Chapter 15
Acoustic Behavior and Midbrain Function

TOM C.T. YIN AND BRADFORD J. MAY

1. INTRODUCTION

This chapter provides an overview of the role of the central nucleus of the inferior colliculus (ICC) in auditory behavioral tasks. This question must be addressed to understand the function of this large structure. The substantial literature on the anatomy, physiology, and pharmacology reflect its importance as a nexus for ascending and descending auditory information processing.

A primary goal is to relate these anatomical and physiological properties of the ICC to acoustically dependent animal behavior. For this, studies of the ICC that incorporate behavior are critical and must address the relationship between neuronal activity and behavior. Given the difficulty in quantifying behavior in animals and recording neural activity in humans, many early studies related human psychophysics to recordings from anesthetized animals (Siebert 1970). This is not an ideal combination, as the behavioral "function" of a neuron in the awake brain and anesthetized brain is different. These ambiguities are compounded when the animal's auditory behavioral ability is unknown.

Traditionally, the behavioral function of neural tissue has been inferred from the effects of activation (electrical stimulation in intact animals) or inactivation (lesions or cooling) on neurons. Such manipulations, although useful, are constrained by the virtual impossibility of electrically stimulating neurons with naturalistic stimuli and because lesions cause loss of neurons but also elicit compensatory responses in the brain.

The development of techniques to record from neurons in awake, behaving animals, particularly in the visual system, has enabled striking advances in relating neural activity with behavior. Major advances in understanding include the neural basis for saccadic eye movements (Wurtz 1996; Sparks 2002), the linkage between single-cell responses and visual motion perception (Parker and Newsome 1998), the neuronal substrate for directed visual attention (Maunsell and Cook 2002), and neuronal processing of intended movements (Andersen and Buneo 2002). Studies in the somatosensory system have related single-neuron discharges to the perception of vibration (LaMotte and Mountcastle 1975; Vallbo and Johansson 1984). Deciphering the relationship between perceptual state and neural activity is a central goal of modern neurobiology.

Unfortunately, the auditory community has lagged behind the visual and the somatosensory communities in relating neural activity and behavior in animals. It was noted that "Remarkably, we have been unable to identify studies of the auditory pathways in which neural signals have been measured at the same time as the subject is performing at near-threshold levels in a detection or discrimination task" (Parker and Newsome 1998, p. 260). The few behavioral studies of the ICC and its input systems from a functional point of view limit our understanding of its function.

This chapter summarizes experiments that have been directed toward the functional organization and processing in the ICC with respect to behavior, sound localization, and on the coding of localization cues. Classically, the duplex theory posits that the important cues for sound localization are interaural time and level disparities (Rayleigh 1907). Since about 1980 it has become clear that additional cues are necessary for localization in elevation, as can be readily appreciated by considering localization of sources that vary in elevation along the midsagittal plane, where interaural cues are minimal. The spectral filtering by the head, shoulders, and external ears is now considered important for localization in elevation (May 2000) while the interaural cues are critical for azimuthal localization (Yin 2002).

2. SOUND LOCALIZATION AND THE INFERIOR COLLICULUS

2.1. CONTRALATERAL ENCODING OF SPACE

Most mammalian sensory and motor systems are organized in a contralateral fashion: the left brain receives input from the right side of the body and extrapersonal space, and controls the muscles on the right side of the body. This contralateral representation is documented in the visual, somatosensory and skeletal motor systems, for example, the precise partial decussation of fibers at the optic chiasm, such that the right side of visual space is projected to the left lateral geniculate body and visual cortex, is well known. That the auditory system follows a similar contralateral representation is less obvious but not unexpected.

However, the auditory system differs markedly from the visual and somatosensory systems in the manner in which space is encoded. In vision and touch the spatial location of the stimulus is naturally encoded by receptor location: the retinal map of the visual field and the somatosensory receptors in the skin are naturally topographically arranged. Retinotopic and somatotopic organization is preserved in both systems by the anatomical projections at successive nuclei to the sensory cortices, and in both systems there is a precise projection of the appropriate fibers across the midline such that the cortex has a topographical representation of the contralateral visual field and body.

On the other hand the auditory system initially encodes frequency, not spatial location. The auditory system must compute the location of the stimulus based on the interaural cues of time, intensity, as well as spectral cues. The result of this neuronal computation also provides for a contralateral representation of auditory space.

2.2. *Coding of Interaural Localization Cues*

2.2.1. Interaural Time Disparities

It has been known since about 1900 that the interaural time (ITD) and interaural level differences (ILD) of sounds in free field provide the critical cues for localization of sound sources along the horizontal dimension (Rayleigh 1907). Numerous studies have shown that ITDs are first encoded by cells in the medial superior olive (MSO; Goldberg and Brown 1969; Yin and Chan 1990), which receives bilateral input from the spherical bushy cells of the anteroventral cochlear nucleus (AVCN; Fig. 15.1A; Warr 1966; Tolbert et al. 1982; Cant and Casseday 1986; Smith et al. 1993). Cells in the MSO project to the ICC so that ITD sensitivity is also a common feature of low-frequency ICC cells (Rose et al. 1966; Kuwada and Yin 1983). The physiological properties of these cells are described in more detail elsewhere (see Chapter 13) (Yin 2002).

For pure tone stimuli, which were used by most of the early studies, auditory nerve fibers preserve timing information in the stimulus by discharging over a limited range of phase angles of the input sinusoid, a feature usually called phase locking. Phase locking in mammals is limited to low frequencies <3 to 4 kHz (Johnson 1980) and it is preserved, indeed, enhanced, by AVCN spherical bushy cells (Joris et al. 1994) so that the bilateral inputs arriving at the MSO are highly phase-locked. A fundamental feature of binaural ITD-sensitive MSO cells is that they behave like coincidence detectors in accord with the original model (Jeffress 1948): they respond maximally when the inputs from the left and right sides coincide in time (Goldberg and Brown 1969; Yin and Chan 1990; Batra et al. 1997). Thus, when both ears are stimulated at the same frequency and the delay between the onset of the tones is varied, an MSO cell will respond maximally at a particular interaural phase angle, which corresponds to the condition when the arrival of the left and right inputs is in coincidence. For each ear a time delay results from the angular position of the stimulus with respect to the midsagittal plane, cochlear delays, and the path length between the AVCN on that side to the MSO cell. When the time delays on the two sides are equal, then the inputs arrive in phase and the MSO cell will discharge maximally.

A fundamental concept, first proposed on the basis of observations in only four cells, was characteristic delay (CD) (Rose et al. 1966). CD refers to what happens in a cell as the frequency of the tone is varied since changes in frequency also result in changes in phase. Thus, the interaural phase difference of the stimulus at which the maximal response is obtained may vary with the stimulus frequency for any given MSO cell. A cell that shows CD is one in

