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Subunits of the primary auditory cortex (AI) of the cat distinguished by segregated thalamic input sources and functional specialization

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SUBUNITS OF THE PRIMARY AUDITORY CORTEX (AI) OF THE CAT DISTINGUISHED BY SEGREGATED THALAMIC INPUT SOURCES AND FUNCTIONAL SPECIALIZATION

by

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DISSERTATION

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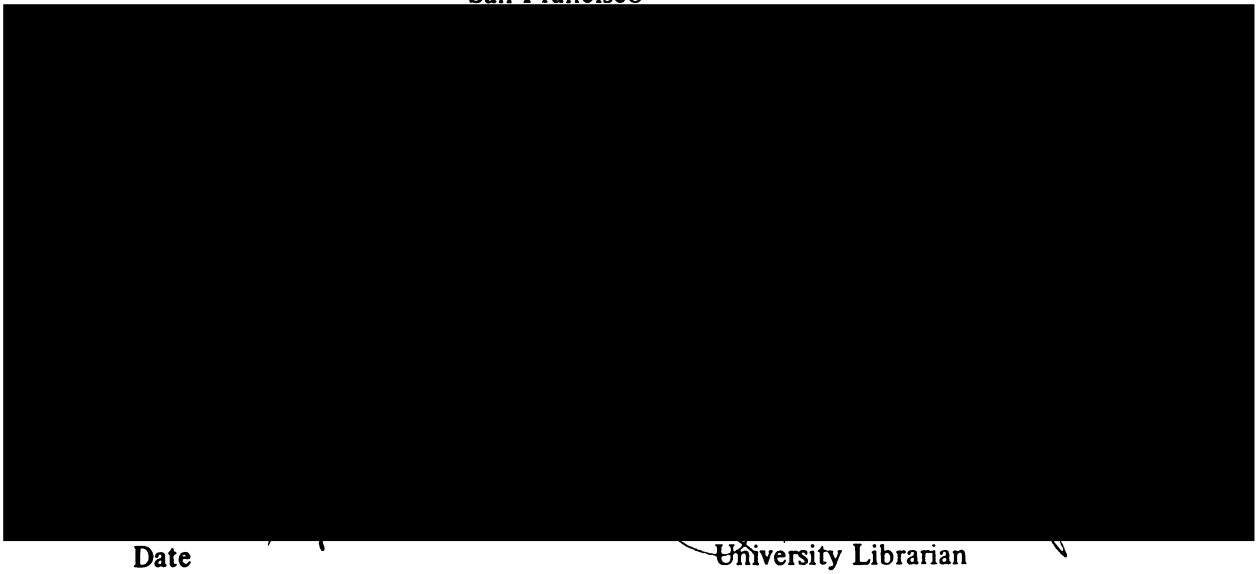
GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA

San Francisco



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I am grateful for the continuing support of my wife, Sylvia. She has shown tremendous patience, and even helped with some of the histology.

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ABSTRACT

The rostrocaudal dimension of the cat's primary auditory cortex (AI) contains an orderly representation of the audible frequency range (i.e., a topographic representation of the cochlear sensory epithelium). Three series of anatomical and physiological experiments have addressed the problem of organization within the orthogonal, isofrequency dimension. Binaural response-specific subdivisions have been defined, the sensitivity of neurons in each subdivision to sound location has been characterized, and a spatial segregation of the thalamic input sources to the cortical subdivisions has been demonstrated.

The primary field was mapped with microelectrodes, using diotic tonal stimulation. Excitatory/excitatory (EE) neurons were segregated from excitatory/inhibitory neurons within the plane of AI. Binaural response-specific regions (binaural interaction bands) were found to be elongated rostrocaudally. Multiple alternating EE and EI bands subdivided the isofrequency dimension of AI.

The sensitivity of neurons in AI to sound location was measured by recording from single neurons while presenting tonal stimuli in a free sound field. Within the population of neurons that were sensitive to any particular frequency range, approximately half of the neurons were insensitive to sound location, and the other half had

delimitable threshold receptive fields. Location sensitive neurons that responded to high frequency tones all had receptive fields that were aligned with the axis of greatest sensitivity of the contralateral pinna. From the response properties of units distinguished by sensitivity to sound location, it is apparent that the location sensitive and location insensitive units correspond to EI and EE units, respectively.

The sources of input to binaural bands were characterized by mapping the borders of bands with microelectrodes, then introducing multiple injections of retrograde tracers into different bands. Within the ventral division (V) of the medial geniculate body, the sources of input to EE bands were strictly segregated from sources to input to EI bands. All EI bands apparently receive convergent projections from three discrete regions in V, while areas within the single EE-projecting region project preferentially to particular EE bands. The EE- and EI-projecting neurons in V occupy alternating slabs which are oriented approximately horizontally.

These observations suggest that the higher frequency representations in AI and the ventral division of the medial geniculate body may be regarded as assemblies of spatially discrete, functionally distinguishable subunits. The data suggest a model of function organization in the auditory forebrain in which EI bands confer information relevant to

sound location upon the products of non-spatial, perhaps spectral, analysis that is carried out within EE bands.

LIST OF ILLUSTRATIONS

CHAPTER ONE

BINAURAL RESPONSE-SPECIFIC BANDS IN PRIMARY AUDITORY CORTEX (AI) OF THE CAT: Topographical Organization Orthogonal Isofrequency Contours

ABSTRACT

The spatial distribution of neurons with different binaural resonse properties has been studied within the three dimensions of the primary auditory cortex (AI) in the cat. Using diotic stimulation, 92% of neurons encountered could be classified into either the excitatory/excitatory (EE) or excitatory/inhibitory (EI) interaction class. In nearly all of almost 800 penetrations introduced along radial axes, all neurons encountered along a given penetration were of the same binaural response class. Neurons of different binaural interaction classes were spatially segregated within the plane of the cortex. Electrode penetration made parallel to isofrequency contours traversed the mediolateral extent of AI through the middle layers of the cortex. A sharp segregation of units by binaural response class was observed in these penetrations, i.e., sequences of neurons that were all of the EE class alternated with sequences of EI neurons. The regions of uniform response to binaural stimulation formed radially organized topographical subunits that were elongated along the rostrocaudal dimension of AI. These binaural interaction bands intersect the lines of re-representation of the cochlear sensory epithelium ('isofrequency contours') and, thus, create subdivisions of AI that each contain a representation of the entire audible frequency domain. The implications of these results for the concept of AI as a unitary element in auditory processing are discussed.

INTRODUCTION

The primary auditory cortex (AI) of the cat contains a systematic representation of the cochlear sensory epithelium (Woolsey and Walzl, '42; Merzenich et al., '75). The apical cochlea (low frequencies) is represented at the caudal aspect of the field, and the basal cochlea (high frequencies) is represented rostrally. A striking feature of this topographical organization is that the one dimension of organization of the cochlea is expanded ("re-represented") in the mediolateral dimension of AI. Thus, any given point along the basilar membrane (any given frequency) is represented along a medio-laterally-oriented cortical line (an "isofrequency contour"; see Tunturi, '50 and Merzenich et al. ,'75). The functional significance of the re-representation of points of the cochlea along lines in the cortex has remained obscure.

Tunturi ('52) first addressed the question of the functional significance of this re-representation of the cochlear sensory epithelium in AI. He found in the auditory cortex of the dog that while the characteristic frequencies and thresholds for contralaterally evoked cortical surface potentials are constant all along any given isofrequency contour, the threshold for ipsilateral stimulation increases systematically with lateral shifts along isofrequency contours. Tunturi speculated that a differential

representation of the two ears (encoding, in some way, sound location) might form a basis for topographic organization of the auditory cortex orthogonal to the frequency organization. However, studies of AI in the cat using binaural stimuli and single unit recording techniques have not revealed any mediolateral spatial progression of ipsilateral thresholds (Hall and Goldstein, '68; Brugge et al., '69; Abeles and Goldstein, '70).

These and other single unit studies in AI in the cat have revealed that neurons in this field fall within a few binauralresponse specific classes. The responses of cortical neurons to contralateral stimulation commonly are facilitated (excitatory-excitatory, or "EE" neurons) or inhibited (excitatory-inhibitatory, or "EI" neurons) by simultaneous stimulation of the ipsilateral ear (Hall and Goldstein, '68; Brugge et al., '69). Some neurons are sensitive to the time differences between the stimuli to the two ears (Brugge et al., '69). Apparently, by virtue of their EE or EI interaural delay sensitivity, some cortical neurons are sensitive to the spatial location or direction of motion of a sound source (Eisenman, '74; Sovijari and Hyvarinen, '74).

Abeles and Goldstein ('70) first reported evidence indication that neurons located within the same radial chain of neurons extending through the cortex are all of a single

binaural class, i.e., that there are binaural "columns" in AI. Imig and Adrian ('77) subsequently studied the spatial distribution of neurons of different binaural interaction types in more detail.

In their study, most of the units encountered were categorized into one of two classes, based on their responses to binaural stimuli: a) summation units were driven more effectively by both ears than by either ear alone; b) suppression units responded best to stimulation of only one ear (i.e., the other ear inhibited this driven response). Units in the same binaural interaction class were found to be clustered together in spatial blocks that extended throughout the depth of the cortex and were elaborated for variable distances in the plane of the cortex. These spatial blocks were referred to as "binaural interaction columns". In one illustrated case, a "suppression column" formed a band elongated along a rostrocaudal axis and crossing the axis of isofrequency contours. The areas that were mapped in other illustrated cases were too small to indicate whether or not this elongated shape is characteristic of binaural interaction columns.

How are neurons of different binaural response classes arrayed relative to the frequency representation in AI? Is the segregation of different types of binaural

neurons similar in all regions of the frequency range? Could the topographical distribution of neurons of different binaural response types constitute a basis for topographical organization orthogonal to the representation of sound frequency? These questions must be addressed as the obvious next step in understanding the functional organization of the primary auditory cortex.

In the series of experiments reported here, we have determined the distribution in AI of neurons of different binaural response types by making numerous closely-spaced radial electrode penetrations oriented parallel to isofrequency contours. Our results reveal a pattern of repeating binaural response-specific bands that intersect the pattern of isofrequency contours. Some of the implications of these results relative to the functional units of the primary auditory cortical field will be discussed. A preliminary report of this work has appeared elsewhere (Middlebrooks et al., '78).

METHODS

Animal Preparation

The results reported here are based on experiments conducted in 32 adult cats. Anesthesia was induced prior to surgery with intraperitoneal injections of sodium pentobarbital (40 mg/kg). A surgical level of anesthesia was maintained throughout the experiment with supplemental doses of sodium pentobarbital (I.V.) or ketamine hydrochloride (I.M.). A venous cannula and an endotracheal tube were inserted, and a slow, sustaining infusion of lactated Ringer's solution was begun. Individual experiments lasted 16-24 hours.

The animal's head was supported rigidly in a head holder designed to leave the ear canals unobstructed. Pinnae were resected bilaterally and sound delivery tubes were sealed into the acoustic meati. The temporal muscle was retracted on one side and a craniotomy was made to expose the dorsal tip of the middle ectosylvian gyrus. A well was constructed around the skull opening with dental impression wax and was filled with warm mineral oil or isotonic saline. The dura was resected, and a magnified photograph was made of the cortical surface. The photograph was used to record the sites of all electrode penetrations relative to features of the surface vasculature.

Sound Stimulation and Unit Recording

Cats were stimulated with pure tone bursts that were 200 msec in duration, presented one per second, with rise and fall times of 10 msec. The tones were generated with an audio oscillator (General Radio, model 1309A), shaped with a bank of electronic timers and switches, and passed into two attenuators (Hewlett Packard, model 350D). Thus, the intensity of otherwise identical stimuli to each ear could be controlled independently. The electronic signals were delivered to audiometric drivers (Telex, model 61470) enclosed in small chambers that were sealed to the sound delivery tubes. The tubes, in turn, were sealed into the acoustic meati.

The activity of single units and of small clusters of units was recorded with glass-insulated platinum-iridium or tungsten electrodes (impedances at 1 kHz were 1.5 to 3.0 megohms). Neural activity was amplified, band-pass filtered, and monitored on an oscilloscope and an audio monitor. The electrodes were advanced with a hydraulic microdrive (Kopf) which itself was positioned with use of a micromanipulator.

Two types of electrode penetrations were used in this series of experiments. In some experiments, the electrodes were advanced through the cortex along axes

perpendicular to the pia, i.e., parallel to the radial cell columns; this type of penetration will be referred to as a "radial penetration". In other experiments, the electrodes were oriented approximately parallel to the plane of the pia and in the frontal plane (i.e., roughly parallel to the isofrequency contours); these penetrations are referred to henceforth as "tangential penetrations". The locations of all tangential penetrations were marked in the brains by placing electrolytic lesions at their point of termination (and usually at one or two other points) in each penetration.

The data indicating relative frequencies of occurence of different types of binaural responses was compiled only from tangential electrode penetrations, and represents the relative lengths along electrode tracks that were occupied by neurons of each class. This protocol estimates the relative areas of AI containing each class of binaural neuron.

Sampling Protocol

The data presented in this report are descriptive for recordings from the primary auditory field (AI) of the cat. The location of AI can be estimated only crudely from the sulcal pattern on the temporal cortex (Rose, '49). Merzenich et al. ('75) have shown that the exact position of

the field relative to surface landmarks is quite variable between individual cats, and that it must be defined operationally in each case. In our experiments, AI was identified by the sharp frequency specifically of its units and low thresholds (marking its dorsal and ventral borders; see Merzenich et al., '75) and by the caudal-to-rostral increase in the "characteristic frequency" (CF) of units (caudally and rostrally bordering fields have reverse frequency sequences; see Knight, '77; Reale et al. '77). On these bases, we were confident that all of the recordings reported here were from AI.

The data in these experiments were obtained largely from neurons with CFs in the range of 3 to 20 kHz. This sample space was chosen to avoid the range of low frequencies in which interaural time differences are important (Brugge et al., '69), to avoid recording from neurons located on the banks of the posterior ectocylvian sulcus (in which units with lower CFs were usually predominant), and to take advantage of the frequency range over which our sound stimulation equipment had a relatively wide dynamic range.

Under the condition of anesthesia used, we observed that driven unit activity was not evoked by tonal stimulation when the electrode tip was located in the superficial layers of the cortex. Thus, the data reported

here refers to activity recorded from cortical depths greater than approximately 500 microns.

All determinations of binaural responses were made with characteristic frequency tones. The CF in these experiments was defined as the frequency of the least intense stimulus that would evoke a neural response detectable by the investigator on the oscilloscope or audio monitor. Previous experiments (e.g., Brugge et al., '69) have shown that many neurons display quite non-linear and non-monotonic relationships between stimulus intensity and spike rate at stimulus levels well above threshold intensity. To avoid complications introduced by these characteristics of intensity functions, most determinations of responses were made at intensities within 20 dB of threshold.

Evaluation of Binaural Responses

The objective of these experiments was to observe the topographical distribution of neurons of different binaural response classes. Thus, we assigned responses to one of a small number of general binaural classes rather than testing a wide variety of binaural stimulus configurations. The binaural interaction, in most cases, was determined by noting how the response to near-threshold stimulation of the most sensitive ear was affected by

stimulation of the other ear. The latter procedure was followed in all cases, except when a response could be evoked only by simultaneous stimulation of both ears. We have chosen to use a nomenclature similar to that commonly used in studies of auditory structures of the brainstem (Goldberg and Brown, '69; Aitkin and Webster, '72) in referring to the types of binaural interaction observed. Thus, "excitatory/excitatory" neurons (EE) were those excited monaurally by either ear and displaying facilitation in response to a binaural stimulus. "Excitatory/inhibitory" neurons were excited monaurally by the contralateral ear, not excited by monaural stimulation of the ipsilateral ear, and displayed a weaker response to binaural stimulation than to contralateral stimulation alone. "Inhibitory/excitatory" neurons (IE) were driven monaurally by the ipsilateral ear and inhibited by the contralateral ear. A fourth class of responses, "EO", included the neurons that were responsive to monaural stimulation of either ear but whose binaural response was equal to the responses to the most effective monaural stimulus ("occlusion" neurons; see Imig and Adrian, '77).

Histological Procedures

In all experiments in which tangential penetrations were used, the electrode tracks were reconstructed from histological sections. At the end of each of these

experiments, the cat was sacrified with a lethal dose of barbituate, the craniotomy enlarged and the head immersed in a large volume of phosphate buffered 4% paraformaldehyde. Several days thereafter, the brain was removed from the cranium and further fixed in additional buffered paraformaldehyde. Fixed brains were rinsed, passed through buffered sucrose solutions, and cut frozen (50 micron sections). Brains were cut in a near-frontal plane, parallel to tangential recording penetrations.

Brain sections were mounted on gelatinized slides and stained with cresyl violet. Tangential penetrations were reconstructed using a projection microscope. A NOVA 1220 computer was used to plot the locations of all recordings along tangential penetrations, using the measurements from the histological reconstructions and the distances from the electrode microdrive for positional references. The location of the terminal lesion of each penetration was projected along the line of the radial cell columns to the pial surface, and the distance between this point and the starting point of the penetration was used to scale a projection of each track onto the pial surface. In this way, all tracks were projected onto a single plane and, at the same time, the data was adjusted for tissue shrinkage and for the angle of the electrode relative to the pial surface.

RESULTS

A. Radial Organization of Binaural Responses

In initial experiments, unit responses were recorded at several depths along each radial penetration through the thickness of the cortex. In the superficial 500 microns of a typical radial penetration, graded cortical evoked potentials were recorded in response to the presentation of adequate tonal stimuli. Within AI, these evoked potentials were tuned sharply with regard to stimulus frequency, and the CF for this intracortical evoked response was approximately the same as that determined for unit responses observed in the underlying layers of the cortex. Surprisingly, the cortical evoked response usually displayed binatural summation regardless of the binaural response type of neurons encountered later in the penetration. Action potential seldom were recorded in these superficial layers of the cortex; neurons only responsed to stimuli of moderate or high level. (This lack of responsiveness was presumable due to the use of barbituate and/or ketamine anesthesia, as the superficial layers of the cortex are active in the unanesthetized preparation, e.g., Abeles and Goldstein, '70.) As the electrode tip was advanced deeper into the cortex (into layers 3-4) neurons were strongly driven by low level contralateral monaural stimuli of appropriate frequency.

The use of stimuli of intensities near the contralateral threshold facilitated the categorization of binaural responses. Typically, we would adjust the intensity of the contralateral stimulus until a unit or small cluster of units was discharging a few spikes per presentation (approximately 10-20 dB above threshold), then would add an ipsilateral stimulus. If the ipsilateral stimulus facilitated the response, we often found that the threshold for simultaneous stimulus of the two ears was significantly lower than that for a monaural contralateral stimulus: such behavior indicated an EE response. A complete cessation of firing accompanying the addition of the ipsilateral stimulus indicated that the cell or cluster was of the EI class. The ipsilateral intensity was sometimes raised as much as 10 dB louder than the contralateral stimulus in order to confirm the identification of an EI response. By adjusting the interaural intensity difference in this way, it was possible to make unequivocal determinations of response class on the basis of the amplitude of the response judged from the activity displayed on the oscilloscope and audio monitor.

A conspicuous feature of the radial electrode penetrations was that all units encountered along a given radial electrode penetration tended to have the same type of response to binaural stimulation. Thus, AI is radially (or

vertically) organized with regard to binaural interaction. In five initial cases comprising 73 radial penetrations (average of 3.3 recordings per penetration), 43 penetrations had EE responses and no EI responses, 24 had EI responses and no EE responses, and only 6 of the penetrations had both EE and EI responses. In five of the six penetrations in which more than one type of binaural responses was recorded during a given penetration, the type of response changed only once along the electrode track. In the sixth, a recording of one type of response was preceded and followd by recordings of another response type. Although histological confirmation of the exact angle of the radial tracks were not obtained, we presume that in these few cases the changes in the type of binaural response along a penetration were due to deviations of the electrode array from precisely radial trajectories.

B. Topographical Distribution of Binaural Responses

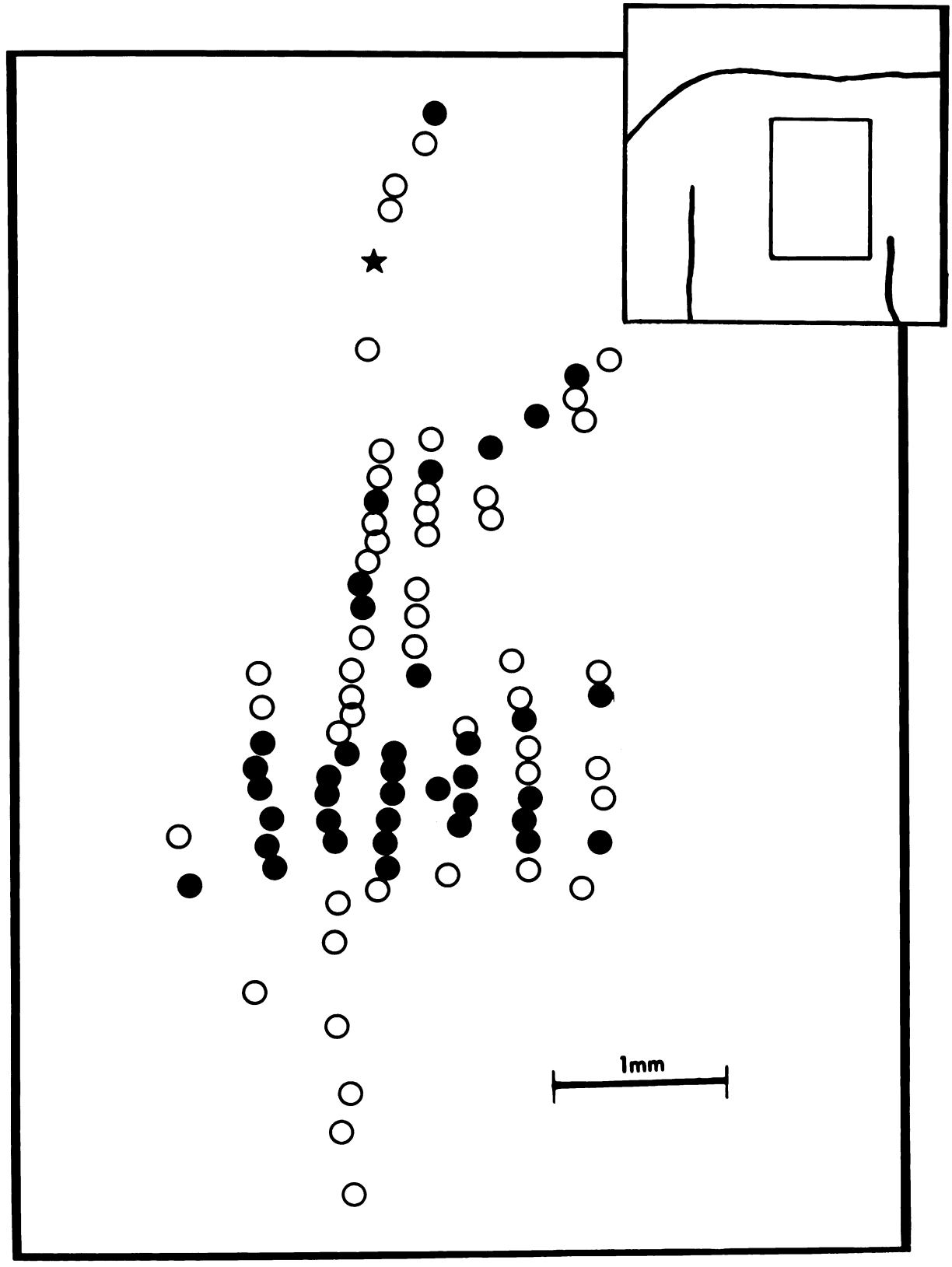
Because the responses of neurons in AI to binaural stimulation are relatively constant along any radial electrode penetration, it is sufficient to record at only one or two depths at each penetration site in order to determine the binaural responses of all neurons at that location. In this way, AI was surveyed in nine cats, with 34 to 150 closely spaced radial electrode penetrations in each animal. The locations of all penetrations were

recorded on photographs of the cortical surfaces, using the surface vasculature for positional references. The produce of such an experiment is a map of a region of AI showing the binaural interaction class of neurons at each point where a penetration was made.

In maps of binaural responses in AI, there was a clear topographical segregation of EE and EI responses. An example of such a map is shown in Figure 1. In this type of map, each circle indicates the binaural response class of all units located at a given point in the cortex. Filled circles represent EI responses, and open circles represent EE and EO responses. In this particular map (fig. 1), there is a large area in the ventral half of the field in which only EI units were encountered. This group of EI units appeared to form a broad band, approximately 1mm across at its widest point, stretching along a rostrocaudal axis. It appeared to divide into two narrower bands at its caudal end. A distinct, narrow line of EI units is seen in the dorsal half of this field.

