

# THE SENSES: A COMPREHENSIVE REFERENCE

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Volume 3  
AUDITION

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## 3.46 Sound Localization and the Auditory Cortex

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### Glossary

**artificial neural network** A computer algorithm that has been applied to the study of cortical representation of sound-source locations. The network first is trained with examples of cortical responses to particular sound sources, and then the trained network is used to estimate the source location producing other cortical responses.

**azimuth** The horizontal dimension of space. In the context of this review, azimuth is the location of a sound source relative to the frontal midline measured as the angle about the vertical axis.

**maximum likelihood estimator** A statistical procedure that can be used to determine which of a set

of stimuli is most likely to have produced a particular neural response.

**precedence effect** Refers to a group of phenomena in which two spatially discrete sound sources are perceived as a single source. Depending on the relative timing of the two sounds, the fused source is reported as intermediate in location between the two sources or at the location of the leading sound.

**spatial receptive field** The region of auditory space within which presentation of a sound elicits a criterion response from a cortical neuron.

**tonotopic organization:** A neural representation of the audible frequency range in which individual neu-

rons are sharply tuned for frequency and the tuning of neurons varies systematically as a function of location within a brain nucleus or cortical area.

**virtual auditory space:** A simulation of a spatially localized sound source produced by sounds

presented through headphones. A virtual target is synthesized by filtering an arbitrary sound source with the directional filter properties of the head and external ears that have been measured previously for an actual sound source.

### 3.46.1 Introduction

One can say with some confidence that an intact auditory cortex is essential for normal sound localization. That assertion is based on studies of behavioral consequences of lesions and on studies of functional inactivation (reviewed in Section 3.46.4). Beyond that, however, the specific role of auditory cortex in sound localization, and more generally in spatial hearing, is not so clear. We know that acoustic cues for sound localization are encoded in patterns of activity in the two auditory nerves, we can point to specific brainstem nuclei that extract particular binaural and spectral shape cues for sound-source location, and we infer that those cues are integrated in the ascending auditory pathway to at least begin to form the neural correlates of auditory objects. Nevertheless, one cannot say with certainty how much of that integration is accomplished by the brainstem and how much remains to be done at the cortical level. Neither is it clear to what extent spatial processing might take place in a hierarchical manner among various cortical fields nor, indeed, is it clear whether any particular cortical area or areas have a special role in spatial hearing.

Although many questions remain, substantial progress has been made on these issues in the past 5–10 years, due in part to developments in virtual auditory space technology, computational algorithms for recognition of patterns of cortical activity, methods for functional inactivation of specific cortical areas, and functional imaging of the human brain. This chapter begins by reviewing the spatial sensitivity of auditory cortical neurons, including responses to stimuli that vary dynamically in space and time. We then explore how it is that the location of a sound source is written down in patterns of cortical activity and how one might read those patterns. Next, we review the behavioral consequences of destruction or inactivation of particular auditory cortical areas. We review briefly the rapidly growing body of results from studies of the human brain using functional imaging techniques. Finally, we draw

some broad conclusions and list some key areas for future research.

### 3.46.2 Spatial Sensitivity of Cortical Neurons

The cat and, to a lesser degree, the ferret have been favored for research on cortical mechanisms of sound localization because those species have well-developed auditory cortices and because, as nocturnal predators, they have evolved accurate sound-localization behavior. We focus on the cat and the ferret, summarizing results from nonhuman primates at the end of the section.

#### 3.46.2.1 Spatial Receptive Fields in the Primary Auditory Cortex

Early studies of the spatial sensitivity of neurons, perhaps inspired by visual cortical studies, attempted to map the borders of spatial receptive fields of neurons. Evans E. F. (1967) reported that the majority of the neurons in his sample showed a preference for the location of a handheld transient sound source and that the majority of spatially sensitive neurons preferred sound sources located on the side contralateral to the recorded cortical hemisphere. Similarly, Eisenman L. M. (1974) found a mixture of spatially sensitive and insensitive neurons, with most of the spatially sensitive neurons responding best to sounds at contralateral locations. Middlebrooks J. C. and Pettigrew J. D. (1981) mapped receptive fields using pure tones presented from a movable loudspeaker in an anechoic chamber. Stimulus levels were 10 dB above each neuron's threshold; additional levels were tested in some cases. About half of the neurons were classified as omnidirectional because they responded with at least occasional spikes to sound sources located anywhere within the 180° arc tested in front of the cat. The remaining neurons had hemifield or axial receptive fields. The hemifield receptive fields encompassed most locations contralateral to

the recording site and had borders coinciding approximately with the vertical midline. Axial receptive fields were contained entirely within the frontal contralateral quadrant of space and were centered on the acoustic axis of the pinna on the side contralateral to the recording site. The acoustic axis was defined in that study as the direction for which the pinna contributed the maximum acoustic gain at any particular frequency. Neurons with hemifield receptive fields tended to have characteristic frequencies below 12 kHz, and neurons with axial receptive fields typically were tuned to frequencies above 12 kHz. In later experiments using broadband sound sources and higher sound levels, described below, the various receptive field classes have been less distinct, tending to form a continuum from axial, through hemifield, to omnidirectional depending on the stimulus level and bandwidth and on the characteristics of particular neurons.

The results of the Middlebrooks J. C. and Pettigrew J. D. (1981) study illustrated the importance of the passive directionality of the head and external ears in shaping the directional sensitivity of cortical neurons. In that study, for example, the centers of axial receptive fields tended to vary among cats according to how the contralateral pinna was positioned, and deflection of the contralateral pinna resulted in a shift of the locations of cortical spatial receptive fields. In subsequent studies that tested multiple sound levels, sharply bounded axial receptive fields have been evident only at stimulus levels within  $\sim 10$  dB of neural thresholds (Imig, T. J. *et al.*, 1990; Rajan, R. *et al.*, 1990b). Nevertheless, the imprint of pinna acoustics on spatial receptive fields is evident at levels as high as 50 dB above neural thresholds (Brugge, J. F. *et al.*, 1996; Reale, R. A. *et al.*, 2003). That most auditory spatial receptive fields are centered in front of one or the other pinna is a conspicuous difference in comparison with receptive fields in the visual and somatosensory systems. That issue will be considered further in Section 3.4.6.2.3.

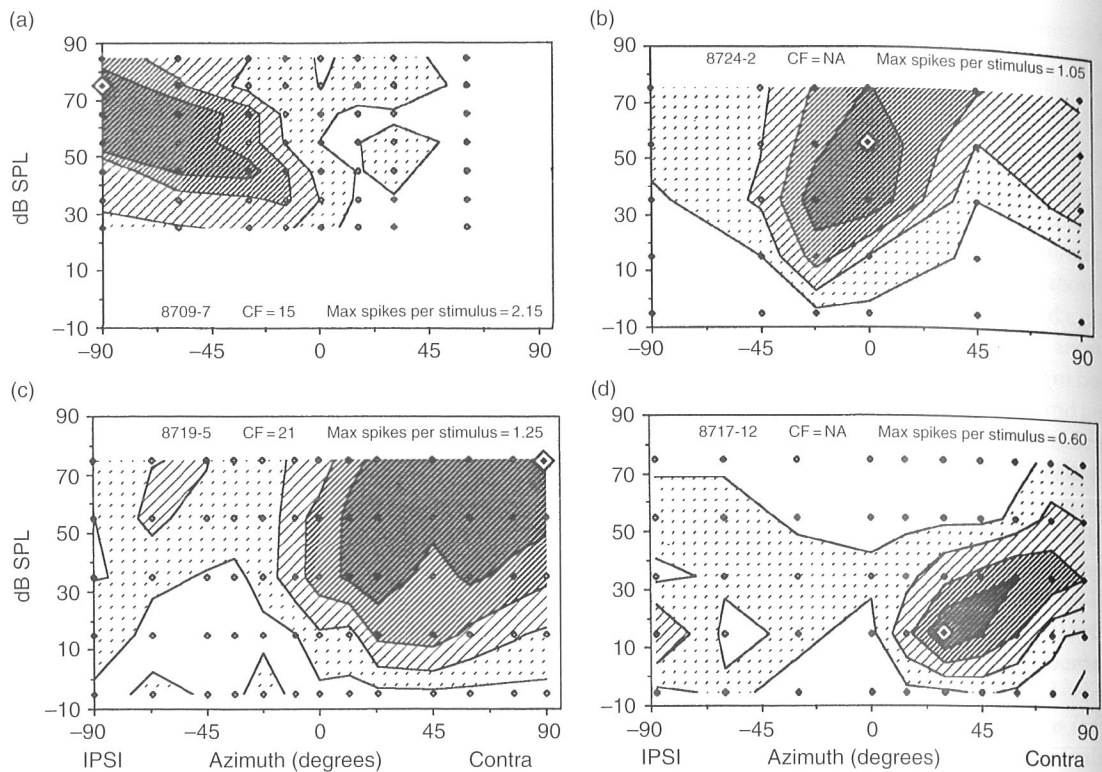
Several groups have quantified spike rates of neurons in cat area A1 (primary auditory cortex) as a function of sound-source azimuth (i.e., the location in the horizontal dimension) and sound level (Imig, T. J. *et al.*, 1990; Rajan, R. *et al.*, 1990b; Poirier, P. *et al.*, 1997; Eggermont, J. J. and Mossop, J. E., 1998; Middlebrooks, J. C. *et al.*, 1998). As in previous qualitative studies, the distribution of spatial tuning among neurons was dominated by contralateral preferred locations. Nevertheless, a sizable number of neurons responded preferentially to sound sources near the frontal midline (17% in Imig, T. J. *et al.*, 1990) and to sources located on the ipsilateral side (23% in Imig, T. J. *et al.*, 1990).

Figure 1 shows examples of an ipsilaterally tuned neuron (Figure 1(a)), a midline neuron (Figure 1(b)), and two contralaterally tuned neurons (Figures 1(c) and 1(d)). Spatial receptive fields tend to grow in size to varying degrees with increasing sound level. Rajan R. *et al.* (1990b), for instance, reported that 60% of spatially selective neurons showed receptive field borders that were constant across a 20–40 dB range of sound levels. Imig T. J. *et al.* (1990), in contrast, reported that the spatial sensitivity of only a minority of their sample was level invariant over a 40–60 dB range.

Virtual auditory space technology has been applied in several experiments for study of spatial sensitivity of neurons (e.g., Brugge, J. F. *et al.*, 1994; 1996; Mrsic-Flogel, T. D. *et al.*, 2001; 2003; 2005). In that approach, broadband sounds are presented sequentially at many locations around an animal, and the resulting sounds are recorded with miniature microphones placed in the animal's ear canals, thus capturing the direction-dependent transfer functions (DTFs) of the external ear. In a later step, arbitrary test stimuli (usually clicks or noise bursts) are filtered by the DTFs and presented to the animal's ears through sealed earphones while recording spike activity from the auditory cortex or other neural structure. The virtual auditory space technique facilitates rapid mapping of spatial sensitivity in azimuth and elevation. The majority of neurons studied with virtual auditory space techniques show receptive fields that are restricted to the contra- or ipsilateral frontal quadrant of space for sound levels no more than  $\sim 30$  dB above neural thresholds. At those levels, the spatial medians of receptive fields tend to coincide with the acoustic axis of one or the other pinna. At higher sound levels, receptive fields tend to broaden, often expanding to encompass all tested locations.