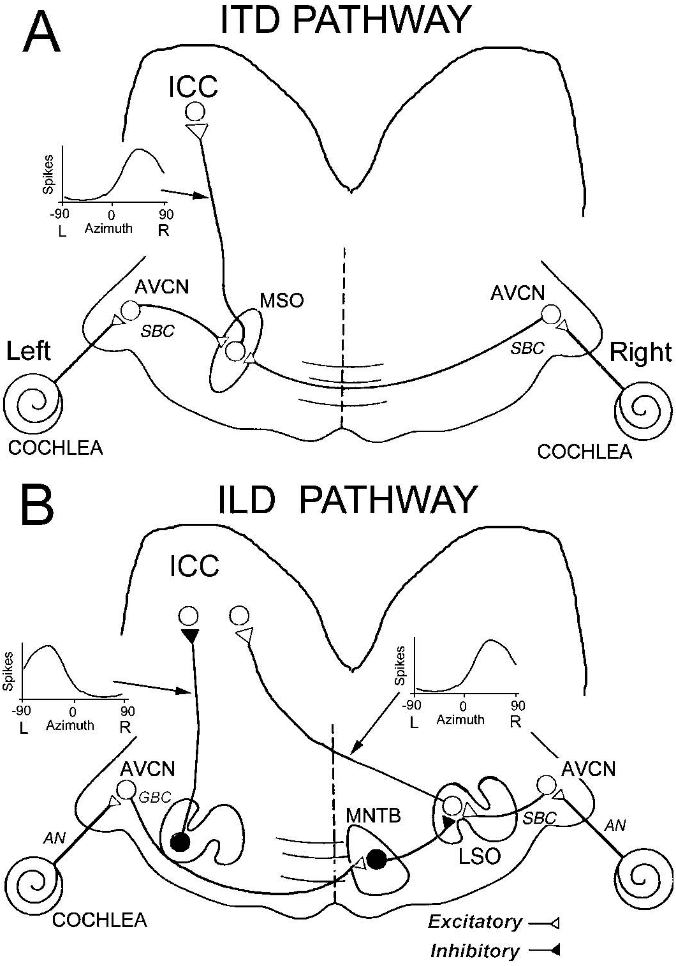

Figure 15.1. Parallel circuits in the superior olive for encoding interaural time (**A**) and interaural level (**B**) disparities in the medial and lateral superior olive, respectively. *AN,* Auditory nerve; *AVCN,* anteroventral cochlear nucleus; *GBC,* globular bushy cell; *ICC,* central nucleus of the inferior colliculus; *LSO,* lateral superior olive; *MNTB,* medial nucleus of the trapezoid body; *MSO,* medial superior olive; *SBC,* spherical bushy cell. Inset diagrams indicate how the neuron would be expected to respond to sound sources delivered in free field.

which the same relative discharge rate (e.g., maximum) is reached at the same ITD at all stimulus frequencies (Rose et al. 1966). This concept was quantified by showing that cells with CD had a linear relationship between interaural phase and stimulus frequency (Yin and Kuwada 1983). The slope of the phase-frequency plot corresponds to the CD while the phase intercept is the characteristic phase (CP) and specifies whether the point of common relative discharge is at the peak (CP = 0.0 or 1.0), trough (CP = 0.5), or in-between. Cells sensitive to ITD and exhibiting CD have been described in the MSO, ICC, dorsal nucleus of the lateral lemniscus (DNLL), medial geniculate body, and primary auditory cortex (Kuwada et al. 1987; Reale and Brugge 1990; Yin and Chan 1990; Stanford et al. 1992).

For stimuli with multiple spectral components, such as noise, a composite curve can be calculated by averaging all the ITD curves at the different frequencies. This composite curve resembles the ITD obtained using the broadband stimulus (Yin et al. 1986; Palmer et al. 1990). This relationship suggests that the individual frequency components of the stimulus are summed in near-linear fashion. An important feature of these responses to broadband stimuli is that the maxima of the composite curves of MSO cells tend to fall in the contralateral sound field, that is, with the ipsilateral ear delayed. This is expected, as the bushy cell axons from the contralateral AVCN must travel further to reach the ipsilateral MSO and hence coincidence would be expected if the contralateral stimulus is given a lead in time. Because the MSO projects to the ipsilateral ICC, we predict that ICC cells would also respond best to sound stimuli in the contralateral sound field, which is indeed the case. Thus, in ICC there is a representation of the contralateral sound field in terms of ITD (Fig. 15.1A).

2.2.2. Interaural Level Disparities

The other important cue for localization in the horizontal plane is created by the reflection and diffraction of sound by the head, shoulders, and external ears. Because the degree of reflection depends on sound wavelength, and hence on its frequency, the ILD cue is highly frequency dependent, with significant ILDs only at high frequencies where the wavelength is short (Blauert 1997). The neural circuit thought to be important for encoding ILDs involves lateral superior olive cells (LSO) which receive excitatory input from the ipsilateral spherical bushy cells and inhibitory input from the medial nucleus of the trapezoid body (MNTB), which is in turn driven by globular bushy cells of the contralateral AVCN with a large calyx of Held synapse on the MNTB cells (Fig. 15.1B; Warr 1966, 1972; Cant and Casseday 1986; Guinan and Li 1990; Smith et al. 1991, 1993). Thus, LSO cells are excited by a sound source in the ipsilateral sound field, where the excitation exceeds the inhibition, and inhibited when the source is in the contralateral sound field (Fig. 15.1B; Tsuchitani and Boudreau 1966; Tollin and Yin 2002a,b; Tollin 2003).

The projection of the LSO to the ICC is unusual and complex. LSO axons project bilaterally to the ICC, but some axons are glutamatergic and excitatory while others are glycinergic and inhibitory (Glendenning and Masterton 1983; Saint Marie et al. 1989). In the cat the crossed projection originates primarily from the medial, high-frequency limb and is excitatory while the uncrossed projection from the lateral, low-frequency limb is both excitatory and inhibitory. Because LSO cells are excited by sound sources in the ipsilateral sound field, an excitatory crossed projection or an inhibitory uncrossed projection will result in ICC neurons that are excited by sound sources in the contralateral sound field (Fig. 15.1B; Glendenning et al. 1992). Note two caveats to this scheme. First, the inhibitory uncrossed projection will not result in an ICC cell that responds to sounds in the contralateral field alone: it needs to act on spontaneous activity or other driven excitation. Second, the excitatory uncrossed projection (not shown in Fig. 15.1B) provides inputs to the ICC that are excited by sounds in the ipsilateral sound field. Thus, most, but not all, ICC cells receive inputs that are responsive to stimuli in the contralateral, but not the ipsilateral, sound field.

Most binaural ICC cells respond to ITDs and ILDs that represent the contralateral sound field, like their visual and somatosensory counterparts. To ensure a unified perception of space, it is not surprising that all modalities follow the contralateral representation of space. What is remarkable is that the auditory system achieves this representation using a computational scheme that involves a massive, but precisely ordered, array of bilateral cochlear nucleus projections to the LSO, and in turn from the LSO to the ICC. This representation is important behaviorally because it predicts that a lesion above the level of the superior olive should affect localization in the contralateral sound field with little ipsilateral effect.

2.3. Perception and Processing of Spectral Cues for Sound Localization

Anatomical projections for the binaural processing of ITD and ILD cues converge on the superior olive from the two cochlear nuclei (Ramón y Cajal 1909; Cant and Gaston 1982; Glendenning et al. 1985; Cant and Casseday 1986). By contrast, sound localization pathways with a selectivity for spectral information do not have overt anatomical features and have been inferred from the unusual spectral integration properties of populations in dorsal cochlear nucleus neurons (Nelken and Young 1997; Spirou et al. 1999; Imig et al. 2000) and ICC (Ehret and Merzenich 1988; Leroy and Wenstrup 2000; Davis et al. 2003). The anatomical specializations that subserve spectral processing may appear less differentiated than those for the binaural brain stem, but the functional enhancements are equally important in natural behavioral contexts where survival mandates the accurate localization of complex sounds.

2.3.1 The Head-Related Transfer Function of the Cat

Our description of spectral cues for sound localization emphasizes the large body of behavioral and physiological evidence from domestic cats. These directional cues are described by the head-related transfer function (HRTF), which is the filter function characterizing relative spectral changes in complex sound propagating from the free field to the ear drum (Wightman and Kistler 1989a,b; Musicant et al. 1990). With ITD and ILD cues that are inherent in binaural comparisons of the HRTF, directionally dependent spectral features encode sound source location (Kulkarni and Colburn 1998). These spectral cues are critical for monaural sound localization, but binaural comparisons of HRTF spectral shapes also provides spatial information (Rice et al. 1992).

The HRTFs of a representative adult cat (Rice et al. 1992) were measured by recording sound energy near the ear drum with a miniature implanted microphone (Fig. 15.2). Rather than focusing on the specific directional properties of individual functions, several functions from the horizontal and median planes are juxtaposed to show generalized localization cues. One transfer function (Fig. 15.2, bold line) in both data sets indicates the ear's filtering effects for a broadband sound directly in front of the head (0° AZ, 0° EL). By convention, a 0-dB gain indicates the HRTF has neither amplified nor attenuated the sound relative to its free-field sound pressure level.