The elongation of EE and EI regions along a rostrocaudal axis was a consistent feature of these binaural response maps. In the case shown in figure 2, a region of EI units was traced out in the ventral aspect of AI. Like the region in figure 1 described above, this region took the form of a band, elongated along a rostrocaudal axis. In

Figure 1. Map of responses of neurons in AI in the left hemisphere. Plane of the paper represents all planes parallel to the pial surface. Each circle represents the response class of units encountered in one radial electrode penetration perpendicular to the cortical surface. Filled circles represent columns of EI responses (see text for definitions). Open circles represent EE and EO responses. Star represents a column of IE responses. CF's ranged from 5 to 13 kHz (increasing caudal to rostral). Insert: location of sampled area of AI in temporal cortex of left hemisphere.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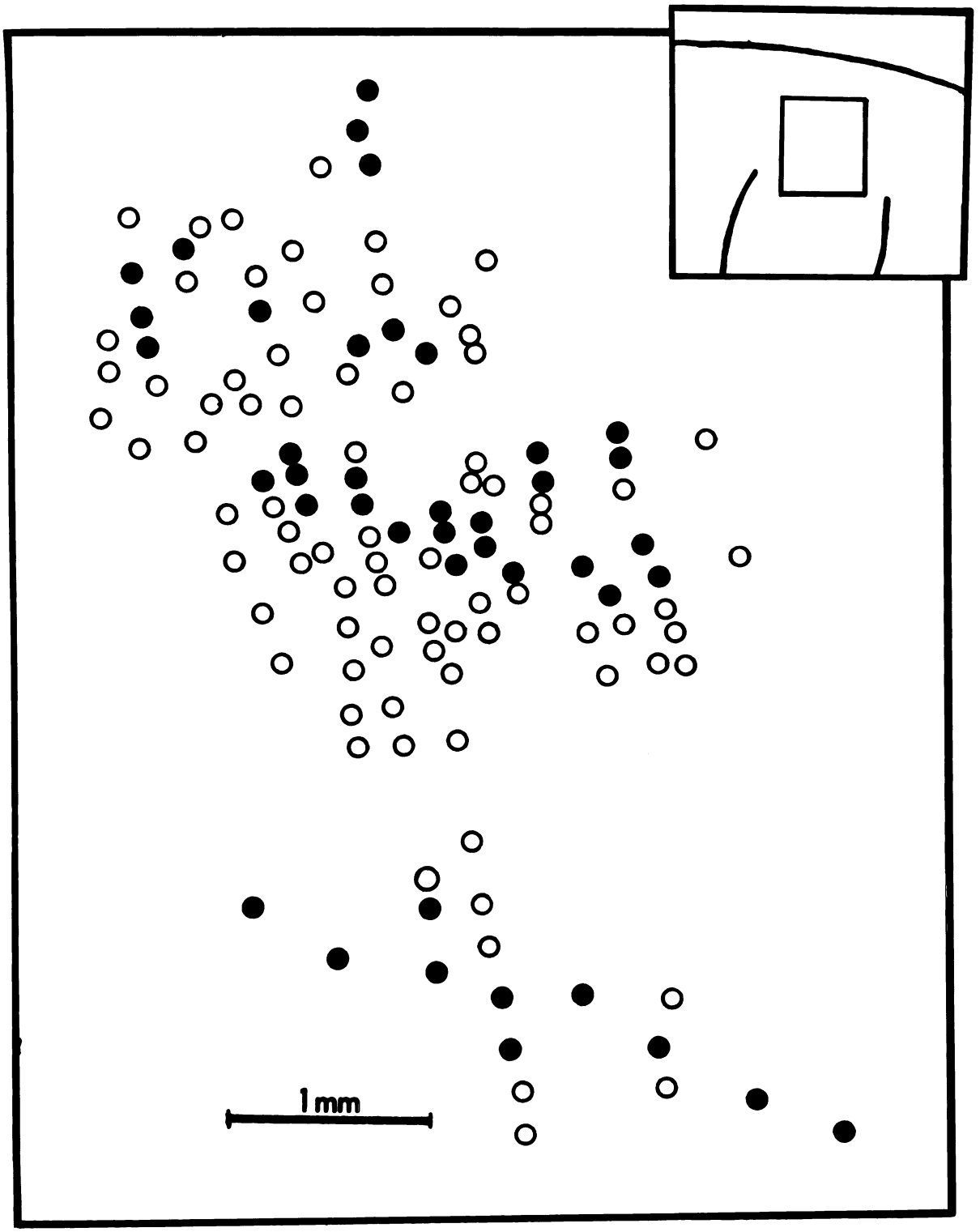
this case, there was an indication of two additional EI bands, located more dorsally and separated by bands of EE responses. The region of AI sampled in the case shown in figure 2 encompassed the representation of frequencies from 4 to 15 kHz.

C. Distribution of Binaural Responses along Isofrequency Contours The results of experiments in which AI was mapped with radial electrode penetrations suggested that regions of EE responses and regions of EI responses form patterns of alternating bands oriented orthogonal to the axis of isofrequency contours. However, the method of surveying a cortical field with multiple radial electrode penetrations has several fundamental limitations. It was difficult to make a sufficiently large number of penetrations in the auditory cortex of one cat to map a large portion of AI with adequate resolution. In addition, the surface blood vessels presented obstacles to the placement of penetrations. In the case shown in figure 2, an attempt was made to define the extent of a band of EI units in the ventral half of the field. In this case, ten points were studied in an EI region, but there was not time in the experiment to make the additional penetrations necessary to determine the width of this EI band.

To circumvent these limitations, tangential electrode penetrations were made in a plane through the

Figure 2. Map of responses in AI. Same symbols as in fig. 1. CF's ranged from 4 to 15 kHz.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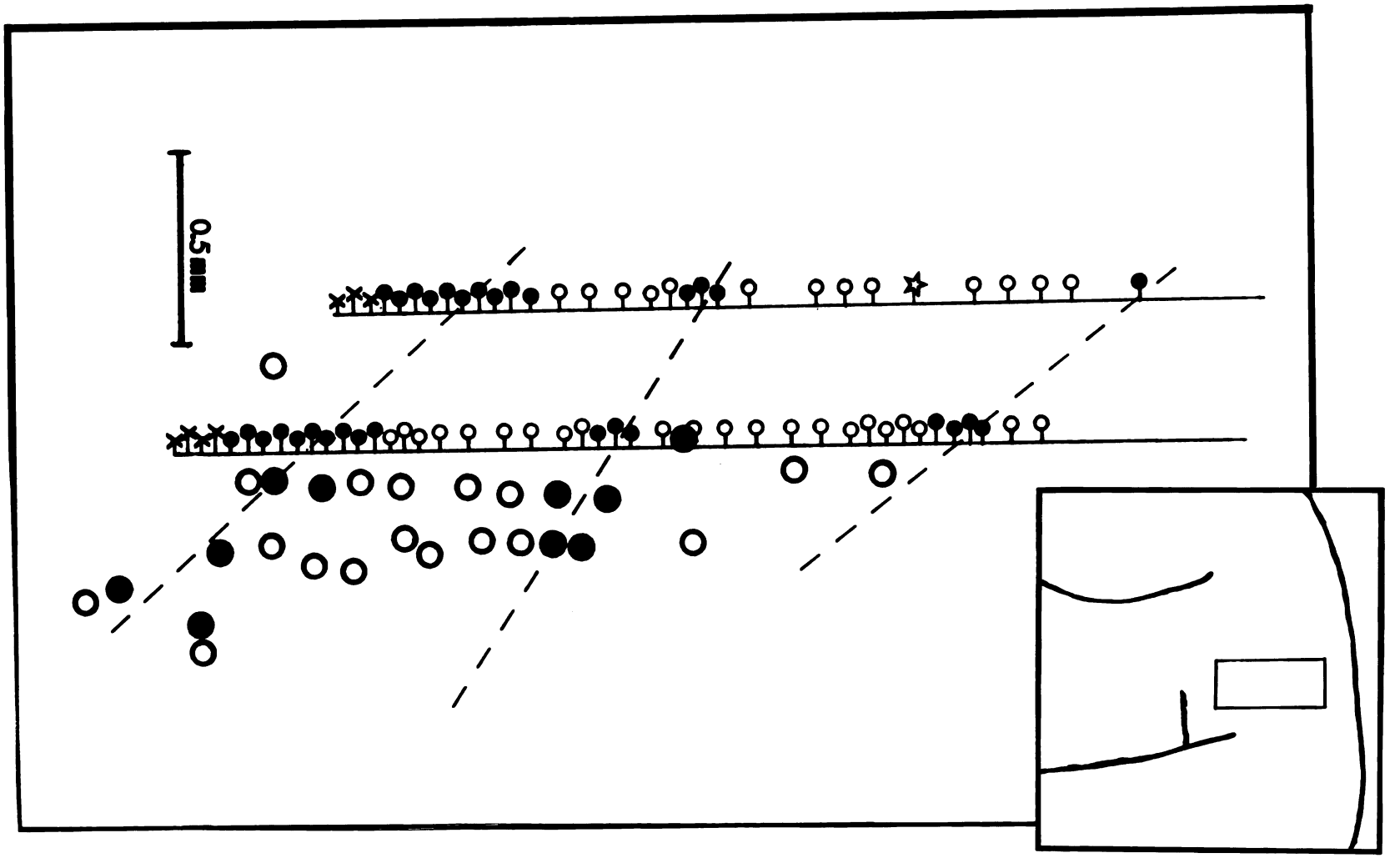
middle layers of the cortex, oriented roughly parallel to isofrequency contours. The electrode was advanced in steps of 50 to 100 microns and the responses of single neurons and clusters of neurons were recorded after each advance. This method of recording along long penetrations through the middle cortical layers made it possible to determine the binaural responses of units in large areas of AI with resolution limited only by the step length of the electrode advances. In addition, by orienting the penetrations along axes roughly parallel to isofrequency contours the variable of characteristic frequency was constrained so that any changes in responses that were observed along a given penetration were independent of stimulus frequency.

Along penetrations that crossed the width of AI, long sequences of units were frequently observed that all had the same binaural response properties. Sharp transitions occurred between different response-specific regions. In the early experiments. regions of EI responses were crossed with electrode step lengths of 50 microns. However, after it was clear from these recordings that these EI regions contained only EI neurons, the step length was increased to 100 microns. In these horizontal penetrations, EE regions were from 200 to 3400 microns wide, and sequences of EI neurons ranged from 100 to 2000 microns in width across AI.

Figure 3. Map of AI in left hemisphere. Same notation as in fig. 1. Large circles represent responses encountered along radial electrode penetrations. Two lines of smaller circles represent reconstructions of tangential penetrations. Crosses indicate sites where CF and binaural interaction class could not be determined, i.e., recordings from outside of AI. Interrupted lines suggest the orientation of EI bands.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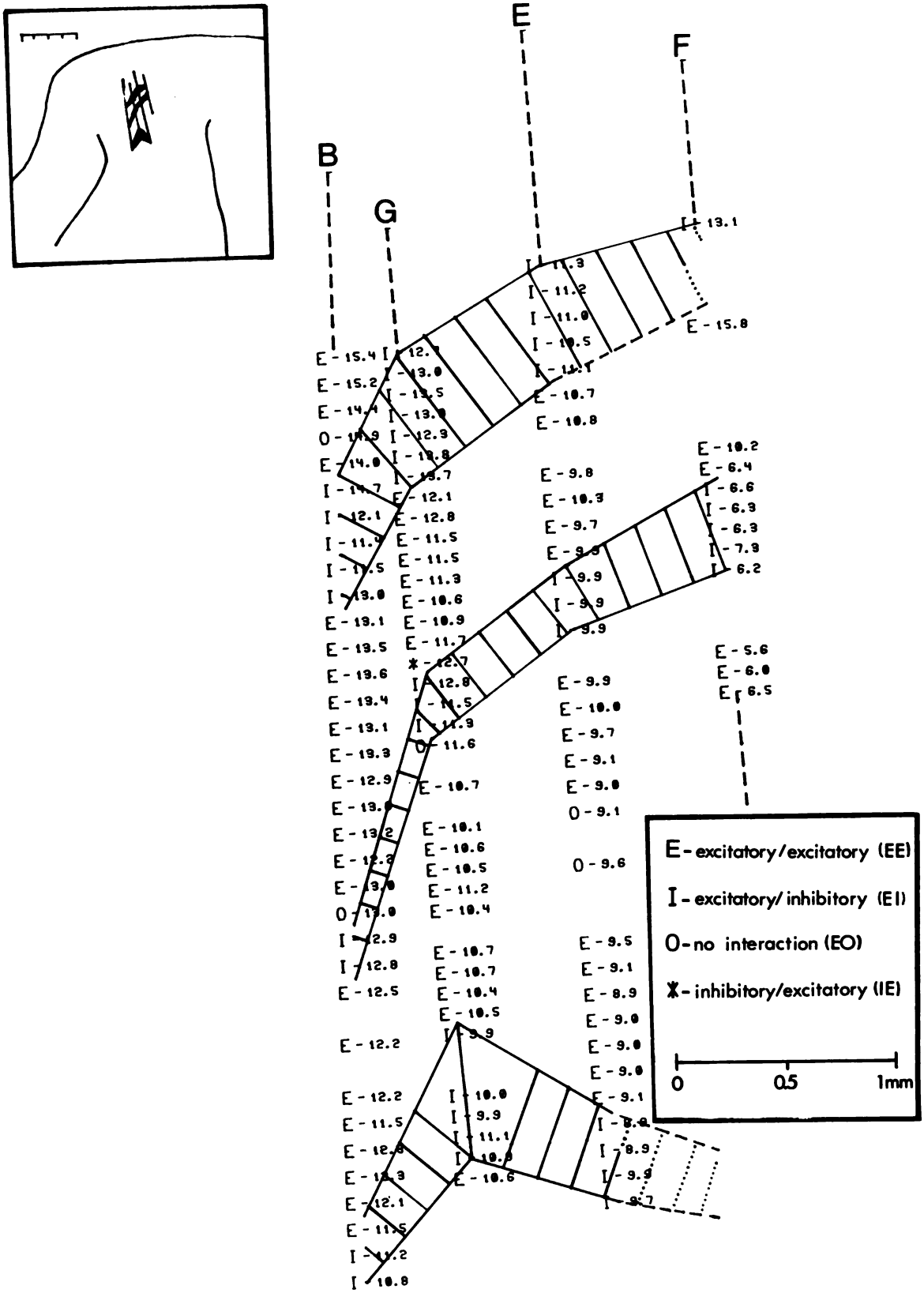
In case 77-126, illustrated in figure 3, 34 radial penetrations were introduced into the sector of AI representing frequencies from 8 to 13 kHz. Two long tangential penetrations were made through this area. The paths taken by these two penetrations are represented by the two lines that traverse the figure. Response properties are represented by the columns of smaller circles. There is a clear correspondence between the distribution of binaural interaction classes revealed by the two different sampling methods. It is noteworthy that there is a region of EI neurons in the dorsal aspect of the field that was detected with tangential penetrations but was missed in the vertical penetration map. This demonstrates a limitation of the latter method. This particular map indicates the presence of two (possibly three) bands of EI neurons oriented along the rostrocaudal axis.

A map based on four tangential electrode penetrations across the width of AI is shown in figure 4. In this case, three of the penetrations each encountered three sequences of EI responses. These sequences of EI alternated with continuous sequences of EE units. The caudal-most penetration encountered only two sequences of EI units. This penetration was placed too superficially, so that the tip advanced into the molecular layer of the cortex before the entire width of the field was traversed. Along

Figure 4. Map of AI in left hemisphere. Lines of letters and numbers represent classes of responses recorded along four electrode penetrations that crossed the width of EI through the middle cortical layers. EI bands are indicated with cross-hatching. Numbers correspond to CF (in kHz). Insert: location of sampled area of AI in temporal cortex of left hemisphere.

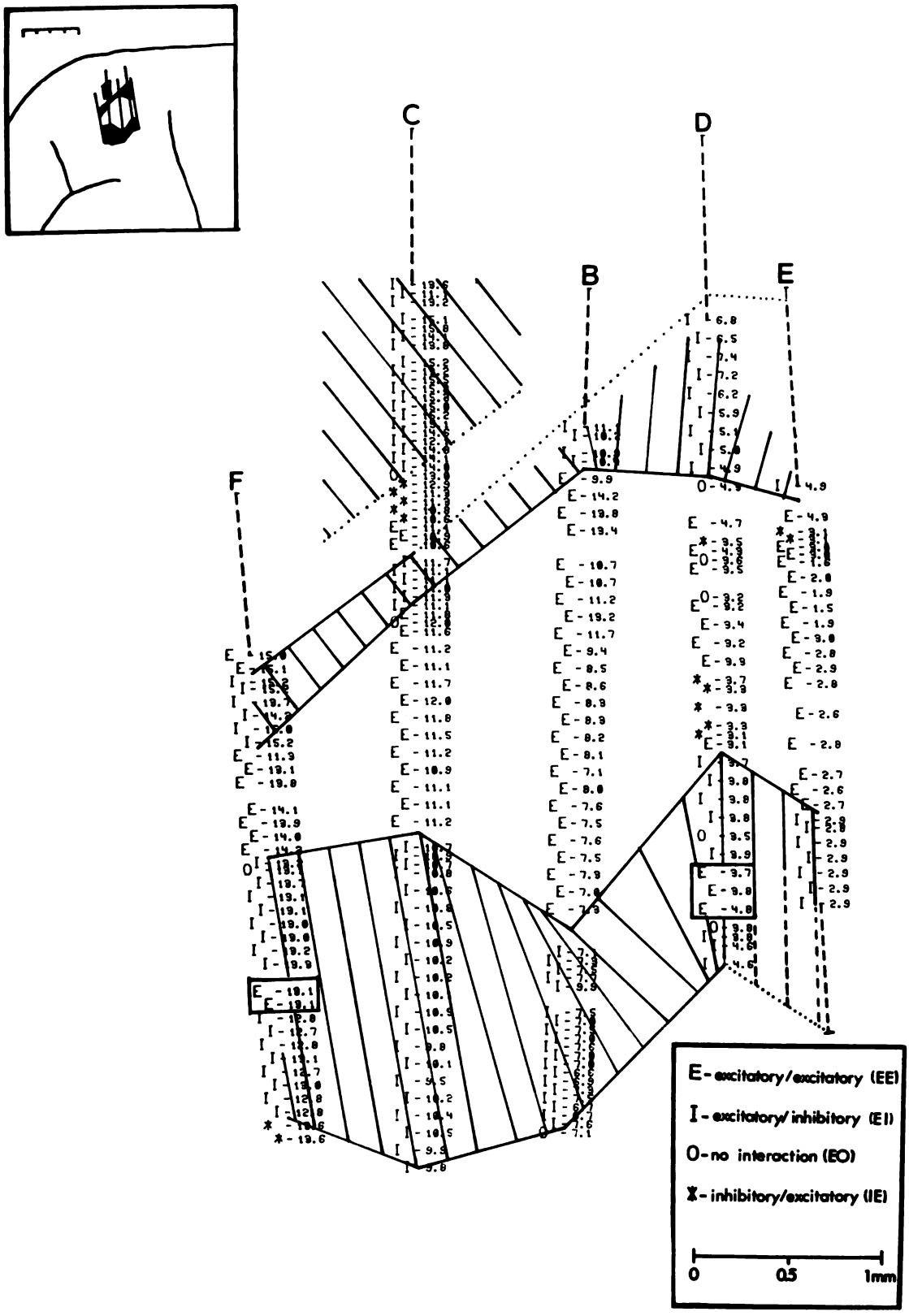

B
G
E
F
E - excitatory/excitatory (EE)
I - excitatory/ inhibitory (EI)
O - no interaction (EO)
✱ - inhibitory/excitatory (IE)
0
0.5
1mm

each of the four penetrations in this case, the characteristic frequencies remained relatively constant, indicating that the electrode penetrations had been placed closely parallel to the isofrequency contours. In this figure, the regions of EI units have been crosshatched.

In another illustrated case (fig. 5), five penetrations were placed through AI. Again, sharp transitions were observed between sequences of EI units and sequences of EE units. In penetrations F, B, D, and E, the first action potentials encountered were from units with responses characteristic of AI neurons; apparently, the electrode did not pass through any other active cortical area before entering AI. Presumably, these penetrations were placed too far ventrolateral in the cortex so that the electrode tracks failed to pass through the dorsal aspect of the field. In all penetrations in this case, long sequences of EI responses were encountered at the ventrolateral end of each penetration.

In the case shown in figure 5, an unusually large number of IE units (units excited by the ipsilateral ear and inhibited by the contralateral ear) were encountered. Like EE and EI units, the IE units were clustered together in sequences that were clearly segregated from sequences of other types of units. Units with IE responses were encountered in only 2 or nearly 800 radial electrode

Figure 5. Map of AI in left hemisphere. Five tangential penetrations. Further details as in fig. 4.


C
D
B
E
F
E - excitatory/excitatory (EE)
I - excitatory/inhibitory (EI)
O - no interaction (EO)
* - inhibitory/excitatory (IE)
0
0.5
1mm

penetrations made in this entire series of experiments. However, all responses encountered in those 2 radial penetrations were from IE neurons.

A total of 24 tangential penetrtions were introduced into AI of six cats. These 24 penetrations constitute a total traverse of 95 millimeters through the middle layers of AI. Recordings were made at nearly 1100 sites along these tracks. Excitatory/excitatory responses occupied 57.7%, and EI responses 34.3%, of the length of these tracks. The EO and IE types of response occupied 6.4% and 1.6% respectively.

In every tangential penetration, strictly delimitable sequences of EE and EI neurons were encountered. A pronounced variation in the lengths of such sequences was noted, both within a single case and between different cases. However, in every case, the locations of EE and EI sequences were consistent with the hypothesis that they form a pattern of alternating EE and EI bands that sub-divide the isofrequency contours in AI.

DISCUSSION

These experiments reveal that the neurons of different interaction classes are topographically segregated into bands or slabs of neurons within which all neurons have similar binaural responses. These repeating EE and EI "binaural interaction bands" intersect isofrequency contours: the alternating pattern of contrasting binaural response classes imposes an organization upon the dimension of AI orthogonal to the dimension in which the cochlea is represented.

In their study of columnar organization in AI, Abeles and Goldstein ('70) found that, along any given electrode penetration that was closely aligned to the axis of the radial cell columns, all neurons encountered tended to display similar responses to binaural stimulation. These investigators suggested that AI possesses a "columnar organization" of binaural neurons. Imig and Adrian ('77) confirmed that binaural interactions are similar for all neurons located along radial lines through AI, and showed that the boundaries between regions of different binaural interaction classes correlate with the lines of radial cell columns. Our results from radial electrode penetrations further support the concept that binaural interactions are radially organized in AI.

Phillips and Irvine ('79) recently have presented evidence that is inconsistent with the existence of radial organization of binaural interactions in AI: they conclude that binaural interactions are not radially organized. It is difficult to reconcile their conclusions with the current observations and with those of Imig and Adrian ('77). However, it appears that the methods used by Phillips and Irvine would have made it difficult to distinguish EE and EI responses. Some of their electrode penetrations (see fig. 1 in their report) were restricted to the superficial 500 microns of the cortex, the cortical laminae that we found to be unresponsive in the barbituate-anesthetized cat. Apparently, determinations of binaural response classes always were made using equal contralateral and ipsilateral intensities. At least some of the determinations of binaural response classes were made on the basis of differences of only 10% in spike counts collected in 50 stimulus presentations. In our hands, the differences between EE and EI responses were <u>always</u> unequivocal. There never was a need to compare slight differences in spike counts.

Phillips and Irvine ('79) specifically challenge the method of recording from clusters of units. In our experiments, <u>all</u> units in a given cluster of EI neurons were inhibited by adequate ipsilateral stimulation: any neuron

facilitated by such stimulation (i.e., and EE unit) was easily detected. When we observed a cluster of predominantly EI units in which not all units were inhibited by ipsilateral stimulation, we usually found that the next advanceof the electrode (along a tangential penetration) brought the tip into an EE region. Thus, for the method of categorizing binaural responses used in the current experiments, we find that all units encountered along a given radial penetration almost invariably displayed the same responses to binaural stimulation.

Imig and Adrian ('77) showed that neurons belonging to different binaural interaction classes are segregated within the plane of AI. They presented an example in which a region of EI (suppression) units occupied a band elongated along a rostrocaudal axis. Our results extend this observation to reveal a fundamental feature of organization of AI: the primary field is subdivided by repeating binaural response-specific bands that transet the pattern of isofrequency contours.

In the data from the six experiments in which tangential penetrations traversed the width of AI, we observed no systematic correlation of frequency coding with binaural interaction. The binaural interaction bands encountered stretched continuously along the entire rostrocaudal extent of the portion of AI that was mapped

intensively in these experiments (i.e., in the frequency range of 3 kHz): each interaction band crossed all isofrequency contours. The converse also was true; i.e., each isofrequency contour crossed all interaction bands. Thus, at any point within AI, a radial column of neurons shares a common characteristic frequency and binaural interaction characteristic. It should be noted that in the current experiments, we are capable of making only a coarse analysis of the homogeneity of detailed response characteristics of neurons within EE or EI bands.

What is the basic processing unit in the primary auditory cortex? Is "AI" the functional unit, or do the binaural response-specific bands constitute independent processing modules?

The demonstration that AI is topographically subdivided into regions containing neurons with different binaural interaction characteristics each containing a complete representation of the cochlear sensory epithelium leads us to reconsider the functional unity of this auditory cortical field. The classical view of the auditory region of the cat, based upon cyto-architectonic criteria (Rose, '49), the projection anatomy (Rose and Woolsey, '49), and the single representation of the cochlea (Woolsey and Walzl, '42), is that AI is a unitary element in sensory processing (see Woolsey, '61). However, in light of current results,

it may be morecorrect to regard AI as a conglomerate of independent processing units. Is "AI" the functional unit? Or are the bands within AI the functional units? There is evidence to support both views from studies of cellular architecture, connectivity, and sensory coding properties of bands within AI.

A. Cytoarchitectonic subdivisions within AI. The auditory region of the cortex has been parcelled, on cytoarchitectonic criteria, into a central auditory sector and a peripheral auditory region; this is the case in human (Campbell, '05; Brodmann, '09; Economo, '27; Bailey and Bonin, '51), a variety of non-human primates (Bonin and Bailey, '47; Bailey et al., '50; Pandya and Sanides, '73; Imig et al., '77), and in cat (Rose, '49; Sousa-Pinto, '73). The central sector, the "auditory koniocortex", is coextensive with the physiologically-defined primary auditory cortex (Rose, '49; Bailey et al., '50; Pandya and Sanides, '73; Imig et al., '77). The auditory koniocortex has been considered to be a single cytoarchitectonic field (see Rose, '49).

Nevertheless, there are many references to the irregularity of cellular architecture within auditory koniocortex. For example, Economo ('27) remarked that the koniocortex in man (TC) is intermixed with "bands and islets" of cortex characteristic of the adjacent

parakoniocortex (TB). Bailey and Bonin ('51) found (also in man) that "around and amongst" the "patches" of koniocortex is a zone of parakoniocortex characterized by large pyramidal cells in the deepest aspect of lamina 3. Bonin and Bailey ('47) found that the auditory koniocortex in the macaque monkey was also patchy and was intruded upon by regions of TB-like cortex. Pandya and Sanides ('73) divided the koniocortex of the macaque into medial (Kam) and lateral (Kalt) strips. The Kalt region was characterized by relatively less dense supragranular layers and by the presence of large pyramidal cells in the deep part of lamina 3. Transcallosal fibers were found by these authors to project preferentially to Kam. This is reminiscent of the observation that only EE regions in the cat are connected transcallosally (Imig and Brugge, '78). A single continuous map of cochlea was found to overlie both Kam and Kalt (Merzenich and Brugge, '73). Concerning the cortex of the chimpanzee, Bailey et al. remarked: "...TC does not cover Heschl's gyrus continuously. Large cells are interspersed in the deeper part of the third layer so that one can easily parcel off narrow strips which might be called TB." ('50; pg.72). Imig et al. ('77) also observed that AI of the owl monkey was not cytoarchitectonically uniform, reporting that large pyramidal cells appeared in clusters in the lower part of lamina 3 in some regions, but were absent in others.

