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Neurobiology of vocal communication: mechanisms for sensorimotor integration and vocal patterning

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This review will focus on recent developments in the sensorimotor integration of vocal communication. Two broad themes are emphasized: the evolution of vocal production and perception, and the role of social context. Advances include: a proposal for the emergence of vocal patterning during vertebrate evolution, the role of sensory mechanisms such as categorical perception in decoding communication signals, contributions of sensorimotor integration phenomena including mirror neurons and vocal learning, and mechanisms of hormone-dependent plasticity in both auditory and vocal systems. Transcriptional networks activated in humans but not in chimps by the FoxP2 gene suggest molecular mechanisms underlying vocal gestures and the emergence of human language.

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Introduction

A complex system of vocal communication, whose form is sculpted by its evolutionary history and experience, is the hallmark of language and the human species. While we have many examples of disorders of language and language development induced by brain injury, until recently our understanding of fundamental mechanisms for vocal communication was meager. Which neural circuitry generates speech sounds? How is hearing matched to utterance for appropriate social discourse and for language learning? How did language evolve?

Experimental model systems provide powerful approaches to answering complex questions in neuroscience, especially when, as is the case for language, direct experimentation is not possible. Vertebrate model systems that have led to recent advances in understanding

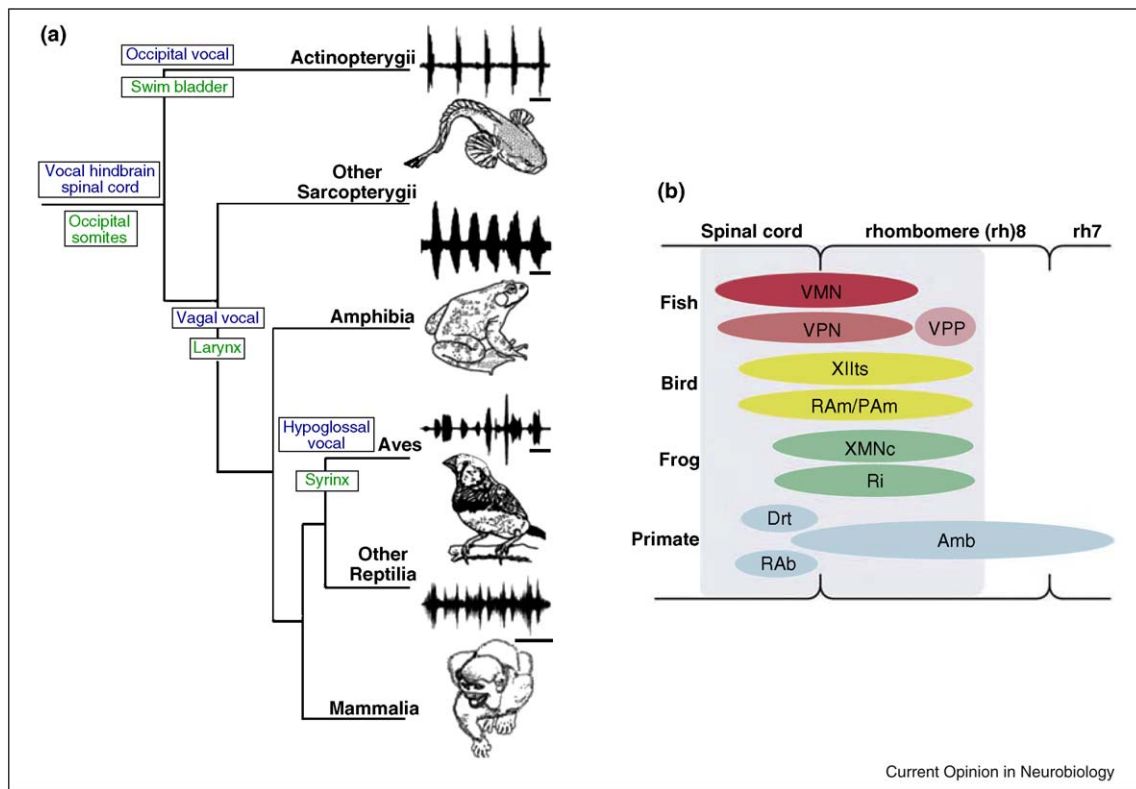
the neurobiology of vocal communication include a wide range of non-mammalian, sonic species from fish and frogs (also see paper by Wilczynski and Ryan in this issue) to songbirds (especially valuable as many species learn their songs). The identification of some potential genetic contributions to language in humans, the increasing availability of genetic and genomic information for vertebrate model systems, and the ability to probe the operation of vocal circuits *in vivo*, have advanced the field over the past five years and form the basis for this review. If insights from model systems are to be widely applicable, there must be some common neural ‘core’ that underlies the way in which social communication functions evolve across species; Goodson and Thompson evaluate evidence for this idea in this issue. Failures of social communication are common in human psychiatric disorders, especially those that manifest in early development, such as autism (see Levitt, this issue). Understanding the neurobiological basis of vocal communication, including the ‘sociogenomics’ of its implementation [1,2] should contribute fresh ideas to these and other disorders.

