monolayer culture (*21*, *22*). Glucocorticoid receptor was detected in cells that were immunoreactive for α-MSH (Fig. 3), an indication that the immunoreactive cells were IL POMC–containing cells. The presence of glucocorticoid receptor was evident in cells after 3 days in culture, the earliest time point examined, and could still be detected after 12 days in culture.

In all of these experiments, rigorous immunocytochemical control experiments, similar to those described in Fig. 3C, were performed to determine the specificity of the immunocytochemical staining. In addition, we used two different monoclonal and two different polyclonal antibodies to glucocorticoid receptor in all of these studies and obtained similar results with all of them. This strongly indicates that the antigen detected in the IL was indeed the glucocorticoid receptor. Furthermore, in parallel experiments (*28*), we used Western blot analysis (*29*) to show that the immunoreactive glucocorticoid receptor found in the NIL cultures had a molecular weight identical to that of the receptor in AL and liver. In other parallel studies, we found that incubation of primary NIL cultures with 100 n*M* dexamethasone for 30 minutes resulted in a significant attenuation (30 to 50 percent) of corticotropin-releasing factor (CRF)–stimulated secretion (10 n*M* CRF for 30 minutes) of immunoreactive β-endorphin and α-MSH from primary NIL cultures (4 days). In contrast, less than 10 percent inhibition occurred in 1-day NIL cultures. These data demonstrate that the induced receptor is functional.

We have shown that glucocorticoid receptor expression can be induced in a normally nonexpressing tissue. This finding may provide a working hypothesis for the study of the molecular basis of glucocorticoid resistance in normal and neoplastic tissues.

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Auditory Responses in Avian Vocal Motor Neurons: A Motor Theory for Song Perception in Birds

Abstract. *The hypoglossal motor neurons that innervate the vocal organ (syrinx) of the male zebra finch show a selective, long-latency (50-millisecond) response to sound. This response is eliminated by lesions to forebrain song-control nuclei. Different song syllables elicit a response from different syringeal motor neurons. Conspecific vocalizations may therefore be perceived as members of a set of vocal gestures and thus distinct from other environmental sounds. This hypothesis is an avian parallel to the motor theory of speech perception in humans.*

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Acoustically different components of human speech are at times perceived as a single phoneme. What these components have in common is the articulatory gesture that produces them. This view, known as the motor theory of speech perception, has been advanced to account for the phonetic decoding of speech (*1*). In this context, speech is perceived not just as a sound but as a series of articulatory gestures (*1*, *2*). We now report observations on songbirds that suggest that they too may decode conspecific sounds by reference to the vocal gestures used to produce them.

Recordings from the tracheosyringeal (ts) branch of the hypoglossal nerve (NXIIts) of anesthetized adult male zebra finches have shown that units in this nerve and in the XIIts motor nucleus (nXIIts) respond to pure tones (Fig. 1, A and B) (*3*). The latency of this auditory response is 45 to 60 msec (*4*), an order of magnitude greater than the latency of a similar auditory response in the laryngeal motor nucleus of the bat (*5*). This

long latency suggested the hypothesis that forebrain song-control nuclei—such as the hyperstriatum ventralis pars caudalis [HVc, a nucleus known to have auditory units (*6*)] and the robustus archistriatalis (RA)—that project nXIIts may form part of the pathway that mediates the NXIIts auditory response (Fig. 1D) (*7*).

Our results appear to support this hypothesis. Auditory activity in the HVc preceded that in the XIIts nerve by 12 to 18 msec, with the individual variation corresponding to differences in latency for the response evoked in the XIIts