The HRTFs suggest three domains of spectral information. Frequencies <5 kHz are amplified, rising to an energy peak at about 4 kHz. Middle frequencies (5 to 20 kHz) usually have one deep and narrow energy trough, or spectral notch. Frequencies >20 kHz manifest a complex spectral shape with multiple peaks and notches. HRTF gain falls with increasing frequency, implying a reduced salience for the high-frequency spectral cues of broadband sounds.

Directional features of the HRTF are revealed by comparing transfer functions across sound locations. The functions represent different azimuthal locations in the horizontal plane ($\pm 75°$ in 15° increments) (Fig. 15.2A) as well as different elevations in the median plane (–30° to 90° in 7.5° increments) (Fig. 15.2B).

The HRTFs (Fig. 15.2) suggest that its low-frequency components are either amplified by the pinna when the sound source azimuth is in the near field, or attenuated by the head's "sound shadow" when it is in the far field. The difference in gain between the ears is equivalent to the ILD cue. This frequency region is virtually unaffected by elevation changes in the median plane.

The mid-frequency HRTF spectrum provides rich directional information for both azimuth and elevation. As a sound source moves in the horizontal or median plane, changes in location are reflected in notch frequency. This feature is critical for encoding sound source elevation, but it also may contribute to the identification of azimuth because horizontal plane spatial acuity improves with increasing stimulus bandwidth (Heffner and Heffner 1988).

The high-frequency HRTF displays complex and less systematic filtering properties. Consequently, directionally dependent relationships between energy peaks and notches have not been established. Nevertheless, high-frequency sounds tend to impart the perception of high elevation (Pratt 1930; Butler and Belendiuk 1977; Blauert 1997), presumably because they are less attenuated by the HRTF at such elevations (Wightman and Kistler 1989a; Rice et al. 1992).

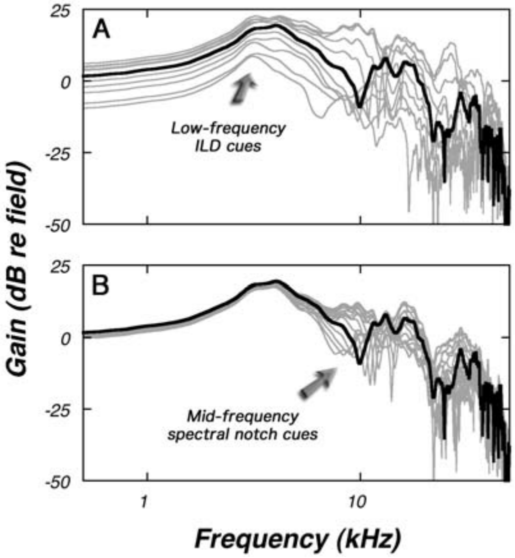

Figure 15.2. Head-related transfer functions (HRTFs) of an adult cat for sound locations in the interaural horizontal plane **(A)** and median vertical plane **(B)**. The transfer function for a sound source directly in front of the subject is repeated in both panels *(bold line).* Filtering effects fall into three frequency domains. At low frequencies, the HRTF gain increases as the sound source moves from contralateral to ipsilateral locations in the horizontal plane. These gain changes create interaural level differences (ILDs). At mid-frequencies, the frequency of a prominent spectral notch increases as the sound rises from low to high elevations in the median plane. At high frequencies, spectral peaks and notches display a less orderly relationship to the direction of the sound source. (Adapted from Rice et al. 1992.)

2.3.2. Role of High-Frequency Spectral Information in Spatial Discrimination

The spectral notches of the HRTF are conveyed to the brain by the discharge rates of auditory-nerve fibers (Poon and Brugge 1993). Computational models suggest a dichotomous role for spectral information in the high- vs. mid-frequency HRTF domains (Nandy and Ben-Arie 1996; May and Huang 1997). Although the high-frequency HRTF components are robust, individual spectral features are not unambiguously associated with discrete sound locations and thus are most effective for the simple detection of a change from one location to another. Mid-frequency spectral notches, in contrast, influence fewer auditory neurons but create more spatially localized response patterns, dictating performance in behavioral tasks that demand the absolute identification of sound source location.

The most common metric for evaluating the perceptual significance of HRTF-borne directional information is the minimum audible angle (MAA; Mills 1958), the threshold for detecting directional changes between paired sound sources. Relative localization tasks are often used in animal behavioral studies because they require less training and are easily related to psychophysical thresholds.

MAA tasks have been used extensively in cats (Martin and Webster 1987; Heffner and Heffner 1988; May et al. 1995). Behavioral results using noise bursts with different frequency domains were used to isolate the frequency dependence of HRTF filtering effects (Fig. 15.3) (Huang and May 1996a). Broadband noise contained spectral cues >5 kHz. Mid-frequency noise was limited to the spectral notch region from 5 to 20 kHz. High-frequency noise conveyed only complex spectral cues >20 kHz. For each stimulus, the MAA was defined as the smallest elevation change that elicited correct responses with a probability corresponding to the signal detection criterion *d*' = 1.

Correlations between directional acuity and the spectral domain of complex sounds have been demonstrated in cats (Martin and Webster 1987; Populin and Yin 1998a) and humans (Musicant and Butler 1984; Carlile et al. 1999; van

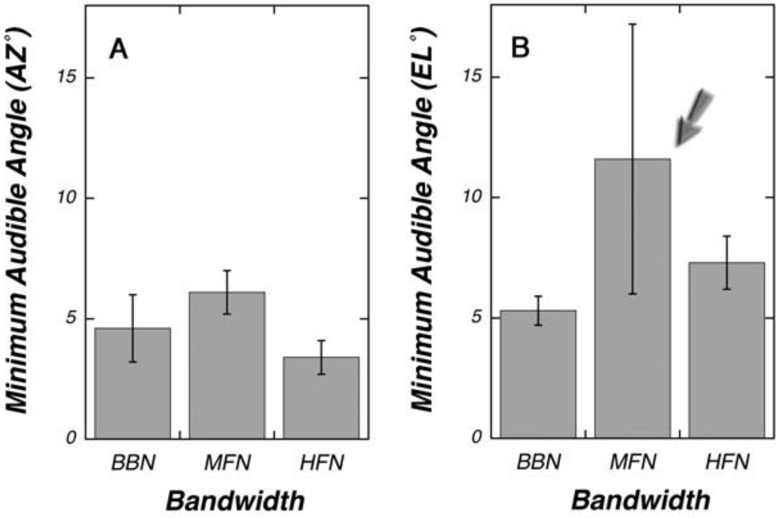

Figure 15.3. Effects of spectral frequency on minimum audible angles (MAAs) in the horizontal **(A)** and median planes **(B)**. MAA is the smallest change in location relative to a reference speaker at 0° AZ, 0° EL that elicited threshold performance (*d*' = 1). Histograms indicate the average thresholds (±SD) of three cats. Largest performance deficits were noted for tests in the median plane with mid-frequency noise (*arrow*). *BBN*, Broadband noise (>5 kHz); *HFN,* High-frequency noise (>20 kHz); *MFN,* mid-frequency noise (5 to 20 kHz). (Adapted from Huang and May 1996a.)

Schaik et al. 1999) and are replicated by responses to mid- and high-frequency noise bursts (Fig. 15.3). As predicted by the quality of directional information inherent in the HRTF (May and Huang 1997), high-frequency noise bursts contain many spectral cues for directional change. Their thresholds were similar to broadband performance. Cats showed deficits when tested with noise that conveyed the more singular mid-frequency notch cue. The relationship between behavioral performance and sound spectra was clearer for sound sources varying in elevation in the median plane than those varying in horizontal plane azimuth.

2.3.3. Role of Mid-Frequency Spectral Cues in Sound Orientation

Natural sound localization behaviors are concerned with the determination of actual locations, not the detection of spectral differences between paired sound sources. The unnatural aspects of the MAA task are circumvented in behavioral paradigms that require the subject to indicate the apparent location of an auditory stimulus by indicating or approaching the sound source. Such procedures are especially useful when directional percepts are predicted to change with modifications of acoustic parameters or lesions. Thus, limiting spectral content to high frequencies provides enough information to convey relative positional changes in the MAA task (Fig. 15.3), but does this manipulation preserve the absolute directionality of an auditory stimulus?

