thermore, the presence of sodium cromoglycate, which stabilized the membrane of mast cells, did not influence the observed hyperpolarization. However, the role of mediators such as vasoactive intestinal peptide or substance P was not tested.

Stimulation of the electrogenic Na^+ pump could occur through binding of antibodies or circulating immunocomplexes to the cell membrane. This could increase membrane permeability for sodium with a consequent stimulation of the electrogenic Na^+ pump. This possibility is consistent with the observation that a receptor-ligand type of interaction between immunocomplexes and polymorphonuclear leukocytes also leads to hyperpolarization (*15*). In macrophages, the Fc receptor is a ligand-dependent sodium channel (*16*). After binding of specific reaginic antibodies on Fc receptors, an increase in Na^+ influx was observed, followed by an increase in Na^+- and K^+-dependent adenosinetriphosphatase activity and consequent increases in the resting membrane potential of macrophages (*16*). Thus, the alteration in the Na^+ gradient which occurs as a result of membrane permeability for Na^+ may lead to the increase in the calcium influx through the Na^+-Ca^{2+} exchange. This may cause the airway smooth muscle to be more responsive to stimulation. Furthermore, the binding of specific antibodies on the membrane may result in an increase in Ca^{2+}-activated K^+ conductance (*16*).

Calcium flux across rat mast cell membrane is promoted by cross-linking IgE receptors (*17*). In addition, the interaction of circulating immunocomplexes with complement during sensitization could activate complement (*18*) with the possible formation of the anaphylatoxin component of complement, C5a. It has been indeed shown (*19*) that C5a and the synthetic bacterial factor analog fMet-Leu-Phe can induce a hyperpolarization of macrophages or polymorphonuclear leukocytes primarily by stimulation of the electrogenic Na^+ pump. Finally, the alteration in function of some receptors, such as beta receptors, that occurs after sensitization may increase the electrogenic Na^+ pump activity. Antibodies to beta receptors may be present in the serum of patients with bronchial asthma (*4*).

It can be argued that alteration of the resting membrane potential is related to the use of pertussis vaccine. However, in a separate series of experiments, guinea pigs were sensitized with ovalbumin only, and we observed a similar increase in the resting membrane potential. Furthermore, in our studies, rabbits were sensitized with ovalbumin only.

In addition to the other factors that are involved in the mechanism of airway hyperreactivity—including the activation of the vagal reflex (*2*), the release of mediators from mast cells and other cells (*3, 8*), and alteration of specific receptors—this study showed that sensitization caused a direct alteration of airway smooth muscle membrane. It is of interest that an alteration of the cell membrane, including the activation of the electrogenic Na^+ pump, was shown recently to exist in vascular smooth muscle of animals with systemic hypertension (*20*).

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Neural Mechanisms of Sound Localization in an Echolocating Bat

Abstract. *The mustache bat emits a three-harmonic echolocation pulse. At the external ear, large interaural intensity differences are generated only when a sound originates within a limited area of two-dimensional space, and this area is different for each pulse harmonic. As a consequence, the external ear generates pronounced binaural spectral cues containing two-dimensional spatial information. This information is encoded in the inferior colliculus by neurons tuned to one of the harmonics and sensitive to interaural intensity differences.*

Many mammals, particularly nocturnal species that rely heavily on audition, can resolve the horizontal and vertical spatial coordinates of a sound source with precision. It is generally accepted that horizontal sound location is determined through a binaural comparison of arrival time, phase, and intensity disparities (*1*). Less is known of the mechanisms underlying vertical sound localization, but psychoacoustic studies in humans suggest that spectral cues may play an important role (*2*). For example, we tend to associate higher frequencies with an elevated sound source. Such studies suggest that sound frequency contains inherent spatial information (*3*).