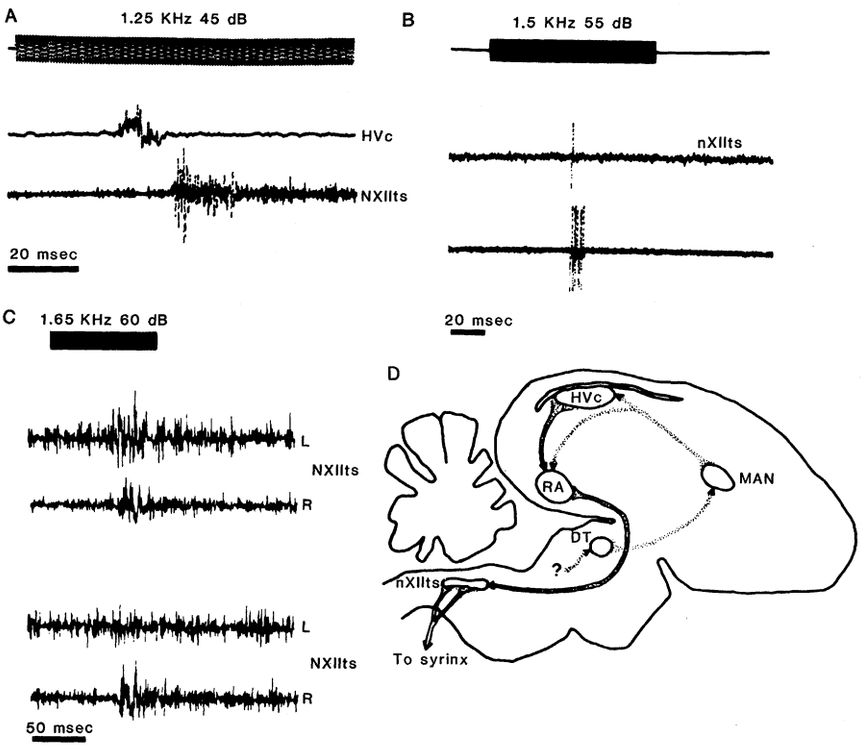

Fig. 1. The tracheosyringeal auditory response. (A) An oscilloscope tracing showing multi-unit activity in the right HVc and XIIts nerve of a male zebra finch in response to a 1.25-kHz, 45-dB sound pressure level (SPL) tone burst. The auditory activity in the NXIIts began 16 msec after that in the HVc. (B, top trace) An oscilloscope trace showing a single-unit response in the ts motor nucleus of a different male zebra finch, elicited by a 1.5-kHz, 55-dB SPL tone burst. Although the latency differs from (A), it is still within the 45 to 60 msec range. (B, bottom trace) The response of the same cell to five successive stimulus presentations. (C) Computer-averaged responses of the left (L) and right (R) ts nerves to ten presentations of a 1.65-kHz, 60-dB SPL tone burst in a male zebra finch before (top) and after (bottom) the left HVc was electrolytically destroyed. The lesion to the HVc eliminated the auditory response in the ipsilateral ts nerve; the remaining activity was respiratory. (D) A sagittal section of a songbird brain, showing the vocal motor pathway (solid lines) and the putative reafferent loop (dotted line). Abbreviations: HVc, hyperstriatum ventralis pars caudalis; DT, the dorsal thalamic region back-filled by horseradish peroxidase injections into the MAN; MAN, nucleus magnocellularis of the anterior neostriatum; RA, nucleus robustus archistriatalis; nXIIts, the tracheosyringeal motor nucleus.