Early studies of cat directional hearing combined an array of sound sources with food or water reward. Sound presentations signaled the active goal box and the subject obtained the reward by approaching the proper speaker (Casseday and Neff 1973). When combined with surgical lesions, this procedure revealed valuable insight into the information processing roles of major auditory centers (Moore et al. 1974; Casseday and Neff 1975; Neff and Casseday 1977).

Unilateral ICC lesions induce only contralateral sound localization deficits in the goal-box task (Strominger and Oesterreich 1970; Goreva and Shcherbakov 1978; Jenkins and Masterton 1982). Robust perceptual deficits are only observed if the subject is forced to make an absolute localization among multiple sound sources (Jenkins and Masterton 1982; Jenkins and Merzenich 1984). Normal performance is achieved if the localization task is a simple spatial discrimination between paired sound sources (Butler and Musicant 1993; Kelly and Kavanagh 1994) and in nonspatial tasks such as the pure-tone discrimination (Neff et al. 1975). In these behavioral contexts, only the multiple speaker goal-box procedure specifically addresses the effects of the lesion on absolute directional hearing.

The dominant role of spectral information in directional hearing exists beyond the horizontal plane. Since flightless animals cannot approach an elevated stimulus, behavioral studies rely on a response in which the subject points to the perceived location of the sound source. In animals, the response is usually based on changes in position of the head (Thompson and Masterton 1978) or eyes

(Populin and Yin 1998a). This reflexive behavior may be used briefly in naive subjects (Sutherland et al. 1998a) or shaped into a food-reinforced operant paradigm for more detailed psychophysical analyses (May and Huang 1996; Populin and Yin 1998a,b; Tollin and Yin 2003a,b).

The effects of spectral content on the accuracy of sound orientation behavior was assessed in cats trained to orient to broadband noise (Fig. 15.4A) (Huang and May 1996b), then probing behavioral performance with occasional bursts of mid-frequency (Fig. 15.4B) or high-frequency noise (Fig. 15.4C). Band-limited stimuli elicited less accurate orientation than broadband noise, but spatially organized responses were maintained when the mid-frequency notches were available. High-frequency probes evoked inconsistent and inaccurate head movements. These deficits confirm that the high-frequency filtering effects of the cat's HRTF fail to impart an absolute directional identity, even though this domain is an excellent source of information for relative directional changes (Fig. 15.3).

The directionally dependent HRTF spectral shapes explain illusory elevation effects seen when paired sounds are presented from two locations in close temporal proximity (Tollin and Yin 2003a). Under summing localization conditions (see Section 3.1.1.), cats unexpectedly localize sounds at higher elevations than predicted by actual locations, a striking effect when both sound sources are located in the horizontal plane. These response errors are correlated with mid-frequency spectral notch alterations arising from the time-delayed summation of energy from the two locations.

Illusions of spatial azimuth and elevation also can be created by synthesizing HRTF-based spectral and binaural cues over headphones (Wightman and Kistler 1989b; Pralong 1996; Langendijk and Bronkhorst 2000). The perceptual realism of the resulting virtual space stimuli implies that the auditory system cannot isolate HRTF directional properties from acoustic source spectrum features. Nevertheless, to function effectively in the biological world, the auditory system must be able to derive the HRTF shape without prior knowledge of the stimulus. This processing dilemma is simplified under normal listening conditions because the amplitude spectra of most natural sounds lack sharp spectral features that may be confused with HRTF-filtering effects (Zakarauskas and Cynader 1993). The source spectrum can be disambiguated further by comparing the multiple directional perspectives provided by the two ears (Rice et al. 1992), head movement (Goossens and van Opstal 1999; Wightman and Kistler 1999), and mobile pinna (Young et al. 1996; Populin and Yin 1998b). Despite these heuristics, optimal localization is achieved when the auditory stimulus is a familiar sound (McGregor et al. 1985; Blauert 1997) and it is filtered by one's own ears (Wenzel et al. 1993; Hofman et al. 1998; Middlebrooks 1999).

2.3.4. Coding of Spectral Cues

Electrophysiological studies of the ICC suggest specializations for processing spectral cues for sound localization. The existence of this discrete information

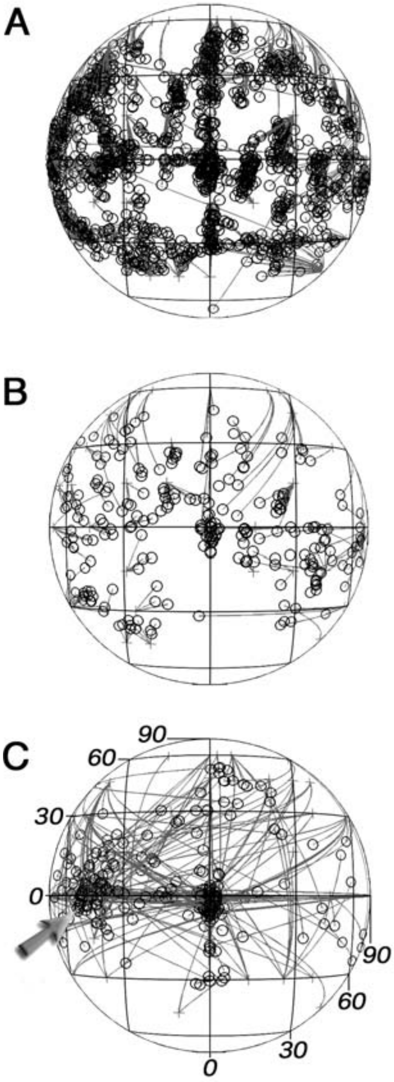

Figure 15.4. Effects of frequency domain on sound orientation behavior. Results from one cat summarized across orientation sessions in which discrete noise bursts were presented from randomly selected speaker locations. *Lines* connect individual responses *(circles)* to stimulus locations *(plus symbols)*. Presentations of broadband noise comprised 85% of the trials **(A)**. Noisebands with mid-frequency spectral notches **(B)** or high-frequency complex cues **(C)** were presented during the remaining probe trials. In this behavioral context, large performance deficits were observed for high-frequency stimuli (*arrow*). *Numerical labels* indicate stimulus azimuth and elevation in double-pole coordinates. (Adapted from Huang and May 1996b.)

processing pathway is based on the physiological classification of inhibitory patterns in the ICC of decerebrate cats (Ramachandran et al. 1999). Type V units have a V-shaped receptive field without strong inhibition. Type I units show a narrow I-shaped excitatory field bounded by lateral inhibitory areas. Type O units may be inhibited by any combination of frequency and level except for an O-shaped excitatory area near threshold.

Similarities in the inhibitory features of frequency response maps have linked type O responses to ascending projections from the dorsal cochlear nucleus (DCN; Davis et al. 1999, 2003; Ramachandran et al. 1999; Ramachandran and May 2002). The response map of a representative type O unit is compared with that of its hypothesized input, a type IV DCN neuron (Fig. 15.5A, B) (Young et al. 1992). The conservation of pure-tone responses between the putative target and source neurons suggests that the DCN spectral processing pathways remain functionally segregated in the ICC (Davis 2002).

The largely inhibitory pure-tone type O responses give way to excitation when the neurons are tested with more natural stimuli (Davis et al. 2003). The response class is particularly sensitive to broadband sounds containing HRTF-filtering effects. The spectral cues influencing these responses have been characterized with parametric stimuli that reduce the complex HRTF to a rectangular notch in broadband noise. A tuned excitatory response is elicited when the notch is swept in frequency across the receptive field of the type O unit (Fig. 15.5C). Because notch frequency is a directionally dependent feature of the cat's HRTF, notch-selective neurons can encode sound location (Young et al. 1992; Imig et al. 2000).