Cortical neurons tend to demonstrate spatial sensitivity not only in terms of their response magnitude (i.e., their spike counts or spike probabilities) but in terms of the latencies of spikes (e.g., Middlebrooks, J. C. *et al.*, 1994; Brugge, J. F. *et al.*, 1996; Middlebrooks, J. C. *et al.*, 1998; Jenison, R. L. *et al.*, 2000; Furukawa, S. and Middlebrooks, J. C., 2002; Reale, R. A. *et al.*, 2003; Stecker, G. C. and Middlebrooks, J. C., 2003). Generally, first-spike latencies vary inversely with spike counts: sounds at preferred locations tend to elicit more spikes with shorter latencies. In some instances, however, spike latencies can show modulation by sound-source location even at high sound levels at which neurons respond with high probability to sounds at all tested locations (Reale, R. A. *et al.*, 2003). An example of spatial gradients of first-spike latencies for a neuron in cat A1 is shown in Figure 2.





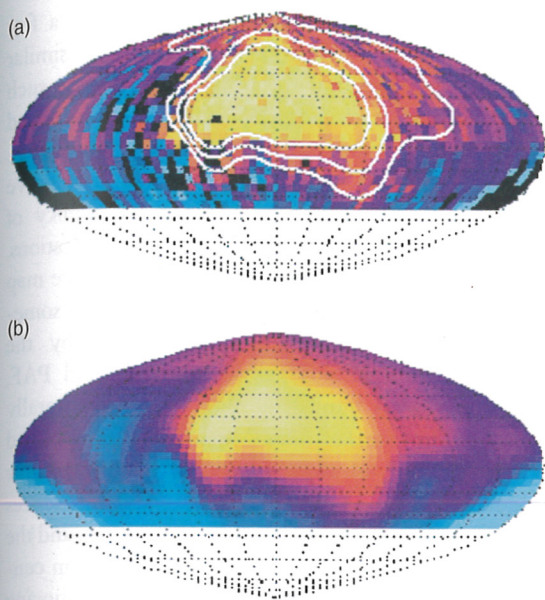
**Figure 1** Spatial sensitivity of four neurons in cat area A1. In each panel, contours represent normalized spike rates as a function of sound-source azimuth (horizontal axes) and sound level (vertical axes). Contours are drawn at 5%, 25%, 50%, and 75% of maximum spike rates. The grids of small diamonds indicate stimulus locations and levels that were tested. Reproduced from Imig, T. J., Irons, W. A., and Samson, F. R. 1990. Single-unit selectivity to azimuthal direction and sound pressure level of noise bursts in cat high-frequency primary auditory cortex. *J. Neurophysiol.* 63, 1448–1466, used with permission from the American Physiological Society.

### 3.46.2.2 Spatial Sensitivity Outside Area A1

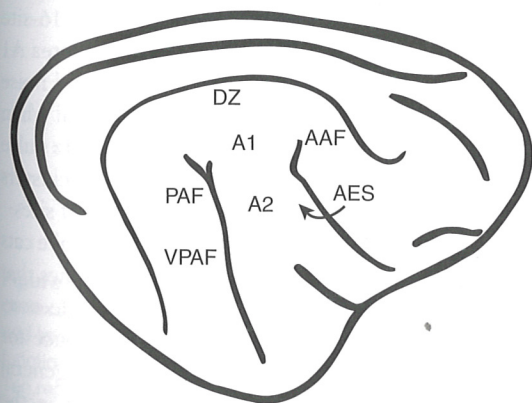
Figure 3 shows the locations of auditory cortical fields on a lateral view of the cat brain. Early studies of spatial sensitivity focused on cortical area A1, perhaps because of its central position in distributing information to other cortical area and because of demonstrations that experimental lesions in A1 result in localization deficits (e.g., Jenkins, W. M. and Merzenich, M. M., 1984). Several more-recent studies have searched beyond the bounds of A1 with the goal of identifying areas that might show enhanced spatial sensitivity. The first such studies examined two nontopographic areas, areas AES (anterior ectosylvian nuclear area) and A2 (second auditory cortex) (Middlebrooks, J. C. *et al.*, 1994; 1998). These are auditory cortical areas in which neurons show broad frequency tuning and robust responses to broadband sounds and in which there is little or no evidence for tonotopic representation of frequency. Perceptual studies of sound localization demonstrate that localization is enhanced by broadband stimuli

(reviewed by Middlebrooks, J. C. and Green, D. M., 1991), presumably indicating that listeners make effective use of location cues across multiple frequencies. The broad frequency tuning of neurons in the nontopographic cortical areas might reflect a neural substrate for integration of multiple location cues. For that reason, the nontopographic cortical areas might seem like a logical place to look for enhanced spatial sensitivity. Also, area AES projects to the deep layers of the superior colliculus (Meredith, M. A. and Clemo, H. R., 1989), which is known to contain a topographic map of auditory space (Middlebrooks, J. C. and Knudsen, E. I., 1984).

Despite the *a priori* speculation that areas AES and A2 might show enhanced spatial sensitivity compared with area A1, the spatial sensitivity observed in those nontopographic areas was qualitatively similar to that observed in A1 (Middlebrooks, J. C. *et al.*, 1994; 1998; Xu, L. *et al.*, 1998; Furukawa, S. *et al.*, 2000). As in area A1, spatial receptive fields tended to broaden as sound levels were increased. Middlebrooks J. C. *et al.* (1998)



**Figure 2** Spatial sensitivity of latencies for a neuron in cat area A1. Transient sounds were presented in virtual auditory space. Latency varied from 11.0 ms (yellow) to 15.0 ms (blue) as a function of virtual source location. Solid white contours are isolatency contours. These quartic authalic (equal-area) projections represent 360° of auditory space. The central vertical meridian represents the vertical midline. (a) Measured data. (b) The data from Figure 1(a) modeled as a linear combination of von Mises basis functions. Reproduced from Brugge, J. F., Reale, R. A., Jenison, R. L., and Schnupp, J. 2001. Auditory cortical spatial receptive fields. *Audiol. Neurootol.* 6, 173–177, with permission from S. Karger A G, Basel.



**Figure 3** Lateral view of the cat brain. The following auditory areas are shown: primary auditory cortex (A1), dorsal zone of A1 (DZ), second auditory cortex (A2), anterior auditory field (AAF), anterior ectosylvian sulcus auditory area (AES), posterior auditory field (PAF), and ventral posterior auditory field (VPAF).

represented the preferred azimuths of neurons by their centroids, defined as the spike-count-weighted centers of mass of their spike-count-versus-azimuth functions. As in area A1, the centroids of the substantial majority of neurons lay in the frontal contralateral quadrant of space, near the acoustic axis of the contralateral pinna. Quantitatively, spatial sensitivity in AES and A2 appeared somewhat greater than in A1, although no direct comparison was made. Spike counts of the majority of neurons recorded in AES and A2 were modulated by >50% by changes in sound-source azimuth. Spatial tuning generally was broad in that, at sound levels >20 dB above neural thresholds, most receptive fields spanned >180° of azimuth. Although failing to demonstrate especially sharp receptive field borders in AES and A2, those studies were the first to demonstrate that spike patterns of neurons varied systematically as a function of sound-source location throughout those large receptive fields, resulting in an effectively panoramic representation of sound locations. That issue is considered further in Section 3.46.3.1.

Area A1 is surrounded by several other auditory cortical areas that are more or less tonotopically organized, including the anterior auditory field (AAF), the dorsal zone of A1 (DZ), and the posterior auditory field (PAF) (e.g., Reale, R. A. and Imig, T. J., 1980; Middlebrooks, J. C. and Zook, J. M., 1983). Recent studies of area AAF indicate that neurons there have spatial sensitivity similar to that of A1 neurons but that AAF neurons tend to show greater broadening of spatial receptive fields in response to increasing sound levels (Harrington, I. A. *et al.*, 2005). Areas DZ and PAF, however, have several features that, *a priori*, make them attractive places to search for enhanced spatial sensitivity. Area DZ was described as a band of cortex dorsal to A1 proper in which frequency tuning was conspicuously broader than in A1 and shifted somewhat to higher frequencies (Middlebrooks, J. C. and Zook, J. M., 1983). Also, in closed-field stimulus conditions, many neurons in DZ failed to respond to either ear alone but showed a strongly facilitated response to equal sounds at the two ears. That binaural response property appeared predictive of sensitivity for free-field sounds located near the midline. Area PAF has been described as having many neurons that show nonmonotonic spike-count-versus-level functions (Phillips, D. P. and Orman, S. S., 1984; Phillips, D. P. *et al.*, 1995). Nonmonotonicity is pertinent to spatial sensitivity because Imig T. J. *et al.* (1990) reported that the most spatially sensitive neurons in A1 also tended to show nonmonotonic level sensitivity. Also, neurons in PAF tend to show rather complex



frequency response areas (Loftus, W. C. and Sutter, M. L., 2001), which might reflect a sensitivity to spectral cues for sound localization.

Recordings in PAF and DZ confirmed the speculation that neurons in those areas might show enhanced spatial sensitivity (Stecker, G. C. *et al.*, 2003; 2005a). Qualitatively, there were no spatial properties that had not been seen at least in milder form in A1 (i.e., no topographic space map; no pin-point receptive fields). Nevertheless, PAF and DZ showed several quantitative differences compared with A1. Figure 4 shows examples of responses in DZ, PAF, and A1. The left column shows frequency response areas, with the typical V-shaped frequency tuning in A1 and more complex multi-peaked frequency tuning in DZ and PAF. Spatial sensitivity is represented by rasters (second column) and rate-versus-azimuth functions (third column). The confusion matrices in the fourth column will be discussed in Section 3.46.3. Compared to those in area A1 (and to areas AES and A2, not shown), spike counts in PAF and DZ were modulated more strongly by sound-source location, spatial gradients were sharper, and (particularly in PAF) spatial tuning was less sensitive to changes in stimulus level. A striking finding in PAF, and to a lesser degree in DZ, was the degree of modulation of spike latencies by sound-source location. Median first-spike latencies were longer in PAF than in A1 (PAF 28.8 ms, DZ 22.0 ms, A1 17.6 ms), and the range of latencies resulting from changes in sound-source azimuth was substantially larger (median ranges: PAF 10.6 ms, DZ 8.4 ms, A1 3.1 ms). The difference between PAF and A1 in the dependence of latency on sound-source location suggests that an intracortical mechanism, as yet unidentified, might act to recode stimulus location as response latency.