Vocal patterning

Vocalizations in many species consist of rhythmic patterns of muscle contractions that produce sounds in various ways (Figure 1a). In a recent study, Bass *et al.* [3**] have proposed that this rhythmicity reflects the emergence of a vocal hindbrain–spinal cord compartment that includes both vocal motor neurons and vocal pacemakers. The signature feature of this compartment is an expansion in size of rhombomere 8, the most caudal of the embryonic hindbrain segments, that contains the ancestral neural pattern generator for vocal–acoustic behaviors mediating social signaling in all extant vertebrates, including humans (Figure 1b). They propose that this neural network for social communication originated over 400 mya in the ancestor of the two major groups of bony vertebrates, the Actinopterygii or ray-finned fishes in which vocal communication is widespread [4] and the Sarcopterygii that include lobe-finned fishes, the living coelacanth *Latimeria* and all of the sonic tetrapods [3].

The development of reduced preparations in amphibians and fish has yielded fundamental insights into how vocal patterns are generated in the hindbrain. In the aquatic frog, *Xenopus laevis*, sounds are generated by the contraction of intrinsic laryngeal muscles innervated by vocal motor neurons originating in rhombomere 8 (XMNc, Figure 1b; [5]). Recordings from the laryngeal nerve of

Figure 1



(a) Evolution of vocal behaviors. Cladogram of living bony vertebrates with oscillograms of a vocalization from representative species. Vocalizations (top to bottom): midshipman fish agonistic ‘grunts,’ bullfrog advertisement call, estrildid finch song, and squirrel monkey cackle. Scale bars (top to bottom) are 500 ms, 1.0 s, 250 ms, and 200 ms. **(b)** Relative positions of vocal neurons in the rhombomere (rh)8–spinal compartment in sagittal view. Vocal motor neurons in fish and birds develop from the occipital/hypoglossal (XII) motor column (VMN/vocal motor nucleus; XIIIts/tracheosyringeal division of XII). Laryngeal motor neurons in mammals and frogs originate in caudal nucleus ambiguus (Amb)/vagal motor nucleus (XMNc). Premotor vocal neurons are also in this compartment: Drt, dorsal reticular nucleus; PAm, nucleus paraambiguus; RAb, nucleus retroambiguus; RAm, nucleus retroambiguus; Ri, inferior reticular formation; and VPP–VPN, vocal prepacemaker–pacemaker neurons. Modified from [3].

vocalizing males and females reveal that nerve activity, the vocal motor volley, predicts vocal patterns: each sound pulse or click is matched 1:1 with each compound action potential or CAP of the volley [6^{••}]. As is also the case for electric fish [7], ion channel expression in male and female effector motor neurons reflects differing requirements for the production of vocal signals in the sexes [8].