The directional sensitivity of type O responses has been demonstrated under closed-field conditions with noise bursts that provide more realistic simulations of binaural and spectral properties of the HRTF (Fig. 15.5E) (Delgutte et al. 1999; Davis et al. 2003). As predicted by the notch frequency sweep (Fig. 15.5C), maximum discharge rates align with a spatial contour that is defined by near-BF spectral notches. Interestingly, the unit exhibits a preferred location along the iso-notch contour that cannot be explained purely by notch directional selectivity. This enhanced spatial tuning may derive from wideband spectral integration properties allowing type O units to analyze the broader spectral context of mid-frequency notches, or a sensitivity to covarying binaural cues in some type O units (Ramachandran and May 2002).

Most type O units are silenced by surgical or pharmacological manipulations that disrupt neural transmission in the dorsal acoustic stria (DAS; Davis 2002), the principal DCN output pathway to the ICC. Although type IV units are distinguished by nonlinear spectral integration properties that endow sensitivity to HRTF-based spectral notches, type O units do not simply recapitulate their DCN inputs. Type IV units (Fig. 15.5D) display a frequency tuned inhibitory response to spectral notches (Young et al. 1992; Imig et al. 2000). Additional excitatory, inhibitory, and binaural inputs are required to transform this DCN pattern into the directionally selective type O unit (Davis et al. 2003).

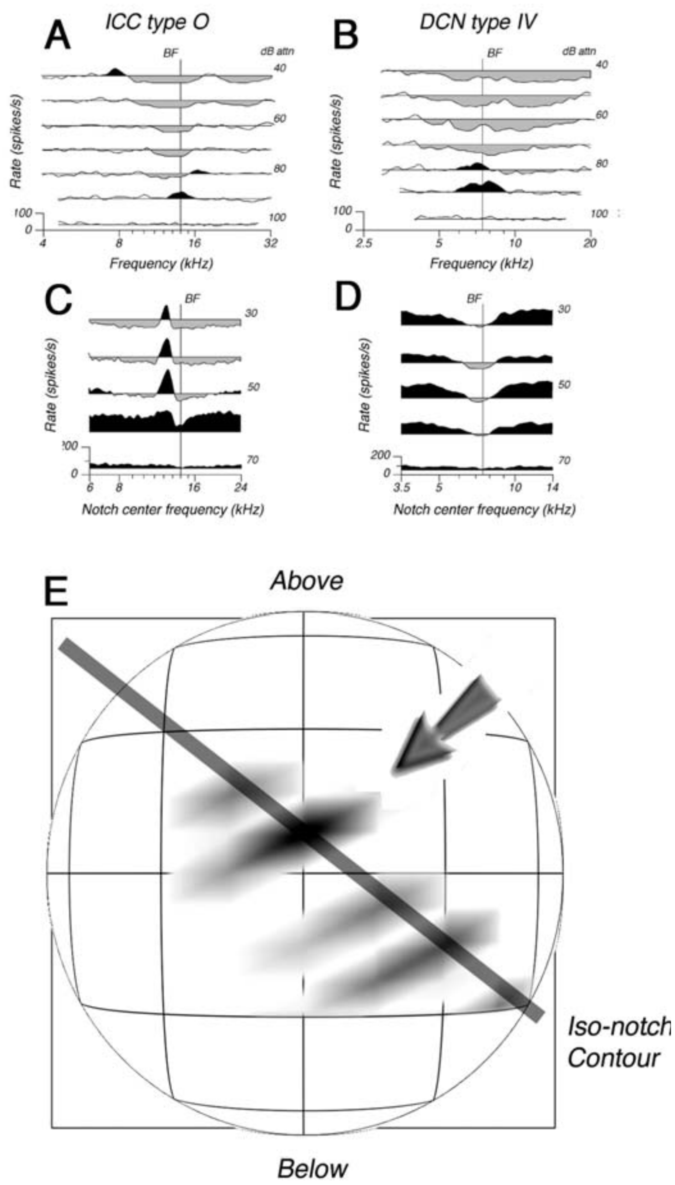

Figure 15.5. Physiological properties of type O units in the ICC and type IV units in the DCN. Each row of the response maps shows driven discharge rates at a different level of attenuation. Inhibitory responses of the two unit types are similar for pure-tone frequency sweeps **(A, B)**, but the type O unit shows a tuned excitatory response for notch frequency that is absent in the type IV unit **(C, D)**. This notch selectivity creates a spatial receptive field when type O units are tested with virtual-space stimuli **(E)**. Responses along the preferred iso-notch contour exhibit a "best location" that implies directional processing beyond notch frequency *(arrow)*. (Adapted from Davis et al. 2003.)

2.3.5. Effects of Dorsal Cochlear Nucleus and Central Nucleus Lesions on Localization Behavior

The functions of DCN projections to the ICC have been investigated by measuring the effects of DAS lesions on localization behavior (Sutherland et al. 1998a,b; May 2000). Unlike trapezoid body lesions that induce deafness, this surgical procedure has little effect on hearing sensitivity in quiet and in background noise (Masterton and Granger 1988; Masterton et al. 1994). Consequently, it is possible to explore the nature of auditory deficits in subjects with bilateral DAS lesions.

A cat with DAS lesions was tested with bandpass noise to restrict spectral cues to HRTF-based notches between 5 and 20 kHz (Fig. 15.6). The subject oriented correctly to random source locations throughout the frontal sound field prior to the lesions (Fig. 15.6A), but had large errors after transecting DCN pathways (Fig. 15.6B) (May 2000). These deficits confirm that DCN/ICC pathways fulfill a critical spectral processing role in feline sound localization (Davis et al. 2003).

Elevation errors are pervasive (Fig. 15.6B). Regardless of the actual elevation of randomly selected sound sources, most responses fell within ±30° of the horizontal plane. The under-estimation of sound source elevations exceeded 60° for extreme locations. These results reproduce the elevation-dependent errors induced when spectral cues are constrained in narrowband stimuli (Middlebrooks 1992). In both situations, the perceptual consequences of impaired spectral information are minimized for testing in the horizontal plane by the normal function of the binaural pathways. The remaining deficits suggest that monaural spectral representations within the DCN/ICC pathway also contribute to the perception of azimuth. This dual role is supported by the observation that most monaural ICC units are sensitive to both azimuth and elevation of virtual-space stimuli (Delgutte et al. 1999).

The functional specificity of DAS sound localization deficits has been evaluated by testing cats with MAA procedures (Sutherland et al. 1998a; May 2000) (Fig. 15.6C). Although these three cats had orientation deficits after the DAS lesion, none showed impaired spatial acuity when tested with mid-frequency noise bursts in the MAA procedure, confirming that DAS lesions do not produce general hearing deficits (Masterton and Granger 1988). These results further substantiate the view that relative spatial acuity and absolute directional hearing utilize different cues and processing pathways (Jenkins and Masterton 1982; May and Huang 1997).