### 3.46.2.3 Spatial Topography

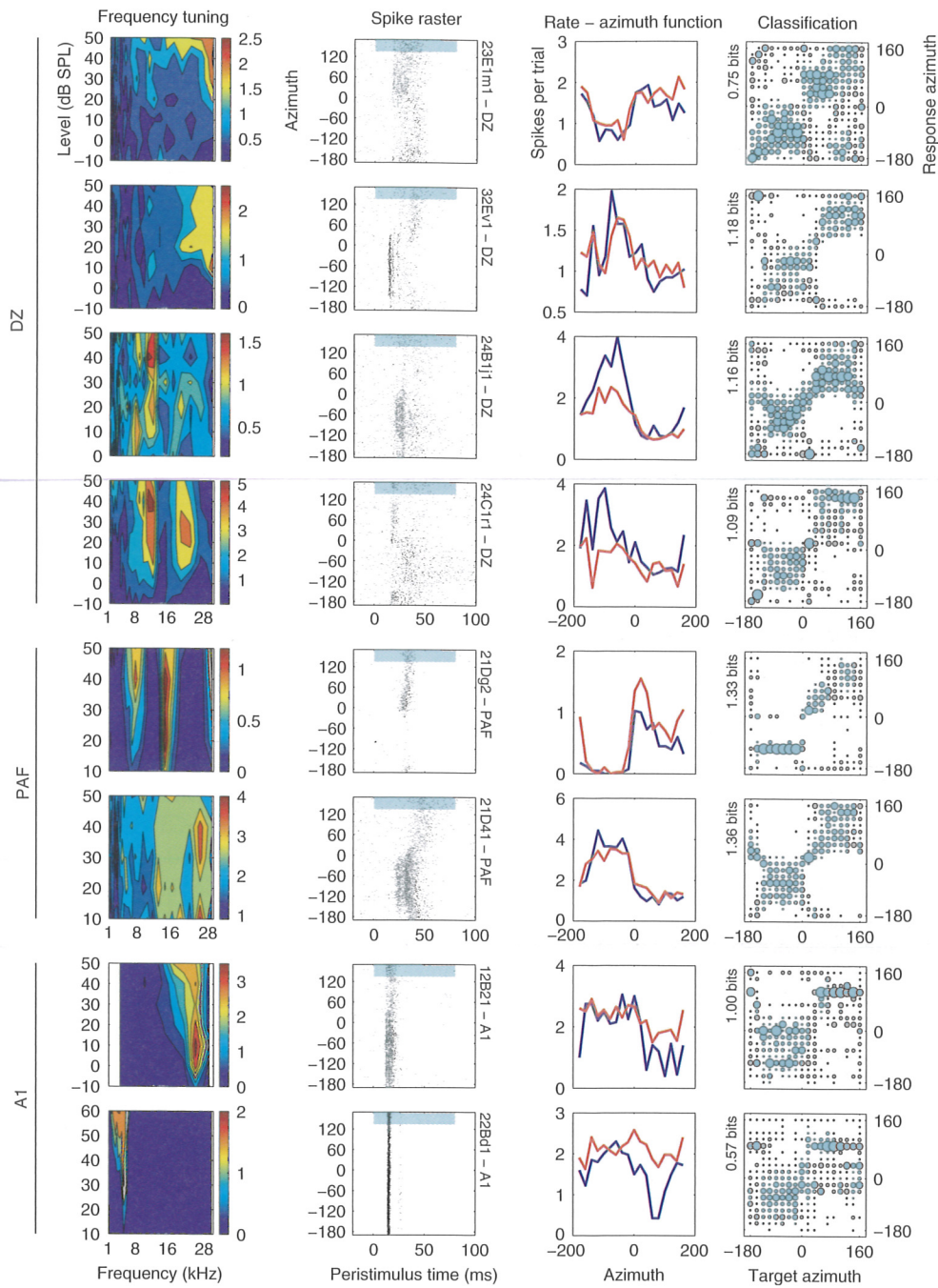
Studies of spatial sensitivity in the auditory cortex consistently have failed to identify a point-to-point map of sound-source location onto cortical place. A point-to-point map would require, first, that the locations of spatial receptive fields vary continuously among neurons and, second, that receptive fields of neurons vary as a function of locations of neurons on the cortex. The first condition is largely unmet, so the second condition is moot. That is, as described above, the distribution of receptive field centroids among neurons is markedly nonuniform, with the majority of centroids located near the axis of one or the other pinna and little coverage of locations across the frontal midline. Regarding the distribution of neurons in the cortex, in A1 one can

identify cortical regions on a scale of one to a few millimeters in which neurons all tend to show similar response properties, but the transition from one such region to another is abrupt (Middlebrooks, J. C. and Pettigrew, J. D., 1981; Imig, T. J. *et al.*, 1990; Rajan, R. *et al.*, 1990a; Clarey *et al.*, 1994). In AES, a quantitative test showed that there is a significant tendency of nearby neurons to have nearby receptive field locations, but there was no indication of a continuous space map (Middlebrooks, J. C. *et al.*, 1998). In DZ, there is somewhat more uniform coverage of azimuth by the distribution of centroids compared to A1 and PAF, especially a larger number of midline and ipsilaterally tuned neurons (Stecker, G. C. *et al.*, 2005a). One can find examples in DZ of sequences of neurons that show progressive shifts in centroid locations. Such sequences are the exception rather than the rule, however, and the sequences tend to terminate with abrupt shifts in centroid location. To summarize, there is no convincing evidence that auditory space is represented in the form of a point-to-point map. Instead, the data are more consistent with a highly distributed representation, as discussed in Section 3.46.3.

### 3.46.2.4 Spatial Sensitivity in Unanesthetized Cats

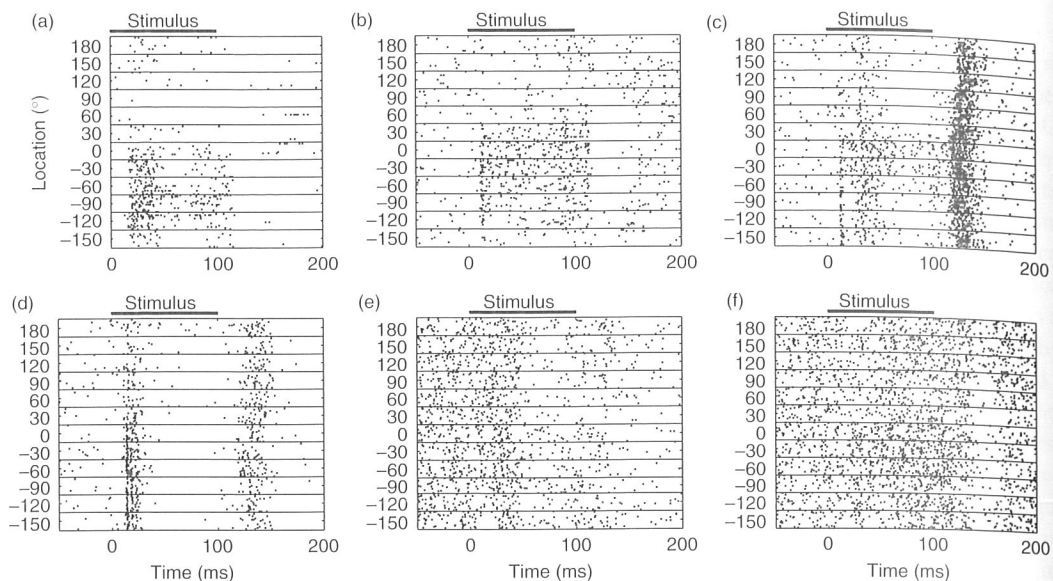
By far, the majority of previous studies of spatial sensitivity have been conducted in anesthetized animals. The use of general anesthesia almost certainly has an impact on the response patterns and on the stimulus sensitivity of cortical neurons. For that reason, there is a growing interest in cortical studies in awake animals. Mickey B. J. and Middlebrooks J. C. (2003; 2005) have used a preparation in which 16-site recording probes are implanted chronically in area A1 of cats. The cat is trained to listen to broadband noise bursts that vary in location and to release a pedal when the sound changes from a noise burst to a 200 Hz pulse train. The activity of single units and multiunit clusters is recorded simultaneously from the 16 cortical sites.

The results from recordings in area A1 in awake cats agree with the major points of the previous studies that used anesthesia. That is, spatial tuning of single neurons generally is broad, and there is no evidence for point-to-point spatial topography. Beyond that general agreement, however, the responses of neurons in the unanesthetized condition are strikingly different from those in the anesthetized condition. Examples of raster plots are shown in Figure 5. In anesthetized cats, nearly all neurons tend to respond with a burst of spikes at the onset of the sound and no continuing (tonic) response



**Figure 4** Examples of neural responses in cat dorsal zone of A1 (DZ), posterior auditory field (PAF), and primary auditory cortex (A1). First column: Frequency-response areas plot mean spike count as a function of stimulus frequency (horizontal axes) and level (vertical axes). Color bars indicate spikes per trial. Second column: Raster plots showing spatial sensitivity as a function of sound-source location (vertical axes). Each row of dots represents spikes resulting from one stimulus presentation. Ten repetitions are shown for each location. Time is represented on the horizontal axes. Blue shading indicates the stimulus duration. Third column: Mean spike rate sound as a function of sound-source location. Blue and red lines represent sound levels 20 and 40 dB, respectively, about neural thresholds. Fourth column: Joint stimulus-probability matrices (confusion matrices) show the accuracy of localization by neural spike patterns, as described in the text. The area of each symbol represents the proportion of trials in which a particular estimated azimuth (vertical axis) was given in response to a particular actual stimulus location (horizontal axis). Transmitted information rates computed from each matrix are given along the left axis. Reproduced from Stecker, G. C., Harrington, I. A., Macpherson, E. A., and Middlebrooks, J. C. 2005a. Spatial sensitivity in the dorsal zone (area DZ) of cat auditory cortex. *J. Neurophysiol.* 94, 1267-1280, used with permission from the American Physiological Society.





**Figure 5** Spatial sensitivity of six neurons in area A1 of the awake cat. Rasters represent responses to 10 stimulus repetitions at each sound-source azimuth. The stimulus duration is given by the bar at the top of each panel. Reproduced from Mickey, B. J. and Middlebrooks, J. C. 2003. Representation of auditory space by cortical neurons in awake cats. *J. Neurosci.* 23, 8649–8663, with permission from the Society for Neurosciences.

(Figure 4, bottom 2 rows). In contrast, the neurons in awake animals (Figure 5) show a diversity of temporal response patterns, including onset bursts, bursts at stimulus offset, tonic responses, stimulus-related inhibition of spontaneous activity, and combinations of those patterns that vary according to stimulus location. Spatial tuning is sharper, partially due to the presence of suppression of background activity by stimuli at nonoptimal locations. Spatial sensitivity is appreciably less vulnerable to changes in sound level. Also in contrast to the anesthetized condition, the peaks of azimuth functions are distributed fairly uniformly throughout the contralateral half of space. These early results from an awake preparation offer the promise of a wealth of new understanding of spatial sensitivity of auditory cortical neurons.

### 3.46.2.5 Dynamic Spatial Sensitivity

The sensitivity of a cortical neural to the location of a particular sound can be influenced by preceding sounds. In this section, we will discuss effects of changes in stimulus location, more or less related to motion sensitivity. In the following section, we will consider cortical responses to pairs of sounds that could result from direct and reflected paths to the ear.

Research on the motion sensitivity of cortical neurons has been hampered by the difficulty of presenting

controlled moving sound sources without introducing other extraneous sounds. One solution has been to use simulated sound motion produced by sequential activation of a series of sound sources located along some particular trajectory. Using such a technique, Poirier *et al.* (1997) showed that about a quarter of neurons sampled in area A1 showed direction sensitivity in the sense that their spike rate was two or more times greater for a sound moving in one direction than the same sound moving in the opposite direction. A larger proportion of neurons (88%) showed such behavior in area AES (Jiang, H. *et al.*, 2000).

