonal reproductive development and song system growth\(^1,2,3,12,14,15\). Each year prior to the breeding effort, the lengthening days of late winter and early spring stimulate gonadal recrudescence, development of secondary sexual characteristics and increases in circulating blood levels of gonadal sex steroids\(^12\). The seasonal growth of the song control system occurs during this early stage of seasonal reproductive development, several weeks before the actual onset of breeding\(^2\). Recent data suggest that the seasonal growth of the song nuclei can also be influenced by social cues other than day length. In the laboratory, social cues from sexually receptive female white-crowned sparrows (Zonotrichia leucophrys gambelii) enhanced the photic-induced growth of two song nuclei in their male cage-mates\(^27\). HVC and RA were 20% and 15% larger, respectively, in males housed with females on long spring-like days than in males housed similarly without females. Future studies should determine whether other seasonal cues such as food availability, temperature or precipitation also influence the neural growth of the song system.

In the laboratory, long spring-like days (LD) and elevated circulating testosterone (see below) stimulate structural changes in the song circuitry that closely resemble those observed in wild animals (Table 3). These changes occur rapidly and sequentially\(^1,2,3\). In captive white-crowned sparrows, HVC volume increased by 69% within seven days of exposure to LD and testosterone. The primary efferent targets of the HVC, RA and area X, appeared to grow more slowly, only achieving 20% and 15% of their pre-breeding male toads\(^4\), claw-closer muscle produce smaller EPSPs, 6

### TABLE 1. Comparative survey of seasonal plasticity in the adult central nervous system*  
<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrodonid</td>
<td>Inhibitors of protein kinases A and C are most effective during the non-breeding season at suppressing egg-laying hormone secretion from the neuroendocrine bag cells of Aplysia californica. A greater percentage of Aplysia californica siphon motorneurons exhibit an excitatory response to PDBFamide treatment during the summer months.</td>
<td>4</td>
</tr>
<tr>
<td>Crustacea</td>
<td>Motor terminals that innervate the crayfish (Procambarus clarkii) claw-closer muscle produce smaller EPSPs, are more resistant to fatigue and have more synaptic varicosities during the summer than during the winter.</td>
<td>5</td>
</tr>
<tr>
<td>Osteichthyes</td>
<td>Androgen-receptor levels peak during spawning in the goldfish (Carassius auratus). The size of pitanal organ cell bodies increases during the fall and winter in goldfish (Carassius auratus).</td>
<td>6</td>
</tr>
<tr>
<td>Amphibia</td>
<td>The volume of the mediod-amphidala-antierior-preoptic-complex is larger in hibernating (pre-breeding) than in post-breeding male toads (Bufo: pteronotus).</td>
<td>7</td>
</tr>
<tr>
<td>Reptilia</td>
<td>The size of the anterior-hypothalamus-preoptic area increases while the size of the ventromedial hypothalamus decreases during the breeding season in male white-throated lizards (Cnemidophorus inornatus).</td>
<td>8</td>
</tr>
<tr>
<td>Aves</td>
<td>The volume of the hippocampal formation and neuronal incorporation into this brain region increase during the fall in black-capped chickadees (Peromyscus leucopus). The volume of several song control nuclei increases during the breeding season in songbirds. GrpH immunoreactivity is decreased, and the number of axo-somatic synaptic terminals contacting GrpH neurons is greatest in photorefractory European starlings (Sturnus vulgaris).</td>
<td>9</td>
</tr>
<tr>
<td>Mammalia</td>
<td>Motorneurons in the spiral nucleus of the bulboconarous area are larger in breeding than in non-breeding white-footed mice (Peromyscus leucopus). Hippocampal neuronal incorporation is greatest during the fall in Syrian hamsters (Mesocricetus auratus). The volume of the hypothalamic suprachiasmatic nucleus and the number of vasopressin-immunoreactive neurons contained within it is greater during the autumn than during the summer.</td>
<td>10</td>
</tr>
</tbody>
</table>

*Note that this list is not exhaustive, but is intended to provide examples from a wide variety of taxa. Abbreviations: AH, anterior hypothalamus; GnRH, gonadotropin-releasing hormone; MBH, mediobasal hypothalamus; POA, pre-optic area.
control nuclei in adults is similar to the sequential ontogeny of these structures in juvenile birds. In young male zebra finches (Poephila guttata, between 12 and 53 days post-hatch), Botter et al. reported that the developmental growth of HVc preceded that of RA and area X (Ref. 52). These observations might suggest that early ontogeny and adult plasticity in the brain exploit similar mechanisms, an idea that dates back to Ramon y Cajal23. Rigorous tests of this hypothesis should be carried out in a species other than the zebra finch because these birds are not typical photoperiodic seasonal breeders24.