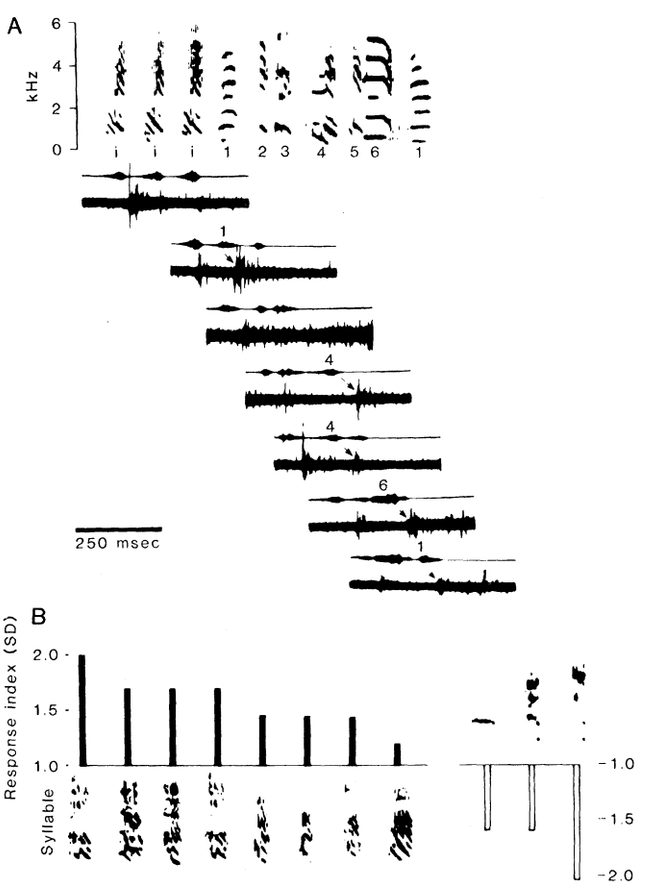

Fig. 2. Auditory response selectivity in the ts motor nucleus. (A) Sonograph showing the structure of a male zebra finch's song (plotted as frequency against time). The introductory notes are labeled i, and the syllables are numbered. The song was edited into three-note sets of introductory notes and syllables. The natural order and spacing of the song elements were maintained within the triplets. Multi-unit recordings were made at a site near the anterior end of the ts motor nucleus while the bird was stimulated with song triplets. Although the units responded to each syllable (or introductory note) when it was presented as the initial member of a triplet, only syllables 1, 4, and 6 evoked firing when they occurred as the second or third members of a triplet. These three syllables are the only ones that contain sustained notes with little or no frequency modulation. (B) A recording site in the posterior portion of the ts motor nucleus of another male zebra finch tested with 27 syllables derived from several songs. Each syllable was presented ten times at each position within a stimulus triplet, and the response index was calculated [see (*10*)]. All syllables with a response index $> +1.0$ or < -1.0 are shown here. The units at this recording site were excited (black bars) by syllables composed of downsweeps; complex downsweeps were more excitatory than simpler syllables. Unmodulated, high-frequency syllables with a relatively simple harmonic structure (open bars) inhibited the ts motor neurons at this recording site.

nerve by microstimulation in the HVc (n = 13 adult male zebra finches; r = 0.94). Lesions to the HVc or RA eliminated the response in the XIIts nerve (Fig. 1C). The XIIts auditory response to pure tones did not habituate, and no such long-latency auditory responses were found in other medullary dorsal column motor nuclei. It would seem, then, that the XIIts auditory response is a reflection of auditory activity in the telencephalic vocal control nuclei.

In experiments to investigate possible response specificity in the XIIts motor neurons, naturally occurring zebra finch songs were edited by computer (*8*) into sequences of three-syllable segments (triplets; see Fig. 2A). These segments were then used as auditory stimuli while recording from multiple units within the XIIts nucleus. Because the nXIIts neurons of anesthetized birds almost invariably responded to the initial syllable of a triplet (*9*), excitatory responses were scored only when the multi-unit activity occurred in response to the second or third syllables of a stimulus triplet (Fig. 2A). Inhibitory syllables were scored when the number of responses evoked by ten repetitions of a stimulus syllable fell more than 1 standard deviation below the mean response level (*10*).

Using this method, we obtained a hierarchy of responses to different types of syllables at a single recording site within the XIIts motor nucleus. Motor neurons in the posterior portion of the nXIIts responded most strongly to syllables composed of downswept frequency transitions (with complex downsweeps producing the strongest responses) and were inhibited by high-frequency unmodulated syllables (Fig. 2B). In contrast, the anterior nXIIts units (Fig. 2A) were excited by unmodulated syllables of the type that was inhibitory for the posterior recording site.

In order to obtain further evidence for differential selectivity within the motor nucleus, we tested a number of syllables at four locations within the posterior half of the motor nucleus and scored them as excitatory or inhibitory (Fig. 3). The response strength varied systematically with the location of the recording site within the nXIIts. Rostro-caudal differences in response selectivity consistent with those described here were obtained for a total of 14 recording sites within the XIIts motor nuclei of four male zebra finches.

Thus hypoglossal motor neurons responsible for song production respond selectively to various naturally occurring song elements, with the locomotion of the recording site within the XIIts nucleus determining the most effective class of auditory stimulus. A specific response to song components was also seen in an unanesthetized adult male zebra finch with an electrode permanently implanted in the nXIIts; this bird showed no response to pure tones. Response to pure tones may reflect an attenuation of selectivity in anesthetized animals.

The ts portion of the hypoglossal motor nucleus of the domestic fowl is organized into discrete pools of motor neurons innervating different syringeal muscle groups (*11*). These pools are arranged in discrete segments at different rostro-caudal levels of the nXIIts (*11*). The differences in the specificity of motor neuron auditory responses along the XIIts motor nucleus in songbirds may therefore correspond to similar discrete pools of motor neurons. If this relation between auditory response specificity and motor neuron pool obtains, it may be that an nXIIts motor neuron responds selectively to the auditory stimuli that are similar to the sounds produced when the same unit fires during vocalization.