A study of low-frequency neurons in area A1 of awake monkeys demonstrated dynamic sensitivity to interaural phase differences (IPDs) that could be taken as indicative of motion selectivity (Malone, B. J. *et al.*, 2002). The response of a particular neuron to a particular static IPD varied according to the IPD of a preceding sound, and the IPD of a preceding sound influenced the IPD that produced the strongest response. Moreover, neurons often showed selectivity for the direction of changing IPD, analogous to selectivity for the direction of azimuthal motion of a low-frequency sound source.

Jenison R. L. *et al.* (2001) used a form of spatial white-noise analysis to study the dynamic spatial sensitivity of neurons in area A1. Identical 10 ms noise bursts were presented from random locations in virtual



auditory space, and space-time receptive fields were computed by compiling the source locations that preceded spikes of cortical neurons. Some 14% of neurons showed receptive fields that were inseparable in that their dynamic space-time receptive fields could not be separated into independent spatial and temporal components. That is, the spatial sensitivity of a neuron at any particular time was influenced by the locations of previous sounds. This implies that neurons are sensitive to the speed and direction of sound motion. Such motion sensitivity was confirmed in tests using simulated motion trajectories.

There is some controversy in the human psychophysical literature regarding the existence of specific motion detectors in the auditory system. One possibility is that neurons in the auditory system might show motion sensitivity analogous to the motion sensitivity that is evident in the visual system. An alternative to a specific auditory motion representation would be that auditory motion is represented only in the comparison of static snapshots of the changing stimulus location (reviews: Middlebrooks, J. C. and Green, D. M., 1991; Grantham, D. W., 1997). A previous review stated: "As yet there is no compelling evidence for motion-sensitive systems in the auditory system" (Middlebrooks, J. C. and Green, D. M., 1991). Subsequent to that review, functional brain imaging has been applied to the problem, but the evidence is so far equivocal. A number of studies have found that moving stimuli activate bilateral loci in the temporal lobe (e.g., Baumgart, F. *et al.*, 1999) and in the right parietal lobe (e.g., Griffiths, T. *et al.*, 1998). The same areas, however, are activated equally well by stationary stimuli that vary randomly in spatial location (Smith, A. L. *et al.*, 2004). It is possible that these cortical areas contain both location-sensitive and motion-sensitive cells intermingled at a scale that cannot be resolved by current imaging methods.

The results discussed above from animal cortical studies showing dynamic spatial sensitivity in addition to recent psychophysical results tend to tip the balance more in favor of motion-sensitive systems. Psychophysical evidence suggests that sensitivity to source motion at relatively low velocities ( $<60^\circ \text{ s}^{-1}$ ) enhances the discrimination of source velocity beyond that observed when only endpoint displacement information is available, although listeners also make use of displacement cues if they are available (Grantham, D. W., 1997; Carlile, S. and Best, V., 2002). Auditory motion adaptation and aftereffect phenomena also suggest the existence of specialized motion detectors (Grantham, D. W. and Wightman, F. L., 1979; Dong, C. J. *et al.*, 1999; Neelon, M. F. and Jenison, R. L., 2004).

### 3.46.2.6 Multiple Sound Sources

In a typical natural environment, a listener must localize sounds in a background of other sounds and must distinguish the actual location of a sound source from multiple reflective surfaces. Several groups have begun to explore the spatial sensitivity of cortical neurons in the presence of continuous background sounds and sensitivity to the locations of leading and lagging pairs of sounds.

Brugge J. F. *et al.* (1998) examined the effect of continuous background noise on the spatial sensitivity of neurons on cat A1. Stimuli were presented in virtual auditory space, and uncorrelated noise at the two ears produced a spatially diffuse background. In the absence of a noise background, spatial receptive fields mapped with transient signals were large, typically occupying a quadrant or more of virtual auditory space. Within those large receptive fields, first-spike latencies formed functional gradients – typically, latencies were shortest for stimuli near the acoustic axis of the contralateral ear and increased with increasing separation from the axis. Introduction of background noise reduced spike counts and increased latencies throughout the receptive field, but the general structure of the receptive field, including the latency gradients, was preserved. That is, increasing the level of a background noise was largely equivalent to decreasing the level of the signal.

Furukawa S. and Middlebrooks J. C. (2001) performed a similar experiment, differing in that the stimuli were presented in a free sound field and the recordings were from area A2. In a condition of diffuse background noise, the result was the same as that obtained by Brugge J. F. *et al.* (1998). Increasing the background noise level simply decreased the effective level of the stimulus such that spike rates were reduced and spatial receptive fields narrowed. A very different result was obtained when the background noise was presented from a discrete location in the free field. In that condition, the background noise tended to mask the signal differentially according to masker location, the masking being greatest when the masker was located near the signal. That means that a masker placed at the centroid of a neuron located near the axis of the contralateral ear could suppress the response to sounds at the contralateral axis, thereby deflecting the centroid toward the axis of the ipsilateral ear. In conditions in which the spatial sensitivity of a neuron in quiet was nearly omnidirectional, the introduction of a focal background noise could suppress responses to signals

near the masker and effectively carve out a rather restricted receptive field. These results from neurons in cat area A2 are analogous to psychophysical demonstrations of spatial unmasking, in which detection of a signal in noise is enhanced by moving the signal away from the masker (Terhune, J. M. and Turnbull, S. D., 1989; Saberi, K. *et al.*, 1991). There are no analogous psychophysical demonstrations, however, suggesting that a focal continuous noise source can produce a systematic deflection of the spatial judgment of a target (Good, M. D. and Gilkey, R. H., 1996; 1997; Lorenzi, C. *et al.*, 1999).

Pairs of sounds separated in time produce in human listeners a variety of spatial percepts that differ according to the interstimulus delay (ISD). Those phenomena are referred to collectively as the precedence effect (reviewed by Litovsky, R. Y. *et al.*, 1999). Physiological analogs to those perceptual phenomena have been observed in the spatial sensitivity of cortical units. When the ISD is less than  $\sim 1$  ms, a human listener will report a single auditory event that is located at a point intermediate between the two sources, biased toward the earlier source. This is summing localization. Mickey B. J. and Middlebrooks J. C. (2001) recorded responses of neurons in cat areas A1 and A2 to sound pairs that produce summing localization. They used a computer pattern-recognition algorithm to identify cortical spike patterns associated with particular locations, thus attempting to recognize the locations signaled by neurons (discussed further in Section 3.46.3). Locations recorded in that way closely followed predictions of summing localization. That is, a 1 ms ISD produced responses signaling the location of the leading stimulus, 0 ms ISDs produced responses signaling the location midway between the two sound sources, and ISDs between 0 and 1 ms produced responses signaling locations biased toward the leading source in proportion to the magnitude of the ISD.

When human listeners are presented with pairs of sounds separated by  $\sim 1$ –4 ms, their localization judgment is dominated by the location of the leading sound. Cortical physiology results in awake rabbits (Fitzpatrick, D. C. *et al.*, 1999) and awake or anesthetized cats (Mickey, B. J. and Middlebrooks, J. C. 2001; 2005) accord with that phenomenon in that most neurons fail to respond at all to sounds that lag a leading sound by several milliseconds. Differences between human psychophysics and animal cortical physiology appear in the ISD range of five to a few hundred milliseconds. A human listener normally can detect a lagging sound after  $\sim 5$  ms and can begin to

localize the lagging sound with some accuracy after  $\sim 10$  ms. In contrast, the animal cortical data show that many neurons still are strongly suppressed during that time range. In a study of area A1 in the awake rabbit, for instance, the median time for 50% recovery of mean spike counts was 21.9 ms, and some neurons showed suppression out to  $\sim 300$  ms (Fitzpatrick, D. C. *et al.*, 1999). In area A1 of the anesthetized cat (Reale, R. A. and Brugge, J. F., 2000), responses to lagging sounds were suppressed over an ISD range of 50–200 ms. Despite the suppression of responses to lagging sounds, however, the spatial sensitivity of neurons in that study (mapped with virtual auditory space techniques) was largely preserved. That is, spatial receptive fields of many neurons in the presence of a sound leading by 100–400 ms resembled receptive fields mapped in control conditions using a lower sound level. Similarly, spatial gradients of first-spike latencies were largely preserved.

In areas A1, A2, and PAF of anesthetized cats, most neurons responded to a leading sound with a burst of spikes followed by a period of suppression lasting 100–200 ms (Mickey, B. J. and Middlebrooks, J. C., 2005). A period of suppression also was seen in awake cats, although the recovery was somewhat faster (Mickey, B. J. and Middlebrooks, J. C., 2005). Only 12% of neurons showed discrete responses to lagging sounds at ISDs of 20 ms, a delay at which human listeners can readily detect and localize a lagging sound. In the ISD range of 1–16 ms, most neurons transmitted considerable information about the location of a leading sound, analogous to performance by human listeners. In contrast with the ability of human listeners to localize sounds at ISDs of 8–16 ms (Yang, X. and Grantham, D. W., 1997), however, there was little information transmitted in the cat cortical spike patterns about the location of the lagging sound. That is, although Reale R. A. and Brugge J. F. (2000) showed that spatial sensitivity is present at long ISDs, there is as yet no evidence for cortical coding of the locations of lagging sounds over a range of delays at which human listeners localize quite accurately.

#### 3.46.2.7 Acoustic Basis for Spatial Sensitivity

The location of a sound source is not mapped directly at the auditory periphery but must be computed based on multiple cues provided by the interaction of the incident sound wave with the

head and external ears. Cortical neurons are well known to be sensitive to one or both of the major cues for azimuth, interaural level differences and interaural time differences. We refer the reader to other recent sources for reviews of the large literature on interaural difference sensitivity in the auditory cortex (Fitzpatrick, D. C. *et al.*, 2000; Zhang, J. *et al.*, 2004). We focus in this review on several studies that have related neuronal spatial sensitivity to the frequency sensitivity of neurons combined with the directional acoustics of the periphery.

The use of virtual auditory space techniques makes it possible to, in effect, exchange the external ear acoustics of one animal for another. That is, one can record the responses of cortical neurons in one animal to stimuli filtered with DTFs measured from another animal. For instance, Mrsic-Flogel T. D. *et al.* (2001) demonstrated that 73% of neurons studied in area A1 of the ferret showed significant changes in the shape or location of spatial receptive fields when stimulated with DTFs measured from another ferret. This approach has been used to explore the development of spatial sensitivity in the cortex (Mrsic-Flogel, T. D. *et al.*, 2003). Cortical neurons in immature ferrets (postnatal age 33–39 days) tend to be broader and to carry less information about stimulus location than do neurons in adult ferrets. When neurons in immature ferrets are tested with stimuli filtered with DTFs from mature ferrets, the spatial sensitivity sharpens. This implies that the relatively poor spatial sensitivity of cortical neurons in immature ferrets is determined by the small size and lack of development of physical structures of the head and external ears more than by immaturity of neural pathways.