2.3.6. The Neurobiology of Spectral Processing

Behavioral and electrophysiological studies suggest that type O units represent a specialized pathway for processing of spectral cues for sound localization. Although type O response patterns are common in decerebrate cats, they are rare in the ICC of some other laboratory species. For example, V-shaped fre-

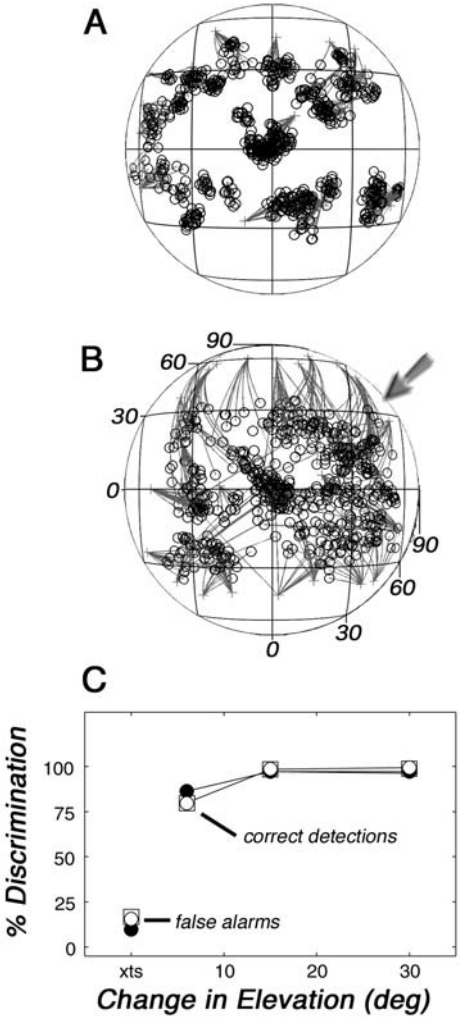

Figure 15.6. Effects of dorsal acoustic stria (DAS) lesions on directional hearing. Orientation responses of a representative cat before **(A)** and after **(B)** bilateral DAS lesions. Elimination of DCN inputs to the ICC disrupted absolute orientation behavior, especially sound source elevation *(arrow)*. Three cats with bilateral DAS lesions had excellent post-lesion performance in MAA procedures **(C)**. Psychometric functions plot the percentage of correct responses relative to changes of elevation in the median plane. False alarms to catch trials without directional changes *(xts)* confirm the low probability of false positive responses in well-trained subjects. (Adapted from May 2000.)

quency response areas comprise most ICC units in anesthetized guinea pigs (Syka et al. 2000; Le Beau et al. 2001). (See Fig. 15.7A.) The remaining non–V-shaped units tend to have narrow tuning like the type I units in decerebrate cats.

Species differences in the prevalence of type O units cannot be explained by the use of anesthesia in guinea pigs, or the surgical elimination of descending projections to the ICC in decerebrate cats. After decerebration, guinea pigs show the same inhibitory patterns described in anesthetized preparations, including a conspicuous absence of type O units in frequency response maps (Fig. 15.7B).

An alternative explanation is that type O units reflect an auditory specialization that is restricted to species that require accurate sound localization, a biological need often associated with predatory lifestyles. The sound localization abilities of laboratory mice support this neuroethological premise. Besides poor directional acuity (Ehret and Dreyer 1984), single-unit recordings suggest an under-representation of type O responses in anesthetized mice (Egorova et al. 2001; Ehret et al. 2003). These species differences do not simply reflect the confounding influences of anesthesia and decerebration on the inhibitory prop-

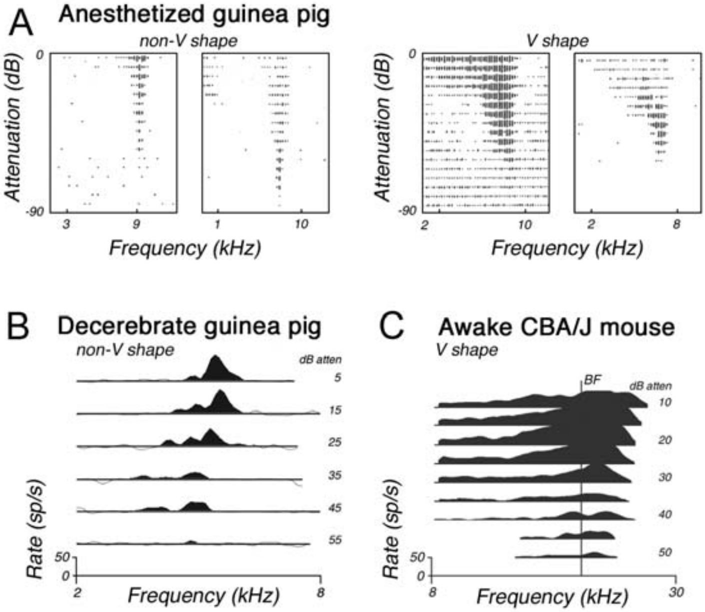

Figure 15.7. Frequency response maps in nonpredatory species. Non–V-shape and V-shape responses are common in anesthetized guinea pigs **(A)**, decerebrate guinea pigs **(B)**, and awake mice **(C)**. Type O units are rare in these species. (**A**: Adapted from Le Beau et al. 2001.) (**B, C**: Unpublished data from BJ May.)

erties of ICC neurons. V-shaped units also represent the most common response type in the ICC of awake, intact mice (Fig. 15.7C; May 2003).

This review relies heavily on research in domestic cats to describe the perception and processing of spectral cues for sound localization. Though regarded as a general model of mammalian hearing, the cat auditory system has evolved to meet the demands of nocturnal predation. These adaptations for prey localization may be species-specific.

Natural behavior provides insights into the functional significance of the common neural pathways and species specializations that remain to be addressed by laboratory studies. An emphasis on comparative behavior, particularly in terms of predator and prey relationships, has contributed greatly to investigations of the brain stem binaural sound localization system (Neff et al. 1975; Heffner and Heffner 1986, 1987, 1989; Moore 1987). A neurobiological perspective ought to prove equally important for understanding the spectral processing pathways of the ICC.

2.4. Effects of Lesions of the Central Nucleus of the Inferior Colliculus on Localization

Physiological studies of the encoding of interaural localization cues suggest that the contralateral sound field is represented in the ICC even though the superior olive has both ipsilaterally and contralaterally driven cells. This dominant innervation has been confirmed by ICC lesions. A contralateral localization deficit followed a unilateral lesion of its output pathway, the brachium of the ICC (Strominger and Oesterreich 1970), and a unilateral lesion that affected LSO output in the lateral lemniscus or ICC caused a deficit in localizing sounds in the field contralateral to the lesion (Jenkins and Masterton 1982) and after large unilateral ICC lesions in the ferret (Kelly and Kavanagh 1994).

Since the ascending projections from the ICC to the medial geniculate body and then to the primary auditory cortex are predominantly uncrossed (see Chapter 7), we predict the same functional contralateral representation in the physiology of thalamic and cortical cells as well as a contralateral deficit in localization following a unilateral lesion of these higher centers. Indeed, most medial geniculate and primary auditory cortex cells have receptive fields in the contralateral sound field (Imig et al. 1990; Brugge et al. 1996; Irvine et al. 1996; Samson et al. 2000) and unilateral auditory cortex lesions create a contralateral localization deficit (Jenkins and Merzenich 1984).

2.5 Effects of Electrical Stimulation of the Inferior Colliculus

There are few studies of behavioral results of electrical stimulation of the ICC. By 1970 (Syka and Straschill 1970; Syka and Radil-Weiss 1971) it was known that head and eye movements could be evoked by stimulation of the ICC and that these effects used connections to the deep layers of the superior colliculus, a well-known sensorimotor integration site (Wurtz 1996; Sparks 2002).

In rodents the ICC has been implicated as one of the sites for abnormal brain activity in the form of seizures. Stimulation of the ICC by acoustic, electrical, or pharmacological means can evoke seizure activity in particular seizure-prone strains of rodents, the genetically epilepsy prone rat (GEPR; Ribak and Morin 1995; Ross and Coleman 2000). This system has been used as a model for studying the interaction between excitatory and inhibitory neurotransmitters in inducing epileptic activity (see Chapter 21).

3. PHYSIOLOGY IN AWAKE AND BEHAVING ANIMALS

In all of the experiments reviewed in the preceding, the physiological responses to localization cues were recorded in anesthetized or decerebrated animals. How anesthesia affects the responses is not understood and undoubtedly depends on the dosage, type, and the site of recording as well as the species. A major advance since 1960 is the development of techniques to record from awake, behaving animals, which avoids the contaminating effects of anesthesia and allows one to study the neural bases of higher-order cognitive effects.

There are few studies since 1980 in awake behaving preparations, even though several earlier studies used this technique. Responses of monkey ICC cells in an auditory reaction time task were compared to responses to the same stimuli when the monkey was quiescent. Discharge patterns resembled those in acute experiments and rates significantly increased during task performance (Ryan and Miller 1977, 1978). Similar comparisons were also made from the cochlear nucleus to auditory cortex (Ryan et al. 1984). Moreover, in behaving animals there are multisensory interactions as eye position affects some ICC neuron responses as much as sound source location in monkeys (Groh et al. 2001).