The isolated *X. laevis* brain can be induced to generate fictive male and female vocal motor patterns by application of the neuromodulator serotonin [9]. In addition to the male advertisement call, the isolated brain also generates a pattern of CAPs that matches the amplexant call made when a male clasps another frog [10[•]]. Two pieces of evidence strongly implicate a rostral hindbrain nucleus, DTAM (the homolog of mammalian parabrachial nucleus), in generating male vocal patterns. Transection of the isolated brain just caudal to DTAM abolishes fictive advertisement calling [9]. Advertisement calling is biphasic; local cooling of DTAM slows both the fast and the slow trill phases [11[•]].

As suggested by a phylogenetic analysis of early development [3^{••}], the hindbrain code for vocalization in frogs (and other tetrapods) emerged from the vocal circuitry of fish. Transection of the caudal hindbrain–spinal region containing the premotor–motor circuitry (Figure 1b) shows that this region alone is sufficient for generating a rhythmic vocal output [12[•]]. As in frogs, CAPs, recorded from vocal nerves in fishes that innervate a pair of ‘drumming’ muscles attached to the walls of the swim bladder, are matched 1:1 with each sound pulse and thus determine the temporal patterning of both advertisement and agonistic calls [13,14]. Putative pacemaker neurons set the firing frequency of adjacent motor neurons that determine vocal muscle contraction rate and, in turn, pulse repetition [13].

Cooling of local brain nuclei ([11], see above) has also made an important recent contribution to understanding the role of forebrain nuclei in generating bird songs. Long and Fee [15^{••}] used a peltier device to cool either HVC or RA (two forebrain vocal ‘motor’ nuclei). While cooling RA did not affect the temporal structure of songs, cooling

HVC slowed songs at all temporal scales: within individual syllables, between syllables, and across groups of syllables or motifs. The control of song in some bird species is lateralized to one hemisphere [16]. When nucleus RA was cooled, production of individual syllables appeared to be lateralized, some being affected only by cooling right RA, and others by cooling the left [15].

Sensorimotor integration and social context

How are vocal communication signals decoded and socially appropriate responses generated? In birds, frogs and fish, two individuals can produce highly synchronized bouts of vocal activity in response to hearing each other [17–20]. The neural substrates for the antiphonal calling that characterizes choruses of male terrestrial frogs includes acoustically evoked inhibition of vocal motor output [21] and timing input from the acoustic–vocal forebrain integrator [22].

In humans and other primates, a class of neurons termed ‘mirror neurons’ has been proposed as part of the machinery for social integration. These neurons fire both when the monkey produces a motor gesture or when it sees or hears another individual do the same thing [23]. These characteristics suggest the possibility that the mirror neuron system participates in empathy and theory of mind. If so, this functionality is not uniquely human as mirror neurons have also been described in swamp sparrows as identical neural responses while singing or listening to their own or similar songs [24••]. Perceptual and sensorimotor phenomena such as categorical perception and mirror neurons have been proposed as contributors to the emergence of language. Categorical perception has long been known to extend widely, present in songbirds [25•] and even in crickets [26]. While confirming the fundamental conservation of mechanisms used for the neural control of social communication ([2,3]; see Goodson and Thompson, this volume), no specialized sensorimotor system has yet been fingered as the key determinant of the evolution of human language. And while social interaction is an essential feature of language learning in children [27], it is also a strong factor in song learning in zebra finches [28].

The songs that male birds produce when alone (undirected song) differ qualitatively from those produced in the presence of a (non-singing) female (directed song; [29]). For the male singer, neural activity in the anterior forebrain nucleus LMAN is less during directed than undirected song [30] as is expression of the immediate early gene (IEG) *egr-1* (avian *ZENK*) [31]. Recognition of social context (a female bird or no bird in this case) is not driven by either visual or auditory stimuli alone but must rather be subserved by a modality-independent neural system responsive to social context [32••].

