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

Darcy B. Kelley^{*} and

Department of Biological Sciences, MC2432, Columbia University, New York N.Y. 10025 USA

Andrew H. Bass^{**}

Department of Neurobiology and Behavior, Mudd Hall, Cornell University, Ithaca, NY 14853 USA

Summary

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.

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. What 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

^{*}Corresponding author: dbk3@columbia.edu.

^{**}ahb3@cornell.edu

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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 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 (Fig. 1A). In a recent study, Bass and colleagues [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 (Fig. 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, Fig. 1B; [5]). Recordings from the laryngeal nerve of 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 (Fig. 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 appears to be lateralized, some being affected only by cooling right RA, and others by left cooling [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 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] in frogs demonstrated 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 [39,41,43-45]. 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 moment-to-moment basis during ongoing social and auditory-dependent behaviors. Subsequent studies have supported estrogen's modulatory-like effects on auditory encoding in NCM [50,51]. Steroids thus act both on conserved vocal networks and on conserved auditory networks, including that of humans (see [52] for evolution of auditory pathways).

Gene expression, social communication and language

One of the genes proposed as a contributor to the evolution of human language is FoxP2. In a large family pedigree, members with a specific allele of the DNA-binding domain showed specific language impairments [53,54]. Strong evidence implicates a selective sweep in the [49] lineage leading to humans in a different exon or its flanking regions [55,56]. The sweep suggests strong selective pressures probably operating during the last 200,000 years. FoxP2 is a transcription factor. Comparison of human-specific and chimpanzee forms demonstrates activation of distinctive transcriptional networks ([57]; Fig. 2). Target genes include several implicated in CNS development and in craniofacial formation. The identification of these gene networks considerably widens the field of potential candidate genes underpinning the emergence of language.

FoxP2 is not expressed uniquely in humans nor in language associated areas of the brain. The gene is expressed widely in vertebrates including songbirds, fish and frogs [58]. In zebra finches it is expressed particularly intensely during song learning [59]. To what extent FoxP2 functions more generally in the control of neural development and whether it has been co-opted by vocal learners remains unclear. The modern variant of FoxP2 is present in the Neanderthal genome [60] but is not present in chimpanzees. We do not know whether the former had language; the latter do not, as strictly defined.

Future directions

The sequencing of whole genomes for many experimental model systems in vocal communication (most recently the zebra finch [61]) will enable us to lift our focus up from individual genes that come to light via human phenotypes to multigene arrays implicated not just in vocal communication but in social interactions as a whole [2].

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Figure 1.

A. Evolution of vocal behaviors. (A) 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; XIIIs/tracheosyringeal division of XII). Laryngeal motor neurons in mammals and frogs originate in caudal nucleus ambiguus (Amb)/ vagal motor nucleus (XMNc) (23). Premotor vocal neurons are also in this compartment: Drt, dorsal reticular nucleus; PAM, nucleus paraambigualis; RAb, nucleus retroambiguus; RAM, nucleus retroambiguus; Ri, inferior reticular formation; VPP-VPN, vocal prepacemaker–pacemaker neurons. Modified from [3].

Figure 2. Gene expression networks driven similarly (red) and differentially (blue) by FoxP2 in humans and chimpanzees. Two “hub” genes (genes with the most connections) are DLX5 and SYT4, known to participate in craniofacial development and synaptic function. (Reproduced with permission from [57]).