In his study of the auditory region of the cat, Rose ('49) did not delineate any particular subdivision of the auditory core region, but he did cite the variation in cellular architecture within AI as a prime example of cytoarchitectonic gradients within a single cytoarchitectonic region. It is conceivable that there are some cytoarchitectonic distinctions within AI which are associated with distinct functions (follow boundaries of binaural interaction bands) in both cats and primates.

B. Differential connections of binaural interaction bands with other cortical and subcortical structures. The auditory system contains numerous spatially isolated nuclei in the pons, each with characteristic responses to binaural stimulation. The similarity of the binaural interactions that take place in some of the brainstem auditory nuclei to those of the different binaural interaction bands in AI suggest that the binaural responses recorded in the cortex are determined by interactions that occur at some lower level of the auditory pathway. Results by Roth et al. ('78) indicate that the central nucleus of the inferior colliculus (ICC) contains at least largely segregated clusters of neurons, each with binaural response properties that appear to be determined by a small subset of the auditory nuclei that project to the central nucleus as a whole. Neurons receiving inputs from a given region of the ICC are

clustered in columns that extend throughout the ventral nucleus of the medial geniculate body (Andersen et al., '80a). Similar patterns of clusters of neurons have been shown to converge onto segments of isofrequency contours in AI (Colwell and Merzenich, '75, '82). Perhaps the columns of neurons in the ventral division that receive inputs from one small portion of the ICC project to a particular binaural interaction band. This organization may be the anatomical substrate for two or more relatively independent, parallel, ascending lines of processing that terminate in different binaural interaction bands in AI.

Imig and Brugge ('78) studied the distributions of the sources and sites of termination of the transcallosal fibers linking AI in the two hemispheres. Transcallosal fibers project from AI in one hemisphere to rostrocaudally elongated bands in the contralateral hemisphere, and sites of termination of transcallosal fibers correspond to regions of summation (EE) and ipsilateral dominant suppression (IE) responses. The sources of transcallosal fibers are located preferentially, although not exclusively, in regions of EE and IE neurons. Hence, this finding indicates that different classes of interaction bands are also distinguished by their transcallosal connections.

Thus, there is growing evidence that EE and EI bands derive their input from spatially distinct populations of

thalamic neurons and have distinct patterns of output projections (at least to the thalamus and to AI in the contralateral hemispher). These differences in the connectional patterns of EE and EI bands support the hypothesis that there are different functional roles for different binaural interaction bands.

C. Implictions of differences in binaural response properties for different auditory perceptual phenomena. It is possible to relate some aspects of auditory sensation to the types of binaural response properties that are necessary and sufficient to encode them. For example, interaural intensity differences are the stimulus cues necessary for localization and lateralization of sound stimuli lacking low frequency components (Mills, '60). Cortical EI neurons are sensitive to interaural intensity differences, while they are relatively insensitive to net binaural intensity (Brugge et al., '69). Ablation-behavior experiments and clinical reports have indicated that AI is essential for normal sound localization (Neff et al., 50; Neff et al., '56; Sancheq-Longo and Forster, '58; Strominger, '69). Thus, one might imagine that one or all of the EI bands in AI of a given hemisphere is particularly involved in sound localization. Conversely, there are many coding problems for which EE neurons are best suited. Tonal perceptions are little affected by a unilateral loss of auditory cortex, but

profoundly affected by a bilateral loss (e.g., Jerger et al. '69). These perceptions (as well as a variety of binaural pitch phenomena) must be encoded by a system with excitatory inputs from both ears. Perhaps the segregation of EE and EI neurons at all points of the frequency representation in AI is the anatomical manifestation of a functional specialization of neuronal populations for specific perceptual contributions.

A major obstacle to understanding the function of AI as a single unit, or as a collection of several functional units, stems from the fact that we do not know the extent to which neurons within the same general functional class actually are alike in function. Are all EI bands functionally equivalent? Do all EE bands perform the same permutation on ascending inputs? In the current experiments, there was some variation noted in the properties of different EI neurons, and it has been suggested that there are two distinct types of ipsilaterally inhibited response (Brugge and Imig, '78), but there has, as yet, been no unequivocal demonstration of a spatial segregation of different subgroups of EI neurons.

One hypothesis is that the sum of all EE and EI bands comprise only two distinguishable populations, but that these two processing units are, for some unkown reason, interdigitated rather than segregated into two circumscribed

modules. It might be the case that EE and EI neurons are located in alternating strips adjacent to each other because this juxtaposition facilitates some sort of complimentary interaction between two types of neurons. An example of such an organization is found in the striate visual cortex of the cat, where monocular inputs from the thalamus are segregated to ocular dominance columns, and monocular neurons in the granular layers of adjacent ocular dominance columns presumably interact to generate binocular responses. This analogy extends only with some difficulty to the auditory system, since both types of binaural interaction columns presumably receive binaural inputs from the thalamus, and because there is not obvious function that would be served by an interaction between EE and EI responding neurons.

This data raises the possibility that AI may be an assembly of independent processing units, each involved in encoding and/or generating different aspects of auditory perception. Obviously, additional experiments are necessary to determine whether or not AI or its parts constitute the elemental processing unit or units. We wish to stress the practical importance of the observations presented here of binaural response-specific subdivisions of AI. This functional subdivision constitutes a basic feature of cortical topology that must be considered in the

interpretation of results of any subsequent studies directed to understanding the functional organization of AI.

CHAPTER TWO

FUNCTIONAL CLASSES OF NEURONS IN PRIMARY AUDITORY CORTEX OF THE CAT DISTINGUISHED BY SENSITIVITY TO SOUND LOCATION

ABSTRACT

Could neurons in the primary auditory cortex (AI) encode the spatial location of sounds? Is location sensitivity a parameter of stimulus coding relevant to topographical organization in AI? We have mapped receptive fields of single units in AI of the cat by varying systematically the location of a tonal stimulus within a sound field free of acoustic obstructions and reflections. By orienting tangential electrode penetrations parallel to the medio-lateral axes along which neurons are tuned to the same stimulus frequency, we have explored the possibility that this axis could be concerned with spatial features of sound stimuli.

Approximately half of the neurons encountered were selective for the location of sounds. The location selective units could be divided into two discrete populations. Hemifield units responded only to sounds presented in the contralateral sound field, with receptive fields extending from a well defined medial border to beyond the contralateral pole of the sound field. Axial units had small, completely circumscribed receptive fields that were constant in location for all such units in each cortical hemisphere studied. The location of axial receptive fields coincided with the acoustical "axis" of the contralateral pinna which was defined by acoustical measurements of the

directionality of the ear. Axial units were restricted to the rostral pole of AI where neurons are tuned for high frequencies, while hemifield units were located more caudal and were tuned for lower frequencies. The location insensitive, omnidirectional, units were distributed across the entire length of AI sampled. Some of the properties of the measured receptive fields could be inferred by comparing the passive acoustical properties of the ear with binaural interactions previously described in AI.

There was no indication of a systematic map of sound space in AI. Instead, the medio-lateral axis of AI contains spatially segregated regions of different unit classes. This organization was consistent with the previously described pattern of binaural interaction bands. The location selective and location insensitive unit classes might represent stages of fundamentally different lines of processing that are segregated within AI.

INTRODUCTION

The primary auditory cortex (AI) of the cat contains a topographical representation of the auditory sensory epithelium, the cochlear partition (Merzenich et al., 1975). This is manifest as a caudal to rostral map of the audible frequency domain (tonotopic organization). In the visual system, the representation of the two dimensions of the retina fills the two dimensions of the visual cortex (e.g., Hubel and Wiesel, 1962). In contrast, the representation in the auditory cortex of the one-dimensional sound frequency domain is expanded laterally so that points on the cochlea (i.e., single frequencies) are represented as medio-laterally oriented lines in AI (isofrequency contours). This re-representation of single frequencies as isofrequency contours could provide a substrate for the topographical representation of some parameter of sound stimuli that is independent of sound frequency (e.g., Tunturi, 1952).

The response to binaural stimulation is one parameter that varies with location within an isofrequency contour. Neurons with similar responses to binaural stimulation form radial columns extending through the depth of the cortex (Abeles and Goldstein, 1970; Imig and Adrian, 1977). Units with different responses to binaural stimulation are topographically segregated within AI, forming rostro-caudally oriented bands ("binaural

interaction bands") that cross the axis of isofrequency contours (Imig and Brugge, 1978; Middlebrooks et al., 1980). It has been suggested that bands of units that are sensitive to different features of dichotic stimuli might form independent processing units within AI (Middlebrooks et al., 1980).

The auditory cortex of the cat has been implicated in the representation of the spatial locations of sounds. For example, single units in AI of the cat tested with dichotic stimuli (sounds delivered independently to the two ears) are sensitive to interaural disparities that provide spatial information which is not available from one ear alone (Hall and Goldstein, 1968; Brugge et al., 1969). Some neurons in the auditory cortex respond preferentially to sounds presented in limited regions of the sound field (Evans, 1968; Eisenman, 1974; Sovijarvi and Hyvarinen, 1974). Bilateral ablations of the temporal cortex cause deficits in the ability of a cat to go to the source of a sound (see Neff et al., 1975 for review).

The present study was undertaken to examine the role of sound location in the functional organization within AI. Can single units in AI of the cat encode the location of a sound source? Might the medio-lateral dimension of AI be concerned with spatial features of sound stimuli? We have

addressed these questions by recording from single units in AI while presenting tonal stimuli in a free sound field. The receptive fields of auditory neurons were mapped by plotting the boundaries of spatial regions within which stimuli elicited a given neural response. Tangential electrode penetrations were oriented medio-laterally, approximately parallel to isofrequency contours, to explore the possibility that the spatial sensitivity of units might vary along the dimension where binaural interactions previously have been shown to vary. Using simple criteria based on characteristics of sensitivity to sound location, we could distinguish three classes of units in AI, two of which had sharply defined spatial receptive fields. These unit types were topographically segregated within isofrequency contours. By comparing the location sensitivity of cortical neurons with the acoustic transfer function of the external ear, we can begin to relate this data to the existing body of data collected in experiments using dichotic stimulation. These results are relevant to the neural bases of auditory behavior in the cat as well as to the understanding of the functional principles of organization within the primary auditory cortex. Preliminary reports of this work have appeared elsewhere (Middlebrooks and Pettigrew, 1980a,b).

METHODS

Animal preparation and single unit recording.

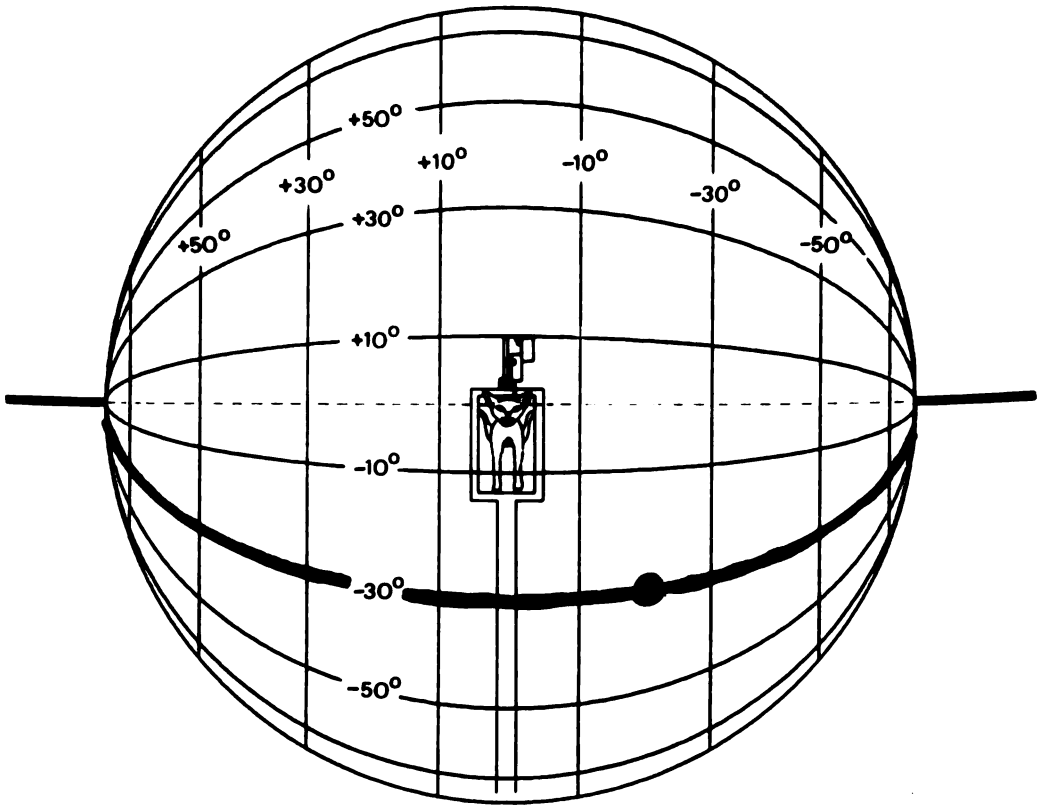
We studied 21 young adult cats from an inbred colony of specific-pathogen-free tabbies. Among these inbred cats we found relatively little variation in the cortical sulcal pattern or in the location of the primary auditory cortical field (AI) relative to the sulcal pattern. This is in contrast to the great variation seen among cats from random sources. In addition, the cats from this closed colony were relatively free from ear mites and other pathology of the external and middle ear that is common among other cats. The neurophysiological data presented here are from 15 cats in which good recordings were obtained from AI. The data on the passive acoustics of the ear are from two additional cats.

Surgical anesthesia was induced with intramuscular injections of ketamine hydrochloride (Ketaset; 20 mg/kg) and diazepam (Valium; 1 mg/kg). Supplementary doses of ketamine were given as needed, with smaller doses necessary once the animal was comfortably suspended in its hammock for recording (see below). Under even the lightest conditions of anesthesia used, we observed no spontaneous movements of the pinnae nor were there any movements observed in response to sound stimuli.

Following induction of anesthesia, cats were positioned temporarily in a stereotaxic device using blunt ear and eye bars. This facilitated alignment of the animal in a standard coordinate system. A stainless steel bar was attached to the skull with screws and acrylic cement. This bar extended behind the cat's head and was used later for holding the head in position in the sound chamber. The skull was opened over the middle ectosylvian gyrus in the left hemisphere and a recording chamber was mounted over the skull opening. The scalp was closed around the chamber and supporting bar, and the pinnae were restored to a normal-appearing configuration. At this point, the cat was removed from the stereotaxic device. Its body was suspended in a canvas hammock and the head was supported, still in alignment with stereotaxic coordinates, by clamping the steel bar from behind the head. Thus, the animal was positioned in a well-defined coordinate frame with no obstructions in the sound path to its ears. This entire setup was positioned in the sound chamber with the cat's Horsley-Clarke horizontal plane parallel to the floor and the interaural axis aligned with the axis of the sound stimulation apparatus (fig. 1).

The activity of single units was recorded with glass-insulated tungsten microelectrodes (Levick, 1972). Neural activity was amplified, band-pass filtered, and

Figure 1. Position of cat within coordinate system. Use of this projection is consistent with directions of motion of the loudspeaker on the hoop. Lines of constant elevation take the shape of the hoop. Movements of the loudspeaker in azimuth are accomplished by movements along a track on the hoop. Rotation of the entire hoop about its lateral poles cause movement of the loudspeaker in elevation with constant azimuth. Center of cat's interaural axis is concentric with center of sphere. 0 elevation is equivalent to intersection of Horsley-Clarke horizontal with surface of the sphere. 0 azimuth is on the mid-sagital plane. Loudspeaker is shown positioned at -20 azimuth and -30 elevation. A. Coordinates projected as if viewed from a point directly in front of cat at an infinite distance. B. Coordinate system rotated 30 about vertical axis. The point directly in front of the cat (0 ,0) is shifted 30 to the reader's right of center.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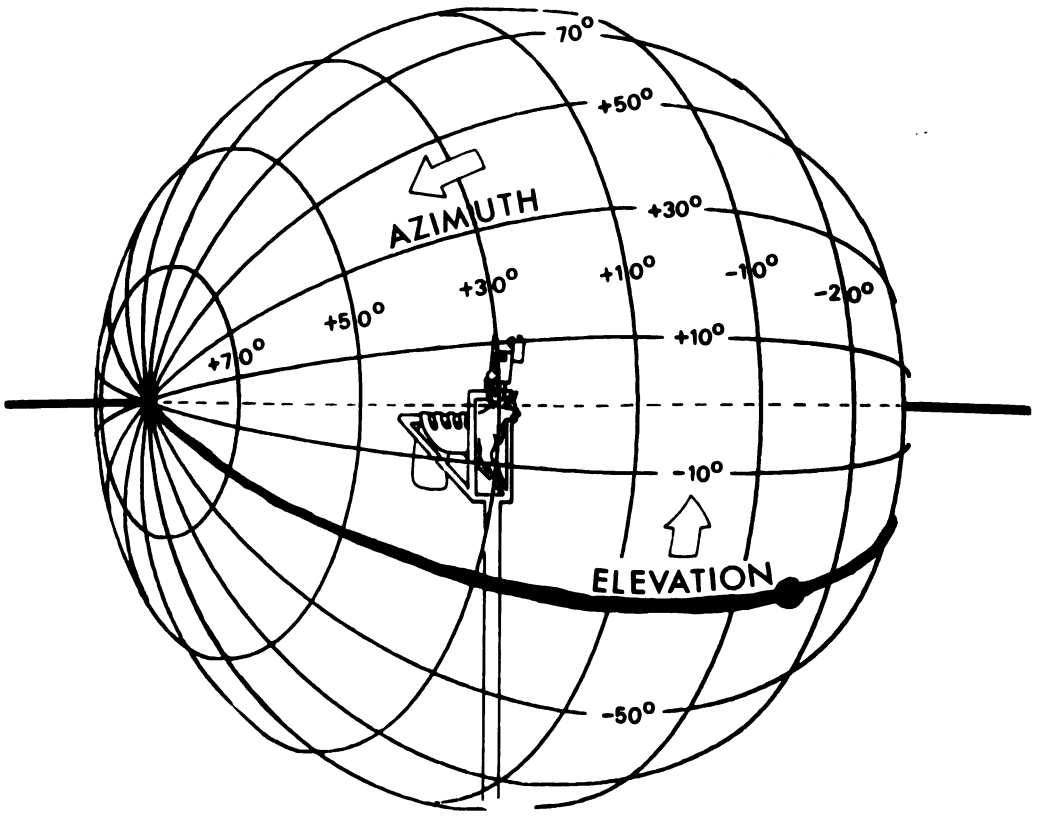
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displayed on an oscilloscope and an audio monitor. In some cases, spikes were isolated with an amplitude discriminator and the output of the discriminator led to an event counter. Electrodes were positioned using a Narashige micromanipulator and a stepping motor microdrive. After the dura mater was opened and the electrode was positioned over the surface of the cortex, the recording chamber was filled with agar (3% in isotonic saline) and covered with wax. This hydrostatically sealed chamber stabilized the brain and facilitated lengthy recordings from single cortical neurons. For most electrode penetrations, the electrode was oriented in the parasagital plane and 10 degrees anterior to the frontal plane (see fig. 7). In this orientation, the electrode passed approximately parallel to the isofrequency contours. In a few penetrations, the electrode was oriented approximately normal to the surface of the cortex, parallel to the axis of radial cell columns.

The locations of electrode penetrations were marked by two or more electrolytic lesions along each penetration (10 microamps of cathodal current for 10 seconds). Following the recording period, the animal was deeply anesthetized with sodium pentobarbital and perfused through the heart with isotonic saline followed by 10% formalin in isotonic saline. Electrode tracks were reconstructed from 50 micron frozen sections stained with cresyl violet.

Sound stimulation.

Sound stimuli were delivered using a system that moved a loudspeaker on the surface of an imaginary sphere, one meter in radius, centered on the middle of the cat's interaural axis (fig.1). In this apparatus, the loudspeaker (Magnavox piezoelectric tweeter) moved along a semicircular track. This track (or "hoop") pivoted about an axis coinciding with the cat's interaural axis. We refer to movements along the track as movements in azimuth, and to movements of the entire hoop about the interaural axis as movements in elevation. When the hoop was held at a constant elevation, movement of the speaker along the hoop described a meridian of isoelevation. Conversely, when the speaker was fixed at a given azimuthal position on the hoop and the hoop was rotated about the axis passing through the interaural axis, the speaker described a parallel to the midsagittal plane (see fig. 1). The coordinate system that we have used thus can be compared to a globe of the earth which has been rotated laterally so that the equator is in the midsagittal plane with parallels of latitude running vertically and the meridians of longitude running approximately horizontally. For simplicity we have used the terms azimuth and elevation in the text, but this unusual usage should be noted. The speaker could be positioned in any direction relative to the cat except for the area

directly beneath the cat and the extreme three degrees of azimuth at the contralateral and ipsilateral poles. In practice, however, the positions of the loudspeaker in the sound hemifield in front of the cat were most intensively studied. The responses of cortical units to moving stimuli could not be studied conveniently, as the responses to tonal stimuli were confounded by responses to the sounds produced by the mechanism moving the speaker.

The sound stimulation hoop and the animal were positioned inside a 5 x 3 x 3 meter anechoic chamber (Industrial Acoustics Co.) rated at 300 Hz. The controls for frequency, intensity, and location of sound stimuli were located outside of the sound chamber as were the recording oscilloscope and audio monitor.

Cats were stimulated with pure tone bursts that were 100 msec in duration, presented one per second, with rise and fall times of 5 msec. The tones were generated with an audio oscillator (General Radio) and controlled in intensity with a decade attenuator (Hewlett Packard). Characteristic frequencies (CF's) of units were determined by noting the frequency at which a given unit responded to the lowest stimulus intensity. Once the CF was determined for a given unit, the tone frequency was maintained constant while mapping that unit's spatial receptive field. Occasionally, responses to noise burst stimuli were observed and such

stimuli were adequate to drive some units. However, no systematic study was made of the responses to noise, and all of the data presented in this report refer to responses to stimulation with tones of characteristic frequency.

Measurement of passive acoustics of head and pinnae.

In two cases, the acoustic transfer function of the head and external ear was estimated by recording from the acoustic meatus with a probe microphone while presenting tones of constant frequency and varying the location of the sound source. The data plotted in figures 8 and 9 are from an isolated cat head and neck. In this case, a small opening was made in the posterior aspect of the right pinna and a slit was cut in the cartilaginous portion of the acoustic meatus. A short length of polyethylene tubing was placed snuggly over the end of a 1/8" B & K microphone, extending approximately 5 mm beyond the diaphragm of the microphone. This probe fit tightly into the slit in the meatus and was cemented in place. The opening in the back of the pinna was closed so that the pinna regained its normal appearance. The cat head was suspended in the usual position in the sound chamber.

The output of the probe microphone was measured with a General Radio wave analyzer set to the 10 Hz bandwidth. The AC output of the wave analyzer was read with a digital

voltmeter. The sound pressure level in the acoustic meatus was measured while moving the piezoelectric loudspeaker systematically in azimuth and elevation in steps of 10 or 15 degrees. For each set of measurements, the frequency and intensity of the input to the loudspeaker were maintained constant and only the location was varied while the values on the voltmeter were recorded. For each frequency, intensities were expressed as decibels below the greatest level recorded. By expressing all the data as relative level for a constant frequency, we avoided errors that might have been introduced by slight deviations from a flat frequency response in our loudspeaker and recording configuration. By recording variations in sound level for a constant input to the loudspeaker, rather than adjusting the loudspeaker input to achieve a constant sound level, we place the requirement for linearity on the B & K microphone rather than on the loudspeaker. In figures 8 and 9, the filled circles indicate the locations of the loudspeaker for which intensity levels were recorded, and the curves are iso-intensity contours interpolated between the data points

Graphic representation of data.

In our sound stimulation apparatus, the loudspeaker moves on the surface of an imaginary sphere centered on the middle of the cat's interaural axis. The intersection of the cat's Horsley-Clarke horizontal plane with the sphere is

defined as zero elevation, with positive elevations above this line. The intersection of the midsagittal plane (vertical plane) with the sphere is defined as zero azimuth, with azimuths on the cat's right side (the reader's left) defined as positive. Because all of the recordings in this study were made from the left cortical hemisphere, the sound hemifield containing positive azimuths is referred to as the contralateral hemifield. The straight line connecting the two lateral poles (± 90 degrees azimuth) passes through the cat's interaural axis.

In the figures in this report, the sphere surrounding the cat is flattened onto two dimensions as if viewed from an infinite distance. In some of the figures (e.g., fig. 1A), the point of zero azimuth and zero elevation is drawn in the center of the figure. In this conformation, lines of constant azimuth (varying elevation) appear as straight, vertically-oriented lines, and lines of constant elevation (varying azimuth) appear as arcs connecting the two lateral poles. Areas directly in front of the animal are most magnified, with more lateral regions appearing relatively compressed. In other figures (e.g., fig. 1B), the coordinate system is rotated so as to bring the contralateral pole 30 degrees out of the plane of the paper. In this scheme, areas in the ipsilateral hemifield appear compressed relative to equivalent areas in the

contralateral hemifield. The vertical midline (0 degrees azimuth) appears as an arc located 30 degrees to the reader's right of center. The advantage of this coordinate system is that more visual emphasis is placed on regions containing the majority of spatial receptive fields.

Receptive fields boundaries are indicated by filled circles located at every point at which the edge of a receptive field was measured. The lines connecting the filled circles are the shortest paths between these points (i.e., great circles).

RESULTS

Under ketamine anesthesia, we found auditory cortex responsive and we were able to verify previously described features of its functional organization (e.g., Merzenich et al., 1975). Within the primary auditory field (AI), neurons were sharply tuned for frequency. Tonotopic organization was observed, with characteristic frequencies (CF's) increasing from the caudal to rostral pole of AI. These two properties, sharp tuning and correct gradient of CF, were used as functional criteria to identify AI. The responses of most neurons in AI to pure tone bursts were transient, although neurons occasionally were encountered whose responses were sustained throughout the duration of the stimulus.

Sensitivity to sound location.

Many neurons in AI were sensitive to the spatial location of a sound source. For those units, spatial receptive fields were plotted by mapping the region within which the presentation of a CF tone elicited a given neuronal response. Unless otherwise stated, receptive fields shown in the figures were plotted using a stimulus intensity 10 dB greater than the threshold found for the most effective location of the loudspeaker within the receptive field. The sound hemifields are identified as

contralateral or ipsilateral relative to the cortical hemisphere containing the recording site.