Activation of the dopaminergic reward system appears essential for context-dependent social signaling. Jarvis

and his colleagues [33] have shown that dopamine release into the basal ganglia-like nucleus, Area X, in the bird forebrain is higher during singing (particularly directed song). Ventral tegmental area neurons are more active during a song, particularly directed song, and their afferents to Area X are thought to enhance singing-regulated gene expression in this nucleus [34••].

Hormone-dependent plasticity of vocal–auditory mechanisms

While hormones have traditionally been studied in the context of their long-term influences on the development of brain and behavior [35,36], recent studies from fish, frogs and songbirds emphasize the relatively rapid, modulatory-like influences of peptide, glycoprotein and steroid hormones on vocalization and hearing [36,37]. For example, Yang and colleagues [38••] demonstrated in frogs that exogenous human chorionic gonadotrophin (hCG) acts within the CNS to induce androgen-dependent increases in advertisement calling. The authors then cloned the luteinizing hormone receptor (LHR) in their study species (*Xenopus laevis*) and demonstrated strong expression in the acoustic–vocal forebrain integrator nucleus. In isolated brains, a brief exposure to hCG upregulates the IEG *egr-1* in the same forebrain region, a time course consistent with behavioral effects.

In vocal fish, systemic steroid injections can induce changes in the duration of fictive calls within 5 min (the temporal sequence of vocal nerve activity/CAPs, see above). Modulation both between and within (male morphs with alternative reproductive tactics) the sexes parallels divergent profiles of circulating steroids [39]. Rapid androgen effects match androgen-induced increases in calling within minutes observed in field studies of nesting males. Similarly fast increases in both plasma androgen levels and calling occur in response to underwater playbacks that simulate vocal challenges from neighboring males [20,40,41]. Direct androgen effects on vocalization in fish, as in frogs and birds, are likely to occur via an evolutionarily conserved pattern of androgen receptor expression in central vocal nuclei [36,42]. Estrogens as well as androgens can have neuromodulatory effects in frogs, fish, and birds [39,41,43,44,45••]. Steroids also synergize with other modulatory agents such as hCG in frogs (above) and opioids in fish [46]. Together, comparative studies in fish, frogs, and birds point to a fundamental and ancient co-evolution of neuroendocrine and vocal behavior networks ([37,36]; also see Goodson and Thompson, this issue).

While behavioral, endocrine, and neuroanatomical studies strongly support a steroid influence on human hearing [47], the neurophysiological evidence for such effects has only just been revealed in studies of fish [48] and songbirds. Remage-Healey *et al.* [49] have shown that steroid levels change within local CNS regions in birds (including an auditory forebrain nucleus, NCM) on a

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Robinson GE, Grozinger CM, Whitfield CW: **Sociogenomics: social life in molecular terms.** *Nat Rev Genet* 2005, **6**:257-270.

2. Robinson GE, Fernald RD, Clayton DF: **Genes and social behavior.** *Science* 2008, **322**:896-900.

3. Bass AH, Gilland EH, Baker R: **Evolutionary origins for social •• vocalization in a vertebrate hindbrain–spinal compartment.** *Science* 2008, **321**:417-421.

Since Darwin's time, there has been speculation on the evolutionary origins of vocal behavior among vertebrates. Fish, like frogs, birds and mammals, vocalize as part of their reproductive and territorial behaviors and have provided a model showing how the central nervous system determines the production of social, context-dependent vocalizations. This study presented evidence that a vocal "compartment" within the developing hind-brain and spinal cord of all sonic vertebrates originated with fishes.

4. Ladich FCS, Moller P, Kapoor BG: **Communication in Fishes.** Enfield, NH: Science Pubs; 2006.

5. Tobias ML, Kelley DB: **Vocalizations by a sexually dimorphic isolated larynx: peripheral constraints on behavioral expression.** *J Neurosci* 1987, **7**:3191-3197.