The sequential seasonal growth of the song control nuclei is consistent with the hypothesis that the seasonal growth of RA and area X requires trans-synaptic support from HVc. In support of this hypothesis, Brenowitz and Lent reported preliminary data that lesions of HVc blocked the seasonal growth of RA and area X in captive white-crowned sparrows25. This result is also reminiscent of developmental studies where HVc lesions can also impair song discrimination26,27. The anterior forebrain circuit (gray arrows) indirectly connects HVc to RA and is essential for song learning and perception22,23. Lesions of anterior forebrain nuclei prevent normal song learning in juvenile birds24,26 and song perception in adult birds22,25. Feedback circuits also exist within the song control system. Neurons in the lateral portion of the magnocellular nucleus of the anterior neostriatum (lMAN) that project to RA send collateral branches to area X in the parolfactory lobe closing one loop. Projections from RA also initiate reentrant thalamo-telesencephalic loops (broken arrows) that might provide indirect feedback to HVc (Refs 33,34). The HVc receives afferent input from two song nuclei that are not shown: nuclei interfacialis of the caudal neostriatum and nucleus uvaeformis. HVc and RA also receive input from several auxiliary forebrain regions that are not shown28. Finally, neurons in the lateral hypothalamus project to the dorsomedial nucleus of the posterior thalamus (DMH), which in turn projects to the medial portion of the magnocellular nucleus of the anterior neostriatum (mMAN), suggesting integration of information between the hypothalamus and the song system22. Abbreviations: DLM, dorsolateral nucleus of the medial thalamus; rMNX, the rostro-medial portion of the hypoglossal nucleus; V, lateral ventricle.

**Fig. 1.** The song control system is organized into two principal circuits. The main descending motor pathway (black arrows) begins in HVc (sometimes referred to as the “high vocal center”) and terminates at the syrinx (the vocal production organ). Neuronal activity in HVc and in the robust nucleus of the archistriatum (RA) is synchronized with sound production from the syrinx21,22, and excitation of either of these nuclei abolishes song production21. HVc lesions can also impair song discrimination26,27. The anterior forebrain circuit (gray arrows) indirectly connects HVc to RA and is essential for song learning and perception22,23. Lesions of anterior forebrain nuclei prevent normal song learning in juvenile birds24,26 and song perception in adult birds22,25. Feedback circuits also exist within the song control system. Neurons in the lateral portion of the magnocellular nucleus of the anterior neostriatum (mMAN) that project to RA send collateral branches to area X in the parolfactory lobe closing one loop. Projections from RA also initiate reentrant thalamo-telesencephalic loops (broken arrows) that might provide indirect feedback to HVc (Refs 33,34). The HVc receives afferent input from two song nuclei that are not shown: nuclei interfacialis of the caudal neostriatum and nucleus uvaeformis. HVc and RA also receive input from several auxiliary forebrain regions that are not shown28. Finally, neurons in the lateral hypothalamus project to the dorsomedial nucleus of the posterior thalamus (DMH), which in turn projects to the medial portion of the magnocellular nucleus of the anterior neostriatum (mMAN), suggesting integration of information between the hypothalamus and the song system22. Abbreviations: DLM, dorsolateral nucleus of the medial thalamus; rMNX, the rostro-medial portion of the hypoglossal nucleus; V, lateral ventricle.

control nuclei in adults is similar to the sequential ontogeny of these structures in juvenile birds. In young male zebra finches (Poephila guttata, between 12 and 53 days post-hatch), Botter et al. reported that the developmental growth of HVc preceded that of RA and area X (Ref. 52). These observations might suggest that early ontogeny and adult plasticity in the brain exploit similar mechanisms, an idea that dates back to Ramon y Cajal23. Rigorous tests of this hypothesis should be carried out in a species other than the zebra finch because these birds are not typical photoperiodic seasonal breeders24.