All units encountered in this study could be grouped into three classes on the basis of their sensitivity to stimulus location. These classes were designated omnidirectional, hemifield, and axial units.

Omndirectional units responded to sounds presented from any direction in front of the cat. Often, a faintly delimited receptive field could be determined for these units at near-threshold intensities, but increases of the stimulus intensity to within 10 dB above threshold caused this 'receptive field' to expand to fill the entire region explored in front of the animal. Although the response thresholds for a given omnidirectional unit were within 10 dB for all stimulus locations, the number of spikes elicited by a supra-threshold tone burst varied somewhat with sound location. For the majority of these units, the most effective stimuli were located in front of the animal near the vertical midline, with the threshold increasing gradually toward the lateral poles. Omnidirectional units were most readily distinguished from hemifield and axial units by their responses to stimuli located well into the ipsilateral sound hemifield.

Hemifield units had receptive fields occupying most

of the contralateral sound hemifield, with sharply defined vertically-oriented medial borders (fig. 2). The azimuth of the medial edge of the receptive field varied somewhat among hemifield units, although for most units it was within 20 degrees of the vertical midline. Laterally, the receptive field extended beyond the extreme contralateral pole of the sound field. These receptive fields sometimes had upper or lower boundaries, rarely both, but this was not a useful defining characteristic. The two receptive fields plotted in figure 2 represent the extremes of variation within this class, one field having boundaries above and below as well as medially, and the other having only a clear medial boundary.

Axial units had completely circumscribed receptive fields located within the frontal contralateral quadrant of the sound field (fig. 3). The location of these receptive fields coincided with the acoustical axis of the contralateral pinna (see RESULTS below for description of the passive acoustics of the pinna). A striking feature of the axial units was that the lateral edge of the receptive field terminated with a border which was as sharply defined as the medial border. These units were readily distinguished from hemifield units by failing to respond to stimuli presented at the contralateral pole of the sound field regardless of their intensity. Axial receptive fields

Figure 2. Two hemifield units. These two units represent the extremes of variation within this class. Cross indicates 0 azimuth, 0 elevation. Filled circles indicate locations where borders of receptive fields were determined. Lines connecting the filled circles are the shortest possible paths on the surface of the sphere (great circles). A. Receptive field has clear upper and lower borders as well as medial border. Receptive field extends beyond contralateral pole. Plotted with characteristic frequency (CF) tone of 11.2 kHz. B. This receptive field extended up as far over cat's head as was explored. Medial border extends slightly beyond midline then sweeps down to make a partial lower border. CF 8.3 kHz.

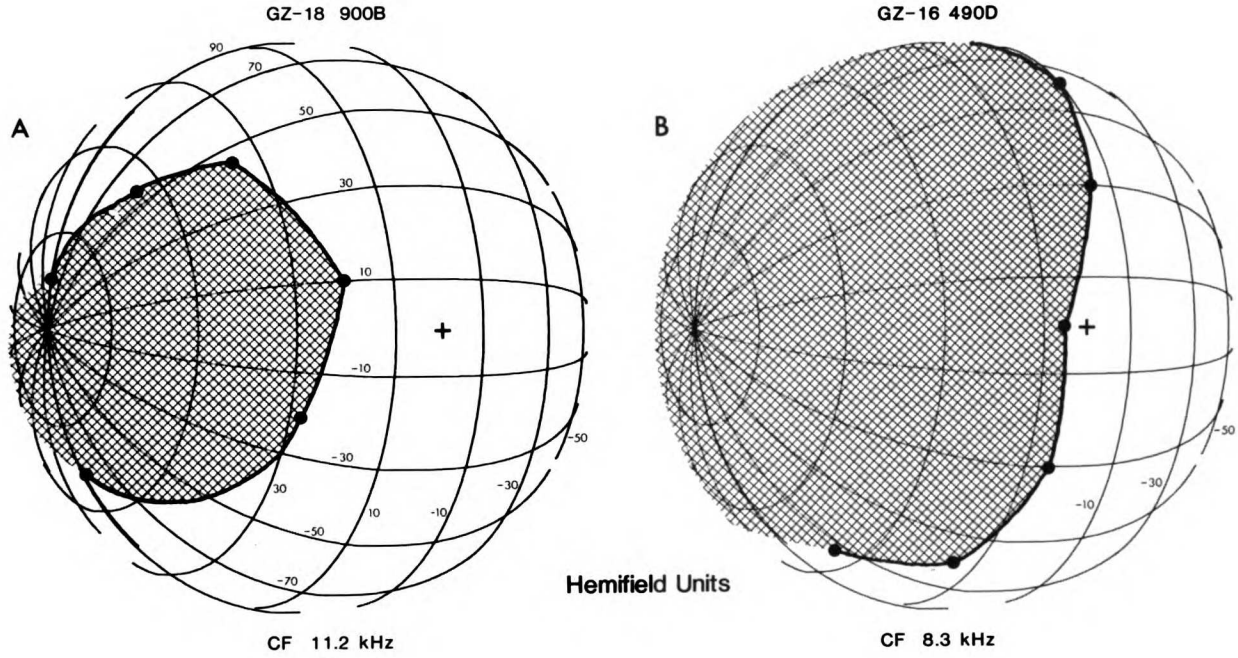
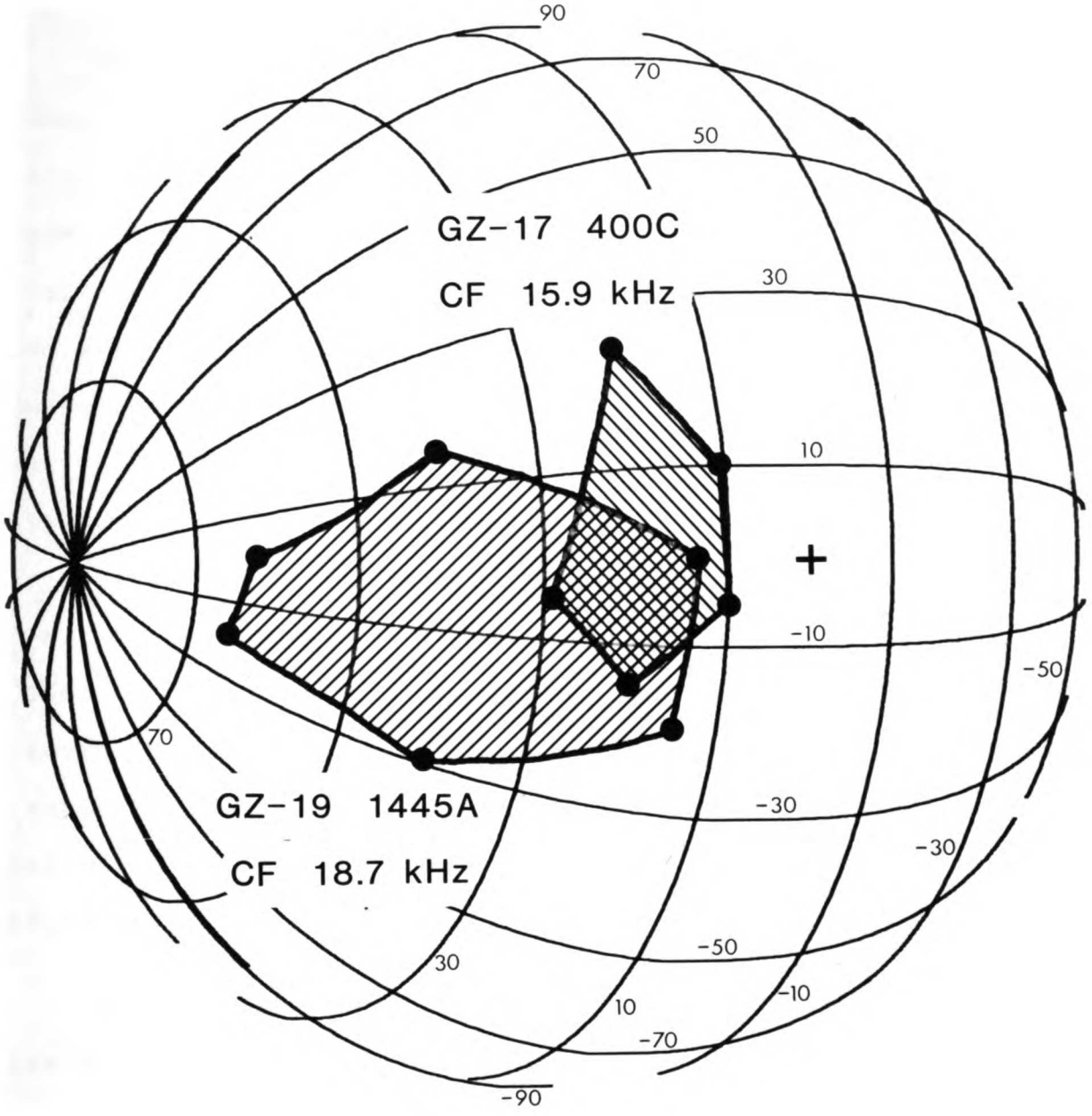

GZ-18 900B
A
90
70
50
30
10
-10
-30
-50
-70
30
10
-10
-30
-50
CF 11.2 kHz
GZ-16 490D
B
-10
-30
-50
CF 8.3 kHz
Hemifield Units

Figure 3. Two axial receptive fields. These two fields represent the extremes of variation within this class. Receptive field of unit 400C is only 20 wide in azimuth at widest point and is elongated in elevation. Receptive field of unit 1445A is centered more laterally and is elongated in azimuth. Note that these two units were recorded in two different cats; within a single cat, axial receptive fields have roughly the same location (e.g., fig. 4A).

Axial Units


90
70
50
GZ-17 400C
CF 15.9 kHz
30
10
+
-10
-50
70
GZ-19 1445A
CF 18.7 kHz
-30
-30
-50
30
10
-10
-70
-90

had both upper and lower boundaries. The width of these receptive fields varied in azimuth from 20 to 60 degrees.

The locations of axial receptive fields varied somewhat throughout the entire course of these experiments, but within a given cat the locations were remarkably constant (fig. 4A). This can be seen in figure 4B, where plotted symbols representing the centers of axial receptive fields are clustered for a given cat, while the locations of the clusters vary from cat to cat. The variation in axial receptive field locations between animals is most likely due to slight variations in the resting position of the pinnae under anesthesia and following the surgery to expose the cortex. The dependence of axial receptive field location on the position of the pinna was tested in one case by mapping the receptive field of an axial unit before and after moving the contralateral pinna with a clamp. Pulling the pinna medially had the expected effect of moving the receptive field medially (fig. 5).

The boundaries of hemifield and axial receptive fields expanded somewhat with increasing stimulus intensity, although the amount of such expansion varied considerably among the units studied. Figure 6 shows examples of the extremes of this variation. For the hemifield unit whose receptive field is shown in figure 6A, an increase in the stimulus intensity from 10 dB above threshold to 20 dB above

Figure 4. Locations of axial receptive fields. A. Boundaries of every axial receptive field encountered along one tangential penetration in cat GZ-18. CF's of these units ranged from 15.7 to 16.1 kHz. The receptive fields are centered approximately on the acoustical axis of the contralateral pinna (see fig. 8). B. Every axial receptive field encountered in each of three cats. Symbols indicate the centers of receptive fields, with a different symbol for each cat. Cat GZ-17: 20 axial units recorded along 900 um of two electrode penetrations; CF's ranged from 15.5 to 16.9 kHz. GZ-18: 8 units; 500 um; one penetration; CF's from 15.7 to 16.1 kHz. GZ-19: 8 units; 1200 um; one penetration; CF's from 14.2 to 19.1 kHz.

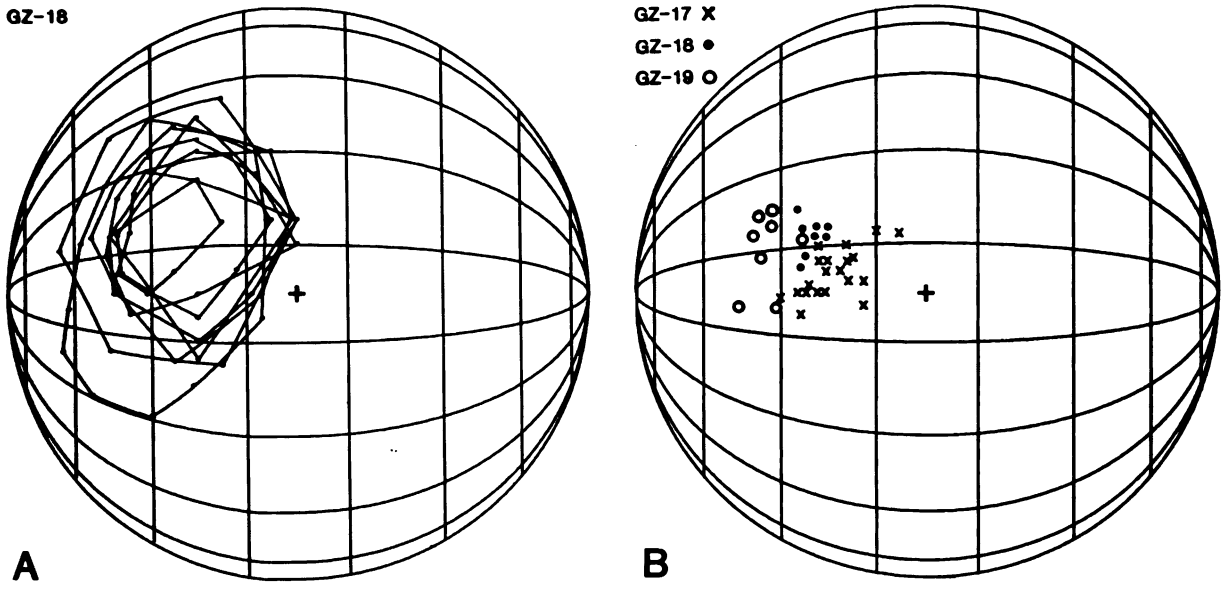
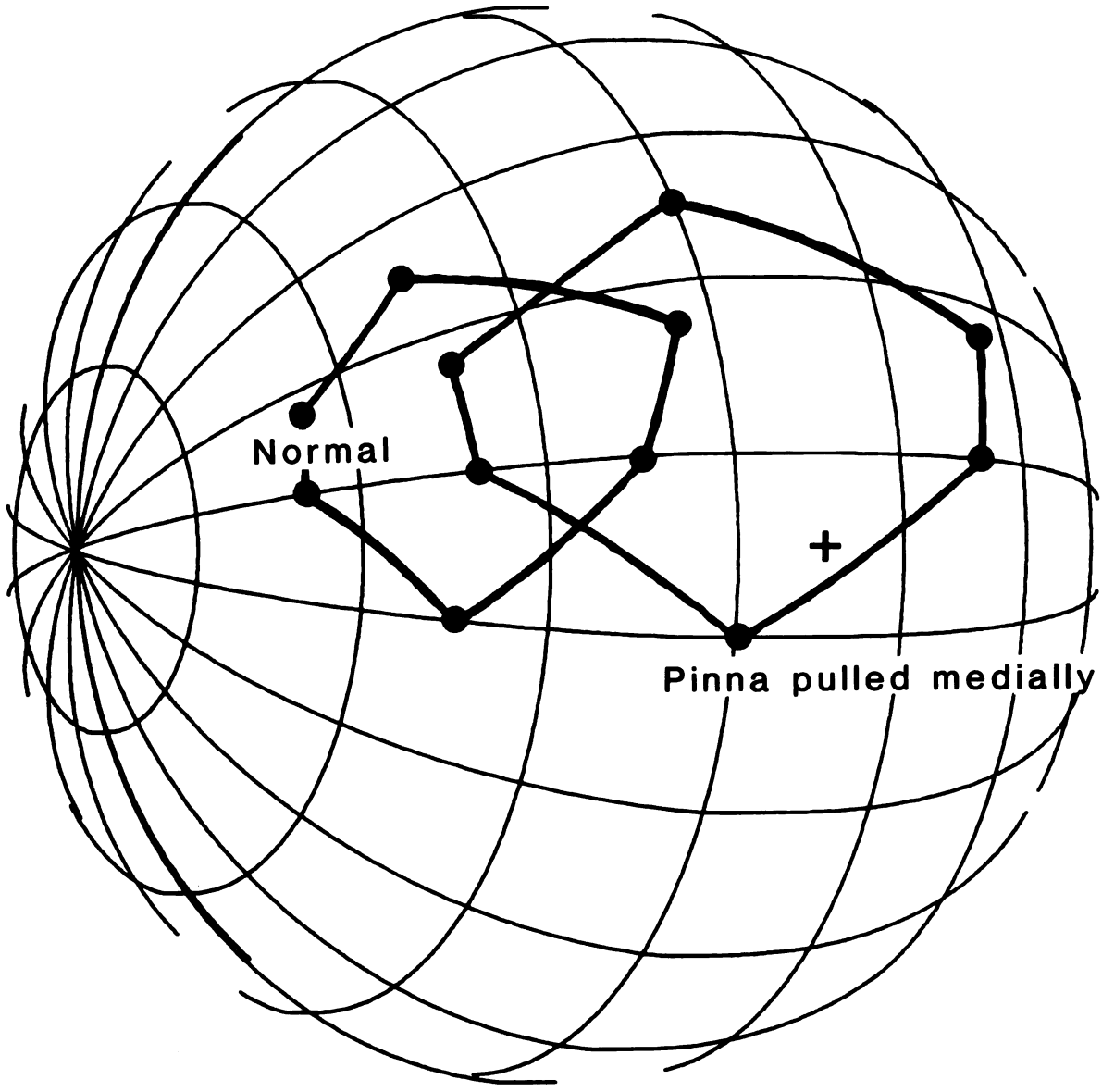
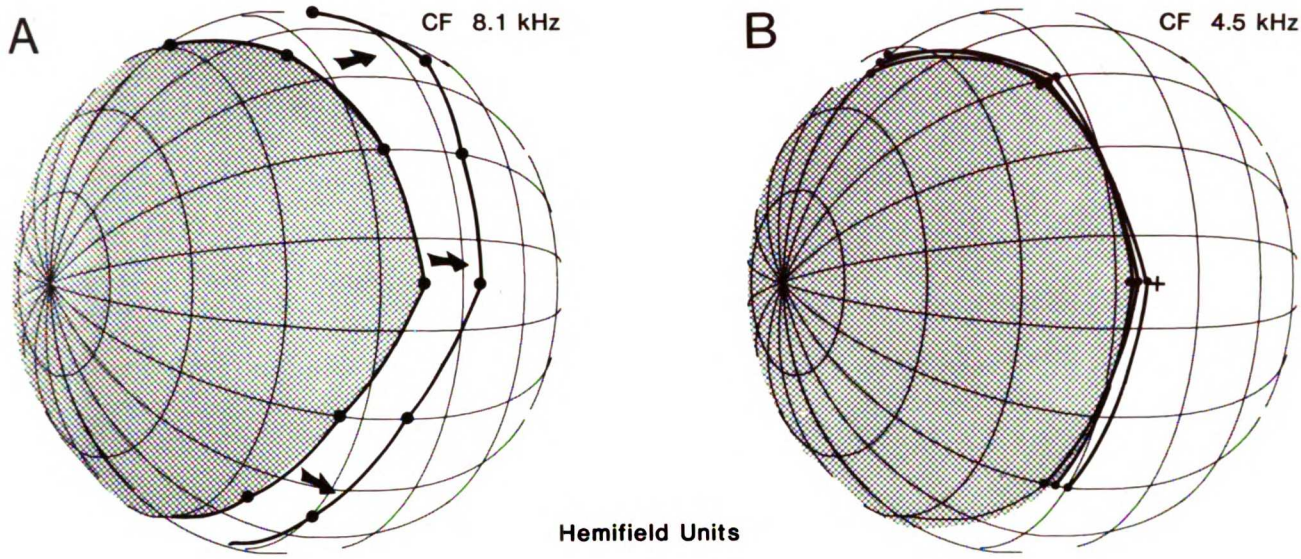

GZ-18
A
GZ-17 X
GZ-18 ●
GZ-19 O
B

Figure 5. Dependence of axial receptive field location on pinna direction. Boundaries of axial receptive fields, both for the same unit, before and after the contralateral pinna was pulled medially with a clamp. Moving the pinna medially caused the receptive field to broaden slightly and move medially. Note that the variation in receptive field location is greater between cats than within a single cat. CF 18.5 kHz.



Effect of Pinna Movement

Figure 6. Expansion of receptive fields with increasing intensity. A. Hatched area is receptive field of a hemifield unit plotted with a CF stimulus of intensity 10 dB greater than the threshold at the most sensitive loudspeaker location. Arrows indicate the medial border of the receptive field of the same unit plotted with intensity 20 dB over threshold. B. Another hemifield unit. Three medial borders plotted for intensities of 10, 20, and 30 dB above threshold. C. Axial unit. Hatched area is receptive field for 10 dB over threshold. Arrows show expansion with increase in intensity to 25 dB over threshold. D. Two receptive fields plotted for an axial unit with intensities of 10 and 25 dB over threshold.

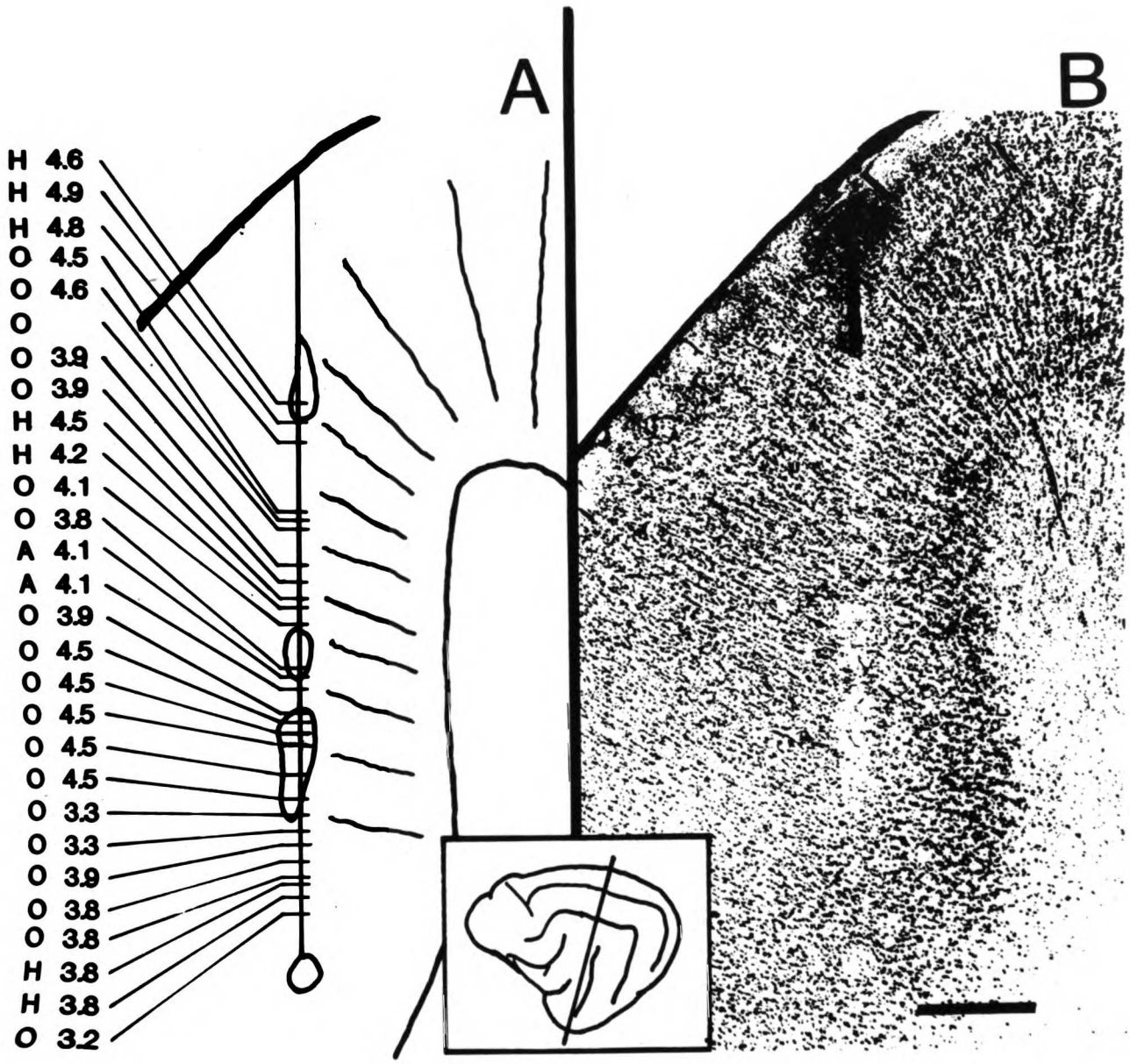

A
CF 8.1 kHz
B
CF 4.5 kHz
Hemifield Units
C
CF 18.5 kHz
D
CF 14.6 kHz
Axial Units

threshold caused the medial edge of the receptive field to move medially approximately 10 degrees. In contrast, the medial borders of the receptive fields for 10, 20, and 30 dB above threshold for the unit shown in figure 6B are virtually identical. Likewise, the axial receptive field shown in figure 6C more than doubled in diameter following a 15 dB increase in stimulus intensity. Over a similar intensity range, the borders of the axial receptive field shown in figure 6D remained nearly unchanged.

Distribution of response classes within AI.

Units with different types of receptive fields were spatially segregated within AI. Most electrode penetrations in this study were oriented oblique to the axis of radial cell columns and approximately parallel to isofrequency contours. In these penetrations, sequences of units displaying one type of spatial receptive field alternated with sequences of units with a different spatial receptive field type. Individual units with different receptive field properties tended not to intermingle along these penetrations. This is shown in figure 7 where a tangential electrode penetration has been reconstructed. The CF's of units varied little along this penetration, indicating that the penetration was oriented along the axis of the isofrequency contours. There was, however, variation of the units' sensitivity to sound location as a function of their

Figure 7. Reconstruction of tangential penetration. A. Numbers indicate CF in kHz. Letters indicate receptive field class: O-Omnidirectional; H-Hemifield; A-Axial. Oblique lines suggest the orientation of radial cell columns. Irregular circles along track indicate approximate extent of marking lesions. Note segregation of different receptive field classes along this medio-laterally oriented penetration. B. Nissl-stained frontal section containing the electrode track drawn in fig. 7A. Scale=1mm. Inset. Lateral view of cat brain with straight line indicating the orientation of the plane of section.