6. Yamaguchi A, Kelley DB: **Generating sexually differentiated •• vocal patterns: laryngeal nerve and EMG recordings from vocalizing male and female african clawed frogs (*Xenopus laevis*).** *J Neurosci* 2000, **20**:1559-1567.

Using an in vitro intact brain preparation, bath application of serotonin evoked fictive calls from male and female brains that resemble, respectively, male advertisement and female release calls. Electrical stimulation combined with transections also showed that the hindbrain nucleus DTAM, together with a more caudal region adjacent to vagal-laryngeal motoneurons, is essential for vocal patterning.

7. Stoddard PK, Zakon HH, Markham MR, McAnelly L: **Regulation and modulation of electric waveforms in gymnotiform electric fish.** *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* 2006, **192**:613-624.

8. Yamaguchi A, Kaczmarek LK, Kelley DB: **Functional specialization of male and female vocal motoneurons.** *J Neurosci* 2003, **23**:11568-11576.

9. Rhodes HJ, Yu HJ, Yamaguchi A: **Xenopus vocalizations are controlled by a sexually differentiated hindbrain central pattern generator.** *J Neurosci* 2007, **27**:1485-1497.

10. Zornik E, Kelley DB: **Regulation of respiratory and vocal motor • pools in the isolated brain of *Xenopus laevis*.** *J Neurosci* 2008, **28**:612-621.

The isolated brain of *X. laevis* was shown to generate both fictive amplectant calling and respiration. The evolution of the uncoupling of calling and breathing in this aquatic frog likely involved inhibition of glottal motor neurons by the hindbrain vocal pattern generator, DTAM.

11. Yamaguchi A, Gooler D, Herrold A, Patel S, Pong WW: **Temperature-dependent regulation of vocal pattern generator.** *J Neurophysiol* 2008, **100**:3134-3143.

Bilateral cooling of DTAM (a parabrachial nucleus homolog) slowed both the fast and slow trill phases of the male advertisement call, implicating DTAM in generation of both patterns.

12. Remage-Healey L, Bass AH: **Rapid, hierarchical modulation of • vocal patterning by steroid hormones.** *J Neurosci* 2004, **24**:5892-5900.

Steroid hormones were shown to rapidly modulate vocal motor patterning (fictive calls), most likely through non-genomic mechanisms. Responses were steroid-specific, suggesting multiple classes of membrane-bound steroid receptors in the vocal circuit. Transection experiments also showed that steroids act independently at midbrain and hindbrain-spinal levels of the vocal pattern generator.

13. Bass AH, Baker R: **Sexual dimorphisms in the vocal control system of a teleost fish: morphology of physiologically identified neurons.** *J Neurobiol* 1990, **21**:1155-1168.

14. Rubow TK, Bass AH: **Reproductive and diurnal rhythms regulate vocal motor plasticity in a teleost fish.** *J Exp Biol* 2009, **212**:3252-3262.

15. Long MA, Fee MS: **Using temperature to analyse temporal •• dynamics in the songbird motor pathway.** *Nature* 2008, **456**:189-194.

A novel peltier-like device was used to locally cool individual forebrain regions of the song control system of male zebra finches. Temperature manipulations in HVC, but not RA which receives input from HVC, led to a slowing down in the temporal patterning of motifs and their component notes/syllables. The results also suggested hemispheric lateralization in controlling subsyllabic structure.

16. Nottebohm F: **Asymmetries in neural control of vocalization in the canary.** In *Lateralization in the Nervous System*. Edited by Harnard S. Academic Press; 1977:23-44.

17. Thorpe W: *Duetting and Antiphonal Song in Birds: its Extent and Significance* Leiden: E.J. Brill; 1972.

18. Tobias ML, Viswanathan SS, Kelley DB: **Rapping, a female receptive call, initiates male–female duets in the South African clawed frog.** *Proc Natl Acad Sci U S A* 1998, **95**:1870-1875.