Human listeners make systematic errors in vertical localization when presented with sounds that have been processed with a narrowband filter (Middlebrooks, J. C., 1992). It was hypothesized that the narrowband filter mimics an aspect of the directional filter properties of the external ears. That hypothesis was supported by a computational model that predicted localization judgments on the basis of correlation of the narrowband filter shape with the DTFs of individual listeners. An analogous procedure was tested in the cat, using recordings of neurons in area A2. The elevation sensitivity of neurons was measured using broadband and narrowband sounds presented in a free field. When tested with narrowband sounds, neural responses tended to signal particular elevations that depended on the center

frequency of the stimulus, not on the actual location of the source. The computational model from the human study (Middlebrooks, J. C., 1992) was adapted to cats by applying DTFs of individual cat's ears. That model could effectively predict the spatial sensitivity of the cortical neurons, indicating a straightforward relationship between external ear acoustics and elevation sensitivity.

Schnupp J. W. H. and colleagues (Schnupp J. W. H. *et al.*, 2001; Mrsic-Flogel, T. D. *et al.*, 2005) attempted to account for the spatial sensitivity of neurons in area A1 of ferrets on the basis of a linear combination of the frequency sensitivity of the two ears and the directional acoustics of the auditory periphery. Frequency–time response fields (FTRFs) were measured using a reverse correlation analysis of responses to multiple random-frequency tone pips presented to the two ears. The FTRFs captured the frequency-dependent excitatory and inhibitory contributions of each ear. Sensitivity to interaural level differences presumably was captured by the use of stimulus sets presented simultaneously to the two ears, but sensitivity of neurons to interaural differences in temporal fine structure (i.e., IPD sensitivity) was not captured. The FTRF for each ear was multiplied by the DTF of that ear, yielding an estimate of the directional sensitivity of neuronal responses. The estimates of spatial receptive fields provided by this simple model were remarkably good for the majority of high-frequency neurons, which were said to exhibit linear processing of spatial cues. For many neurons, the procedure could estimate the growth of spatial receptive fields with increasing sound pressure level, although that estimation was more successful for neurons that receive predominantly excitatory input from the contralateral ear and inhibitory input from the ipsilateral ear (EI neurons) than for neurons that derive predominantly excitatory input from both ears (EE neurons). Performance was less satisfactory for low-frequency neurons that, presumably, derive spatial sensitivity largely from IPD cues. Also, the linear estimation procedure failed to duplicate the location dependence of first-spike latencies that commonly is observed in empirical data.

Macpherson E. A. *et al.* (2004) applied a similar linear estimation procedure to characterize elevation sensitivity of several auditory cortical fields in cats. The elevation sensitivity of neurons in areas A1 and AAF was predicted accurately by a simple linear model, but the linear model worked poorly for neurons in areas DZ and PAF. One possible explanation for those results is that neurons in DZ and PAF exhibit



greater nonlinearity than do A1 and AAF neurons, perhaps reflecting greater nonlinearity in the processes within DZ and PAF or indicating that nonlinear processes are added on in a projection from A1 to DZ and PAF. A second possibility is that spatial sensitivity in all fields incorporates similarly nonlinear processing but that the nonlinearity is not as evident in A1 and AAF neurons because those neurons tend to show relatively narrow frequency tuning.

### 3.46.2.8 Nonhuman Primates

In nonhuman primates, spatial sensitivity of cortical neurons has been studied in temporal lobe auditory areas and in multimodal areas of the frontal and parietal cortex. We will focus on the auditory areas and refer the reader elsewhere for a brief overview of auditory spatial sensitivity in multimodal areas (Middlebrooks, J. C., 2000). Kaas J. H. and Hackett T. A. (Chapter 3.45) review the organization of the auditory areas in primates. Briefly, there is a core area containing two or more tonotopic representations; the core area in primates is homologous to region comprising areas A1, AAF, and PAF in the cat, although homologies among specific fields are unclear. The core area in primates is bordered by medial and lateral belt areas that, in turn, are bordered by parabelt areas.

In two early studies in unanesthetized macaques, stimuli were restricted to a limited number of locations in a frontal segment of the horizontal plane (Benson, D. A. *et al.*, 1981; Ahissar, M. *et al.*, 1992). Both studies showed that the majority of neurons in area A1 responded more strongly to contralateral than to ipsilateral sounds. The Benson group reported that neurons were more active when monkeys were engaged in an auditory task than when the monkeys were idle, but few neurons showed a significant difference in neuronal responses between a sound-localization task and a simple auditory detection task. The Ahissar group reported that some neurons showed a preference for a particular direction of sound-source motion, but those researchers declined to conclude that there were separate mechanisms for localization and for motion discrimination.

Recanzone G. H. *et al.* (2000) studied the spatial sensitivity of cortical neurons in awake behaving macaques. Recordings were from area A1 and from the caudomedial (CM) area of the medial belt region. Stimuli varied in azimuth and elevation, all within 30° of the origin at 0° azimuth, 0° elevation. Most

neurons in A1 and CM showed a robust response across the entire tested area. The majority of neurons in A1 and CM were spatially tuned in the sense that regression analysis showed a significant correlation of spike count with stimulus azimuth and/or elevation. A statistical procedure was performed to determine the minimum change in sound-source location that could be detected on the basis of a change in the spike counts of single neurons. Those neuronal spatial discrimination thresholds were compared with analogous behavior thresholds from the same monkeys. Generally, the thresholds of CM neurons tended to correlate more closely with the behavioral thresholds than did those of A1 neurons.

Tian B. *et al.* (2001) compared spatial sensitivity among three of the lateral belt areas in anesthetized macaques: anterolateral (AL), middle lateral (ML), and caudolateral (CL). Stimuli were a selection of monkey calls presented in 20° steps of azimuth from -60° to +60° in the frontal horizontal plane. Based on histograms of spatial-tuning widths, it appears that the majority of neurons responded with at least half-maximal spike counts across more than half of the tested locations, with the half-maximum response area extending off one or both edges of the tested range. There was no indication of any striking qualitative difference in spatial sensitivity among the three tested cortical areas, but tuning widths in CL were significantly narrower than in AL and ML.

### 3.46.3 Reading the Location of a Sound Source from Patterns of Neural Activity

Studies of spatial sensitivity like those described above implicitly address the question: "Given this stimulus, what is the likely neuronal response?" A question that perhaps is more relevant to perception and behavior is: "Given this neuronal response, what was the most likely stimulus?" Research by several groups has begun to address this latter question, attempting to understand how response patterns of single cortical neurons or of neural populations could signal the location of a sound source.

#### 3.46.3.1 Sound Localization by Single Neurons

Although many cortical neurons exhibit restricted spatial receptive fields at near-threshold sound levels, receptive fields measured at moderate sound levels

typically extend throughout  $180^\circ$  to  $360^\circ$  of azimuth. Nevertheless, even within an omnidirectional receptive field, the number and latency of spikes of a single neuron can vary systematically with sound-source location. Middlebrooks J. C. *et al.* (1994) adopted an artificial neural network as a spike-pattern classifier and attempted to estimate sound-source locations by recognizing sound-location-specific spike patterns of neurons in cortical area AES of anesthetized cats. That work demonstrated that the spike patterns of neurons could signal sound-source locations with variable amounts of accuracy throughout up to  $360^\circ$  of azimuth. This was referred to as panoramic location coding. The accuracy with which a computer-based classifier can estimate sound localization on the basis of neural spike patterns can be taken as a measure of the information contained with those spike patterns – information that presumably could contribute to an animal's perception and behavior.

Similar analysis has subsequently been applied to cortical areas A1 (Mickey, B. J. and Middlebrooks, J. C., 2001; 2003; Stecker, G. C. *et al.*, 2003), A2 (azimuth: (Middlebrooks, J. C. *et al.*, 1998); elevation: (Xu, L. *et al.*, 1998)), PAF (Stecker, G. C. *et al.*, 2003), DZ (Stecker, G. C. *et al.*, 2005a), and AAF (Harrington, I. A. *et al.*, 2005). There have been differences in the classifiers that have been used and in other details of analysis, but the general analysis procedure has been as follows. Spike patterns are recorded in response to multiple repetitions of sounds at multiple locations. The spike patterns are divided into 'training' and 'test' sets. The training set is used to train a computer-based classifier (typically a form of artificial neural network), then the trained classifier is used to estimate the sound-source location that elicited each pattern in the test set. For convenience in presentation, we will refer to this estimation of the sound-source location as sound localization by the cortical neuron. The localization performance of each neuron is assessed either with a measure of the magnitude of errors or by a measure of transmitted information (i.e., how much information about sound-source location is transmitted by the animal's auditory system to the recording electrode in the auditory cortex).

The rightmost column of Figure 4 shows examples of sound localization by neurons in areas A1, PAF, and DZ. Each panel shows a confusion matrix in which the area of each circle indicates the proportion of spike patterns that were localized to a particular estimated location (plotted on the vertical axis) in response to a stimulus at a particular target

location (horizontal axis). Correct estimates of the target location fell on the major diagonal with positive slope; the DZ unit shown in the third row is an example with many correct estimates. Points lying on one of two minor diagonals with negative slope are instances in which the estimate of the lateral position was correct but in which front and back were confused; the PAF unit shown in the sixth row shows many such front/back confusions. We note that front/back confusions often are observed in human sound-localization judgments (e.g., Middlebrooks, J. C. and Green, D. M., 1991). In some instances, neurons discriminated left targets from right fairly accurately but could not discriminate locations within one hemifield; the A1 units in the bottom two rows are examples.

Qualitatively similar sound localization by single neurons has been observed in all auditory cortical areas in which this sort of analysis has been performed. That is, there is no indication that one area is doing something dramatically different from the others. Nevertheless, one can rank the localization performance of the areas, with areas A1 and AAF showing the least accuracy, areas AES and A2 intermediate, and areas DZ and PAF showing the most accurate localization. PAF in particular exhibits localization that is least vulnerable to changes in sound-source level.

As discussed in Section 3.46.2.3, the responses of neurons are not consistent with the existence of a topographic, point-to-point, map of auditory space. That is, one cannot identify particular neurons that are watching over particular sound-source locations. Instead, all the data are consistent with a highly distributed representation, in which each neuron transmits at least partial information about nearly all source locations and the representation of each source location is distributed among most of the auditory cortical population.

### 3.46.3.2 Information-Bearing Features of Spike Patterns

Cortical neurons exhibit spatial sensitivity both in terms of the magnitude of responses (i.e., spike count or spike probability) and in terms of the timing of spikes, as described in Section 3.46.2 and as is clearly evident in raster plots like those in Figure 4. Response magnitude is widely accepted in sensory neuroscience as representative of the response of a neuron to a particular stimulus. The pattern classification schemes used in studies discussed in Section



3.46.3.1 potentially exploit both magnitude and timing information. In this section, we consider the relative amounts of location-related information transmitted by response magnitude and timing.

The importance of cortical spike timing for location representation can be demonstrated by reducing spike patterns to simple spike counts, thus eliminating any temporal dimension of responses. Localization by classification of spike counts of neurons in areas AES and A2 was substantially inferior to that by spike patterns that preserved spike timing (Middlebrooks, J. C. *et al.*, 1994; 1998). Furukawa S. and Middlebrooks J. C. (2002) quantified the amounts of location-related information that were transmitted by intact spike patterns of neurons in area A2 and by the same patterns degraded in one of two ways. In one condition, spike times were interchanged randomly among trials, thus preserving response magnitudes but eliminating any timing information. In that condition, there was a ~35% decrease in transmitted information. In the other condition, all spikes after the first spike were deleted, thus preserving first-spike latencies and the dispersion of first-spike latencies but eliminating information from spike counts. That resulted in a decrease in transmitted information of only ~11%. In tests of information transmitted by unidimensional terms, spike count or first-spike latency, latency transmitted significantly more information than did spike count.