A
B
H 4.6
H 4.9
H 4.8
O 4.5
O 4.6
O
O 3.9
O 3.9
H 4.5
H 4.2
O 4.1
O 3.8
A 4.1
A 4.1
O 3.9
O 4.5
O 4.5
O 4.5
O 4.5
O 4.5
O 3.3
O 3.3
O 3.9
O 3.8
O 3.8
H 3.8
H 3.8
O 3.2

medio-lateral position along the penetration. Omnidirectional, hemifield, and axial units clearly were separated into clusters along this five millimeter track. Along each of the few radial electrode penetrations which we made, all units encountered tended to belong to the same location-sensitive class.

Sequences of units of a given receptive field class sometimes were encountered more than once along a single tangential electrode penetration. This is demonstrated in the penetration reconstructed in figure 7, where hemifield units were found in three discrete segments of a penetration, with the segments of hemifield units demarcated by sequences of omnidirectional or axial units. In each of four tangential penetrations that were oriented approximately parallel to isofrequency contours, two or more sequences of hemifield units were encountered, separated by 300 to 1000 microns in which omnidirectional or axial units were recorded. In each of three other tangential penetrations, two segments of axial units were separated by 350 to 1250 microns of recordings of omnidirectional or hemifield units.

Relative sizes of unit populations.

In tangential electrode penetrations, the percentage of each penetration in which units of a given receptive

field class were recorded should be proportional to the area of AI occupied by units of that class. In the nine cats in which units were recorded for more than 900 microns of a tangential penetration (12 penetrations, all oriented approximately parallel to isofrequency contour), 52% of the total length was occupied by omnidirectional units, 23% by hemifield units, and 25% by axial units. These values should be taken only as a rough estimate of the relative areas occupied by each unit class, as few of the penetrations traversed the entire medio-lateral extent of AI, i.e., the medial and lateral extremes of the field were under-sampled. This estimate of the relative area of AI devoted to each unit class is averaged over the entire portion of the rostro-caudal axis sampled (i.e., CF's from 3-20 kHz).

When the sampled population is divided into two groups on the basis of characteristic frequency greater than or less than 12 kHz, proportions are skewed heavily toward more hemifield units with lower CF's and more axial units with higher CF's. We chose 12 kHz as the cutoff point for CF in the analysis because that frequency divides our data approximately in half, and because no tangential penetrations crossed a 12 kHz isofrequency contour. The ratios are 56:42:2 for omnidirectional:hemifield:axial units with CF's below 12 kHz (6 penetrations in 6 cats; total of

9650 microns of tangential penetrations), and 49:5:46 for units with CF's above 12 kHz (6 penetrations in 4 cats; total of 10,000 microns). We lack the very large amount of data necessary to report the relative frequencies of occurence of each unit class within more limited frequency bands. However, a striking feature is revealed by comparing the half of the sampled population having the lowest CF's with the half having the highest CF's. While the fraction of the population occupied by omnidirectional units is approximately independent of CF, the fraction occupied by hemifield units at low frequencies is taken over by axial units at higher frequencies.

We cannot exclude the possibility that axial and hemifield receptive fields represent two ends of a continuum, with the lateral border of the axial receptive field gradually appearing as CF increases through the range around 12 kHz. However, spatial tuning does not seem to be strictly correlated with CF, as the axial receptive fields encountered in one tangential penetration (figure 4A) varied in diameter by a factor of three even though the CF's were restricted to a range of 15.7 to 16.1 kHz.

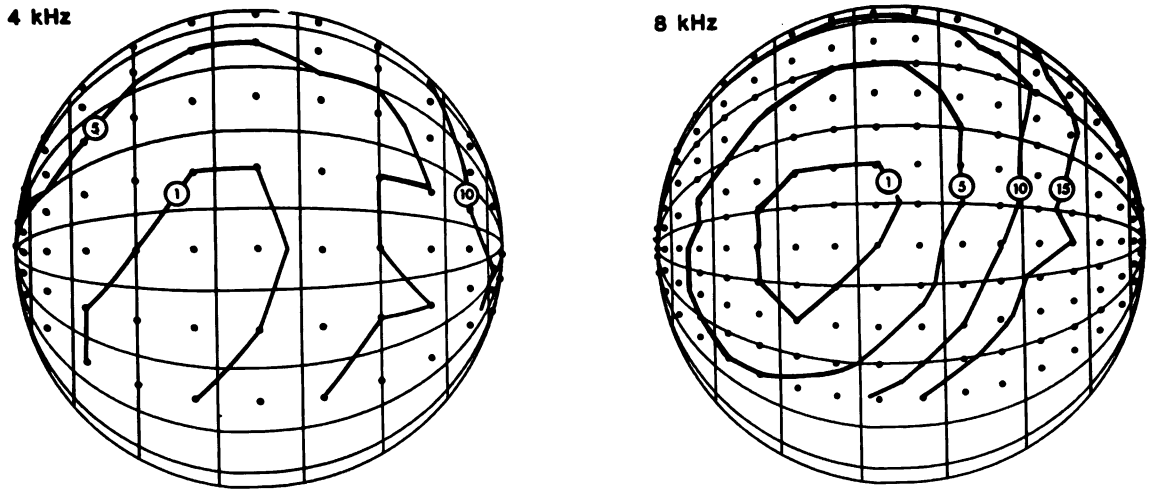
Passive acoustics of the head and pinna.

The passive acoustical properties of the head and external ear must have a prominent effect on the spatial

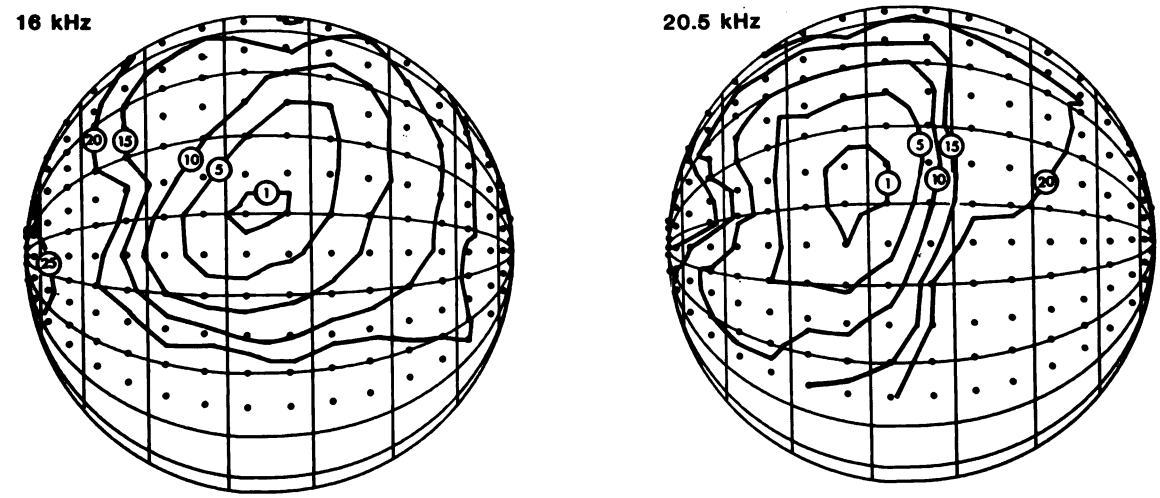
sensitivity of auditory neurons. This acoustic transfer function was estimated by measuring the sound pressure level inside the acoustic meatus with a probe microphone while presenting pure tones in the free sound field. The location of the loudspeaker was varied systematically while holding the tone frequency constant. For each frequency, data were plotted as decibels below the greatest level recorded, i.e., the datum for each point represents an attenuation relative to the level recorded for the most sensitive "axis" of the pinna. Iso-intensity contours are interpolated between the loudspeaker locations at which intensity levels were recorded.

The direction sensitivity of the right pinna at 4, 8, 16, and 20.5 kHz is shown in figure 8. The greatest ratio of maximum to minimum intensity levels measured for 4 kHz was 15 dB, 32 dB for 8 kHz, 38 dB for 16 kHz, and 40 dB for 20.5 kHz. The iso-intensity contours tend to form ovals with the major axis oriented from superior and medial to inferior and lateral. For the greatest levels (the most sensitive direction of the pinna), the contour lines form closed loops centered on approximately 10-20 degrees azimuth and 5-15 degrees elevation. These closed contours resemble the shape and location of axial receptive fields (e.g., fig. 4B). With increases in frequency (decreases in sound wavelength), the sensitivity gradient of the pinna becomes

Figure 8. Directionality of the pinna. Intensity levels measured with probe microphone inside right acoustic meatus for 4, 8, 16, 20.5 kHz. Intensity levels are expressed as decibels below the greatest level recorded for each frequency. Filled circles indicate positions of the loudspeaker for which levels were measured. Curves are iso-intensity contours interpolated between data points. Numbers in circles indicate intensity level for each contour. The innermost closed contours encircle the acoustical axis centered at approximately 10-20 azimuth and 5-15 elevation.



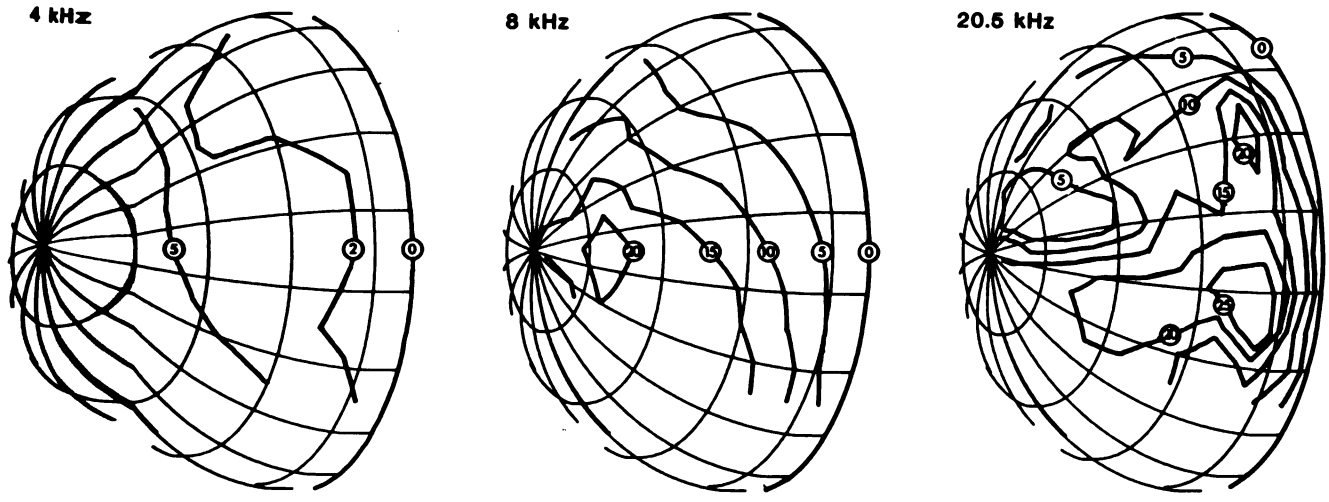
ISO-INTENSITY CONTOURS



steeper, yet the center of the innermost contour line, the pinna's acoustical "axis", remains approximately constant in location. The centers of these contours, particularly for 16 kHz, seem displaced medially like the most medial of the axial receptive fields (e.g., fig. 5A, GZ-17). The insertion of the probe microphone from behind the pinna may have inclined the pinna slightly medially causing this apparent displacement. Note however that the elevation of the acoustical axis is very similar to the elevation of the centers of axial receptive fields in all cats and this elevation also is close to that of the visual axis of the cat's eye (13 ; Bishop et al., 1962).

In figure 9, the data for 4, 8, and 20.5 kHz are replotted as interaural intensity difference (IID) versus location in the contralateral sound hemifield. This figure is derived from the data shown in figure 8 by assuming that the two pinnae are symmetrical and subtracting the sound levels (expressed in dB) for loudspeaker locations that are mirror symmetrical with respect to the mid-sagittal plane (0 degrees azimuth). Contours of constant IID are drawn. In those plots, the contours for zero IID, by definition, fall on the midsagittal plane. In the plots for 4 and 8 kHz, the contour lines are oriented from superior and lateral to inferior and medial, with an even gradient of increasing IID oriented inferiorly and laterally. The plot for 20.5 kHz is

Figure 9. Interaural intensity differences for sounds located in cat's right sound hemifield. Values are derived from figure 8 assuming that the two ears are symmetrical with respect to mid-sagital plane. Each level recorded for a loudspeaker position in the contralateral hemifield is divided by the level for a mirror-symmetrical position in the ipsilateral hemifield and value is expressed in decibels. Curves are contours of constant IID. Numbers in circles indicate IID for each contour.



INTERAURAL INTENSITY DIFFERENCE (IID)

much more complicated, with reversals in the IID gradient and isolated IID maxima.

DISCUSSION

The results of this series of experiments indicate that single units in the primary auditory cortex (AI) of the cat are sensitive to the location of sound stimuli. The characteristics of spatial receptive fields form a set of functional criteria by which every unit encountered in this study can be placed into one of three classes: 1) Omnidirectional units were relatively insensitive to sound locations. They responded to stimuli presented anywhere in the sound field, although the relative effectiveness of stimuli varied somewhat with sound location. These units made up 52% of the area of AI within the entire range of CF's sampled (approx. 3-20 kHz). 2) Hemifield units had receptive fields occupying all or most of the contralateral sound hemifield, extending beyond the extreme contralateral pole, and with a well defined border near the vertical midline. These units occupied 42% of the population of units with CF's below 12 kHz, but only 5% of the population with CF's greater than 12 kHz. 3) Axial units had completely circumscribed receptive fields that encircled the acoustical axis of the contralateral pinna. The receptive field location was approximately constant for all such units within a single cat. Axial units occupied 46% of the population of units with CF's greater than 12 kHz and only 2% of the population with CF's below 12 kHz. Units with

different types of spatial sensitivity were segregated from each other within the cortex. Iso-intensity contours derived from physical measurements of the directionality of the ear form closed curves with some spatial features in common with the observed spatial receptive fields.

Comparison with previous reports of location sensitivity.

Several previous reports have indicated that auditory cortical neurons are sensitive to sound location. Evans (1968) reported that approximately half of the units encountered in cat auditory cortex that were tested with "transient sound complexes" (snapping of fingers) gave preferential responses for particular stimulus locations. Some units responded only to stimuli presented in the contralateral hemifield, displaying a sharp diminution in their responses as the stimulus was moved a few degrees into the ipsilateral sound field.

Eisenman (1974) tested the responses of units in the auditory cortex of the cat to the presentation of tone and noise bursts He found that for many units, plots of the number of spikes elicited by stimuli as a function of the azimuth of the source showed sensitivity to sound location. Notably, 33% of 43 units studied responded more strongly to contralateral stimuli, and 16% displayed a peak response near zero degrees azimuth. There were no spatial response

profiles comparable to our axial receptive fields, although this might be expected since the separation of the loudspeaker positions in the previous study was larger than the size of many of the axial receptive fields.

Sovijarvi and Hyvarinen (1974) studied the responses of units in cat auditory cortex to continuous tonal stimuli presented from a hand-held loudspeaker. They found some units that responded only to stimuli moving in a particular direction in space. No indication was given in this report of the extent or location of regions from which stimuli were effective. In the current study, we found that most cortical units responded reliably only to the onset of our 100 msec tone bursts. The onset of a stationary tone burst which was an adequate stimulus in our experiments might be equivalent to the effect of moving a continuous tone source past a receptive field as in the study by Sovijarvi and Hyvarinen.

In the three earlier studies cited above, the location of AI was defined by cortical surface landmarks or by cytoarchitecture. Such anatomical criteria have since been demonstrated to be unreliable in locating the single cortical representation of the cochlea defined functionally (Merzenich et al., 1975). Data from a unit were included in the present study only if its response met the dual criteria of sharp tuning for frequency and correct position in the

gradient of CF's increasing from caudal to rostral. Thus, some of the responses reported in earlier studies may not be directly comparable to those recorded in our experiments, as different criteria were used for defining "AI".

Absence of a space map in AI.

Microelectrode recordings from the forebrain auditory structure, field L, of the owl have revealed the presence of single neurons with small, sharply delimited spatial receptive fields (Knudsen et al., 1977). In an auditory structure of the owl's midbrain, the MLD, units with small spatial receptive fields form a neural map of sound space, with an orderly shift in receptive field locations accompanying a shift in the location of the recording site within the nucleus (Knudsen and Konishi, 1978). No comparable map of sound space was observed in our recordings from AI of the cat. The most spatially restricted receptive fields, those of the axial units, were found in a location in the sound field that was constant for each cat. There was some variation in the location of the medial border of hemifield receptive fields, but we noted no orderly progression of these borders associated with advances of the recording electrode. Furthermore, the medial border of nearly all hemifield receptive fields fell within 20 degrees of the vertical midline.

Directionality of the ear.

Previous studies of the passive acoustics of the external ear have concentrated on directionality in the horizontal plane. In one such study, Wiener et al. (1966) measured the sound pressure level within the cat's acoustic meatus as a function of tone frequency at each of five azimuths (±90, ±45, and 0 degrees), all in the horizontal plane. For all frequencies, the greatest level was recorded when the sound was presented 45 degrees from the vertical midline. This is consistent with our observation that the center of iso-intensity contours for the directionality of the pinna, the acoustical "axis", remained approximately constant for all frequencies tested.

It is interesting to compare the acoustics of the cat's pinna with that of the human pinna. Shaw (1965) plotted the sound pressure recorded in the human acoustic meatus as a function of frequency for five different angles in the horizontal plane (±90,±45, and 0 degrees). The sound source producing the greatest level in the meatus varied between +45 and +90 degrees as the sound frequency was changed. This variation in the orientation of the axis of the human pinna was substantially greater than that noted in our results and in those of Wiener et al. (1966) for the cat. Hebrank and Wright (1974) have shown that the elevation of the axis of the human pinna is even more

dependent than azimuth on the frequency of a sound. Using artificial ears molded from human pinnae, they showed that the most sensitive elevation in the vertical midline plane changed from 60 degrees above horizontal to 30 degrees below horizontal with a change in sound frequency from 6 to 12 kHz (measured from their fig. 4). The differences between the pinnae of the cat and human could indicate a fundamental difference in the potential use of the external ear by the two species, perhaps also related to the fact that the behaving cat, but not man, is able to make both coordinated movements of both ears and isolated movements of each ear.

The frequency response profile of the human pinna contains narrow-band "notches" that move in the frequency domain as a function of sound source elevation (Hebrank and Wright, 1974). In our measurements of the directionality of the cat's pinna, sounds were varied systematically in the spatial domain for a limited number of frequencies. If such notches are present for the cat, they would appear as local minima in our directionality plots. No such pronounced minima were observed, although they might have been detected had we used a finer "grain" of loudspeaker placements.

Derivation of spatial receptive fields from acoustic cues available to the nervous system.

The spatial receptive fields plotted for auditory

cortical units resemble tactile and visual receptive fields determined for somatosensory and visual cortical units. However, the neural code for the location of acoustic stimuli is fundamentally different from the code for tactile and visual stimuli. Locations on the body surface or in the visual field are encoded directly as locations on the skin or retina, while spatial features of a sound source must be extracted within the central nervous system from multiple monaural and binaural stimulus cues. Among the most significant of these cues are interaural delay, interaural intensity differences (IID's), spectral cues, monaural cues derived from the directionality of the pinna, and cues which rely on scanning movements of the head and pinnae.

Some of the above cues could not have contributed to the spatial sensitivity observed in the current study. 1) In our anesthetized preparation, no movements of the head were possible and no movements of the pinnae were observed in response to sounds. 2) Spectral cues could not have contributed to the sharpness of spatial receptive fields seen in the current experiments, as only pure tone stimuli were presented. We would not expect broad band spectral cues to contribute to the location sensitivity of neurons in AI, as single units in AI are sharply tuned for frequency (Merzenich et al., 1975). If there are cortical neurons that derive location information from a convergence of input

from a broad region of the audible spectrum, they would be more likely to be found in one of the non-tonotopically organized cortical fields such as AII, where single units have relatively flat frequency tuning curves (see Merzenich et al., 1979). 3) Interaural delay cues are a source of spatial information for low frequency sounds. However, in the existing report of delay sensitivity in the auditory cortex of the cat, no units with CF's greater than 2.5 kHz were detected (Brugge et al., 1969), while most of the units sampled in the current study had CF's greater than 3 kHz.

Correlation of location sensitivity classes with classes defined with dichotic stimulation.

The sensitivity of auditory cortical neurons in the cat to some binaural stimulus parameters has been tested in experiments in which sound stimuli were delivered independently to each ear (e.g., Hall and Goldstein, 1968; Brugge et al., 1969; Abeles and Goldstein, 1970). Many units in auditory cortex respond to monaural stimulation of either ear and their responses are facilitated by binaural in-phase stimulation. These units have been called "excitatory/excitatory", or "EE". Other units are excited by contralateral stimulation, but are inhibited by simultaneous ipsilateral stimulation ("excitatory/inhibitory" or "EI"). Some units respond maximally to binaural stimulus pairs containing an

interaural delay ("delay sensitive" units; Brugge et al., 1969).

a) Omnidirectional units and EE units? The omnidirectional units observed in the current experiments were driven by stimuli presented anywhere in front of the cat with thresholds within 10 dB above the threshold for the most effective loudspeaker location. For all frequencies tested, the 10 dB contours for the directionality of the pinna nearly fill the portion of the sound field in front of the cat extending from the vertical midline to the lateral pole. A neuron that could respond to excitatory inputs from the contralateral and/or ipsilateral ears would be expected to have thresholds restricted to a range of 10 dB for stimuli presented anywhere in front of the cat. Thus, it seems likely that the omnidirectional units are equivalent to at least some of the EE neurons described previously.

b) Hemifield units and EI units? Hemifield units were driven by stimuli presented in the contralateral sound field, and the response ceased as the stimulus was moved into the ipsilateral field. Moving the sound source into the ipsilateral sound field is comparable to increasing the intensity of an ipsilateral stimulus in an experiment using diotic stimulation. Thus, the hemifield units may be equivalent to EI neurons. In previous descriptions of EI neurons (e.g., Brugge et al., 1969; Middlebrooks et al.,

1980), the greatest changes in the response rate of EI neurons occurred for contralateral and ipsilateral stimuli that were within 15 dB of equal intensity. This would correspond to a band of loudspeaker locations centered on the vertical midline, the region of the sound field containing the medial borders of most hemifield receptive fields. Brugge et al. (1969) demonstrated with dichotic stimulation that EI neurons in the cortex are most sensitive to changes in IID and are relatively insensitive to the net intensity of a binaural stimulus pair. Thus, one might expect the border of the receptive field of an EI unit to follow a contour of constant IID. The iso-IID contours derived in figure 9 for 4 and 8 kHz tones resemble the medial borders of many of the hemifield receptive fields.

c) Axial units and EI units? The receptive fields of axial units have the shape and location of the innermost iso-intensity contours for the contralateral ear derived from physical measurements of pinna directionality. Most of the axial units had CF's greater than 12 kHz, the range of frequencies for which the pinna is most directional. Both the location of axial receptive fields and the location of the axis of the pinna are approximately constant within a single cat for a range of sound frequencies. When the contralateral pinna is manipulated by the investigator, axial receptive fields move in the same direction as the

pinna. These points argue that the responses of axial units are dominated by excitatory inputs from the contralateral ear. However, the receptive field of such a monaural unit would be expected to expand greatly with increasing intensity, just as the iso-intensity contours in figure 8 expand. In contrast, axial receptive fields expand with intensity no more than the field shown in figure 6C. In experiments using dichotic stimulation, monaural units seldom are recorded in the cortex: most unit responses are either facilitated or inhibited by ipsilateral stimulation (Imig and Adrian, 1977; Middlebrooks et al., 1980). For three axial units studied in the current study, blocking the ipsilateral ear with a ball of cotton made the boundaries of the receptive fields more sensitive to increases in stimulus intensity. This suggests a role of ipsilateral inputs in "sharpening" the spatial tuning of axial units.

Could axial units correspond to EI units? In our protocol, locations of the loudspeaker near the axis of the contralateral pinna, i.e., within axial receptive fields, were the most comparable to a contralateral monaural stimulus, the most effective stimulus for an EI neurons. Movements of the loudspeaker away from this axis would decrease the ratio of contralateral to ipsilateral intensity, somewhat analogous to increasing the strength of the ipsilateral input in a dichotic stimulation experiment.

Such a movement of the loudspeaker would place it outside of an axial unit's receptive field, much as increasing the intensity of an ipsilateral stimulus inhibits the response of an EI unit.

Spatial receptive field properties and functional organization within AI.

Recent experiments using dichotic stimulation and microelectrode mapping techniques have revealed some basic features of functional organization in AI. Imig and Adrian (1977) confirmed earlier indications (Abeles and Goldstein, 1970) that neurons arrayed in radial columns through the depth of AI have similar responses to binaural (dichotic) stimulation, and they showed that these binaural columns are elaborated for varying distances in the plane of the cortex. In each binaural column, all responses encountered were EE (excitatory/excitatory) or all responses were EI (excitatory/inhibitory). Over the range of CF's encountered (approx. 3-20 kHz), EE units occupied two thirds and EI units occupied one third of the sampled population. Middlebrooks et al. (1980) showed that the binaural columns form radially organized bands oriented rostro-caudally across the axis of iso-frequency contours and extending over the length of AI. The primary field in each hemisphere usually contains three EI bands separated by two EE bands. This banded organization also is demonstrable in the pattern

of transcallosal connections between AI in the two hemispheres (Imig and Brugge, 1978). It was suggested from the microelectrode mapping data as well as from existing connectional and cytoarchitectonic evidence that the binaural interaction bands in AI might represent independent cortical processing units with fundamentally different roles in cortical function (Middlebrooks et al., 1980).

In the current experiments, units with different classes of sensitivity to sound location were segregated along both tangential and radial electrode penetrations. At lower frequencies (below 12 kHz), sequences of omnidirectional units alternated along tangential penetrations with sequences of hemifield units. For higher CF's, sequences of omnidirectional units alternated with sequences of axial units. Sequences of units of a given response class were encountered more than once along a single penetration. It was argued above that omnidirectional units probably are equivalent to EE units, and that hemifield and axial units might be equivalent to EI units. Confirmatory experiments remain to be done, but the current evidence is most consistent with the interpretation that AI is subdivided by a pattern of bands of omnidirectional units alternating with bands of hemifield and axial units that is comparable to the pattern of alternating EE and EI bands shown previously.