19. Thorson RF, Fine ML: **Acoustic competition in the gulf toadfish *Opsanus beta*: acoustic tagging.** *J Acoust Soc Am* 2002, **111**:2302-2307.

20. Remage-Healey L, Bass AH: **Rapid elevations in both steroid hormones and vocal signaling during playback challenge: a field experiment in Gulf toadfish.** *Horm Behav* 2005, **47**:297-305.

21. Walkowiak W: **Call production and neural basis of vocalization.** In *Hearing and Sound Communication in Amphibians*. Edited by Naris P, Fay R, Popper A. Springer; 2006:87-112.

22. Walkowiak W, Berlinger M, Schul J, Gerhardt HC: **Significance of forebrain structures in acoustically guided behavior in anurans.** *Eur J Morphol* 1999, **37**:177-181.

23. Kohler E, Keyers C, Umiltà MA, Fogassi L, Gallese V, Rizzolatti G: **Hearing sounds, understanding actions: action representation in mirror neurons.** *Science* 2002, **297**:846-848.

24. Prather JF, Peters S, Nowicki S, Mooney R: **Precise auditory–•• vocal mirroring in neurons for learned vocal communication.** *Nature* 2008, **451**:305-310.

A class of forebrain neurons in swamp sparrows and Bengalese finches responded both during singing and when listening to the bird's own, or similar, songs. These neurons (HVCx) were driven only by corollary discharge during singing and only by acoustic input while listening and thus operated in a manner similar to mirror neurons in primates.

25. Prather JF, Nowicki S, Anderson RC, Peters S, Mooney R: **Neural • correlates of categorical perception in learned vocal communication.** *Nat Neurosci* 2009, **12**:221-228.

Recording of HVCx neurons in swamp sparrows identified a class of neurons that respond to note duration qualitatively rather than quantitatively. Categorical responses revealed a novel dialect feature between sparrow populations.

26. Wyttenbach RA, May ML, Hoy RR: **Categorical perception of sound frequency by crickets.** *Science* 1996, **273**:1542-1544.

27. Kuhl PK: **Is speech learning 'gated' by the social brain?** *Dev Sci* 2007, **10**:110-120.

28. Tchernichovski O, Mitra PP, Lints T, Nottebohm F: **Dynamics of the vocal imitation process: how a zebra finch learns its song.** *Science* 2001, **291**:2564-2569.

29. Bischof HJ, Bohner J, Sossinka R: **Influence of external stimuli on the quality of the song of the zebra finch (*Taeniopygia guttata castanotis* Gould).** *Z Tierpsychologie* 1981, **57**:.

30. Hessler NA, Doupe AJ: **Social context modulates singing-related neural activity in the songbird forebrain.** *Nat Neurosci* 1999, **2**:209-211.

31. Jarvis ED, Scharff C, Grossman MR, Ramos JA, Nottebohm F: **For whom the bird sings: context-dependent gene expression.** *Neuron* 1998, **21**:775-788.