Zebra finches complete the song-learning process approximately 90 days after hatching and show no changes in their song as adults (*12*). The NXIIts auditory response occurred in 22 of 28 zebra finch males (78.6 percent) older than 95 days, while six of eight males (81.8 percent) aged between 60 and 95 days showed auditory responses in the NXIIts. These two distributions are not significantly different (χ^2 = 0.0789, $P > 0.5$). The existence of nonresponding birds may be attributable to nerve damage incurred during surgery. Whereas the NXIIts auditory response of juvenile birds may play a role in song learning as a motor skill, this role would not apply in adulthood since zebra finches retain their songs even after deafening (*12*). The NXIIts auditory response in adult males may then play a role in the perceptual processing of song.

Listening or singing male zebra finches have similar neural circuitry for song production. It should be possible for a listener to convert a song heard into the motor commands necessary to reproduce the same sounds. This is the type of phonetic analysis proposed by the motor theory of speech perception (*1, 2*). If this transformation of sound to motor command is used in the perception of a sound as a vocal gesture, then the information extracted by the nXIIts motor neurons must be transmitted back to the forebrain. This appears to be the case. Electrodes placed within the lateral portion

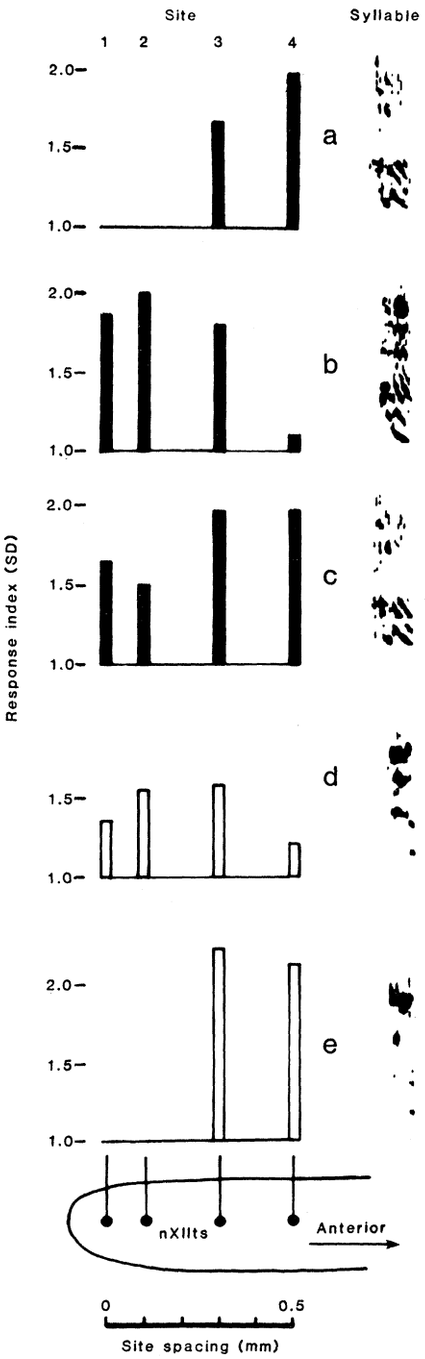

Fig. 3. Auditory response specificity within the ts motor nucleus. An adult male zebra finch was stimulated with triplets derived from his own song while responses were recorded from four sites along the posterior half of the nXIIts. The response strength profiles vary systematically with the location of the recording site; for example, syllable b, with the broadest downsweep, was most effective at exciting the two most posterior recording sites, while two other different syllables (a and c) composed of more complex downsweeps were both most effective in evoking a response at the two more anterior recording sites. The excitatory (black bars) and inhibitory (open bars) responses are consistent with those shown in Fig. 2B, although they were obtained from a different bird.

of the nucleus magnocellularis of the anterior neostriatum (MAN), which is part of the song control system (*7, 13*), recorded multi-unit responses to auditory stimuli with latencies longer than those in the XIIts nucleus or nerve. Furthermore, a restricted area within the dorsal thalamus that is back-filled by injections of horseradish peroxidase into the lateral MAN showed auditory activity that followed the activity in the nXIIts and preceded that in the lateral MAN. Thus part of the dorsal thalamus and lateral MAN may be components of a recurrent loop carrying information derived from analysis of sound stimuli by the XIIts nucleus.