Spectral cues are generated by the frequency-dependent directional properties of the external ear (*4–6*). Maximum acoustic energy reaches the tympanum when a sound originates along the "acoustic axis" of the external ear (*7*). The angles of the acoustic axis, relative to the tympanum, change with frequency (*6*). Different frequencies are therefore perceived as loudest when they originate at different points in space, hence their spatial attributes. It follows, then, that the ear will modify the power spectrum of a broadband sound as a function of sound location. The perceived power spectrum will also differ at the two ears as a function of location, creating binaural spectral cues. Such cues permit a simultaneous comparison of interaural

intensity disparities (IID's) over a number of frequencies; they are theoretically capable of providing the information required for accurate horizontal and vertical sound localization (*8*).

We now report neural correlates of the role of binaural spectral cues in horizontal and vertical sound localization in an echolocating bat, a mammal unsurpassed in acoustic orientation (*9*). The mustache bat (*Pteronotus parnellii*) emits an echolocation pulse containing a long triharmonic (30-, 60-, and 90-kHz) constant-frequency (CF) component, with each harmonic terminated by a short downward frequency-modulated sweep (*10*). We first measured the directional selectivity of the bat's external ears at the three harmonics of the CF component, and calculated the IID's generated at the harmonics. We then evaluated the influence of ear directionality on the spatial selectivity of single neurons in the inferior colliculus. The external ears seem to generate pronounced binaural spectral cues that are encoded within the central auditory system and that provide a possible mechanism for horizontal and vertical sound localization.