32. Hara E, Kubikova L, Hessler NA, Jarvis ED: **Assessing visual requirements for social context-dependent activation of the songbird song system.** *Proc Biol Sci* 2009, **276**:279-289.
This study showed that visual cues have no significant affect on IEG activation in male song nuclei during female directed singing. Along with other studies, these somewhat surprising results lead to the conclusion that no one sensory modality, including audition, plays a predominant role in modulating known social context-dependent differences (i.e., directed vs. undirected song) in IEG expression in song nuclei.
33. Sasaki A, Sotnikova TD, Gainetdinov RR, Jarvis ED: **Social context-dependent singing-regulated dopamine.** *J Neurosci* 2006, **26**:9010-9014.
34. Hara E, Kubikova L, Hessler NA, Jarvis ED: **Role of the midbrain dopaminergic system in modulation of vocal brain activation by social context.** *Eur J Neurosci* 2007, **25**:3406-3416.
One of the first papers to examine mechanisms for social context-determined neural activity. Lesions in midbrain, dopaminergic nuclei abolished social context differences in immediate early gene expression (IEG) in two forebrain vocal efferent nuclei.
35. Moore FL, Boyd SK, Kelley DB: **Historical perspective: hormonal regulation of behaviors in amphibians.** *Horm Behav* 2005, **48**:373-383.
36. Bass AH, Ramage-Healey L: **Central pattern generators for social vocalization: androgen-dependent neurophysiological mechanisms.** *Horm Behav* 2008, **53**:659-672.
37. Goodson JL, Bass AH: **Social behavior functions and related anatomical characteristics of vasotocin/vasopressin systems in vertebrates.** *Brain Res Brain Res Rev* 2001, **35**:246-265.
38. Yang EJ, Nasipak BT, Kelley DB: **Direct action of gonadotropin in brain integrates behavioral and reproductive functions.** *Proc Natl Acad Sci U S A* 2007, **104**:2477-2482.
This study proposes that the hormone gonadotropin (GT), well known for controlling gonadal steroid synthesis, has a novel action within the CNS to stimulate courtship song in *Xenopus*. Stimulation of IEG expression in GT-receptor expressing neurons suggested mediation by the forebrain acoustic-vocal integrator.
39. Ramage-Healey L, Bass AH: **Plasticity in brain sexuality is revealed by the rapid actions of steroid hormones.** *J Neurosci* 2007, **27**:1114-1122.
40. Ramage-Healey L, Bass AH: **A rapid neuromodulatory role for steroid hormones in the control of reproductive behavior.** *Brain Res* 2006, **1126**:27-35.
41. Ramage-Healey L, Bass AH: **From social behavior to neural circuitry: steroid hormones rapidly modulate advertisement calling via a vocal pattern generator.** *Horm Behav* 2006, **50**:432-441.
42. Forlano PM, Marchaterre M, Deitcher DL, Bass AH: **Distribution of androgen receptor mRNA expression in vocal, auditory, and neuroendocrine circuits in a teleost fish.** *J Comp Neurol* 2010, **518**:493-512.
43. Wu KH, Tobias ML, Thornton JW, Kelley DB: **Estrogen receptors in *Xenopus*: duplicate genes, splice variants, and tissue-specific expression.** *Gen Comp Endocrinol* 2003, **133**:38-49.
44. Wu KH, Tobias ML, Kelley DB: **Estrogen and laryngeal synaptic strength in *Xenopus laevis*: opposite effects of acute and chronic exposure.** *Neuroendocrinology* 2001, **74**:22-32.
45. Ramage-Healey L, Oyama RK, Schlinger BA: **Elevated aromatase activity in forebrain synaptic terminals during song.** *J Neuroendocrinol* 2009, **21**:191-199.
Evidence supporting a proposed mechanism for rapid control of local steroid synthesis in the CNS: pre-synaptic action via neurotransmitters and modulators. Singing birds (but not birds just listening to song) had increased levels of the enzyme that converts androgens to estrogens in caudal forebrain synaptosomes.
46. Ramage-Healey L, Bass AH: **Estradiol interacts with an opioidergic network to achieve rapid modulation of a vocal pattern generator.** *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* 2009, **196**:137-146.