The sequential seasonal growth of the song control nuclei is consistent with the hypothesis that the seasonal growth of RA and area X requires trans-synaptic support from HVc. In support of this hypothesis, Brenowitz and Lent reported preliminary data that lesions of HVc blocked the seasonal growth of RA and area X in captive white-crowned sparrows25. This result is also reminiscent of developmental studies where HVc lesions in juvenile male zebra finches blocked the full development of RA and area X (Refs 56,57). In young male zebra finches, HVc neurons produce brain-derived neurotrophic factor (BDNF), which appears to be trans-
Fig. 2. Seasonal volumetric changes in the songbird brain. Wild male spotted towhees were collected and killed during the spring breeding season (left) and during the winter non-breeding season (right). Nissl-stained coronal sections through HVc (a), robust nucleus of the archistriatum (RA) (b) and area X (c) are shown. The overlying hippocampal formation has been removed in (a). Scale bars, 0.5 mm. Modified, with permission, from Ref. 40.

(a) Spring
(b) Winter
(c) Area X

TABLE 3. Experimentally induced plasticity of song control nuclei in captive male songbirds

<table>
<thead>
<tr>
<th>Species</th>
<th>Treatment</th>
<th>HVc*</th>
<th>RA*</th>
<th>Area X*</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canary (Serinus canarius)</td>
<td>Natural photoperiod April versus September</td>
<td>1.99</td>
<td>1.77</td>
<td>nm</td>
<td>3</td>
</tr>
<tr>
<td>Red-winged blackbird (Agelaius phoeniceus)</td>
<td>15 h versus 9.5 h light</td>
<td>1.34</td>
<td>1.28</td>
<td>1.42</td>
<td>43</td>
</tr>
<tr>
<td>Orange bishop (Euplectes franciscanus)</td>
<td>14 h versus 10 h light</td>
<td>1.80</td>
<td>1.60</td>
<td>nm</td>
<td>48</td>
</tr>
<tr>
<td>Eastern towhee (Hylophilus腓orhadinus)</td>
<td>15 h versus 9 h light</td>
<td>1.68</td>
<td>1.54</td>
<td>1.62</td>
<td>49</td>
</tr>
<tr>
<td>Gambel’s white-crowned sparrow (Zonotrichia leucophrys gambelii)</td>
<td>20 h light versus testosterone versus 8 h light*</td>
<td>1.82</td>
<td>1.71</td>
<td>1.57</td>
<td>44</td>
</tr>
<tr>
<td>European starling (Sturnus vulgaris)</td>
<td>P-stim versus P-refrac*</td>
<td>1.44</td>
<td>no change</td>
<td>no change</td>
<td>50</td>
</tr>
<tr>
<td>American tree sparrow (Spizella arborea)</td>
<td>20 h versus 8 h light</td>
<td>1.76</td>
<td>1.46</td>
<td>1.74</td>
<td>46</td>
</tr>
</tbody>
</table>

*Numbers represent song nucleus volume ratios between treatment groups.

1Photostimulated (P-stim) males had testes that were not fully recrudesced (birds might not have been fully stimulated). After six to eight weeks of long days, males became photorefractory (P-refrac) and had fully regressed testes.

2Numbers represent song nucleus volume ratios between treatment groups.
Most investigations of seasonal plasticity in the song system have used Nissl stains to visualize the borders of song nuclei. The reliability of these stains in this context was questioned by Gahr et al. He reported that the Nissl-defined borders of HVc were larger in breeding than in non-breeding male canaries, but that the size of this nucleus did not differ between these groups when measured by estrogen-receptor immunoreactivity. Gahr also reported that area X-projecting neurons lay outside the apparent Nissl-defined borders of HVc in non-breeding birds. Since Gahr’s report, several investigators from different laboratories have compared seasonal volumetric changes of HVc using a Nissl stain and additional histological markers. All of these studies failed to replicate Gahr’s observation and found that the Nissl-defined volume of HVc coincided with the volume defined by other markers, regardless of season or hormone condition (see Table I). These studies demonstrate that the seasonal changes observed in the song nuclei using Nissl-stained tissue represent real changes in the structure of these regions. For a detailed discussion of this issue see Ref. 41.