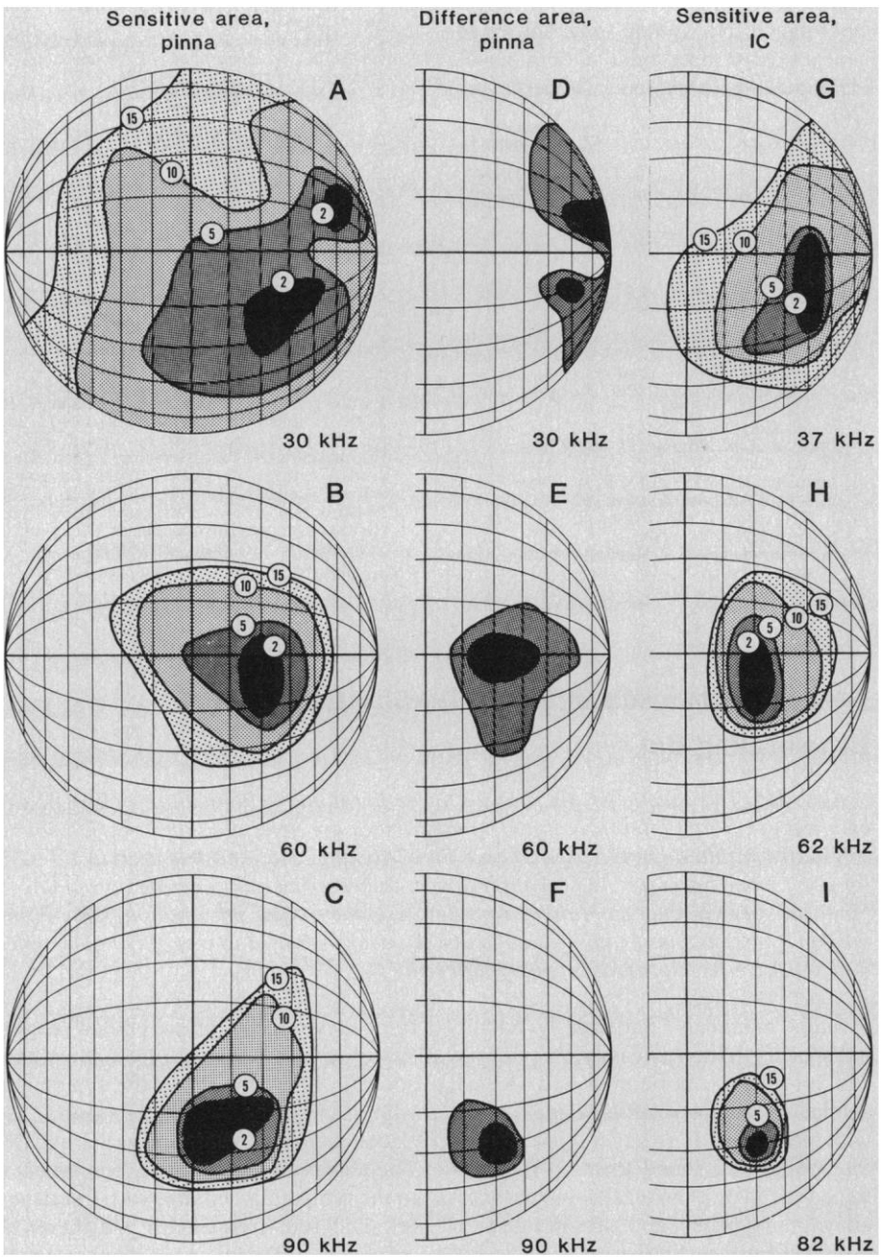

Fig. 1. (A to C) Cochlear microphonic threshold contours in the bat's frontal sound field, showing directional selectivity of the external ear at the three pulse harmonics. The bat is positioned at the center of this hemisphere with its snout pointing at the intersection of the horizontal and vertical midlines. The bat's interaural axis is aligned with the horizontal midline. The numerical values of each contour indicate the decibel value above the lowest recorded threshold. Sensitive areas, where all thresholds are within 2 dB of the lowest value, are shown in black. (D to F) Difference areas of the external ear at the three harmonics, for the same animal shown in parts A to C. The IID's are >20 dB in black areas, >10 dB in the gray areas, and between −10 and +10 dB in the white areas. (G to I) Threshold contours of three inferior colliculus (IC) neurons tuned near the harmonics. Sensitive areas, where thresholds are within 2 dB of the lowest recorded value, are shown in black.

The directional selectivity of the external ear was quantified by recording cochlear microphonic thresholds (*11*) for tone bursts presented at standardized points within the bat's frontal hemisphere of space. Sounds were generated by 15 Polaroid electrostatic transducers (T2004) mounted on a half hoop that could be rotated around the bat's interaural axis. Thresholds were determined at 13° increments along the horizontal axis and repeated at 20° increments of hoop rotation, from 80° below the azimuth to 80° above. These speaker positions are represented by the grid intersections in the figures.

Cochlear microphonic threshold contours generated for each of the three pulse harmonics (Fig. 1, A to C) revealed two trends. First, the sharpness of directional selectivity changed with frequency. At 30 kHz (Fig. 1A), the external ear exhibited a broader directional selectivity than at 60 (Fig. 1B) and 90 kHz (Fig. 1C). Second, the acoustic axis of the external ear changed with frequency, most obviously at the two higher harmonics. The acoustic axes pass through the sensitive areas (black areas in Fig. 1, A to C), in which thresholds were within 2 dB of the lowest value. At 60 kHz, the sensitive area was centered 0° to 20° below the horizon and about 25° off the vertical midline. At 90 kHz, the sensitive area was always lower, between 20° and 40° below the horizon and closer to the vertical midline. The positions of the areas sensitive to 60 and 90 kHz were consistent in all seven cochlear microphonic preparations tested.

Binaural spectral cues were quantified by calculating where the greatest IID's were generated at each harmonic. This was done by subtracting each threshold value in the contralateral half of the frontal hemisphere from its symmetrical counterpart in the ipsilateral half. The area in which IID's were 10 dB or greater is termed the difference area (Fig. 1, D to F). The difference areas of the harmonics occupied discrete regions of the frontal hemisphere and showed less spatial overlap than did the sensitive areas. While the area sensitive to 30 kHz was

broad and variable in position (provided poor spatial information), its difference area was always restricted to the lateral extreme of the frontal hemisphere (Fig. 1D). The 60- and 90-kHz difference areas were located at or near their respective sensitive areas (Fig. 1, E and F).