Comparison of AI with VI.

There are a number of similarities and contrasts to be pointed out between the functional organization just described for AI and the well characterized functional organization of the primary visual cortex, VI. For example, the functional segregation into receptive field classes which has been emphasized in the visual cortex is based on laminar differences in the incidence of neurons with "simple", "complex", and "end-stopped" receptive fields (Gilbert and Wiesel, 1979). In the present case, the functional segregation into omnidirectional, axial, and hemifield units is not based on a laminar subdivision of radial cell columns, but rather upon a topographic subdivision of the medio-laterally oriented isofrequency contours, probably correlated with the system of binaural interaction bands. In this respect, a more appropriate comparison might be made with the functional subdivision of VI into ocular dominance bands which are superimposed on the cortical map of the retina.

Binaural interaction bands and ocular dominance bands both may reflect a substrate for the representation of information extracted by comparison of bilateral inputs: sound location from binaural interaction and visual depth relative to the fixation plane from binocular interaction (e.g., Cooper and Pettigrew, 1979). Although topographic

segregation of binocular units with respect to target depth relative to the fixation plane has not been demonstrated in the visual cortex of the cat, such segregation has been observed in the visual cortex of ungulates (Clarke et al., 1976). This raises the possibility that the functional organization of AI and VI will prove ultimately to be more comparable than present data indicate.

AI and sound localization behavior.

Ablation-behavioral studies have implicated the auditory cortex in the localization of sound. Large bilateral lesion of the temporal cortex can almost completely disrupt the ability of a cat to localize a sound (e.g., Neff et al., 1956; Riss, 1959). Unilateral lesions cause pronounced behavioral deficits only in tests where cats must distinguish between the locations of transient sounds presented within the contralateral hemifield (Jenkins, 1980). It is difficult to compare the classical behavioral studies with the current study of single units in AI, as recent mapping studies have demonstrated that the location of AI is defined only approximately by the anatomical landmarks used for delimiting ablations. There has been no published report of a deficit in sound localization behavior in a cat following the placement of a lesion that was restricted to AI as defined by single unit or other evoked potential recording method.

Axial units have the most restricted receptive fields of all units recorded in AI. Yet all of the axial units in AI of a given hemisphere are trained on the same region of auditory space, presumably the region along the axis of the contralateral pinna. These units would be effective in localizing a sound only if the cat could make scanning movements of the head and pinna, yet a normal cat can identify the source of a sound even if the stimulus is a click so brief that the cat has no time to scan (Jenkins, 1980). Alternatively, hemifield units would at least indicate the laterality of the stimulus. A click presented at the extreme lateral pole of the sound field would be expected to activate hemifield and omnidirectional units in the contralateral cortical hemisphere, but would activate only omnidirectional units in the ipsilateral hemisphere.

The two location selective unit classes found in AI, axial and hemifield, were associated with different ranges of CF, with most axial units displaying CF's higher than the majority of hemifield units' CF's. Presumably, the only location selective units that would be activated in AI by a high frequency tone would be the axial units, and likewise the hemifield units would be the only location selective units activated by lower frequency tones. In nature, a cat rarely encounters a pure tone stimulus, yet cats in a laboratory are able to discriminate the locations of pure

tone stimuli separated by as little as 10-20 degrees (however, this has been shown only when the stimuli were long enough to scan; Casseday and Neff, 1973). It is difficult (as well as unrealistic) to explain the available sound localization data entirely within the context of the location selective units that we have encountered in AI. It would appear that other mechanism must be at work in sound localization, perhaps in one or more of the other auditory cortical fields.

We favor a view of the axial units as part of a mechanism for a cat to scrutinize a sound source of interest. Cats can be observed exploring their environments with independent movements of both pinnae, effectively placing novel sounds into the receptive fields of their axial units. If a sound of particular interest is detected, the cat orients its head and both pinnae toward the source. This motion would devote the bands of axial units in both hemispheres to analysis of the sound, also helping to exclude extraneous sounds located more laterally. In this regard, it perhaps is significant that the axial receptive fields and the acoustical axes of the pinnae are aligned with the cat's visual axes. (Bishop et al., 1962).

Conclusion:

By systematicall varying the locations of sound

stimuli presented in a free sound field, we have revealed the presence in AI of units that are sensitive to sound location in two dimensions, azimuth and elevation. Yet, we also have raised the likelihood that AI is not the principal cortical substrate for an internal map of auditory space. The omnidirectional units, the largest class encountered in these experiments, have little or no selectivity for sound location. The receptive fields of the two location selective unit classes appear not to cover the contralateral sound field with resolution comparable to that observed in behavioral studies. However, the classification of units by spatial sensitivity does reveal a form of topographical organization within the medio-lateral dimension of AI. The unit types distinguished in this way might represent stages of two fundamentally different lines of processing of auditory information that are topographically segregated in AI. One system, represented in AI by the omnidirectional units, appears to contribute to detection and/or analysis of non-spatial features of sounds. The other, location selective, system comprises the hemifield units for lower frequencies and the axial units for higher frequencies. Activity in the hemifield units could signal the approximate location, left or right, of a sound. The axial units constitute a cortical region devoted to the scrutiny of sounds aligned with the axis of the external ear.

CHAPTER THREE

SEGREGATION OF THALAMIC SOURCES TO BINAURAL RESPONSE-SPECIFIC SUBDIVISIONS OF THE PRIMARY AUDITORY CORTEX (AI) OF THE CAT

ABSTRACT

The representation of high frequencies in the primary auditory auditory cortex (AI) of the cat contains functionally defined subdivisions ("binaural interaction bands") within which all recorded neurons display similar responses to binaural stimulation. The purpose of the current study was to identify the thalamic sources of input to identified binaural bands in AI and to characterize the band-specific thalamocortical topography. This was accomplished by mapping the borders of binaural bands in AI using microelectrode recording with diotic tonal stimulation, then introducing injections of one to three retrograde tracers into different bands. We identified binaural bands that were constant in relative location in every studied cat, and regions where the binaural organization was more variable. Within the major thalamic source of input to AI, neurons that projected to different classes of binaural bands were strictly segregated.

In microelectrode maps in 24 hemispheres, excitatory/excitatory (EE) binaural neurons were segregated from excitatory/inhibitory (EI) neurons. In each of these maps, we encountered a ventral pair of rostrocaudally continuous EI and EE bands, a middle area within which the pattern of binaural subdivisions was more variable, and a dorsal zone (DZ) within which the responses of neurons

differed in binaural properties and in frequency specificity from the characteristic AI response patterns. The EI regions in AI apparently all derive input from the same array of projecting neurons in the ventral division (V) of the medial geniculate body. This array consists of three discrete subunits: two horizontally oriented layers of cells in the lateral part of V (Vl) and a column of cells which extends from the ovoidal part of V into the ventral part of the rostral pole of Vl. The EE bands and DZ derive their input from a single continuous structure which comprises the dorsal cap of V (Vdc), a horizontal layer in Vl interposed between the two EI-projecting layers, and a thickened layer which fills the dorsal two thirds of the rostral pole of Vl. Portions of this EE-projecting structure in V were labeled preferentially by injections introduced into particular EE subdivisions in AI. Comparisons of the results of injections that were centered within bands with those introduced on the border between bands indicate a high degree of convergence and divergence in the connections between a single band in AI and its sources of thalamic input.

These observations indicate that the high frequency representation in AI and its principal thalamic source of input, V, may be thought of as assemblies of spatially discrete, functionally distinguishable subunits. The

observed thalamocortical topography, considered with the response characteristics of EE and EI neurons, suggest a model of functional organization in the forebrain representation of high frequencies in which EI bands confer information relevant to sound location upon the product of non-spatial, perhaps spectral, analysis that is carried out within EE bands.

INTRODUCTION

The primary auditory cortex (AI) of the cat contains functionally distinguishable topographical subdivisions. Within each subdivision, all recorded neurons display similar responses to binaural stimulation (Imig and Adrian, '77; Imig and Brugge, '78; Middlebrooks et al., '80; Imig and Reale, '81a). Neurons which respond optimally to stimulation of both ears ("excitatory/excitatory"; "EE") occupy radially organized modules which are segregated from modules of units which are excited by stimulation of the contralateral ear and inhibited by ipsilateral stimulation ("excitatory/inhibitory"; "EI). These "binaural interaction bands" are elongated rostrocaudally, parallel to the axis of representation of the cochlear sensory epithelium (i.e., roughly orthogonal to the isofrequency contours of AI).

The rostrocaudally elongated shape of binaural interaction bands in AI has been described in several reports (Imig and Adrian, '77; Imig and Brugge, '78; Middlebrooks et al., '80; Imig and Reale, '81a). However, the dimensions of bands apparently are highly variable among different cats. Details of the organization of the bands, such as their numbers, dimensions, and neuronal response characteristics beyond the basic EE/EI distinction, have not been determined, nor have the sources of input to different bands been defined. What is the meaning of the apparent

variability in the banding pattern in different cats? Are binaural bands functional subunits which contribute in ensemble to a unified product of AI, or are they largely independent parallel processing regions within AI? By the criteria enunciated by Rose and Woolsey (Rose, '49; Rose and Woolsey, '49), a cortical field is defined by: 1) characteristic neural response properties; 2) distinguishable cytoarchitectonic features; and 3) field-specific input and output connections. How are these criteria met by AI, and by its binaural bands? These studies have been undertaken to begin to address these questions.

Recent studies of the distribution of thalamic input to AI have characterized the basic pattern of projection from isofrequency laminae in the ventral division (V) of the medial geniculate body (MGB) to isofrequency contours in AI (Colwell, '75; Colwell and Merzenich, '75, 82; Andersen et al., '80b; Merzenich et al., '82). Moderate sized injections of retrograde tracers, centered well within AI and spreading over only a fraction of its mediolateral extent, resulted in retrograde labeling of entire isofrequency laminae in V, regardless of the position of the injection along the length of an isofrequency contour. Smaller injections of retrograde tracer introduced at sites of representation of high frequencies sometimes resulted in multiple discrete patches of labeled neurons located within

isofrequency laminae in V. Those results suggested that a single locus in this principal thalamic input source to AI sends divergent projections to repeating subunits distributed along an isofrequency contour in AI; and, conversely, that a narrow zone within an isofrequency contour can receive convergent projections from sources distributed across an entire isofrequency lamina. Merzenich and his colleagues ('82) speculated that the discontinuous patches within an isofrequency lamina in V might be thalamic subunits that provide input to given binaural bands. Does each band (or class of bands) receive its input from a band-specific (or class-specific) neuronal population? Does the intrinsic organization of the thalamus reflect in some way the functionally defined subdivision of AI?

These questions have been addressed in a series of experiments which employed a combination of physiological and anatomical tracing techniques. The boundaries of binaural bands and the tonotopic organization within bands were defined by mapping AI in detail with microelectrodes while presenting diotic stimuli. Subsequently, injections of one to three retrograde tracers were introduced into AI with reference to these functional maps. Two binaural bands in the ventral aspect of AI were identified consistently in mapped hemispheres. The arrays of cells in the MGB that project to these repeatedly encountered EE and EI bands were

found to be largely segregated from each other within an apparently functionally subdivisible ventral division of the MGB. These complex neuronal arrays were remarkably constant in form among different individual cats. Injections introduced into EE and EI subdivisions located farther dorsal in AI demonstrated that bands that are of the same binaural class derive input from common thalamic sources. These results lead to a new view of the functional organization of the MGB and AI.

A preliminary report of these experiments has been presented elsewhere (Middlebrooks and Zook, '81).

METHODS

In each of these experiments, a sector of AI was mapped with microelectrodes, then retrograde tracers were introduced into functionally identified binaural bands. Attention was focussed on the segment of AI in which frequencies greater than 5 kHz are represented. Within this higher-frequency region of AI, binaural interaction bands are best defined and injections of retrograde tracers previously have been shown to produce discontinuous patterns of label in the auditory thalamus (Colwell, '75; Colwell and Merzenich, '75, '82; Andersen et al., '80; Merzenich et al., '82).

Functional mapping.

The results presented here are based on experiments using 38 adult cats. Cats were inspected otoscopically. Animals with apparently normal external ears were anesthetized (I.P.) with sodium pentobarbital, supplemented with IV injections, to maintain an areflexic state. The cortex was exposed and protected with a pool of silicone oil. Hollow ear bars were sealed into the ear canals, leaving the external ears intact.

Sound stimuli consisted of tone bursts shaped with 5 msec rise/fall times. The intensities of stimuli presented to the two ears were controlled independently with decade

attenuators. Tones were generated with headphones (Beyer) that were coupled to the hollow ear bars.

The activity of single units and of small clusters of units was recorded with glass insulated platinum-iridium microelectrodes. Electrode penetrations were oriented approximately normal to the cortical surface. All penetrations in any given experiment were aligned parallel to each other. The locations of penetrations were marked on a magnified photograph of the cortical surface, using the surface vasculature for positional reference. Neural activity was monitored on an oscilloscope and an audio monitor. Best frequencies and binaural response characteristics were defined in the middle cortical layers.

Contralateral monaural tone bursts were used as search stimuli. When no response could be evoked with monaural stimuli, binaural tone pips of equal intensity were used. The characteristic frequencies (CF's) of units and of unit clusters were determined by finding the frequency of the lowest intensity tone burst with which neural responses could be evoked. Once CF was defined, the binaural response class was determined using CF tone pips. Units were assigned to one of two binaural classes by observing the effect of stimulation of the ipsilateral ear on the threshold for contralateral stimulation. Electrode penetrations in which ipsilateral stimulation added to or

facilitated the responses of units to contralateral stimulation were classified as excitatory/excitatory (EE), and penetrations in which ipsilateral stimulation inhibited contralaterally-evoked unit responses were classified as excitatory/inhibitory (EI). In some penetrations that were classified as "EE", units were not driven by stimulation of either ear alone at any stimulus level although they responded with low thresholds to binaural stimulation. In the vast majority of radial electrode penetrations in AI, units recorded along the entire length of the penetration had CF's falling within a narrow range and were of the same binaural class (see Merzenich et al., '75; Imig and Adrian, '77; Middlebrooks et al., '80). Thus, each penetration could be represented by a single point on a map of the cortical surface.

Significant variation was observed in response properties within each binaural class, such as differences in relative thresholds for the two ears, "aural dominance", "facilitation" versus "summation" in EE responses, etc. (see Imig and Adrian, '77; Kitzes et al., '80). A more quantitative characterization of responses probably would have enabled us to distinguish several subclasses. At the same time, the simple dichotomous classification scheme that was used revealed a simple, consistent basis for identifying functional boundaries within AI.

The recognition of constant features of binaural representation was facilitated by determining carefully the location of the border between AI and the second auditory field (AII), which lies ventral to AI. This border was defined in 21 cases. Recordings from AII near the AI/AII border are characterized by broad frequency tuning compared to the sharp tuning characteristics of recordings from AI (see Merzenich et al., '75; Reale and Imig, '80). While unit clusters in AI had clearly defined CF's, clusters in AII often responded to frequencies ranging over an octave at levels only 10 dB above the threshold for the best frequency. In occasional penetrations in which the distinction between characteristic AI and AII neural responses was in question, the effect on neural thresholds of reducing the rise time of the tone burst was tested. The resulting increase in spectral complexity commonly reduced the thresholds of unit clusters in AII by 10 to 20 dB while it had no effect or even increased the threshold of units or clusters in AI. Using one or both of these criteria, the AI/AII border could be defined clearly. Given this boundary definition, specific binaural bands could be identified repeatedly.

Retrograde Tracing

The microelectrode maps of each hemispere were used to guide the placement of microinjections of retrograde

tracers. Injections were positioned with reference to the boundaries of identified binaural bands at sites of known characteristic frequency. Injections were made through glass micropipettes (30-40 um tips, beveled) sealed to a 1 ul syringe (Unimetrics). When care was taken to exclude all air bubbles from the micropipette and syringe, it was possible to make reliable mechanical injections with volumes in the range of tens of nanoliters. In some cases, horseradish peroxidase (HRP) was used as the only retrograde tracer. In other studies, multiple retrograde tracers were used to compare directly the sources of input to several binaural bands in the same preparation. Protocols for single and multiple tracer studies will be described separately.

Single tracer experiments. Horseradish peroxidase (Bohringer-Mannheim grade I) was injected as a 30% solution in distilled water. The injection pipette was advanced 1.0 mm radially into the cortex and was left in place for 5 min following the injection. Injection volumes were 30 or 50 nl. After the pipette was withdrawn, the cortex was covered with Gelfilm (Upjohn), the temporal muscle was sutured in place, and the scalp closed. Local and systemic antibiotics were administered. Following a survival period of approximately 30 hours, cats were anesthetized deeply and perfused transcardially with a wash of warmed 0.1 M

phosphate buffer containing 4% sucrose followed by a fixative of 4% glutaraldehyde, buffered and containing 4% sucrose. Brains were blocked stereotaxically and stored cold in buffered 30% sucrose for two days.

The brains were frozen and sectioned on a sliding microtome at 50 um in the Horsley-Clarke coronal plane. Sections were reacted for peroxidase activity using tetramethyl benzidine (TMB) as the chromagen (Mesulam, 1978). After the reaction, the sections were transferred to cold acetate buffer (pH 3.3), then mounted on subbed slides. In some cases, alternate sections were counterstained with Neutral Red. The air-dried slides were cleared in methyl salicylate, rinsed briefly in xylene, then coverslipped with Eukitt (Calibrated Instruments, Inc.). This coverslipping procedure avoided exposing the tissue to ethanol, which can cause fading of the TMB reaction product (Adams, '80).

Multiple tracer experiments. In some experiments, fluorescent dyes also were used as retrograde tracers. Good results were obtained using Nuclear Yellow (NY; Bentivoglio et al., 1980b) and Propidium Iodide (PI; Sigma; Kuypers et al., 1979), in conjunction with HRP, to trace simultaneously the projections to three sites in the AI. The histological protocol that was used reflects a compromise among the particular requirements for each of the three tracers.

The fluorescent dyes were injected as suspensions in distilled water (1% and 0.75% for NY and PI, respectively) using micropipettes and a 1 ul syringe as described above. Effective injection sites for PI were more restricted than for equal volumes of NY or HRP. Therefore, injection volumes of 30, 30, and 100 nl typically were used for HRP, NY, and PI, respectively, to achieve effective injection sites of comparable size. Post-injection survival periods of 56-60 hrs were used. This longer time was necessary for adequate visibility of transported PI. Transported NY was visible following survival times of 30 hrs, but the transported label was seen more clearly with longer post-injection survivals. With a survival time of 56-60 hrs, HRP-labeled cells were visualized readily in the thalamus; the injection site appeared more diffuse than after 30 hrs.

A modified perfusion and sectioning protocol was necessary to retard the diffusion of NY (Bentivoglio et al., '80a) while maintaining adequate HRP activity. Following an appropriate survival period, cats were anesthetized deeply and perfused transcardially with a washout of 0.1 M phosphate buffer containing 4% sucrose, followed by a fixative of buffered 2% paraformaldehyde containing 4% sucrose and 1.5% dimethyl sulfoxide (DMSO). The DMSO was added as a cryoprotectant in lieu of equilibration in 30% sucrose. Brains were blocked stereotaxically, then removed

from the skull and frozen quickly in heptane on dry ice. Quick freezing was used to retard the formation of large ice crystals. Brains were sectioned on a cryostat at 32 um in the Horsley-Clarke coronal plane and the sections were mounted directly on 2 or 3 sets of subbed slides. One set of slides, for fluorescence microphotography, was left unreacted and uncoverslipped. fluorescence microscopy. Another set of slides was reacted for peroxidase histochemistry as described above, although in this case the reaction was carried out with the sections mounted on slides. This set of slides was cleared and coverslipped as described above.

The method of tissue preparation described here minimized the problem of migration of NY from labeled neurons into adjacent glial cells (Bentivoglio et al., '80b). In good cases, NY label was concentrated within neurons and only faint NY label was seen in glia located in NY-labeled projection areas. In all cases, it was necessary to straighten occasional wrinkled sections using a small brush and a drop of distilled water. In these sections, NY-labeled glial nuclei were seen more commonly and the intensity of label in neurons seemed somewhat reduced.

In the tissue reacted for HRP, the NY label survived remarkably well, although NY-labeled glia were abundant in that material and NY label appeared less concentrated in

neurons. PI-labeled cells could not be identified in tissue reacted for HRP. The TMB reaction product in the tissue reacted on slides did not label neuronal processes as reliably as tissue processed more conventionally, but the patterns of label within the thalamus and the average densities of labeled cells were comparable.

Data analysis.

HIstological materials were examined using transmitted light and fluorescence microscopy. A microprojector was used to draw the outlines of sections and the positions of HRP-labeled cells. Bright field photomicrographs were made with a Nikon Multiphot macrophotography system. Fluorescence-labeled tissues were observed and photographed with a Zeiss Universal fluorescence microscope using excitation wavelengths of 360 nm for NY and 550 nm for PI. With these excitation wavelengths, NY-labeled cells appeared yellow against a blue background and PI-cells were bright red against a dull red background. Fluorescence-labeled tissue was photographed on color positive film (Ektachrome 400, processed to yield a speed of ASA 800). The positions of fluorescence-labeled cells were marked on drawings of the section outlines by projecting the color film with a photographic enlarger and using blood vessels for alignment. Three dimensional reconstructions of histological materials were made using a

computer graphics system.

Interpretation of neuroanatomical experiments of this type is limited fundamentally by the ability to limit the size of the effective injection site. The apparent sizes of the injection sites were much greater than the area of cortex contributing to thalamic labeling and varied with the post-injection survival time, the fixation protocol (in the case of NY), and the sensitivity of the histochemical protocol (for HRP). Nevertheless, two lines of evidence indicate that injections could be restricted to single binaural interaction bands: 1) In cases where injections were placed within several hundred microns of the border of AI with AII, no labeled cells were seen in subunits of the MGB that are labeled by injections into AII (Andersen, '79; Andersen et al., '80). 2) From the known tonotopic organization of AI (Merzenich et al., '75) and the ventral division of the MGB (Colwell and Merzenich, '75, '82; Andersen et al., '80; the current results), one can calculate the relative magnification of the frequency representation in these two structures. Using this factor, the mediolateral thickness of the labeled isofrequency lamina in the ventral division (i.e., the amount of spread along the axis of tonotopic representation) can be related to the size of the effective injection site in AI. This calculation commonly yielded effective injection sites of

the order of 500 um in diameter.

Subdivision of the auditory thalamus. The nomenclature that we use for subdivision of the auditory thalamus follows the definitions of Morest ('64, '65), and Jones and Powell ('71). The MGB has ventral (V), medial (M), and dorsal (D) divisions. The ventral division is the principal source of input to AI (e.g., Rose and Woolsey, '49; Neff et al., '56; Colwell, '75; Colwell and Merzenich, '75, '82). It occupies the lateral and ventral aspect of the rostral two thirds of the MGB and may be subdivided into lateral (Vl), transitional (Vt), and ovoidal (Vo) parts and a dorsal cap (Vdc). The visualization of these subdivisions was facilitated in this retrogradely labeled material by the variation within V of the pronounced laminar arrangement of perikarya and dendrites and of the orientation of the arrays of cells that project to the representation of a single frequency in AI. In Vl, located lateral and dorsal in V, the orientation of the apparent cellular laminae lies approximately parallel to the lateral margin of the MGB. In the dorsal aspect of Vl, the laminae turn medially to form Vdc which abuts the fibers of the acoustic radiation. In the ventral aspect of Vl, the cellular laminae curve medially to form Vt. The ovoidal part of V lies ventral and somewhat medial to Vl. Descriptions of Vo in Golgi material have emphasized the coiled appearance of the laminae, but in

material in which the projection for a single frequency is labeled retrogradely, a single laminae oriented from dorsomedial to ventrolateral is more apparent (Colwell, '75; Colwell and Merzenich, '75, '82; Andersen et al., '80; the current results).

The medial division consists of a population of large cells located among the fibers of the brachium of the inferior colliculus in the ventromedial aspect of the MGB. In our material, retrogradely labeled cells in M formed a cluster that lay lateral to Vt, separated from V by bundles of fibers. In D, only the deep dorsal nucleus (Dd) was labeled retrogradely by injections in AI. This subdivision lies dorsal to M and medial and dorsal to V in the rostral two thirds of the MGB. Laminae of retrogradely labeled cells in Dd were oriented from dorsolateral to ventromedial, while laminae in the dorsal part of Vl were oriented dorsomedial to ventrolateral. The fibers of the acoustic radiation delimit Dd and Vdc. The lateral part of the posterior thalamic group (POl) is continuous rostrally with Dd and lies medial to the fibers of the acoustic radiation. This is the subdivision of the posterior group which receives ascending input from the brachium of the inferior colliculus (Moore and Goldberg, '63) and descending input from the auditory cortex (Jones and Powell, '71).

RESULTS

Sectors of AI were mapped in 24 hemispheres in detail sufficient to identify binaural bands and to position injections of retrograde tracers. Best frequencies and binaural response classes were defined at 32 to 120 cortical sites in each of these experiments. Injections of one to three retrograde tracers were introduced in each of 17 of these cats. In every cat, units that exhibited similar responses to binaural stimulation occupied regions ("binaural interaction bands") that appeared to be elongated rostrocaudally. The border between AI and the second auditory field (AII) was defined in 21 cases. In all of these cats, a band of excitatory/inhibitory (EI) units was identified at the ventral margin of AI; in every cat, it was bordered dorsally by a band of excitatory/excitatory (EE) units. In many of these cases, the dorsal part of AI also was explored. Along the dorsal margin of AI, a region was encountered within which responses differed in frequency specificity and binaural response (as described in more detail below) from those recorded elsewhere in the field. This region is referred to here as the dorsal zone (DZ). In the region of AI lying between DZ and the ventral binaural bands, the dimensions of alternating binaural "bands" were somewhat more variable; these bands often were not continuous rostrocaudally. Injections of retrograde tracers

centered in the ventral EE and EI bands, in DZ, and in the "middle binaural "bands" each resulted in characteristic arrays of retrogradely labeled neurons in the thalamus. Neurons in the ventral division (V) of the medial geniculate body (MGB) that projected to EI bands were segregated from those that projected to EE bands and to DZ (which was principally EE in binaural response character).