3.1. THE PRECEDENCE EFFECT

3.1.1. Psychophysics

There has been considerable interest in an auditory illusion known as the precedence effect (PE), or law of the first wavefront (Wallach et al. 1949), shown by placing a subject between two speakers (Fig. 15.8A) and delivering the same transient sound to both speakers with a variable interstimulus delay (ISD) between the sounds. An idealized plot (Blauert 1997) of the perceived location of the sound as a function of ISD (Fig. 15.8B) shows that, if both speakers are activated simultaneously, the observer will localize the sound to a single phantom source midway between them. As ISD gradually lengthens the perceived source moves towards the leading speaker until, at approximately 1 ms ISD the sound is perceived near the leading source. The interval between about ±1 ms

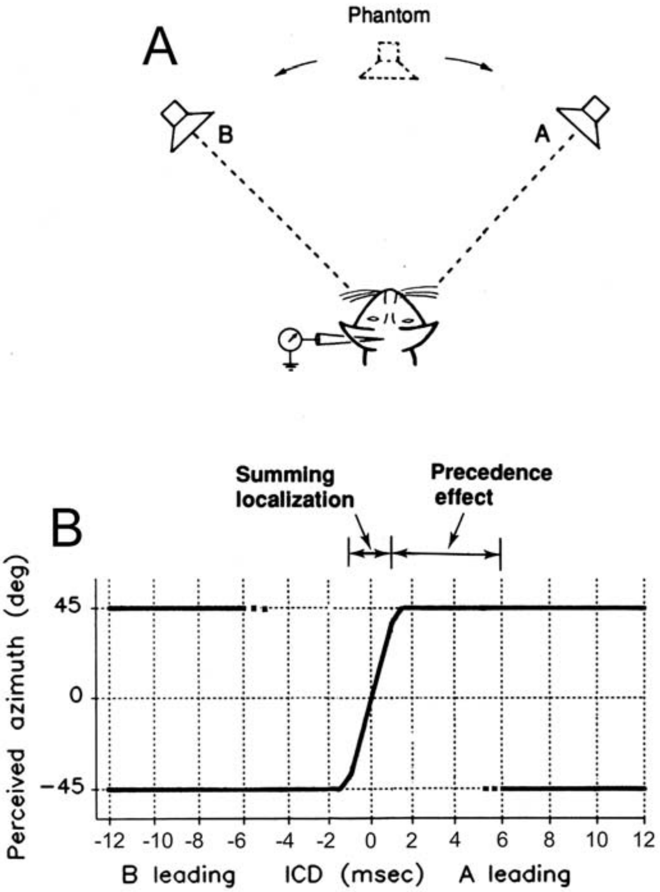

Figure 15.8. The precedence effect. **(A)** Diagram of the stimulus configuration in free field with the subject midway between two speakers (A, B) *(top)* and **(B)** the perceived azimuthal location of the sound as a function of the interclick delay. By convention negative delays correspond to speaker B leading. (Adapted from Blauert 1997 and Yin 1994.)

has been termed summing localization. ISDs between 1 and 5 to 10 ms represent the period of the precedence effect, or localization dominance: the sound is localized to the position of the leading source even though the lagging source is readily localized when presented alone. At longer ISDs the subject hears both sounds at their respective positions, and the shortest ISD at which this occurs is the echo threshold. In practice the echo threshold value is variable and depends on the instructions given to the subject and on the duration and type of acoustic stimulus. Sustained and complex sounds (music, speech) usually have longer echo thresholds.

The term, precedence effect, refers to the way in which the leading sound appears to take precedence over the lagging one in judgments of sound location, as if the lagging sound's location were suppressed by the auditory system. However, the lagging source still plays a role in perception other than localization: for delays in the range of localization dominance, the fused sound can be readily discriminated from the leading sound by a change in timbre, although it is localized to the position of the leading sound. It is thought that the precedence effect is critical for accurately localizing sound in a reverberant environment, such as a room, where any sound will produce time-delayed echoes from many different spatial locations.

An important question regarding the neural bases of PE is how it is experienced by animals. PE has been demonstrated in cats (Populin and Yin 1998a; Tollin and Yin 2003b), birds (Keller and Takahashi 1996; Dent and Dooling 2003), dogs (Ashmead et al. 1986), rats (Kelly 1974), and crickets (Wyttenbach and Hoy 1993). Mean horizontal eye position as a function of ISD of a cat trained to fixate sound sources when presented with pairs of short noise bursts to simulate the PE (Tollin and Yin 2003b) demonstrates this effect (Fig. 15.9). With the head held, all cats consistently undershoot the target (Fig. 15.9A, B: leftward arrows).

The cat (Fig. 15.9) and human (Fig. 15.8B) responses are similar during the localization summing period except that the period is only ±400 μs in the cat because of its smaller head width. For delays between 1 and 10 ms, the cat showed localization dominance to the position of the leading speaker and at delays >10 ms it often made saccades to the location of the lagging sound or double saccades to both the leading and lagging sounds, resulting in mean responses near 0 and large variability. We infer from this behavior, never seen for

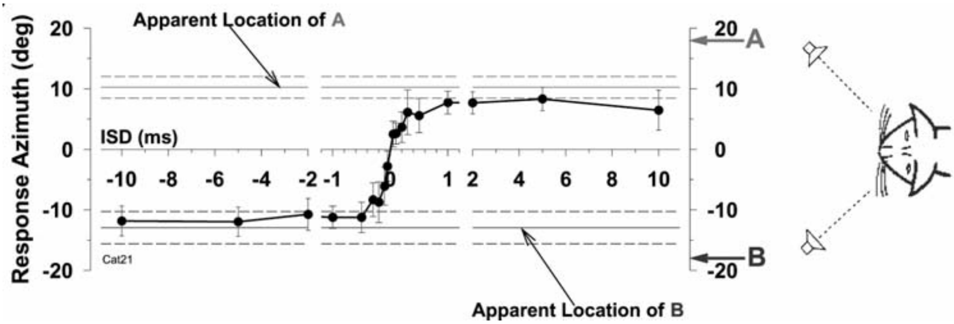

Figure 15.9. Responses of a cat to the PE stimuli. Azimuthal final eye position as a function of interstimulus delay (ISD). The locations of the speakers A and B are indicated by the arrows on the right and the horizontal lines (± standard deviation) show the mean eye position for the two speakers when delivered in isolation. (Adapted from Tollin and Yin 2003b, used with permission.)

shorter delays, that the cat was perceiving both sounds and was unsure which to look at. Thus, the cat echo threshold is between 10 and 15 ms.

3.1.2. Physiology

The first studies of the physiological responses to PE stimuli were in anesthetized animals (Yin 1994). ICC cells respond to click pairs delivered dichotically (Fig. 15.10). A +400 μs ITD, an effective stimulus for this cell, was imposed on both pairs of clicks while the interclick delay (ICD) varied from 1 to 101 ms. At long ICDs the response to both pairs of clicks is clear, but as the ICD decreases gradually the response to the lagging click declines until it disappears at ICDs <7 ms, while there is little change in the response to the leading one. A recovery curve plot shows the response to the lagging click normalized by the response to the same click when delivered in isolation (Fig. 15.9B). The delay at 50% recovery is often used as a metric for half-maximal suppression, and in this cell is 11 ms.

Suppression of the response to the lagging click was common in the ICC and has been studied in other species (rabbit: Fitzpatrick et al. 1995; barn owl: Keller and Takahashi 1996) and extends from the auditory nerve to the cortex (Parham et al. 1996, 1998; Fitzpatrick et al. 1999). Spatial location, ITD, level, duration, and binaurality of the leading sound can each affect suppression (Litovsky and Yin 1998a,b; Litovsky and Delgutte 2002). The half-maximal delay values in different cells were variable, with significant differences in the degree of suppression in the anesthetized cat and unanesthetized rabbit (Yin 1994; Fitzpatrick et al. 1995, 1999; Litovsky and Yin 1998a,b).