At each harmonic, large IID's were created only when a sound originated within a limited area of the bat's frontal hemisphere, and this area was different for each harmonic. This spatial discretion was particularly pronounced for large IID's of greater than 20 dB (black areas in Fig. 1, D to F). Because these areas differed in both their horizontal and vertical positions, a simultaneous comparison of the IID's at the three harmonics could potentially provide cues for two-dimensional sound localization, a mechanism previously proposed by Grinnell and Grinnell (*8*). The centers of the difference areas of the three harmonics may act as spatial reference points, three in each half of the bat's frontal hemisphere. An idealized model of this scheme is shown in Fig. 2A, in which the concentric circles radiating out from each reference point represent progressively decreasing IID values. An echo originating at or among these reference points would theoretically generate a unique ratio of IID's among the harmonics (*12*). For example, if an echo returned from a point in space corresponding to one of these reference points, the IID of that harmonic would be maximal, whereas IID values at the other harmonics would be minimal or zero (*13*).

These results suggested that the harmonic difference areas might be represented in the central auditory system by neurons tuned to one of the harmonics and sensitive to their IID's. Such neurons would be expected to have a spatial selectivity similar to the difference area of the harmonic to which they are tuned. To test this, we correlated the binaural response properties and best frequencies of neurons in the bat's inferior colliculus with their two-dimensional spatial selectivity. This was done with a combined dichotic and free-field stimulation procedure. First, with dichotic stimulation, we determined the neuron's best frequency and binaural response properties (*14*). Stimuli were presented through two Polaroid transducers fitted with 1/4-inch funnels. These transducers were positioned at the entrance of the external meatus and could be rotated away from the ear at the end of a test series. After evaluation of frequency tuning and binaural sensitivity, the dichotic speakers were removed from the ears, and the neuron's two-dimensional spatial selectivity was determined by recording response thresholds to sounds presented by the hoop array (*15*).

Neurons excited by input to one ear and inhibited by input to the other (E-I neurons) and tuned near one of the pulse harmonics exhibited spatial selectivities similar to the difference area of that harmonic (compare Fig. 1, D to F, with Fig. 1, G to I). This relation was consistent in all recorded neurons (n = 51) (Fig. 2B).

We have established that the bat's external ears generate binaural spectral cues containing two-dimensional spatial information and that these cues are encoded in the central auditory system through neuronal spectral and binaural selectivity. How might the bat extract this information? One possibility is that the ratio of harmonic IID's characterizing a particular point in space could be encoded by the relative levels of excitation in populations of inferior colliculus E-I neurons tuned to different harmonics. The final analysis may be performed by neurons receiving converging input from such populations. Possible candidates for such a function are the CF-CF facilitation neurons reported in the auditory cortex of the mustache bat (*16*). These neurons are tuned to two or more of the constant frequency harmonics in the echolocation pulse, and some require the simultaneous presence of these harmonics to be excited. Furthermore, they are also sensitive to the relative intensities of the harmonics as well, suggesting that they could encode harmonic intensity ratios. Whether they are also sensitive to IID's has not been determined (*17*).

The pronounced frequency-dependent directionality of the bat's external ears has a profound influence on the spatial selectivity of central auditory neurons, to the extent that a neuron's spatial selectivity is dictated as much by its frequency selectivity as by its binaural response properties. An important consequence is that excitation within a tonotopically organized population of neurons will vary systematically as a function of sound location. To underscore a point previously made by Bulter (*3*), these results support the concept that the orderly tonotopic organization of the mammalian auditory system may contribute an anatomical substrate for the systematic representation of external space.