Microelectrode maps of AI are illustrated for four representative cases in figure 1. Symbols indicate the sites of radial electrode penetrations and the class of binaural responses that was recorded at each site. Irregular vertical lines indicate isofrequency contours that have been interpolated between recorded CF's. In some penetrations, unusually broad frequency tuning was encountered (indicated in fig. 1 with triangles). These penetrations fell within DZ, described below. Again, ventral EI and EE bands were identifiable in each illustrated map. The maps in figures 1B, C, and D extended across the full width of AI, into DZ.

The composite AI projection pattern. In the case represented in figure 2, an attempt was made to define the entire array of cells in the thalamus that projects to the representation of a single frequency in AI (Colwell, '75; Colwell and Merzenich, '75, '82). Five injections of horseradish peroxidase (HRP) were placed at even intervals

Figure 1. Maps of AI in the right hemisphere in four cases. Lateral view. Symbols indicate the positions of radial electrode penetrations. Circles and triangles indicate penetrations where the frequency tuning of neurons was sharp or broad, respectively. Open and filled symbols indicate EE or EI, respectively, responses to binaural stimulation. Crosses indicate penetrations where recorded neuronal activity was characteristic of AII. Vertical lines with numbers indicate isofrequency contours with CF's specified in kHz. The location of the ventral border of the dorsal zone (DZ) is indicated in B, C, and D. The map in A was not continued dorsally to DZ. dm=dorsomedial; r= rostral.

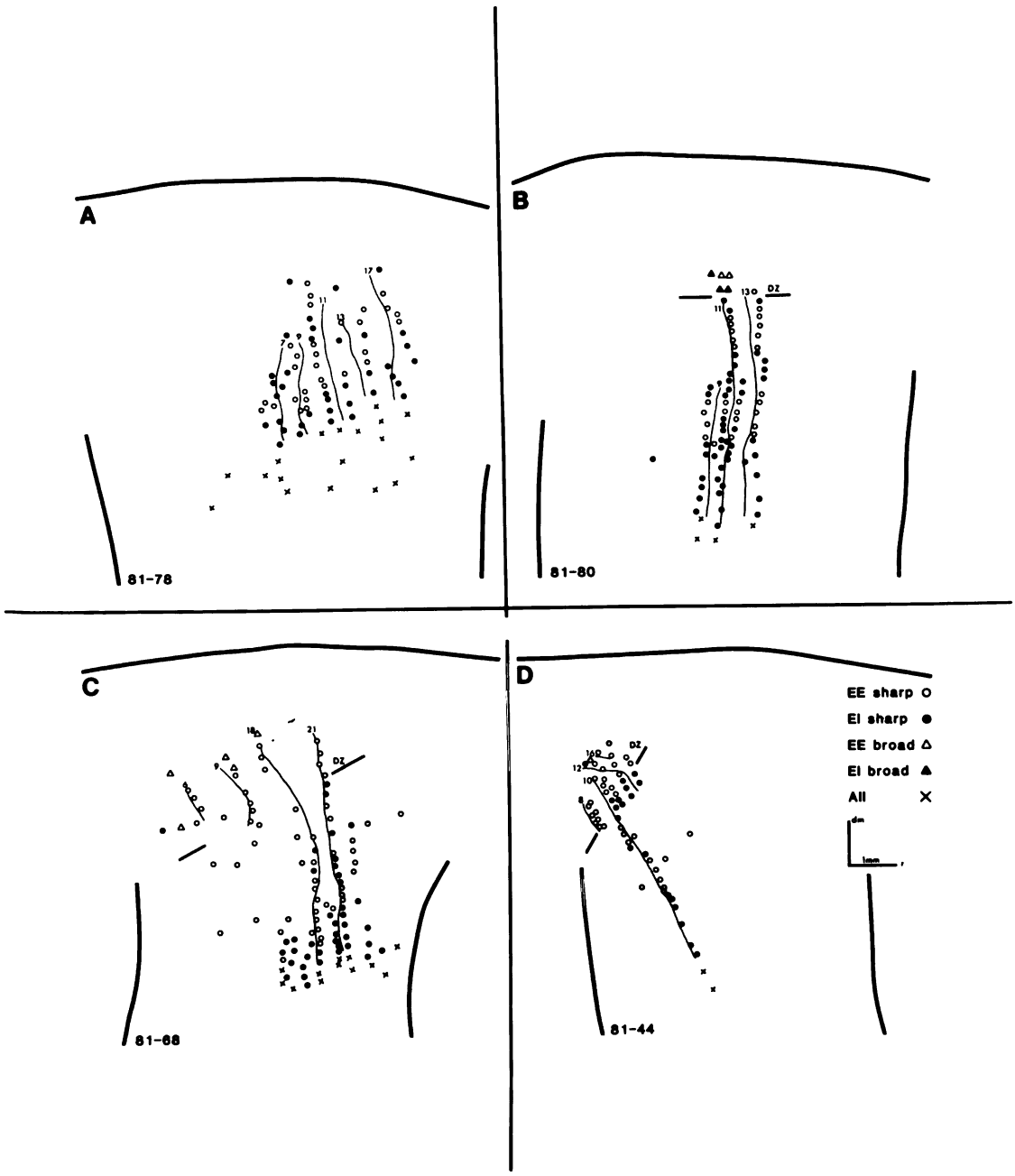
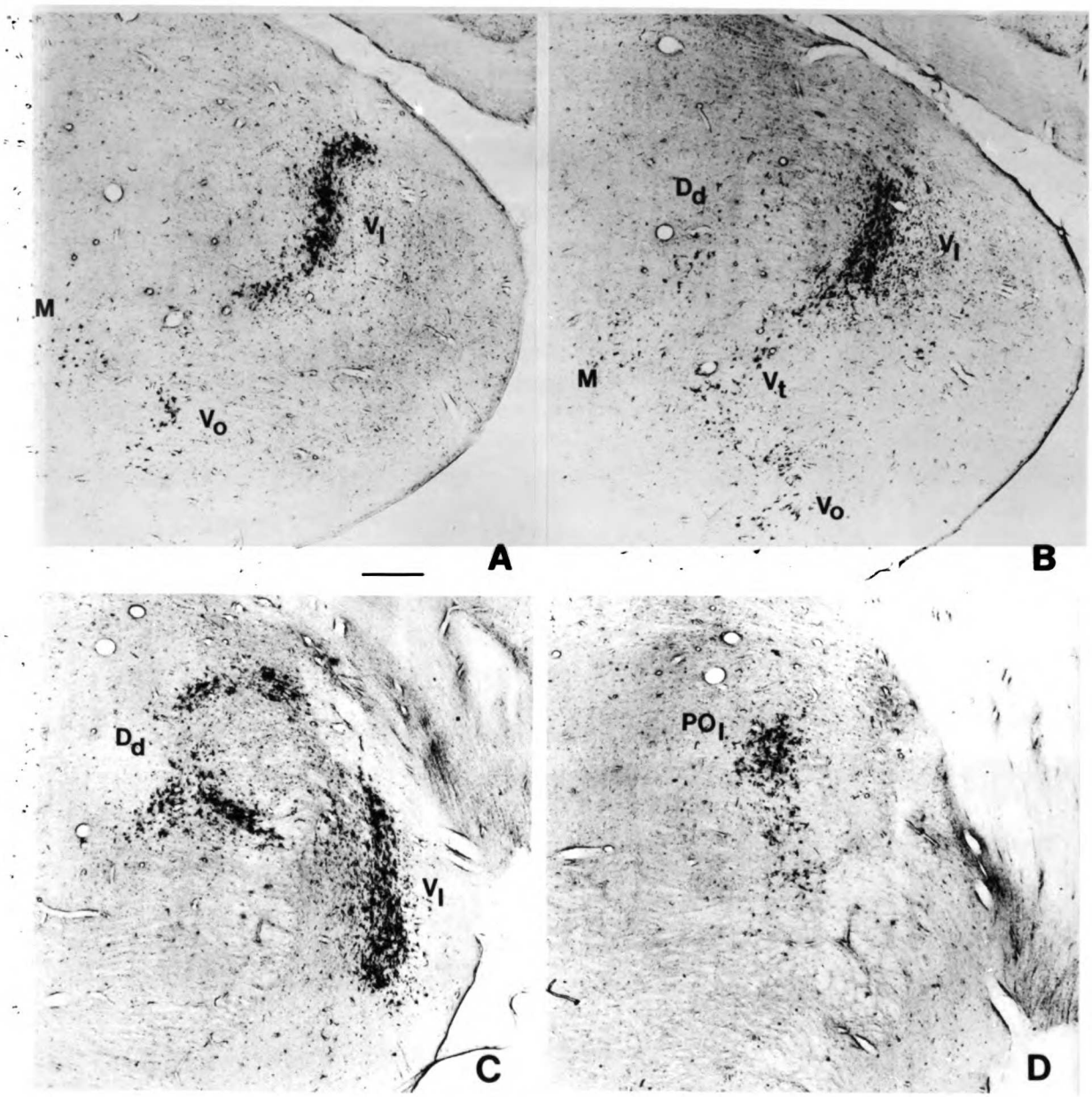

A
B
C
D
81-78
81-80
81-68
81-44
DZ
EE sharp
EI sharp
EE broad
EI broad
All
1mm

Figure 2. Retrogradely labelled cells in the thalamus resulting from 5 injections of HRP along a 17 kHz isofrequency contour in AI. Case 81-70. Horsley-Clarke coronal plane; no counter-stain. The medial division (M), deep dorsal nucleus (Dd), lateral (Vl), ovoidal (Vo), and transitional (Vt) parts of the ventral division (V), and lateral part of the posterior thalamic group (POl) are indicated. Sections are arranged from caudal to rostral. Scale=500 um.


M
V_l
V_o
A
D_d
V_l
M
V_t
V_o
B
D_d
V_l
C
PO_l
D

along the length of the 17 kHz isofrequency contour. Labelled cells were found in all three major divisions of the MGB and in the lateral part of the posterior thalamic group (PO1). As in all AI injection cases, labeled cells in the MGB were restricted to the rostral two thirds of the structure. The major projection to AI was from V. There, labeled cells occupied a lamina which appeared in coronal section as a folded band caudally (fig. 2A) and as a straight band rostrally (fig. 2C). In the caudal and central areas of the array (see fig. 2A, B), the line of labeled cells passed from dorsolateral to ventromedial in the pars lateralis (Vl) and the transitional zone (Vt), then curved laterally to end in the pars ovoidea (Vo). At some levels (fig. 2A), there was an interruption between the band of labeled neurons in Vt and that in Vo. At other levels (fig. 2B), the pattern of labeled neurons was continuous through this region making it difficult to define a Vt/Vo border. More rostral (fig. 2C), the sheet of labeled cells in Vl moved progressively nearer the lateral margin of the nucleus. Here, the labeled neuronal sheet straightened and assumed a parasagittal orientation. A cluster of labeled cells in the medial division (M) lay across the brachium of the inferior colliculus from Vt (fig. 2A, B). At more rostral levels (fig. 2B, C) labeled cells occupied an often discontinuous sheet or column in the deep part of the dorsal division (Dd). The pattern of label in Dd varied

considerably between cases, sometimes filling a narrow lamina or column and other times appearing to be discontinuous, as in this case. The column of label in Dd continued rostrally into PO1 (fig. 2D).

The arrays of labeled cells in Vl that resulted from injections centered on single isofrequency contours in AI correspond in position and orientation to the morphological laminae defined in cytoarchitectonic studies (see Morest, '65). They will be referred to here as "isofrequency laminae". Our data for injections made at various locations along the cortical axis of representation of frequency are consistent with previous descriptions of tonotopic organization in the MGB (e.g., Colwell, '75; Colwell and Merzenich, '75, '82). The most prominent effect of shifts of injection sites along the tonotopic (rostrocaudal) axis of AI was in the location and size of labeled isofrequency laminae in V. For injections located at cortical sites of representation of successively higher frequencies, labeled isofrequency laminae in V were found farther medial, dorsal, and rostral, and grew in total area. A retrogradely labeled isofrequency lamina in V accounts for the representation of a limited range of frequency. Given the tonotopic organization of AI and V, we infer that the thickness of the lamina is roughly proportional to the spread of retrograde tracer along the tonotopic (rostrocaudal) axis of AI.

When injections were restricted to single binaural bands, the resulting retrograde label in the thalamus occupied restricted fractions of the array of neurons that project to an entire cortical isofrequency contour. Nearly all such restricted injections labeled at least a few cells in M, Dd, and PO1. The form and amount of label found in those divisions varied considerably between cases. The patterns of label in those divisions were difficult to correlate absolutely with particular AI injection sites, given the apparent variability in these projections and the limited number of injections that were introduced into each binaural band. However, a clear correlation was recorded between injection site locations (into particular binaural bands) and the characteristic patterns of labeled neurons in V. In the descriptions below, we shall focus on band-specific neuronal arrays in V.

The ventral EI band. The AI/AII border was identified in 19 binaural maps. Sectors of the ventral part of AI as large as the representation of about two octaves were mapped in some experiments. In each of these cases, a band of EI units occupied the ventralmost region of AI. Apart from an occasional anomalous penetration, this ventral EI band appeared to be continuous in its rostrocaudal (tonotopic) dimension in every studied cat. Depending on the aim of a particular experiment, as many as 29 electrode

penetrations were placed into this ventral EI band.

The ventral EI band typically was the largest region of EI responses encountered in AI. In a few instances, it narrowed in its dorsoventral (isofrequency) dimension to as little as 0.5 mm, but it was typically 1 to 2 mm wide. In many animals (but not all), the width of the ventral EI band appeared to increase in more rostral, higher frequency, regions of AI.

Injections of retrograde tracers were centered in the ventral EI band in seven cases. In each of these experiments, labeled cells occupied discontinuous areas within an isofrequency lamina in V. In the experiment illustrated in figure 3, a single injection of HRP was centered in the ventral EI band at the site of representation of 11 kHz. At caudal levels of the projection array, labeled cells formed two discrete clusters in Vl (fig. 3A, B) and a cluster in Vo (fig. 3B). Further rostral (fig. 3C), the ventral label in Vl was continuous through Vt with the labeled cells in Vo. Still more rostral (fig. 3D), the folded sheet of labeled cells in Vl began to straighten to lie in a parasagittal orientation. The labeled array of neurons in ventral Vl continued to the rostral pole of that division (fig. 3E).

The discontinuous clusters of labeled cells in V

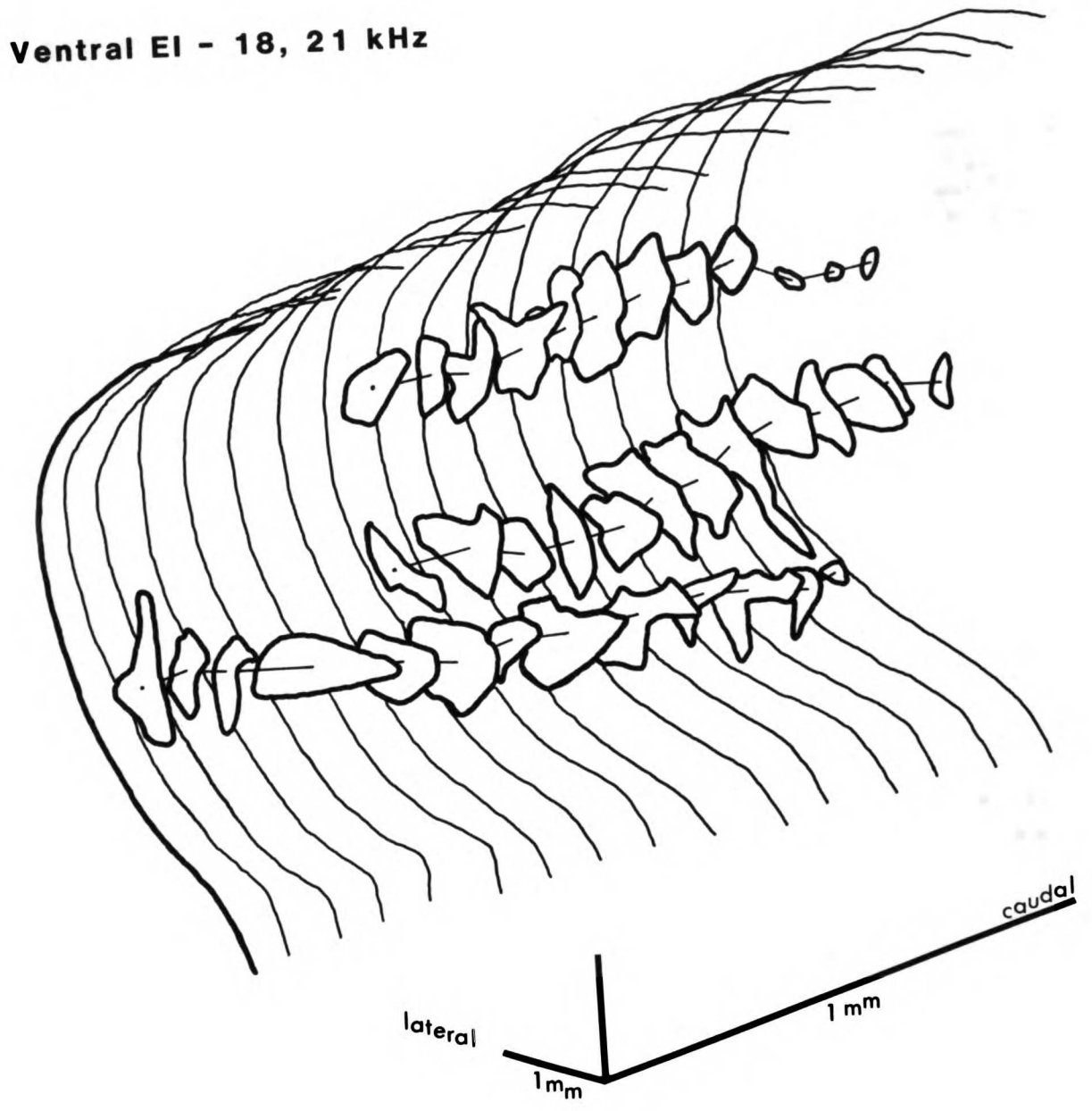
Figure 3. Label in the ventral division resulting from an injection of HRP in the ventral EI band at 11 kHz. Case 81-62. Horsley-Clarke coronal plane. Open circles indicate retrogradely labelled cells. Numbers next to the section outlines indicate distance in um from the caudal aspect of the MGB. Sections are arranged from caudal to rostral. Scale= 3 mm. Short vertical lines on the scale represent the rostrocaudal position of the illustrated section, where the left end of the scale represents the caudal tip of the MGB. A, At the caudal pole of the projecting array, labelled cells occupy 2 columns in Vl. B, A cluster of labelled cells is found in Vo. C, A line of labelled cells passes nearly continuously from the ventral column in Vl, through Vt, and into Vo. The dorsal column in Vl is still present. D, The two columns in Vl are beginning to merge. E, Label is restricted to a single lamina in the rostral pole of Vl.


Ventral EI - 11 kHz
A
B
C
D
E
1696
1888
2080
2463
2656

that resulted from ventral EI injections at single frequencies (or restricted bands of frequency) were reconstructed in three dimensions to reveal rostrocaudally oriented columns of labeled cells. This is demonstrated in figure 4, which shows the pattern of label in V resulting from two injections of NY in the ventral EI band at 18 and 21 kHz loci. The arrays of labeled cells in V resulting from the two injections fused together because of the close spacing of the injections along the tonotopic axis of AI, so the double injection resulted in a thickening of the projection in V along the thalamic tonotopic dimension. In the illustration, the clusters of labeled cells are outlined and the rostrocaudal axis is expanded by a factor of five. In the caudal 400 um of the projection, two columns of label are present in Vl. Further rostral, these columns are joined by a third column in Vo. At some levels, the ventral column in Vl (or Vt) is nearly contiguous to the Vo column. In the rostral 300 um of the projection, label is restricted to the single column which passes from Vo into the ventral and rostral part of Vl.

This basic pattern was common to all of the ventral EI band injection cases in this series. In V, arrays of neurons projecting to the sites of representation of narrow ranges of frequency always comprised three discrete rostrocaudally oriented columns. At caudal levels, there

Figure 4. Three dimensional reconstruction of the pattern of label in V resulting from injections of Nuclear Yellow (NY) in the ventral EI band at 18 and 21 kHz. Case 81-68. The patterns of retrograde label resulting from the two injections are fused because of the close spacing of the injections along the tonotopic axis of AI. Clusters of labelled neurons are indicated with outlining. The ventral division is viewed as if from a point inside the thalamus at an angle 45 from the parasagittal plane and 20 above the horizontal plane. The rostrocaudal axis is expanded by a factor of 5. Retrogradely labelled cells occupy 2 columns in Vl and one column passing from Vo into Vl.

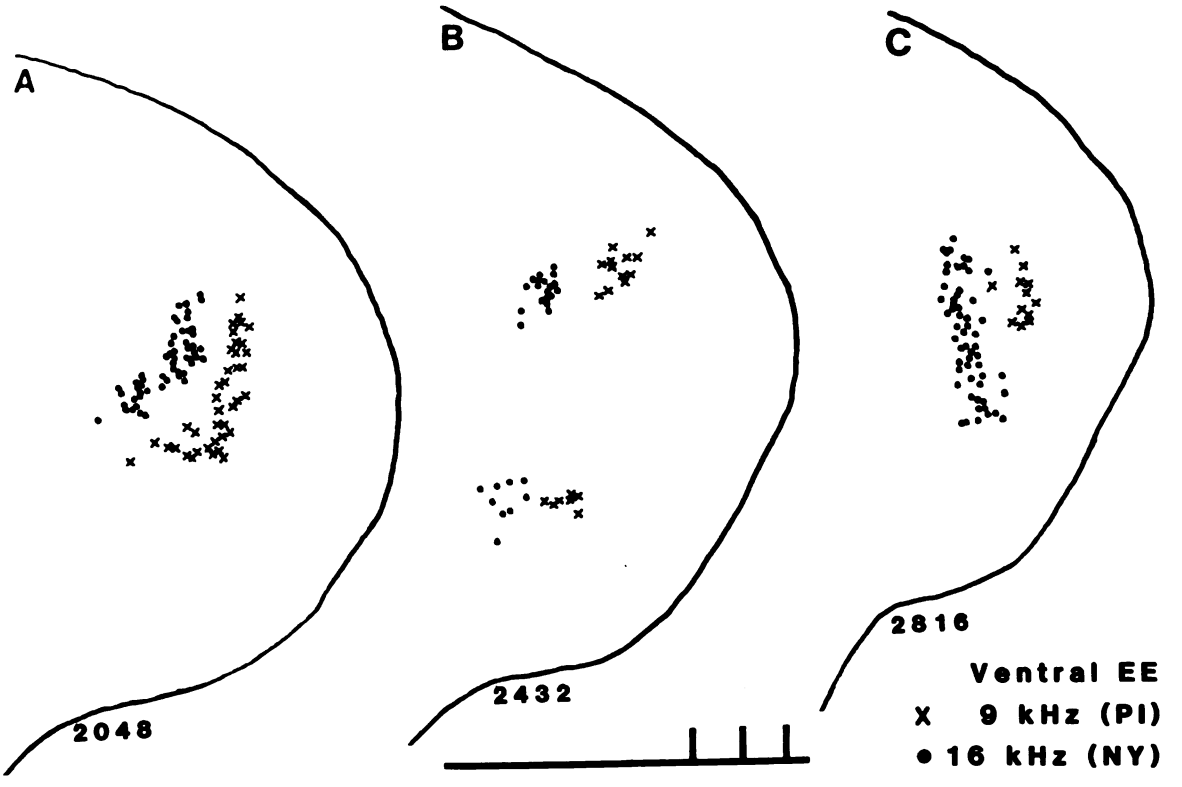

Ventral EI - 18, 21 kHz
caudal
lateral
1 mm
1 mm

were two stubby columns in Vl (again, note the 5X expansion of the rostrocaudal axis in fig. 4). The more ventral column was continuous with Vt and Vo at some levels, and often could be further subdivided along some fraction of its length. Injections into the ventral EI band always produced robust labeling in Vo. The Vo column continued rostrally into Vl, where it extended to the rostral pole Vl. In several cases (e.g., fig. 3), the two columns see in caudal Vl fused at more rostral levels to form a single column which extended as far or farther into the rostral pole of Vl as the Vo-Vl column.

The ventral EE band. A ventral band of EE units consistently was found immediately dorsal to the ventral EI band in AI. Like the ventral EI band, this ventral EE band was continuous along its tonotopic axis and was identified in every case in which the ventral aspect of AI was mapped in detail. This band usually was not the widest band of EE responses that was encountered in AI. It ranged from approximately 0.5 mm to 1 mm in its isofrequency dimension. Within a single case, the width of this band could be quite variable, sometimes broadening or narrowing abruptly for short segments of its length.