**References**


**Box I. Reliable anatomical markers of song control nuclei**

<table>
<thead>
<tr>
<th>Species</th>
<th>Histological markers used</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canary (Sturnus canarius)</td>
<td>Nissl stain, TH/DHT and E₂ accumulation, RA and area X-projecting neurons</td>
<td>c,d,e</td>
</tr>
<tr>
<td>European starling (Sturnus vulgaris)</td>
<td>Nissl stain, α₁-adrenoceptor autoradiography.</td>
<td>f</td>
</tr>
<tr>
<td>Gambel’s white-crowned sparrow (Zonotrichia leucophrys gambelii)</td>
<td>Nissl stain, area X-projecting neurons, TH/DHT or E₂</td>
<td>g</td>
</tr>
<tr>
<td>Gambel’s white-crowned sparrow (Zonotrichia leucophrys gambelii)</td>
<td>Nissl stain, androgen-receptor autoradiography.</td>
<td>h</td>
</tr>
<tr>
<td>Western song sparrow (Melospiza melodia melodia)</td>
<td>Nissl stain, Mu immunocytochemistry.</td>
<td>i</td>
</tr>
</tbody>
</table>

Abbreviations: DHT, dihydrotestosterone; E₂, estradiol; RA, robust nucleus of the archistriatum.

The effects of testosterone on HVc neuronal survival and the volumetric growth of this nucleus appear to be mediated (at least in part) through BDNF. Treatment with testosterone increases protein synthesis18 and BDNF-like immunoreactivity in HVc (Ref. 87). Intaparenchymal BDNF infusion adjacent to HVc mimics the effects of testosterone, enhancing neuronal survival in HVc and increasing its volume. Finally, and most interestingly, neutralizing antibodies to BDNF block the effects of testosterone on neuronal survival within HVc and the volumetric growth of HVc. Insulin-like growth factors 1 and 2 have also been identified in the HVc and the volumetric growth of HVc. Insulin-like growth factors 1 and 2 are known to stimulate neuronal survival in the striatum increase with the onset of photorefractoriness. Emerging evidence suggests that the sensitivity of the song nuclei to circulating testosterone might vary seasonally. At the end of the breeding season birds become refractory to the stimulatory effects of long days and the tests regress, sex steroid levels decrease in the blood and feather molt ensues41. During this photorefractory period, androgen- and estrogen-receptor production in HVc appear to be diminished41,42 (Fig. 3). One study has demonstrated that 5α-reductase levels in the hyperstriatum with the onset of photorefractoriness

![Fig. 3. Androgen-receptor immunoreactivity in HVc of a wild white-crowned sparrow.](image-url)
in European starlings (Sturnus vulgaris)²⁹, perhaps indicating that testosterone inactivation is enhanced in the brains of photorefractory birds. In another study, Bernard and Ball implanted photorefractory starlings with exogenous testosterone and reported no increase in HVC volume²⁸.

Non-steroidal cues contribute to seasonal plasticity

The seasonal plasticity in the song control system is not governed solely by gonadal steroids. Studies from two laboratories have indicated that manipulations of day length can induce changes in the song nuclei of castrated animals. Long days increased the volume of HVC slightly in castrated white-crowned sparrows³⁸ and starlings³⁹. Another study suggested that photostimulation increased the volumes of HVC, RA and area X in castrated American tree sparrows (Spizella arborea)²⁸. These researchers all pointed out that the gonad-independent effects of photoperiod were much less pronounced than those observed in gonadally intact birds. The interpretation of results from these studies of castrated animals must be tempered by reports of non-gonadal sources of sex steroids³⁸.

Several non-steroidal endocrine signals have been identified as potential mediators of non-gonadal song system plasticity. Melatonin binding in HVC and RA is photoperiodically regulated in captive house sparrows (Passer domesticus)³⁹, and exogenous melatonin can inhibit photo-induced song system growth in castrated starlings³⁸. Preliminary evidence suggests that thyroid hormones might also influence seasonal plasticity in the song control system, especially considering their involvement in seasonal plasticity of the avian gonadotropin system⁴⁰,⁴¹,⁴². Why does the structure of the song system change seasonally? An hypothesis

The sustained peak performance of a seasonally predictable behavioral task is often preceded by hypertrophy of the organs or tissues, that support that task⁴³. For example, the size of the gonads and other reproductive structures increases dramatically in preparation for the annual breeding season and these organs regress when the breeding season is terminated⁴⁴,⁴⁵. Long-distance migration in birds is preceded by a host of physiological changes including elevated fat stores and increased flight muscle mass⁴⁶,⁴⁷. Anticipatory changes such as these are stimulated by seasonal environmental cues and mediated by neural and endocrine signaling mechanisms. The maintenance of hypertrophied organ systems and tissues is thought to be energetically expensive and so these systems regress when peak performance is not required⁴⁸,⁴⁹.