The telencephalic nuclei that control learned song are several times larger in adult male zebra finches, which sing, than in adult females, which do not (*14*). This sexual dimorphism is mirrored by the distribution of birds with auditory responses in the NXIIts: 53 of 68 male zebra finches and 0 of 12 females showed auditory responses in the ts nerve, which is a significant difference ($\chi^2 = 28.2$, $P < 0.001$). If nXIIts-mediated song perception is related to the potential for song production, then females and males might differ in their perception of song. We do not know whether this is the case for zebra finches, but there are suggestions of such a sexual perceptual dimorphism in other species of songbirds (*15*). Bird song, as well as other animal vocalizations, may only be totally intelligible to a neural system that is capable of producing the same vocalizations. Birds that perceive song as a series of articulatory gestures may have their own particular form of phonetic analysis.

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3. The anesthetic used was 5 mg of Ketamine and 5 mg of Xylazine per kilogram of body weight, administered together; this combination spared most auditory responses. Birds were placed in a stereotaxic apparatus (Kopf) with especially designed perforated and hollow earbars (which allow direct transmission of sound to the ear) and a bill clamp. The ts nerves were prepared for recording according to the procedure described in J. A. Paton and K. R. Manogue [*J. Comp. Neurol.* **212**, 329 (1982)]. Glass-insulated metal electrodes [H. Asanuma, in *Electrical Stimulation Research Techniques*, M. M. Patterson and R. P. Kenner, Eds. (Academic Press, New York, 1981)] were placed according to stereotaxic coordinates developed during the course of the study and used for single and multi-unit recordings as well as for microstimulation (single bipolar pulses between 5 and 50 μA). Tone bursts (500 Hz to 7 kHz) were obtained from a waveform generator, attenuated, and delivered through a Nagra speaker 1 m directly above the bird's head. A computer averaging program (developed by Dr. David S. Vicario) was used to collect some of the data. The data were all obtained from zebra finches, although the NXIIts auditory response was also seen in the canary, catbird, and white-throated sparrow.
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9. Inhibitory syllables or introductory notes did not evoke multi-unit activity whether they were presented in positions 1, 2, or 3 of a triplet. Syllables that were excitatory or neutral in triplet positions 2 and 3 evoked multi-unit responses when presented in position 1.
10. The mean response levels for the first, second, and third positions within a triplet were calculated for each recording site. The number of positive multi-unit responses to all syllables presented at a single position was divided by the total number of trials. Each syllable was presented at each triplet position for a minimum of ten trials. The mean total response was subtracted from the number of positive responses to the syllable; this difference was then divided by the standard deviation of the total response to yield the response index for the syllable. Negative response indices indicated an inhibitory effect. Response indices that differed from the mean response level by <1.00 standard deviation were ignored.
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Sequence Homology Between Certain Viral Proteins and Proteins Related to Encephalomyelitis and Neuritis

Abstract. *Post-infectious or post-vaccinal demyelinating encephalomyelitis and neuritis may be due to immunological cross-reactions evoked by specific viral antigenic determinants (epitopes) that are homologous to regions in the target myelins of the central and peripheral nervous systems. Such homologies have been found by computer searches in which decapeptides in two human myelin proteins were compared with proteins of viruses known to infect humans. These viruses include measles, Epstein-Barr, influenza A and B, and others that cause upper respiratory infections. Several regions identified in myelin basic protein and P_2 protein can be related to experimental allergic encephalomyelitis or neuritis in laboratory animals*

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Encephalitis, myelitis, and neuritis are well-known complications of certain viral infections and vaccines (*1*), especially vaccinia, measles, infectious mononucleosis, and influenza. The most recent example of such a complication is the Guillain-Barré syndrome (GBS), which followed the national swine flu vaccination program of 1976 (*2*). Experimental allergic encephalomyelitis (EAE) and neuritis (EAN) have provided precise histopathologic models in many species of animals for these post-infectious and post-vaccinal neural complications in humans (*3*). These experimental auto allergic diseases are caused by hypersensitivity to special antigens, myelin basic protein (BP) and P_2 protein, in the target myelins of the central (CNS) and peripheral (PNS) nervous systems, respectively (*4*).

The manner in which a virus could be related to these myelin antigens is open to speculation. Because measles antigens cannot be detected in the CNS in cases of measles encephalitis and sensitization to myelin BP can be detected in many such cases, the suggestion has been made that a nonspecific liberation of BP-sensitive lymphocytes follows the early lymphopenia of measles and that