Similar results pertaining to spike timing, and some differences, were obtained in area A1 of awake cats (Mickey, B. J. and Middlebrooks, J. C., 2003). Complete elimination of the stimulus dependence of spike timing reduced transmission of stimulus-related information by ~50%. The awake cat A1 results differed somewhat from the results from A2 in anesthetized cats in that a substantial decrease in transmitted information was evident in the awake A1 study only when spike times were degraded on a scale of greater than ~16 ms, whereas in the anesthetized A2 study (Furukawa, S. and Middlebrooks, J. C., 2002), a substantial decrease in transmitted information was observed for degradation of timing on a scale as fine as 4 ms. Also different from the A2 study, spike count alone on average transmitted more information than did first-spike latency alone. The result likely reflects the fact that response patterns tended to be more sustained in the awake condition than in the anesthetized condition, resulting in higher spike counts and greater potential for modulation of spike counts by sound-source location.

First-spike latency typically shows a strong negative correlation with spike counts. For that reason, the amount of information transmitted in area A2 by two-dimensional vectors of spike count and spike latency is substantially less than the sum of the information transmitted by either term alone (Furukawa, S. and Middlebrooks, J. C., 2002). Location-related variation of first-spike latency is appreciably greater in area PAF than in areas A1 and A2 (Stecker, G. C. *et al.*, 2003). Correlation between spike count and first-spike latency is significantly weaker in PAF, suggesting that latency contributes a greater increment in transmitted information in PAF than is the case in A1 or A2.

Estimates of transmitted information that rely on first-spike latency require knowledge of the time of onset of the sound, which is not directly available to an animal. A more biologically plausible approach would be to examine stimulus-related information that could be carried by the relative timing of spikes among neurons. Stecker G. C. and Middlebrooks J. C. (2003) compared information transmitted by patterns of spikes timed relative to stimulus onset (absolute spike times) with information transmitted by patterns of spike-time differences between pairs of spikes. When pairs of neurons were selected both from area A1 or both from PAF, information transmission by relative spike times was reduced compared to the absolute-time condition, although the relative times did transmit appreciable amounts of information. In contrast, when pairs of neurons were formed by one A1 neuron and one PAF neuron, relative and absolute spike times transmitted roughly equal amounts of information. It appears that the somewhat restricted range of spike latencies in A1 served as an adequate temporal reference by which to measure the widely varying latencies in PAF. Additional studies of information transmission by relative spike times are considered in the context of location signaling by populations of neurons, discussed in the next section.

### 3.46.3.3 Location Signaling by Populations of Neurons

Despite the potential for single neurons to signal sound locations throughout auditory space, no single neuron can do so accurately enough to account for the accuracy observed in behavioral trials. Hypothetically, that additional accuracy could be gained from the coordinated activity of populations of neurons. That hypothesis has been explored with

classifiers that act on simple combinations of spike patterns of multiple neurons (Furukawa, S. *et al.*, 2000; Mickey, B. J. and Middlebrooks, J. C., 2003; Stecker, G. C. *et al.*, 2003) and with classifiers that exploit some particular differential response among neurons (Jenison, R. L., 1998; 2000; 2001; Stecker, G. C. and Middlebrooks, J. C., 2003; Stecker, G. C. *et al.*, 2005b).

Furukawa S. *et al.* (2000) explored azimuth signaling by ensembles of 2–128 neurons in area A2 of anesthetized cats. Neuronal single- and multiunit data were recorded from multisite recording probes that enabled simultaneous recordings at 16 sites spaced in 100  $\mu\text{m}$  intervals (i.e., all recordings were along a 1500  $\mu\text{m}$  oblique line through the cortex). Ensemble spike patterns were formed either by concatenating patterns of single neurons or by compiling multiple random samples of 1–128 neural units from a pool of 377 units. Ensemble spike patterns were classified using techniques like those described in Section 3.46.3.1. Relative spike timing and spike counts among neurons were preserved by that procedure, but there was no explicit procedure to differentiate timing or count among neurons. Localization signaling performance improved rapidly with increases in the size of ensembles from 1 to about 8 or 16, then improved more slowly beyond that size. An ensemble of 128 units produced localization performance comparable to cat localization behavior (May, B. J. and Huang, A. Y., 1996). It has been noted that a substantial fraction of stimulus-related information in spike patterns is carried by spike timing (discussed in Section 3.46.3.3). The study by Furukawa and colleagues demonstrated that a similar amount of information is carried by times measured relative to the onset of the stimulus or by times measured relative to the first spike across the ensemble of neurons.

Localization signaling performance in the study by Furukawa S. *et al.* (2000) was better when units were drawn from across all recording-probe locations in multiple animals than when all units were recorded with the same 16-site probe. That suggests that localization is enhanced by neural ensembles that exhibit a greater diversity in spatial sensitivity of single units. Neurons in area PAF of anesthetized cats (Stecker, G. C. *et al.*, 2003) and A1 in awake cats (Mickey, B. J. and Middlebrooks, J. C., 2003) show substantially greater diversity of spatial sensitivity and spike patterns than do neurons in areas A1 and A2 in anesthetized cats. Analysis of location signaling by neural ensembles using procedures similar to that introduced by

Furukawa and colleagues showed enhanced growth of signaling accuracy associated with increasing ensemble size in area PAF in anesthetized cats (Stecker, G. C. *et al.*, 2003) and A1 in awake cats (Mickey, B. J. and Middlebrooks, J. C., 2003) compared to areas A1 and A2 in anesthetized cats.

As noted in Section 3.46.2.1, the first-spike latencies of cortical neurons typically vary with sound-source location. Jenison R. L. *et al.* (1998) explored location signaling by the first-spike latencies of ensembles of neurons in area A1 of anesthetized cats. The spatial sensitivity of the latency of each neuron was measured with virtual auditory space techniques, then that sensitivity was modeled using a form of spherical approximation with von Mises basis functions (as in Figure 2; Jenison, R. L. and Fissel, K., 1995; 1996). A maximum-likelihood estimator then was used to estimate sound-source locations based on modeled latencies from ensembles of neurons. Performance was quantified by Monte Carlo simulations and by analytic computation of the Cramer–Rao lower bound (CRLB; Blahut, R. E., 1987), which is a measure of the variance of an unbiased estimator. Neural ensembles of varying sizes were drawn from a population of 65 single neurons studied in area A1 of anesthetized cats (Brugge, J. F. *et al.*, 1996). Performance improved rapidly with increases in ensemble size up to about 20 neurons. Asymptotic values of localization error for targets at 0° azimuth and 0° elevation were comparable to psychophysical values reported in humans (Makous, J. C. and Middlebrooks, J. C., 1990) and cats (May, B. J. and Huang, A. Y., 1996).

Jenison has extended his work in several ways. First, he showed that very similar localization performance is obtained if latencies are expressed relative to the stimulus onset (absolute latencies) or are expressed relative to the first spike in the ensemble (relative ensemble latencies) (Jenison, R. L., 2001). That result is consistent with the results of Furukawa S. *et al.* (2000) obtained with a very different form of classifier. Second, he added a sound-level term to the radial-basis-function representations of spatial receptive fields (Reale, R. A. *et al.*, 2003). Localization performance initially improved with increasing sound level, consistent with human psychophysical results (Sabin, A. T. *et al.*, 2005). Further increases in level tended to result in decreases in performance, which is not seen psychophysically except for localization of transients in elevation (Hartmann, W. M. and Rakerd, B., 1993; Macpherson, E. A. and Middlebrooks, J. C., 2000).

Finally, he demonstrated the interesting and rather unexpected result that localization by the first-spike latencies of an ensemble of neurons is enhanced by correlation among the individual neurons (Jenison, R. L., 2000).

#### 3.46.3.4 An Opponent Process Model

Stecker G. C. *et al.* (2005b) have evaluated an opponent-process model of spatial representation. That model is based on the observation that auditory space is sampled quite nonhomogeneously by receptive fields. Indeed, as noted in Section 3.46.2, the spatial receptive fields of the large majority of neurons are centered on the acoustic axis of one or the other pinna, and few receptive fields are centered on the midline. The tendency of receptive fields to lie off the midline means that the steepest spatial gradients of neurons' spike counts or latencies tend to lie on or near the midline. The near-midline locations of steep response gradients are reflected in the tendency of spike-pattern classifiers (as in Section 3.46.3.1) to discriminate left from right with great acuity while often failing to discriminate locations within one or the other sound hemifield (e.g., see Figure 4, right column). Moreover, specific tests of the discrimination of pairs of locations by neurons in areas A1, PAF, and DZ of anesthetized cats showed that the greatest spatial acuity was for pairs of locations that straddled the frontal midline.

The opponent process model asserts that sound-source locations could be represented by the relative activity of a small number of discrete populations of neurons, as small as two, each population defined by tuning to a particular region of space. Inasmuch as the majority of neurons in each cerebral hemisphere are tuned to locations in the contralateral frontal quadrant, one might think first of a comparison of activity between left and right hemispheres. That notion is untenable, however, because it predicts that a unilateral lesion would produce a bilateral localization deficit, contrary to the largely contralateral deficits that are observed (see Section 3.46.4). Instead, Stecker G. C. *et al.* (2005b) argue that an opponent process localizer could be constituted from contralaterally tuned and the relatively few ipsilaterally tuned neurons within each hemisphere; ipsilaterally tuned neurons are particularly prevalent in area DZ (Stecker, G. C. *et al.*, 2005a). As a proof of concept, they tested a simplified model that summed normalized spike counts from contralaterally tuned neurons and subtracted them from summed counts

from ipsilaterally tuned neurons. Classification of those difference terms provided localization performance that was clearly superior to classification of simple summed spike counts, particularly in conditions of varying sound levels. That test dealt only with overall levels of activation among two populations. One assumes that performance could only be better if the complexity of interconnections among neurons were to be exploited in a more realistic manner.

The opponent process model may be regarded as an extension of the panoramic coding described in Section 3.46.3.1. Results presented in that section indicate that spike patterns of many neurons can signal the locations of sound sources throughout as much as 360° of space. The opponent process model simply points out what is clear in most of the cited publications, that most of those neurons discriminate near-midline locations more accurately than they discriminate locations far off the midline. We note that the enhanced discrimination of midline locations by neurons fits with psychophysical evidence that spatial discrimination is most acute (Mills, A. W., 1958) and that localization is most accurate (Makous, J. C. and Middlebrooks, J. C., 1990; Stevens, S. S. and Newman, E. B., 1936; May, B. J. and Huang, A. Y., 1996) for near-midline targets. Furukawa S. *et al.* (2000) demonstrated that ensembles of panoramic neurons signal sound locations more accurately than do single neurons. The opponent process model extends that observation by suggesting a particular way in which information might be combined across populations – that is, as a differential between populations tuned to left or right hemifields.