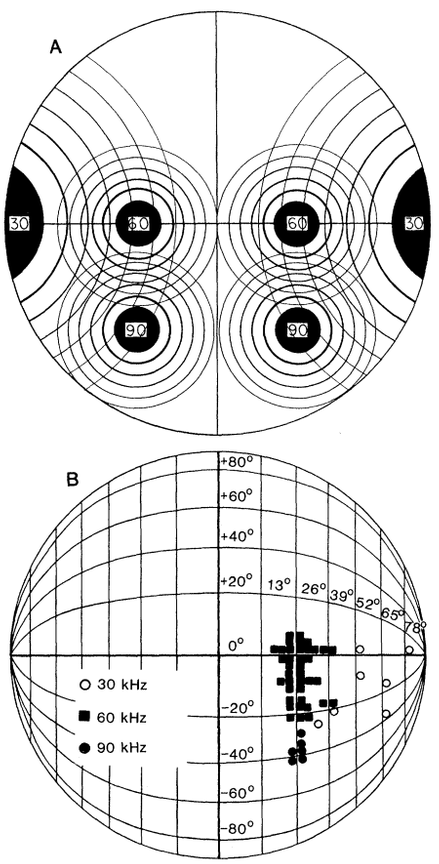

Fig. 2. (A) Conceptual model of the difference areas of the three harmonics as spatial reference points, showing the three difference areas for each ear. Numbers refer to the harmonics. The IID values are maximum at black circles and decrease progressively at each concentric circle. (B) Points in the frontal sound field at which the lowest thresholds were recorded for 51 E-I neurons in the inferior colliculus tuned near one of the pulse harmonics.

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11. This relatively simple procedure causes no dam-

age to the middle or inner ears. A tungsten electrode is advanced through the skull to a point near the cochlear aqueduct [O. W. Henson and G. D. Pollak, *Physiol. Behav.* **8**, 1185 (1972)].

12. This model deals only with the spatial information contained in the difference areas. As such, it does not provide a mechanism for localization along the vertical midline, where IID's at all frequencies will be 0 at all elevations. Such neural mechanisms have been presented [*Soc. Neurosci. Abstr.* **9**, 213 (1983)].
13. The concept of fixed spatial reference points is most plausible if the external ears are immobile. Pinna mobility in the mustache bat is limited. The very tips of the pinnae can be moved laterally, but there is very little rotation of the entire external ear. Pinna movement could have two influences on the proposed reference points: (i) the points could maintain their relative positions with respect to one another, but encode a different region of space relative to the bat's head, or (ii) their relative positions could be altered as a result of a change in pinna configuration. Whether the mustache bat moves its ears at all during flight is not known.
14. Experiments were conducted in a soundproof chamber. Hoop rotation and electrode advance were accomplished from outside the chamber. Single-unit activity was recorded with 3*M* KCl glass microelectrodes. Binaural response properties were quantified by comparing the number of impulses generated by sounds delivered to either ear alone with sounds presented to both ears. In dichotic tests, the intensity at one ear was fixed at 10 dB above threshold, while intensity at the other ear was varied in 10-dB increments. Spike counts were obtained with an on-line computer. Because of the high degree of directionality and rapid attenuation of ultrasonic frequencies, cross talk between the two ears was limited to 35 dB, as measured by cochlear microphonic threshold responses.
15. Spatial selectivity of neurons was determined by measuring threshold at each speaker position. Threshold criterion was a response to each of ten consecutive stimulus presentations.
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17. Primarily for simplicity, we have emphasized the spectral cues derived from the CF harmonics of the echolocation pulse. Also, the frequency dependence of ear directionality is most pronounced when compared at the CF harmonics. The frequency-modulated harmonics also contribute spectral cues likely to further enhance spatial resolution. Most bats emit pulses dominated by a frequency-modulated sweep, and Grinnell and Grinnell (*8*) have proposed that they obtain similar binaural spectral cues from these signals.
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Bimodal Distribution of Dopamine Receptor Densities in Brains of Schizophrenics

Abstract. *The dopamine hypothesis of schizophrenia was examined by measuring the density of dopamine receptors in the postmortem brains of 81 control subjects and 59 schizophrenics from four different countries. The densities of dopamine receptors in the tissues from the schizophrenic patients had a bimodal distribution in the caudate nucleus, putamen, and nucleus accumbens. One mode occurred 25 percent above the control density, and a second mode occurred at a density 2.3 times that of the control density for all three regions. Although almost all the patients had been medicated with neuroleptics, the two modes had the same dissociation constant for the labeled ligand used, suggesting that the neuroleptic doses were similar for the two populations of schizophrenics. The results thus provide direct evidence for two distinct categories of schizophrenia.*