To investigate whether the differences between the cat and rabbit results were due to the species difference or to the anesthesia, recordings were also made in the ICC while the cat was awake and performing a sound localization paradigm. The distribution of half-maximal delays for cells in the anesthetized cat (Litovsky and Yin 1998b; Fig 15.11, gray bars), for unanesthetized, quiescent rabbit (Fitzpatrick et al. 1995; Fig. 15.11, white bars) and in awake, behaving cats (Fig. 15.11, black bars) are available. The half-maximal delays in the behaving cat (circles representing mean and s.d.) were significantly different than in the anesthetized cat but similar in the awake rabbit and suggest that the differences reflect anesthesia. Mean recovery curves for the population of ICC cells in the awake animal were computed separately for either ipsilateral side or contralateral side-leading speaker and show significantly stronger contralateral leading suppression (Fig. 15.10B). The PE period (Fig. 15.10, shaded region) shows considerable suppression in the response of the population of ICC cells when PE is behaviorally effective.

4. FUTURE DIRECTIONS

We have focused on the relationship between sound localization behavior and neural response patterns in the ascending pathways of the auditory midbrain.

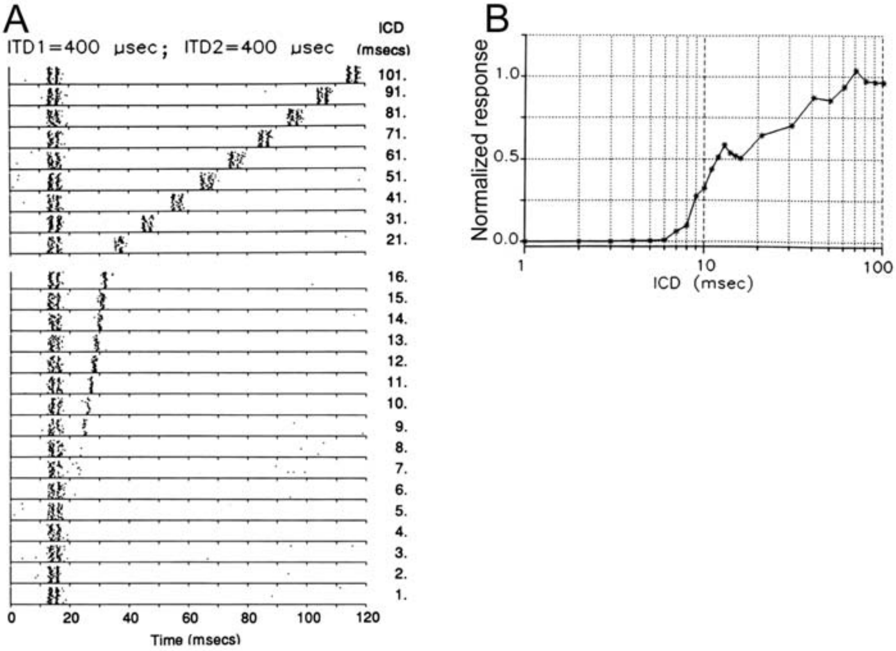

Figure 15.10. Echo suppression in the ICC under dichotic stimulation. **(A)** Dot rasters show the responses to 40 repetitions of ICDs ranging from 1 to 101 ms. Each dichotic click had an ITD of +400 µs. **(B)** Recovery curve of the data in **(A)**. The response to the lagging click was normalized by the response to the same click without the leading click. Half-maximal delay was 12 ms. (Adapted from Yin 1994.)

This emphasis reflects the prominent role the ICC has played in current behavioral and physiological assessments of the inferior colliculus. It is almost certain that the midbrain is involved in other auditory behaviors and that these processes reflect descending influences from higher auditory centers.

Physiological studies find that the auditory processing of a meaningful sound is enhanced by corticofugal pathways that terminate in the dorsal cortex of the inferior colliculus (Zhang et al. 1997; Jen et al. 1998; Yan and Ehret 2001, 2002). When repeating tones are paired with noxious shocks, neurons encoding the fear-conditioned stimulus show an expanded reorganization in the inferior colliculus of big brown bats (Gao and Suga 1998). Analogous changes in frequency tuning are evoked by electrical stimulation of auditory cortex (Chowdhury and Suga 2000), or abolished by pharmacological inactivation of the same locations (Gao and Suga 2000). By contrast, specialized echolocation areas in the inferior colliculus of mustached bats show increased activity and sharper frequency tuning when matching cortical frequency regions are stimulated (Zhang and Suga

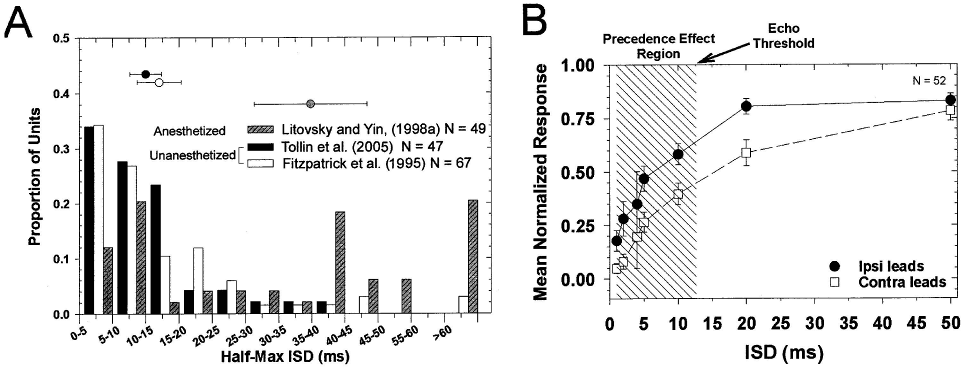

Figure 15.11. **(A)** Histogram of the half-maximal delays in anesthetized cats (Litovsky and Yin 1998b; *gray bars*), awake rabbits (Fitzpatrick et al. 1995; *white bars*), and awake, behaving cats (black bars). The means and standard error of the mean of the distributions are shown by the *circles above*. **(B)** Mean normalized recovery curves of all cells as a function of ISD with the ipsilateral *(filled circles)* or contralateral *(open squares)* speaker leading. (Adapted from Tollin et al. 2005.)

2000), and those of unmatched neurons are suppressed. This compressive reorganization creates a more selective representation of biosonar signals (Suga et al. 2002).

The physiological correlates of attentional filtering were predicted by the classic behavioral paradigms (Jane et al. 1965), in which reciprocal functional roles for the central nucleus and dorsal cortex were proposed. Unlike the deafening effects of ICC lesions, surgical manipulations of the dorsal cortex do not impair sound localization but diminish auditory attention. When redundant auditory and visual cues signal an impending electrical shock, intact cats tend to base their avoidance behaviors on auditory information. This natural "prepotency" of the auditory stimulus is supplanted by visual information in cats with lesions of the dorsal cortex.

Cognitive influences such as learning, attention, and compensation represent exciting new directions for future studies of the physiological underpinnings of acoustic behavior. Within the auditory midbrain, it is becoming increasingly clear that while these complex processes are driven by ascending sensory representations, a set of descending perceptual filters that are suppressed by anesthesia, silenced by decerebration, and altered by experience operate in parallel. From this perspective, acoustic behavior provides an essential context for understanding midbrain function.

Abbreviations

AN	auditory nerve
AVCN	anteroventral cochlear nucleus
CD	characteristic delay
CP	characteristic phase
DAS	dorsal acoustic stria
DCN	dorsal cochlear nucleus
DNLL	dorsal nucleus of lateral lemniscus
GBC	globular bushy cell
HRTF	head-related transfer function
IC	inferior colliculus
ICC	central nucleus of inferior colliculus
ILD	interaural level difference
ISD	interstimulus delay
ITD	interaural time difference
LSO	lateral superior olive
MAA	minimum audible angle
MSO	medial superior olive
PE	precedence effect
SBC	spherical bushy cell

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