47. Hultcrantz M, Simonoska R, Stenberg AE: **Estrogen and hearing: a summary of recent investigations.** *Acta Otolaryngol* 2006, **126**:10-14.
48. Sisneros JA, Forlano PM, Deitcher DL, Bass AH: **Steroid-dependent auditory plasticity leads to adaptive coupling of sender and receiver.** *Science* 2004, **305**:404-407.
49. Ramage-Healey L, Maidment NT, Schlinger BA: **Forebrain steroid levels fluctuate rapidly during social interactions.** *Nat Neurosci* 2008, **11**:1327-1334.
50. Ramage-Healey L, Coleman MJ, Oyama RK, Schlinger BA: **Brain estrogens rapidly strengthen auditory encoding and guide song preference in a songbird.** *Proc Natl Acad Sci U S A* 2010, **107**:3852-3857.
Using microdialysis, local changes in neurosteroid concentrations were determined in forebrain regions with well-known roles in audition and vocal communication in songbirds. The authors show that estrogen concentrations in the caudo-medial nidopallium or NCM of zebra finches, increased within 30 min in males in response to female presentations or playback of either male song or colony sounds.
51. Tremere LA, Jeong JK, Pinaud R: **Estradiol shapes auditory processing in the adult brain by regulating inhibitory transmission and plasticity-associated gene expression.** *J Neurosci* 2009, **29**:5949-5963.
Demonstration of the acute modulation of neural activity by local estradiol synthesis in an auditory nucleus. Local or systemic estradiol increased auditory activity and song-induced IEG expression in a forebrain auditory association area (NCM) of zebra finches by suppressing inhibition.
52. Bass AH, Rose GH, Pritz MB: **Auditory midbrain of fish, amphibians and reptiles: model systems for understanding auditory function.** In *The Inferior Colliculus*. Edited by Winer JA, Schreiner CE. Springer-Verlag; 2005:459-492.
53. Hurst JA, Baraitser M, Auger E, Graham F, Norell S: **An extended family with a dominantly inherited speech disorder.** *Dev Med Child Neurol* 1990, **32**:352-355.
54. Lai CS, Fisher SE, Hurst JA, Vargha-Khadem F, Monaco AP: **A forkhead-domain gene is mutated in a severe speech and language disorder.** *Nature* 2001, **413**:519-523.
55. Zhang J, Webb DM, Podlaha O: **Accelerated protein evolution and origins of human-specific features: Foxp2 as an example.** *Genetics* 2002, **162**:1825-1835.
56. Enard W, Przeworski M, Fisher SE, Lai CS, Wiebe V, Kitano T, Monaco AP, Paabo S: **Molecular evolution of FOXP2, a gene involved in speech and language.** *Nature* 2002, **418**:869-872.
57. Konopka G, Bomar JM, Winden K, Coppola G, Jonsson ZO, Gao F, Peng S, Preuss TM, Wohlschlegel JA, Geschwind DH: **Human-specific transcriptional regulation of CNS development genes by FOXP2.** *Nature* 2009, **462**:213-217.
Differential regulation of transcriptional CNS networks by human- and chimp-specific forms of the FoxP2 gene implicated in language development. Hub genes include those implicated in craniofacial development and synaptic transmission.
58. White SA, Fisher SE, Geschwind DH, Scharff C, Holy TE: **Singing mice, songbirds, and more: models for FOXP2 function and dysfunction in human speech and language.** *J Neurosci* 2006, **26**:10376-10379.
59. Haesler S, Wada K, Nshdejan A, Morrisey EE, Lints T, Jarvis ED, Scharff C: **FoxP2 expression in avian vocal learners and non-learners.** *J Neurosci* 2004, **24**:3164-3175.
60. Krause J, Lalueza-Fox C, Orlando L, Enard W, Green RE, Burbano HA, Hublin JJ, Hänni C, Fortea J, de la Rasilla M *et al.*: **The derived FOXP2 variant of modern humans was shared with Neandertals.** *Curr Biol* 2007, **17**:1908-1912.
Did the common ancestor of humans and Neandertals speak? The FoxP2 gene underwent a selective sweep (indicated by two signature amino acid substitutions) at some point after the chimpanzee and hominid lineages diverged. The Neanderthal genome codes for the signature amino acids, placing the sweep within the last 260,000 years.
61. Warren WC, Clayton DF, Ellegren H, Arnold AP, Hillier LW, Kunstner A, Searle S, White S, Vilella AJ, Fairley S *et al.*: **The genome of a songbird.** *Nature* 2010, **464**:757-762.