The most consistent neurochemical finding relating to schizophrenia has been an increased density of dopamine receptors in postmortem brain tissue from schizophrenic patients (*1*). Although this finding has been generally confirmed (*2*), a few early reports were unable to reproduce it (*3*); subsequent research has revealed elevated densities of dopamine receptors in the brain tissues of schizophrenics treated with neuroleptics (*4*). These elevations are selective for type D_2 dopamine receptors (labeled by tritiated neuroleptics), no changes being detected in the D_1 or D_3 dopaminergic sites or other neurotransmitter receptors (*5*). Although neuroleptic treatment seems to elevate receptor density (*4*), brain tissues from neuroleptic-free schizophrenics can occasionally show markedly elevated densities (*1*). Thus, to obtain further data on the relative effects of illness and neuroleptic medication on these changes, we studied a new series of tissues under improved experimental conditions. We now report a bimodal distribution in the elevated densities of striatal dopamine receptors of neuroleptic-treated patients.

The dopamine receptors were measured by modifications of previous methods (*6*), with a final concentration of less than 1 mg of original tissue per final milliliter of incubate. Table 1 summarizes the results. We analyzed tissue from 71 controls for the caudate nucleus, 56 for the putamen, and 47 for the nucleus accumbens. Some control subjects had received neuroleptics before death. For example, three of the Toronto subjects with Alzheimer's disease had received neuroleptics (40 mg of trifluperazine per day for over a year; 2 mg of haloperidol per day for 2 years; the third individual, an unknown amount of neuroleptics). One Los Angeles subject (control, diagnosis of drug abuse) had received perphenazine (16 mg per day) for at least 2 months. The densities of D_2 dopamine receptors for these subjects, however, were within normal limits. Almost all of the schizophrenic patients had been treated with neuroleptics (Table 1). Although 15 schizophrenic patients had not received neuroleptics in the last month, we considered only those patients who had been off neuroleptics for at least 6 months as being truly drug-free. When such information was uncertain, we assumed that the patient had taken neuroleptics.

Figure 1 indicates the bimodal pattern of the dopamine receptor densities of schizophrenics. The two caudate modes were about 13 and 127 percent higher than the control mode. Table 2 summarizes the data. The distribution of the control values for the caudate nucleus was not statistically significantly different from a normal distribution [$\chi^2(6) = 4.13, P = 0.5$]. For schizophrenics, however, caudate values differed significantly from a single normal distribution [$\chi^2(6) = 11.6, P = 0.05$].

The distribution of densities in the control putamens did not statistically differ significantly from a normal distribution [$\chi^2(6) = 5.46, P = 0.5$]. The putamens from schizophrenics had modes that were 39 and 154 percent above that of the control mode (Fig. 1), a distribution that was statistically different from a single normal distribution [$\chi^2(7) = 14.86, P < 0.05$].

The control values for the nucleus accumbens were not statistically significantly different from a normal distribution [$\chi^2(6) = 2.8, P = 0.8$]. The distribution of values for the schizophrenic accumbens tissues exhibited modes that exceeded the control mode by 25 and 102 percent and thus differed significantly from a single normal distribution [$\chi^2(8) = 13.41, P = 0.05$].

The lower modes for the tissues from schizophrenics were thus elevated from 13 to 39 percent (mean, 26 percent) above the control values. This elevation is within the range seen in rat striatum after long-term administration of neuroleptics, namely between 10 and 50 percent (*7*). It is possible, therefore, that this low-density mode represents a population of D_2 receptors that is normal but that has been elevated by the long-term administration of neuroleptics during the patient's illness.

The higher modes of 23 to 25 pmol/g (in the schizophrenic patients) represent about a 2.3-fold increase in receptor density relative to the control value.

The two modes of brain dopamine receptor densities reported here in schizophrenic patients are consistent with, but not necessarily synonymous with, the two-syndrome concept of