#### 3.46.4 Impact of Cortical Inactivation on Localization Behavior

The ability to localize sounds in space has long been known to depend on intact auditory cortex (e.g., Neff, W. D. *et al.*, 1956). In general, the removal or inactivation of auditory cortex in one hemisphere renders animals unable to approach, or even discriminate, the locations of sound sources in the contralateral hemifield, whereas localization performance in the ipsilateral hemifield is largely unaffected (e.g., Jenkins, W. M. and Masterton, R. B., 1982; Thompson, G. C. and Cortez, A. M., 1983; Heffner, H. E., 1997). When the auditory cortex is removed or inactivated bilaterally, the animals are rendered



unable to approach or discriminate sound sources within either lateral hemifield but generally can discriminate whether a sound source is located on the left or right, albeit with reduced acuity (Heffner, H. E. and Masterton, B., 1975; Heffner, H., 1978; Heffner, H. E. and Heffner, R. S., 1990). In what follows, we will review some of the effects of cortical lesions, as well as acute and chronic cortical inactivation, on the sound-localization behavior of species including cats, ferrets, dogs, and monkeys. It should be emphasized that although the effects of cortical lesions are similar among these species, they cannot be generalized to all species.

#### 3.46.4.1 Role of the Auditory Cortex in Reflexive Orientation to Sound Sources

Not long after the auditory cortex was first implicated in the operant auditory spatial behavior of the cat (Neff, W. D. *et al.*, 1956; see Section 3.46.4.2), researchers began to address its role in reflexive orientation to sound sources. In the first of these studies, Riss W. (1959) observed the orienting responses of cats with bilateral auditory cortex lesions and concluded that the auditory cortex was necessary for "localizing the instantaneous position of a sound source," even when the ability was assessed in terms of reflexive orientation. Indeed, when the animals were deprived of all visual cues, their orienting responses were unrelated to the actual location of the sound source. In contrast, several later studies concluded that while the orienting responses of cats with large bilateral lesions were often abnormal, they were not entirely absent (Thompson, R. F. and Welker, W. I., 1963; Thompson, G. C. and Masterton, R. B., 1978; Beitel, R. E. and Kaas, J. H., 1993). Specifically, although most responses were generally toward the appropriate lateral hemifield, the accuracy of the final head position within that hemifield was often diminished. Indeed, in the study by Beitel and Kaas, the position of the animal's head following an orienting response was unrelated to the position of the sound source, beyond being within the appropriate hemifield. However, Thompson G. C. and Masterton R. B. (1978) observed that when the initial direction of a head turn was appropriate (e.g., turning left for a leftward source), so too was the remainder of the response. The fact that orienting responses could appear normal on one trial and aberrant on the next led those authors to suggest that the systems involved in reflexive responses to sound, although not cortical *per se*, might be under cortical

control (Thompson, G. C. and Masterton, R. B., 1978). These results suggest that while bilateral lesions might impair the ability of cats to accurately orient to sound sources within a lateral hemifield, they have only a slight effect on the ability to orient appropriately to the left or the right side of the midline.

#### 3.46.4.2 Role of the Auditory Cortex in Operant Localization of Sound Sources

In the earliest lesion study of sound localization, bilateral auditory cortex lesions impaired the ability of cats to approach a target on the left or right when it was identified by an auditory, but not a visual, cue (Neff, W. D. *et al.*, 1956). Despite their impairment, however, cats were often able to perform the task above chance levels when just two targets were used, located close to the animal on the left and right. A similar observation was later made in dogs (Heffner, H. E., 1978). Neff proposed that the deficit might reflect an inability to maintain attention between the initiation and completion of an operant response. When the target was closer to the animals, the attentional demands of the task were reduced, and performance improved. Whatever its explanation, the demonstration of an auditory localization deficit, however incomplete, supported the involvement of auditory cortex in sound-localization behavior.

Following the study by Neff W. D. *et al.* (1956), Strominger N. L. (1969a; 1969b) provided additional evidence for the preservation of left-right discrimination following bilateral lesions in cats, as well as the first evidence for an impairment following unilateral lesions (Strominger, N. L., 1969b). Cats were again trained to approach targets on the left and right. Following unilateral lesions, although some animals expressed a bias toward targets on the same side as their lesion (i.e., opposite their intact hemisphere), their behavior was otherwise unremarkable. Following bilateral lesions, however, the animals were unable to perform the discrimination except at the largest separation of 180° (Strominger, N. L., 1969b). Later studies of monkeys, dogs, and ferrets also demonstrated that while the ability to perform left-right discriminations persists following bilateral lesions, the animals' spatial resolution often was deficient and, at least in monkeys, that the degree of deficiency may be task dependent (Heffner, H. E. and Masterton, B., 1975; Heffner, H. E., 1978; Kavanagh, G. L. and Kelly, J. B., 1987; Heffner, H. E.

and Heffner, R. S., 1990). Indeed, the observation that monkeys with bilateral lesions were able to indicate whether a sound came from the left or right by making a corresponding (left or right) lever press, but not by approaching the source of the sound led to the suggestion that, "... what auditory cortex lesions seem to produce ... is an inability to demonstrate sound localization in some tasks" (Heffner, H. E. and Masterton, B., 1975; 1978, p. 742).

These and other studies suggested that cortical lesions impair but do not eliminate the ability of cats, dogs, ferrets, and monkeys to reflexively orient toward, identify, or discriminate sound sources between the left and right hemifields. It was only when animals began to be tested for the ability to localize sound sources within a lateral hemifield, however, that the severity of sound-localization deficits, particularly those that follow unilateral lesions, was made apparent. Jenkins W. M. and Masterton R. B. (1982) required cats to walk to a sound source within an array of speakers spanning 180°, a task that normal animals performed well. Following unilateral lesions, however, the accuracy of their responses was profoundly diminished in the contralesional, but not the ipsilesional, hemifield. This test procedure was later used to demonstrate contralesional deficits of tone localization that were limited to frequencies whose cortical representation in the primary field (A1) had been removed (Jenkins, W. M. and Merzenich, M. M., 1984), as well as a contralesional localization deficit in squirrel monkeys (Thompson, G. C. and Cortez, A. M., 1983). Interestingly, as with the cats tested by Strominger N. L. (1969a), when presented with a contralesional sound source, the squirrel monkeys often responded to ipsilesional sources (Thompson, G. C. and Cortez, A. M., 1983). Subsequent studies have demonstrated that monkeys and ferrets are not only unable to approach contralesional sound sources accurately, they are unable to discriminate them using simpler operant procedures (Kavanagh, G. L. and Kelly, J. B., 1987; Heffner, H. E. and Heffner, R. S., 1990).

Although each hemisphere is primarily responsible for spatial behavior in the contralateral hemifield, regions of space near the midline appear to be represented bilaterally. This ipsilateral spillover is evident when the spatial deficits that follow unilateral lesions in monkeys are mapped by fixing the location of one sound source and systematically varying the location of another sound source in a discrimination task (Heffner, H. E. and Heffner, R. S., 1990; Heffner, H. E., 1997). When both sound sources are more than

15–30° into the contralesional hemifield, they can no longer be discriminated regardless of how widely they are separated within that hemifield. In cases of bilateral lesions, discrimination fails as soon as the two sources are on the same side of the midline, again regardless of their separation (Heffner, H. E. and Heffner, R. S., 1990; Heffner, H. E., 1997). This suggests that each cerebral hemisphere represents the entire contralateral hemifield in addition to the 15–30° of the ipsilateral hemifield closest to the interaural midline. In the absence of auditory cortex in both hemispheres, the animals are only able to distinguish sounds on the left from those on the right. It is possible, however, that the animals might be performing this left–right discrimination on the basis of nonspatial cues. That is, although dogs and monkeys can learn to approach a left and right sound source with persistent training, their ability to rapidly transfer this spatial response to the discrimination of nonspatial stimulus features suggests that they may be making a spatial response to what is for them a nonspatial stimulus (Heffner, H. E., 1978).

#### 3.46.4.3 Reversible Cortical Inactivation

Reversible inactivation techniques have emerged as a powerful tool for the investigation of brain–behavior relationships and have been used to study the role of auditory cortex in sound-localization behavior (Malhotra, S. *et al.*, 2004; Smith, A. L. *et al.*, 2004; Malhotra, S. *et al.*, 2005; Malhotra, S. and Lomber, S. G., 2007). One obvious advantage of these techniques is that the inactivation is fast-acting and reversible and thus should not lead to plastic reorganization (at least when used in the short term). They also allow for the immediate assessment of behavior during the inactivation, in contrast to lesion studies in which a period of postoperative recovery is often necessary, and allow the same experimental animals to be tested repeatedly in their normal and inactivated state (Lomber, S. G., 1999). Malhotra S. *et al.* (2004) have used cryogenic deactivation to study the involvement of individual auditory cortical fields in the localization behavior of the cat. The animals were trained to approach sound sources before, during, and after the unilateral inactivation of individual cortical fields. Of all the areas tested, only inactivation of areas A1, PAF, and AES resulted in auditory-specific localization deficits; the inactivation of two motor areas, 5L and 6m, produced modality-nonspecific deficits (Malhotra, S. *et al.*, 2004). Consistent with the effects of cortical lesions, deficits were restricted to the contralateral hemifield during



unilateral deactivations of A1, PAF, or AES (Malhotra, S. *et al.*, 2004) and were present in both hemifields during bilateral inactivations of A1, PAF, or AES (Malhotra, S. and Lomber, S. G., 2007). The latter deficits were observed following either homotopic (e.g., A1 on both sides) or heterotopic (e.g., A1 on the left and PAF on the right) inactivation. Despite their inability to accurately approach sound sources, the animals generally were able to orient toward the appropriate lateral hemifield, a finding consistent with lesion studies (e.g., Beitel, R. E. and Kaas, J. H., 1993). Thus, the deficits that occur during acute unilateral and bilateral inactivations of auditory cortex are similar to those that follow cortical lesions. It remains to be seen, however, whether the same inactivations would also impair the discrimination of sound-source locations.

Physiological results suggest that areas PAF and DZ might have particular importance for localization behavior (see Section 3.46.2.2). The expectation regarding PAF is supported by the reversible inactivation results (Malhotra, S. *et al.*, 2004). The inactivation of area A1 by Malhotra and colleagues did not distinguish the main (ventral) portion of A1 from DZ. Ongoing studies suggest that inactivation of ventral A1 alone increases the proportion of incorrect responses, whereas inactivation of DZ results in an increase in the number of very large errors (Malhotra, S. *et al.*, 2005). Physiological results do not predict the localization deficits resulting from AES inactivation in that AES neurons do not show especially strong spatial sensitivity. Those localization deficits might reflect in some way the projection from AES to the superior colliculus (Meredith, M. A. and Clemo, H. R., 1989).