The principles of performance-associated hypertrophy might also pertain to the seasonal plasticity of the song control circuitry. This hypothesis predicts that song performance should be enhanced during the breeding season. This prediction is supported by data from canaries, white-crowned sparrows and song sparrows. In these species, males sing more stereotyped songs (less song-to-song variability) during the spring breeding season, and song production is more frequent (more sustained) at this time of the year²⁸,⁴⁰,⁴³,⁴⁴,⁴⁶,⁴⁷,⁴⁸,⁴⁹, (Fig. 4). During the non-breeding season, birds sing less frequently and with less stereotypy (more variability).

Another prediction of the performance-associated hypertrophy hypothesis is that the growth of the song nuclei should occur in anticipation of behavioral changes. This appeared to be true in a study of captive white-crowned sparrows where seasonal cues initiated rapid song system growth that preceded significant improvements in song stereotypy⁴⁸. This prediction merits further study and does not exclude the possibility that experiential factors might also influence song system growth in complex ways. For example, perhaps singing can provide behavioral feedback that modifies song system growth. This idea has not been directly tested.

A third prediction of the performance-associated hypertrophy hypothesis is that the energetic costs of maintaining a fully developed song system throughout the non-breeding season outweigh those associated with recrudescing the song system each spring. Currently, the relative metabolic costs of maintaining or rebuilding the song system each year are not known.

Concluding remarks and prospects for the future

Seasonal plasticity of the song system can serve as a model to address the following questions, which are of fundamental importance to the study of neural plasticity in general.

- What are the mechanisms that mediate hormone action in the adult brain? Does hormone metabolism contribute to adult brain changes? How does trans-synaptic support from afferent and efferent targets support or influence, hormone action in a given brain region?
- What growth factors and trophic agents influence adult brain plasticity? This question has already received much attention in non-avian models, but the song system can shed light on how these agents synergize with or mediate, the effects of circulating hormones.
- How are neuronal proliferation, incorporation and survival in the adult brain controlled? What is the behavioral consequence of seasonally regulated neuronal turnover?
Do neurons possess different electrophysiological characteristics in different species? To what extent is neural processing (for example, synaptic efficacy) affected by seasonal anatomical and physiological changes in brain regions that may host morphological changes? What is the functional relevance of brain changes in adults? What are the behavioral consequences? Does seasonal plasticity affect brain function in adults? What are the costs and benefits associated with the seasonal growth and regression of brain centers?

Adult brain plasticity is a common phenomenon across a wide variety of animal taxa, and is a rich topic of inquiry with many questions yet unanswered. Future studies should take advantage of the great diversity of seasonally breeding animals that exhibit naturally occurring cyclical brain changes. Such a comparative approach is likely to uncover general principles that govern dynamic events in the adult brain. In addition, this approach will provide fundamental insights into the behavioral consequences of structural changes in the adult brain.

Selected references

1 Altman, J. (1962) Are new neurons formed in the brains of adult animals? Science 135, 1127–1128
9 Nottebohm, F. et al. (1986) Developmental and seasonal changes in caudal song and their relation to changes in the anatomy of song control nuclei. J. Neurobiol. 17, 1147–1167
10 Brotz, S.W. et al. (1990) Seasonal effects in songbirds but not in the canary affect song perception in an operant task. J. Neurosci. (in press)
R is supported by the Eview and grant DGE-9816736/M02 from the NSF.

A.D. Tramontin and E.A. Brenowitz - Seasonal plasticity in the adult brain

The authors’ research is supported by the Virginia Merrill Bloedel Hearing Research Center, grant M01RR000063 from the NIH, and grant EY01656 of the National Eye Institute.