Smith A. L. *et al.* (2004) have determined the effects of the longer-term chemical inactivations on the sound-localization behavior of ferrets. The animals were trained to walk to the source of a sound in a circular arena and then received unilateral or bilateral, slow-release implants over A1 that had been impregnated with the GABA agonist, muscimol. These implants produce tonic inhibition of neural activity in their immediate vicinity and can remain effective for up to 5 months. Although the animals with bilateral inactivations showed substantially decreased localization accuracy, particularly for shorter stimulus durations, their deficits were not complete and diminished with further testing. Again consistent with the contralateral control of spatial behavior evidenced by lesion and cryogenic inactivation studies (e.g., Jenkins, W. M. and Masterton, R. B.,

1982; Kavanagh, G. L. and Kelly, J. B., 1987; Malhotra, S. *et al.*, 2004), animals with unilateral inactivations made larger errors in the contralateral hemifield (Smith, A. L. *et al.*, 2004). There was also a marked tendency for animals to make more front/back confusions following the bilateral inactivation of A1, leading to the suggestion that A1 may be involved in the resolution of the spectral cues that distinguish to the front/back locations of sound sources. It should be noted, however, that the accuracy of the initial head-orienting response to sound source was not affected by the chemical inactivation of A1. Indeed, the animals' initial orienting responses were not only toward the appropriate lateral hemifield but within 30° of the target, suggesting a disconnection between spatial information and certain operant spatial behaviors.

#### 3.46.4.4 Summary of Effects of Cortical Inactivation

The auditory cortex plays a critical role in the sound-localization behavior of cats, dogs, ferrets, and monkeys (e.g., Neff, W. D. *et al.*, 1956; Heffner, H. E., 1978; Kavanagh, G. L. and Kelly, J. B., 1987; Heffner, H. E. and Heffner, R. S., 1990). Although the ability to perform left-right discriminations persists following bilateral lesions, the animals tend to have reduced spatial acuity (as evidenced by increased discrimination thresholds) and may in fact be performing what is for them a quasispatial task (Heffner, H. E., 1978; Heffner, H. E. and Heffner, R. S., 1990). In operant localization tasks, for example, the animals might simply be reinforced for trusting their reflexes, as these reflexes appear entirely sufficient to indicate the hemifield from which a sound originated (Beitel, R. E. and Kaas, J. H., 1993), or they might learn to associate location-dependent stimulus variations with appropriate behavioral responses (Heffner, H. E. and Heffner, R. S., 1990). This might also account for the observation that the left-right discrimination performance of cats and dogs is improved when the target is closer to the initial position of the animal (Neff, W. D. *et al.*, 1956; Heffner, H. E., 1978) – the proximity decreases the likelihood of the animal second-guessing its reflex. Neither of these strategies would require the animal to retain a normal appreciation of left or right or any other spatial quality for that matter. Within a lateral hemifield, however, the animals are completely unable to identify the location of a sound source, regardless of whether the ability is assessed using operant or reflexive methods

(Jenkins, W. M. and Masterton, R. B., 1982; Heffner, H. E. and Heffner, R. S., 1990; Beitel, R. E. and Kaas, J. H., 1993). Following unilateral lesions, localization deficits are restricted to the contralesional hemifield, indicating that each cerebral hemisphere is able to represent independently the contralateral spatial hemifield, as well as the 15–30° of the ipsilateral hemifield closest to the interaural midline (Heffner, H. E., 1997). The effects of acute and chronic inactivations of the auditory cortex are generally similar to the effects of lesions – unilateral inactivations produce contralateral deficits and bilateral inactivations bilateral deficits – but, particularly during longer-term inactivations, may be less severe and may resolve with time (Malhotra, S. *et al.*, 2004; Smith, A. L. *et al.*, 2004). Whether more extensive, chronic inactivations would result in more profound and permanent deficits remains to be seen. It is not surprising that lesions and inactivations produce deficits of differing severity, however, since cortical lesions also result in degeneration within the auditory thalamus and unlesioned cortical areas, thereby increasing the effective size of the manipulation.

### 3.46.5 Spatial Hearing and the Human Auditory Cortex

Invasive techniques for study of cortical function are only rarely applicable to humans, so the study of spatial hearing mechanisms in the human auditory cortex has emphasized different experimental techniques than are favored in animals. Classical studies in humans relied on sensory testing following cortical lesions due to stroke or trauma. With the advent of structural imaging techniques, lesion studies have been enhanced by the ability to better delineate the extents of lesions. Functional imaging studies employing positron emission tomography (PET), functional magnetic resonance imagery (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG) have only recently been applied to studies of spatial hearing in humans. We will begin by considering the functional imaging results, then will compare those results with results from lesion studies. We will focus on unimodal auditory areas of the temporal lobe; the large literature covering spatial neglect and integration of auditory signals into multimodal areas of the parietal and prefrontal cortex is beyond the scope of this chapter.

The prevailing framework for much recent functional imaging work is the hypothesis that the auditory

system possesses segregated what and where pathways analogous to those described in the visual system (Rauschecker, J. P. and Tian, B., 2000; Clarke, S. *et al.*, 2005). Under this model, spatially sensitive and stimulus-feature-sensitive cortical fields are thought to lie posterior and anterior, respectively, to primary auditory regions. Despite methodological differences among studies, a common finding in functional imaging studies is that posterior areas, particularly the planum temporale, are indeed preferentially stimulated by spatially varying or moving stimuli.

Preferential activation in the planum temporale has been found using fMRI and headphone presentation of ear-canal recordings of moving, free-field, amplitude-modulated noise stimuli (Pavani, F. *et al.*, 2002). In a PET imaging study, Zatorre R. J. *et al.* (2002) presented stimuli from an array of small loudspeakers surrounding the listener's head. Regardless of stimulus condition, stimuli produced activation within the superior temporal gyrus, the transverse temporal gyrus (Heschl's gyrus), and posteriorly in the planum temporale. When the source was identical on each trial, they found no cortical areas exhibiting increased activity to more spatially diverse stimulus locations, but when the stimulus varied both spatially and spectrotemporally from trial to trial, foci of activity correlated with spatial diversity were found bilaterally in posterior planum temporale. Similar findings are reported by Warren J. D. *et al.* (2002) using PET and fMRI and are interpreted by the authors as evidence that the planum temporale is involved in the separation of space-related and object-related features of stimuli. Smith A. L. *et al.* (2004) also found activation of that region, but their stimuli were unmodulated wideband noise bursts, which lacked the spectrotemporal variation found necessary by Zatorre R. J. *et al.* (2002).

Using MEG, Fujiki N. *et al.* (2002) recorded auditory mismatch fields for spatial oddball stimuli differing in azimuth or elevation from a standard and found by source analysis that stronger responses to the deviant stimuli were located posterior to those of the standards. Tata M. S. and Ward L. M. (2005), using EEG and electrical source analysis, found that spatial attention can modulate activity near the temporoparietal junction, also posterior to primary auditory areas. All of these results are at least consistent with the existence of a posterior where pathway, although some implicate the planum temporale in both spatial and nonspatial aspects of auditory processing. Hart H. C. *et al.* (2004), using fMRI, observed more

activity in the medial planum temporale for moving stimuli and more activity in the lateral planum temporale for frequency-modulated stimuli, which is suggestive of segregated what and where processing in adjacent posterior areas. In humans and other mammals possessing pinnae, information about sound-source location in the vertical plane is carried by the spectral cues generated by the direction-dependent filtering of the outer ear, but the majority of functional imaging studies have used stimuli varying only in azimuth or in the binaural interaural time- and amplitude-difference cues. Two exceptions to this are the studies by Pavani F. *et al.* (2002; fMRI) and Fujiki N. *et al.* (2002; MEG), both of which employed virtual auditory space stimuli changing location in either azimuth or elevation. The results of both studies suggest activation of similar posterior areas by location changes in either azimuth or elevation. Fujiki N. *et al.* (2002) additionally suggest, however, that monaural spectral cues affect activity more in the right hemisphere than in the left, both in terms of the level and location of activity.

Results from animal studies using electrophysiological (discussed in Sections 3.46.2 and 3.46.3) and lesion (see Section 3.46.4) techniques lead to the conclusion that the representation of each half of auditory space lies primarily in the contralateral cortical hemisphere. A contralateral representation is seen less consistently in human lesion studies (reviewed by Zattore, R. J. and Penhune, V. B., 2001). Substantial individual differences in laterality are seen, due in part to differing etiologies of cortical damage, to the difficulty exactly specifying the lesioned areas, and to possible functional reorganization following cortical damage. Nevertheless, recent well-controlled studies suggest right-hemisphere dominance for auditory spatial representation in humans. Using patients with well-characterized lesions of superior temporal cortex, Zattore R. J. and Penhune V. B. (2001) found that right temporal lobe damage was associated with localization deficits throughout auditory space, whereas similar damage on the left generally resulted in little or no reduction in localization performance. Also, that study showed disturbances in localization in patients with right temporal lobe lesions well anterior to any primary auditory areas. That finding is of course at odds with the consistent identification in imaging studies of posterior, but not anterior, areas as part of the putative where pathway.

### 3.46.6 Summary and Future Directions

All available data point to the necessity of intact auditory cortex for normal sound localization. The results from studies in experimental animals support the view of a contralateral cortical representation of auditory space in which most individual cortical neurons respond to sounds throughout half or more of auditory space and in which the representation of individual points in auditory space is distributed across widespread neural populations. There is no evidence that any particular cortical areas represent sound-source locations in a way that is dramatically different than in other areas, although some cortical areas seem to show quantitatively stronger spatial sensitivity or enhanced transmission of location-related information (i.e., PAF and DZ in the cat; possibly the caudal belt areas in the monkey). Sound localization by cortical neurons with accuracy comparable to behavioral performance clearly requires the coordinated activity of populations of neurons, likely involving the differential activation of neural populations within each cortical hemisphere tuned to left and right halves of auditory space.

In humans, it is clear that information about sound-source information must reach multimodal areas for spatial processing in the parietal lobe, so in that sense it is clear that there is a posterior-dorsal where stream. Whether that implies a hierarchical organization for spatial processing within the temporal lobe auditory areas remains unresolved, particularly in light of data showing localization deficits resulting from lesions in anterior auditory areas. In contrast to experimental animals, humans seem to show pronounced right-hemisphere dominance for sound localization.

The majority of physiological studies of spatial hearing have been conducted in anesthetized conditions. The few studies in awake animals show greater diversity of spatial sensitivity and greater diversity of neural response patterns than is observed in anesthetized conditions. Future studies must further explore spatial representation in awake conditions, extending studies beyond area A1 into the cortical belt areas. Also, the influence of the behavioral/attentional state of the animal is a key variable that has been largely unexplored. Most studies have used sounds presented in anechoic (or virtual anechoic) conditions. There is a need for more work on mechanisms of



sound localization in realistic environments in which most direct sounds are accompanied by later-arriving reflected sounds.

The most detailed studies of sound localization in the auditory cortex at the single-neuron level have been conducted in nonprimates, particularly in cats. Recent advances in functional imaging have begun to yield new understanding of auditory spatial representation at a more macroscopic level in the human brain. Research is needed on possible homologies between cortical areas in carnivore and primate brains so that insights from the studies in carnivores can be applied more readily toward understanding of mechanisms of spatial perception in humans.

Finally, most work on spatial hearing has focused on identification of the locations of sounds. That is an appropriate starting point because sound-source locations are readily quantified and because many experimental animals show accurate sound-localization behavior. Aspects of spatial hearing that arguably are more relevant to humans, however, are the ability to group together sounds that originate from a particular source and the ability to segregate sounds that originate from different sources. We are optimistic that future physiological studies, informed by psychophysical research, will demonstrate cortical mechanisms for grouping and segregation of sounds in complex acoustic environments.

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### Further Reading

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