A consistent pattern of retrograde label was observed following five injections of retrograde tracers into the ventral EE band in four hemispheres. In one case

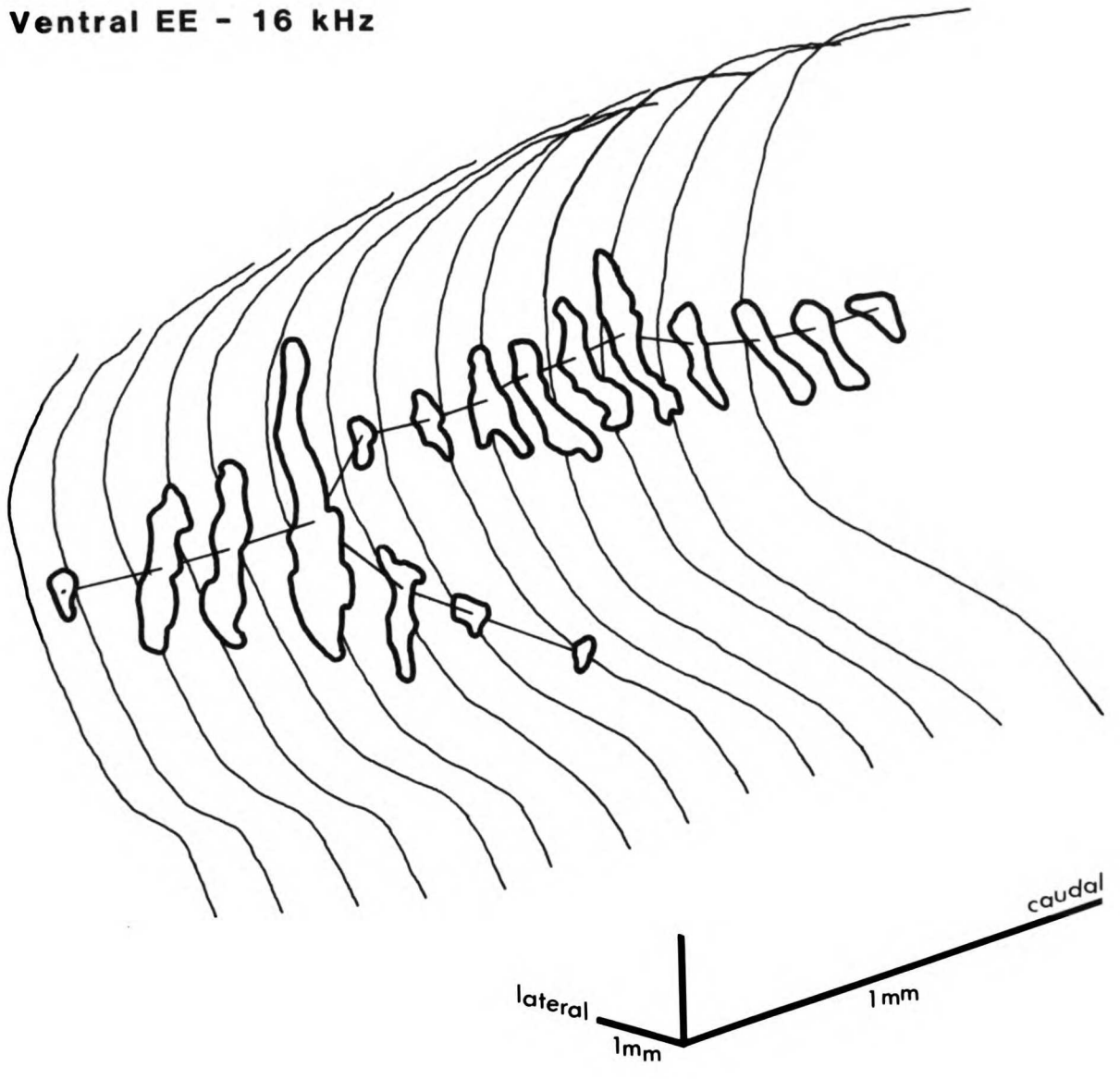
Figure 5. Label in the ventral division resulting from two injections in the ventral EE band: propidium iodide (PI) at 9 kHz and NY at 16 kHz. Case 81-81. Crosses and filled circles indicate cells retrogradely labelled with PI and NY, respectively. For each label, labelled cells are restricted to Vl. Further details as in fig. 4.


A
B
C
2048
2432
2816
Ventral EE
X 9 kHz (PI)
• 16 kHz (NY)

(fig. 5), two injections of retrograde tracers were introduced in the ventral EE band in one hemisphere: NY at 16 kHz and PI at 9 kHz. The labeled cells occupied portions of two parallel isofrequency laminae. At all levels, the projecting array labeled by the injection at the higher frequency lay medial and dorsal to that produced by the lower frequency injection, thus corresponding to the known tonotopic organization of Vl (e.g., Colwell, '75; Colwell and Merzenich, '75, '82; Merzenich et al., '82). In all cases, the arrays of labeled cells in V that resulted from single ventral EE injections could be reconstructed to form single continuous structures. The pattern of NY label resulting from the 16 kHz injection in the case shown in figure 5 is reconstructed in figure 6. Again, note that the reconstruction is expanded by a factor of five in the rostrocaudal dimension. This projection array shared several features with all of the ventral EE projections. At caudal levels of the projection, a single narrow sheet or column of cells was labeled in the ventral part of Vl. Further rostral, this single column shifted dorsally in Vl and merged with a second, shorter, more ventral cell column. At the rostral pole of the projection, the two merged columns form a continuous parasagittally-oriented sheet.

Never more than a few (sometimes no) cells were labeled in Vo by ventral EE injections.

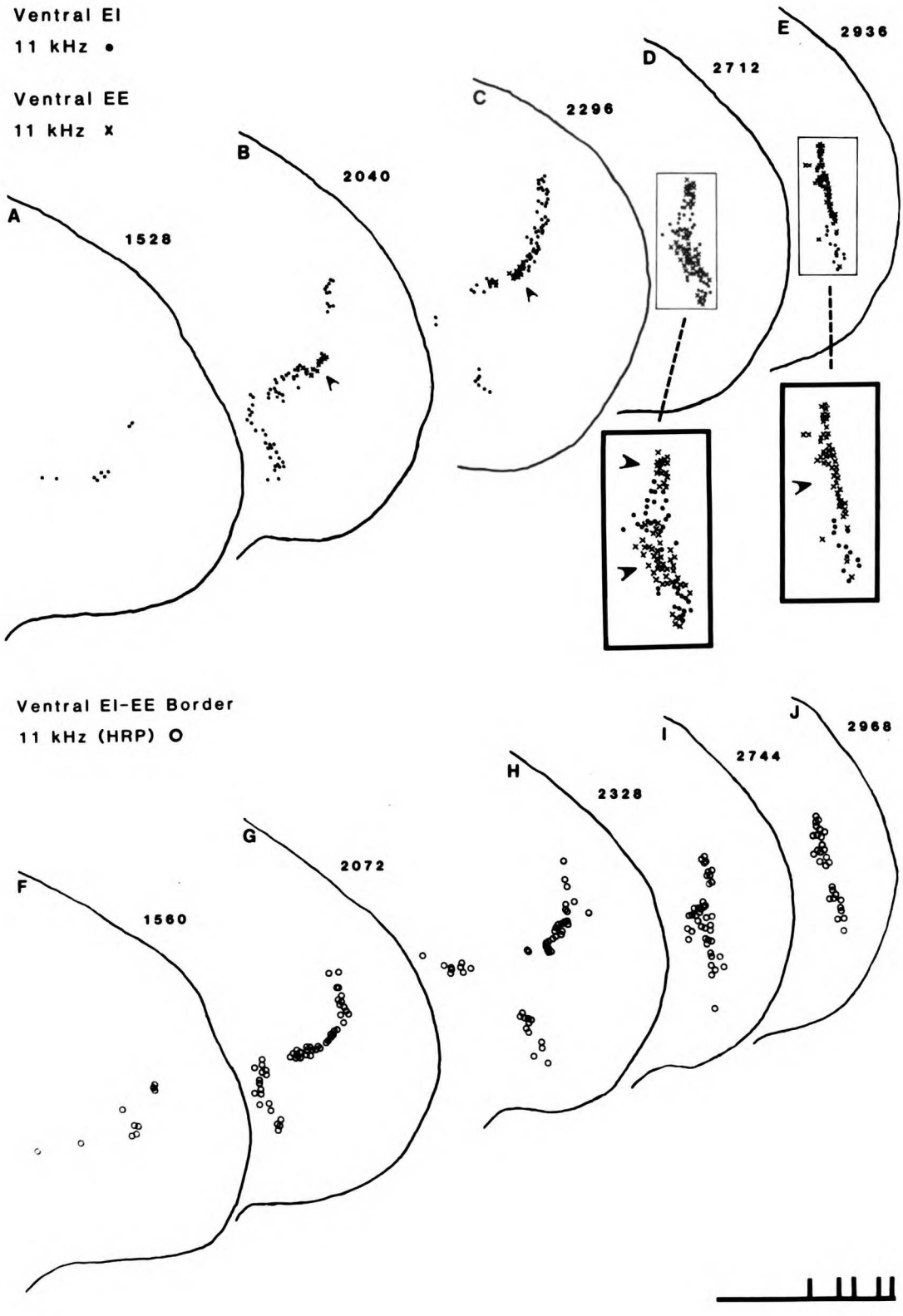
Figure 6. Three dimensional reconstruction of the pattern of label in V resulting from an injection of NY in the ventral EE band at 16 kHz. Case 81-81 (same as fig. 5). Further details as in fig. 4.


Ventral EE - 16 kHz
caudal
lateral
1mm
1mm

The two projecting arrays that were labeled in the case illustrated in figure 5 represent the input from V to two discrete sites along a single ventral EE band. Presumably, the array projecting to the entire rostrocaudal extent of the ventral EE band (i.e., its entire frequency range) occupies a structure that is oriented parallel to the axis of tonotopic organization in V, passing through both of the discrete arrays labeled in the illustrated case.

Segregation in V of the projections to the ventral EI and EE bands. In three cases, the projections to ventral EE and EI bands were compared within single cats. In each of these experiments, different retrograde tracers were injected into different bands along one isofrequency contour. In the case illustrated in figure 7, three injections were placed along the 11 kHz isofrequency contour. Nuclear Yellow was injected into the ventral EI band, PI into the ventral EE band, and HRP on the border between the ventral EI and EE bands. All three resulting projecting arrays lay within the same isofrequency lamina in V. The arrays labeled by the two dyes conformed to the patterns described previously as the characteristic ventral EI and EE projections. The most caudal sections (fig. 7A) contained discontinuous clusters of NY-labeled cells from the ventral EI injection (indicated with filled circles), but no PI label. At more rostral levels (fig. 7B, C), PI-

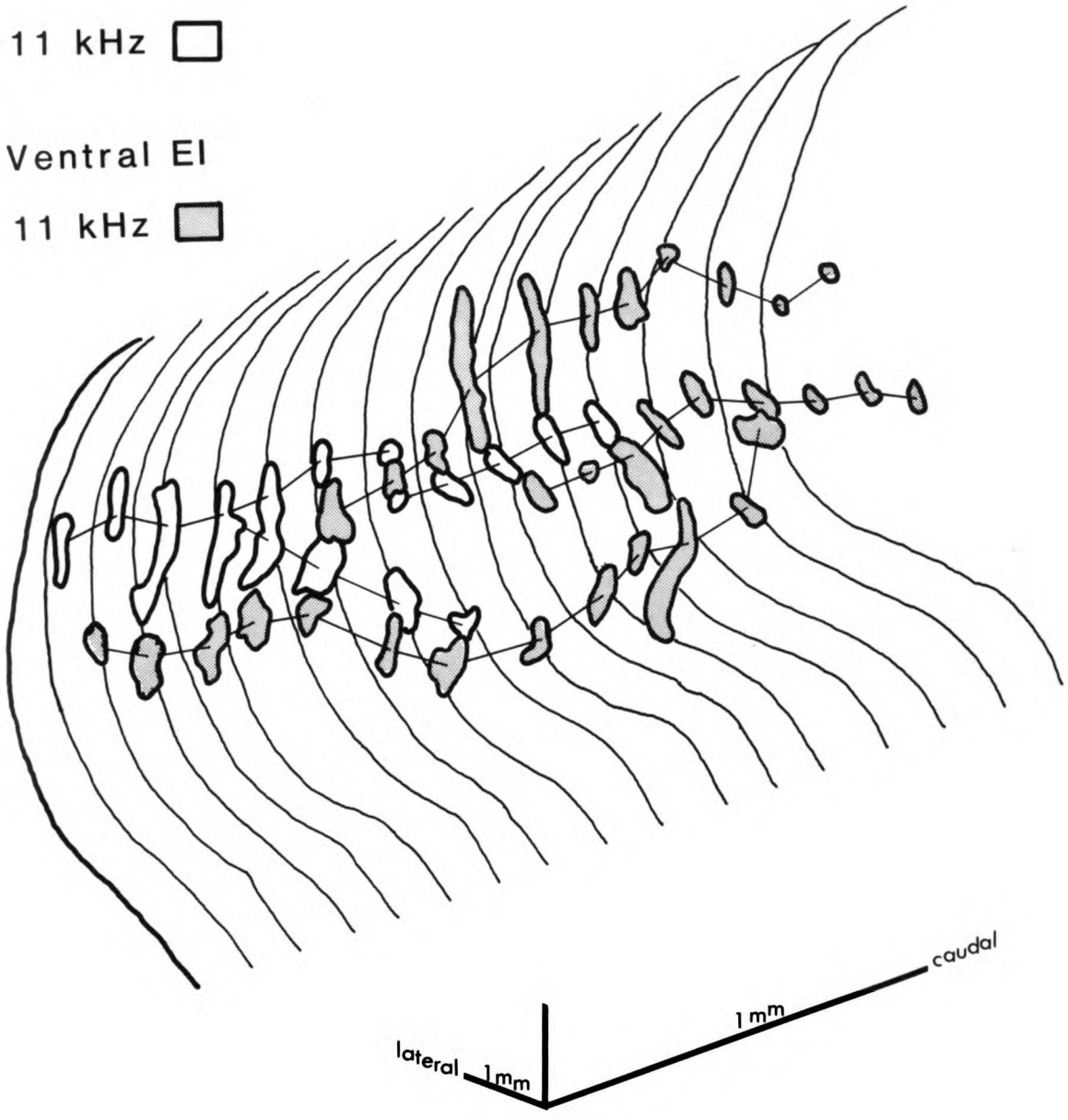
Figure 7. Label in the ventral division resulting from 3 injections along an 11 kHz isofrequency contour: NY in the ventral EI band, PI in the ventral EE band, and HRP on the border between the 2 ventral bands. Case 81-79. A-E, Filled circles and crosses indicate cells retrogradely labelled with NY and PI, respectively. Arrowheads indicate clusters of PI-labelled neurons. Insets show enlargements of the arrays of labelled cells in parts D and E. Note the segregation of clusters of NY- and PI-labelled neurons. F-J, Open circles indicate cells retrogradely labelled with HRP. Note the similarity of the HRP-labelled array to the sum of the arrays labelled with NY and PI. Further details as in fig. 3.


Ventral EI
11 kHz •
Ventral EE
11 kHz x
A
1528
B
2040
C
2296
D
2712
E
2936
Ventral EI-EE Border
11 kHz (HRP) O
F
1560
G
2072
H
2328
I
2744
J
2968

labeled cells from the ventral EE injection (crosses) occupied a narrow lamina that was interposed between the columns of NY label. Further rostral (fig. 7D), the fraction of the area of the lamina labeled within PI increased. At the rostral pole of the projection (fig. 7E), the PI-labeled cells filled the dorsal two thirds of the isofrequency lamina and the NY-labeled cells were restricted to a ventral column.

The HRP injection made in the case illustrated in figure 8 was introduced on the ventral EI/EE border. The effective spread of the HRP injection was comparable to the spread of either of the dye injection sites alone (judging from the extent of the projections in the tonotopic dimension of V). Yet, the HRP-labeled cells occupied approximately the same area of the isofrequency lamina in V as the NY-labeled cells plus the PI-labeled cells. At the most caudal levels (fig. 7F), discrete clusters of HRP-labeled cells were found in correspondence with the ventral EI projection labeled with NY. Rostral to the levels where PI-labeled cells first appeared, the isofrequency lamina is labeled nearly completely by the HRP injection (figs. 7G-J). The single HRP injection in this case could have reached no more than a fraction of each of the ventral EI and EE bands, yet it labeled nearly as much of the area of an isofrequency lamina as five injections placed along the entire length of

Figure 8. Three dimensional reconstruction of the pattern of label resulting from injections of PI and NY into the ventral EE and EI bands, respectively, at 11 kHz. Case 81-79 (same as fig. 7). Open and shaded outlines indicate clusters of PI- and NY-labeled cells, respectively. Note the resemblance of the patterns of NY and PI label to the patterns illustrated in figures 4 and 6, respectively. Further details as in fig. 4.


11 kHz
Ventral EI
11 kHz
lateral
1mm
1mm
caudal

an isofrequency contour (i.e., see fig. 2).

The labeled projection in V from the case shown in figure 7 is reconstructed in three dimensions in figure 8. This drawing illustrates how the ventral EE projection occupies a single branched but continuous region, while the ventral EI projection forms two discrete regions in Vl plus a third column in Vo and the ventral and rostral part of Vl. The patterns of labeled cells in this case are remarkably similar to the patterns of EI- and EE-projecting cells in the cases illustrated in figures 4 and 6. The reconstruction in figure 8 also serves to emphasize that, for a given frequency, the ventral EE neuronal projection is centered rostral to the center of the ventral EI neuronal projection array. This observation was confirmed in every case in which injections were placed in the ventral EI and/or ventral EE bands.

The middle bands. In the area of AI above the readily identified ventral pair of binaural bands, the pattern of binaural subdivisions was somewhat more variable. In all cases, EE-responsive units were segregated from EI units and, commonly, binaural response-specific regions appeared to be elongated rostrocaudally. In some experiments (e.g., fig. 1B) there was evidence of two EI bands and one EE band in the area between the ventral bands and the DZ. At the other extreme, in some cases no single

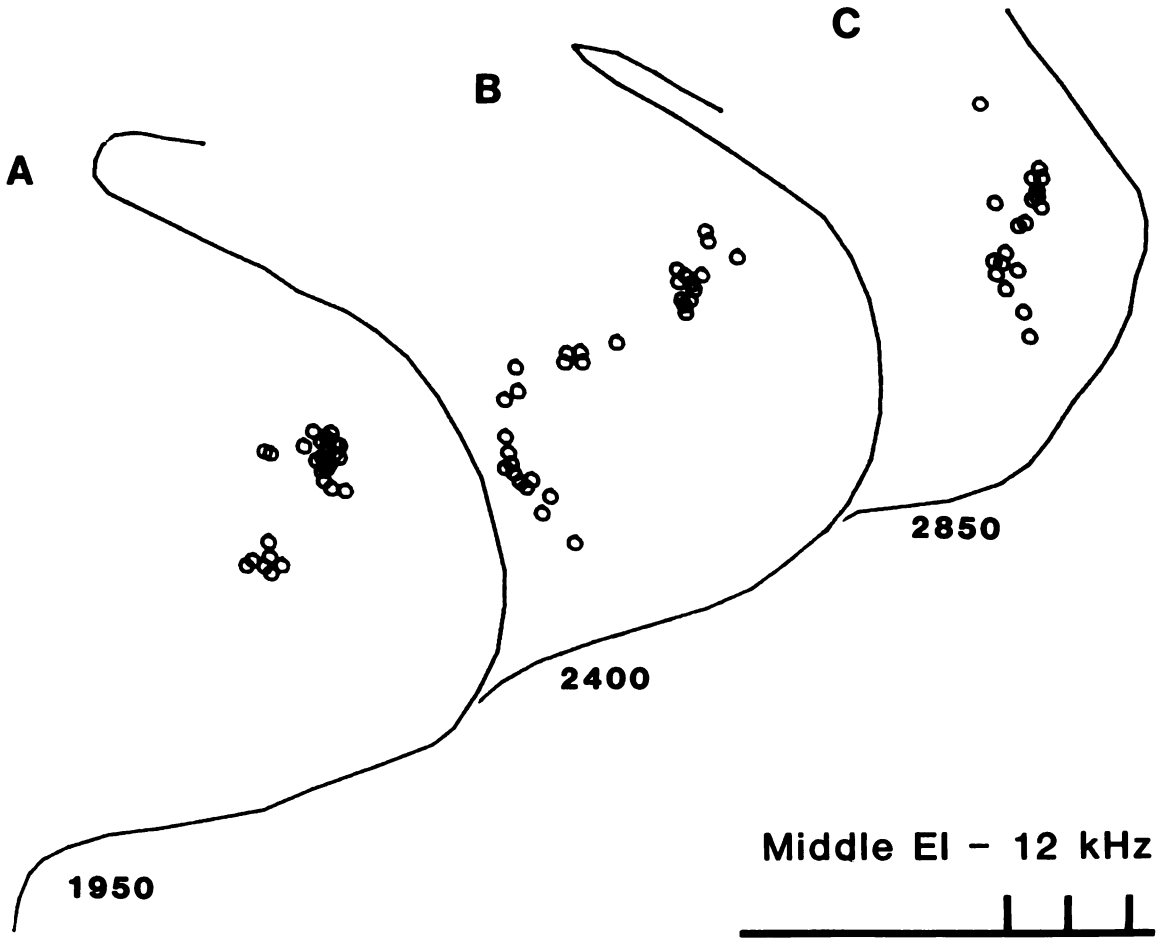
binaural band could be tracked across this middle region (e.g., fig. 1A). To aid description, binaural response-specific regions found between DZ and the ventral EE band will be referred to as "middle EE and EI bands" with the caveat that these bands are much less constant in form than the ventral EE and EI bands.

Injections of retrograde tracers were restricted to single middle bands in several cats in which bands in this middle region could be outlined unequivocally.

In one case, HRP was centered in a middle EI band along the line of representation of 12 kHz (fig. 9). The band in which this injection was introduced was immediately dorsal to the ventral EE band. The thalamic projection labeled in this experiment was very similar to the pattern that resulted from ventral EI injections in other cats. At caudal levels, two columns of cells were found in Vl (fig. 9A). Further rostral (fig. 9B), the sheet of labeled cells was continuous via Vt to Vo. At the rostral pole of the projection, labeled cells were restricted to a single parasagittally oriented lamina in Vl (fig. 9C).

Injections were restricted within middle EE bands in three successful cases. Projection arrays were somewhat different in detail in each of these cases, but in every experiment, labeled cells apparently were restricted to the

Figure 9. Label in the ventral division resulting from an injection of HRP in a middle EI band at 12 kHz. Case 81-56. A, 2 columns in Vl. B, The ventral column in Vl is nearly continuous through Vt with Vo. C, A lamina in Vl. Note the resemblance between this projection pattern and that shown in fig. 3 for a ventral EI injection. Other details as in fig. 3.


A
B
C
1950
2400
2850
Middle El – 12 kHz

regions of V that were labeled by ventral EE and/or DZ injections (described below). Figure 10 illustrates two sections from one of these middle EE injection cases. At caudal levels (fig. 10A), labeled cells were restricted to a single lamina in the ventral aspect of Vl. This lamina resembled the caudal part of the typical projection to the ventral EE band (e.g., see fig. 7B). A few additional cells were found in Vdc (described further below). The rostral pole of the projection in V occupied a single densely labeled lamina oriented parasagittally (fig. 11O). Only five labeled cells were found in Vo in this cat. In another middle EE injection case (case 81-60; not shown), a very similar pattern was observed. However, in the latter case the number of labeled neurons in Vdc was much greater, and the overall pattern of labeled neurons was more closely parallel to that resulting from DZ injections (described below). The label in Vl was relatively sparse.

In a third example, an injection of NY was introduced into a middle EE band at 13 kHz (fig. 11, filled circles) and an injection of PI was introduced into the ventral EE band at the same frequency (crosses). At caudal levels (fig. 11A), the middle EE projection was restricted to Vdc. Rostrally in V (fig. 11B, C), this cluster elongated ventrally to form a parasagittally oriented lamina. The ventral EE projection pattern in this case was

Figure 10. Label in the thalamus resulting from an injection of HRP in a middle EE band at 10 kHz. Case 81-31. Transverse section. A, Label is restricted to a cluster of cells in Vl and a single cell in Vdc. B, A lamina in Vl. Other details as in fig. 3.

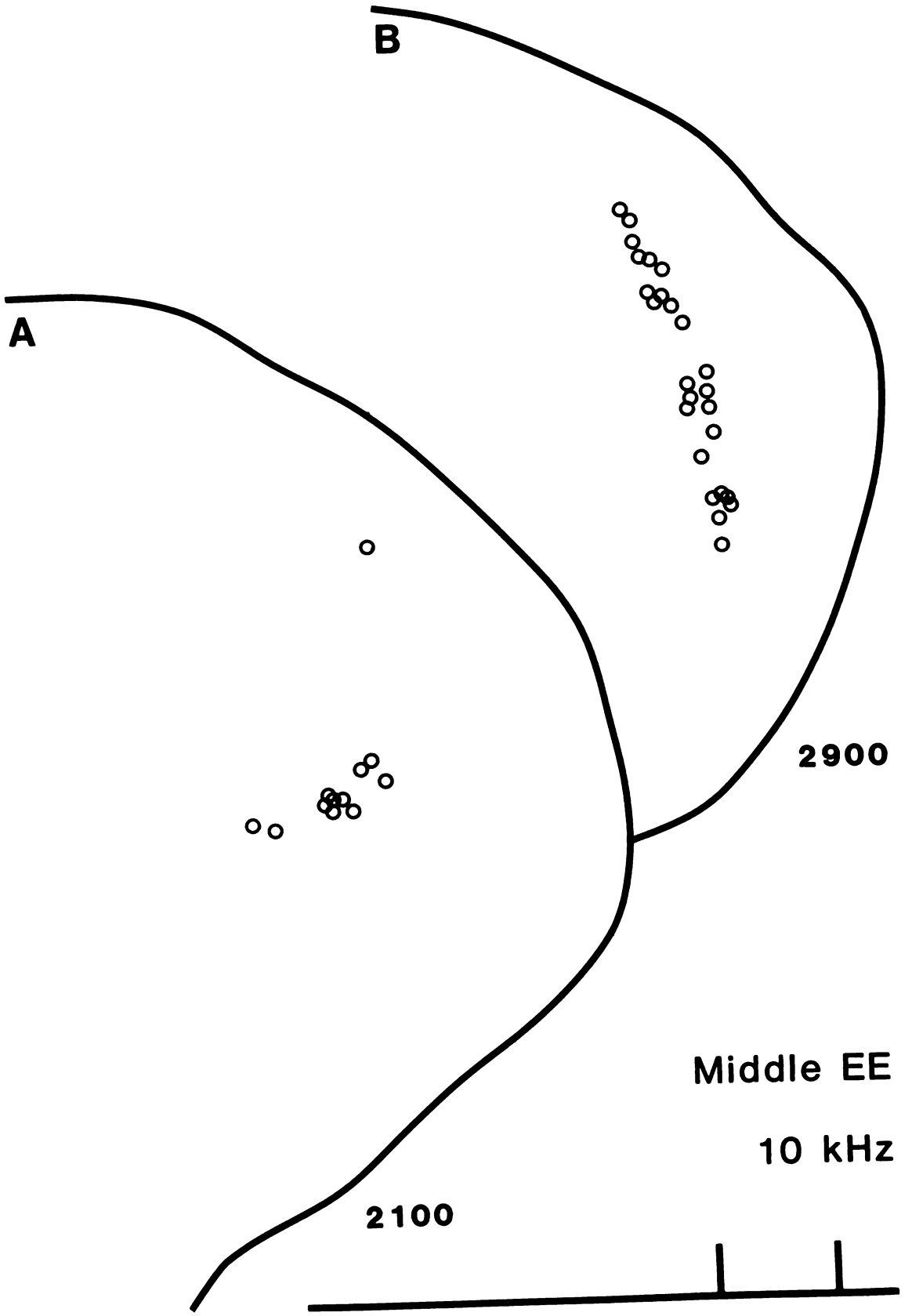
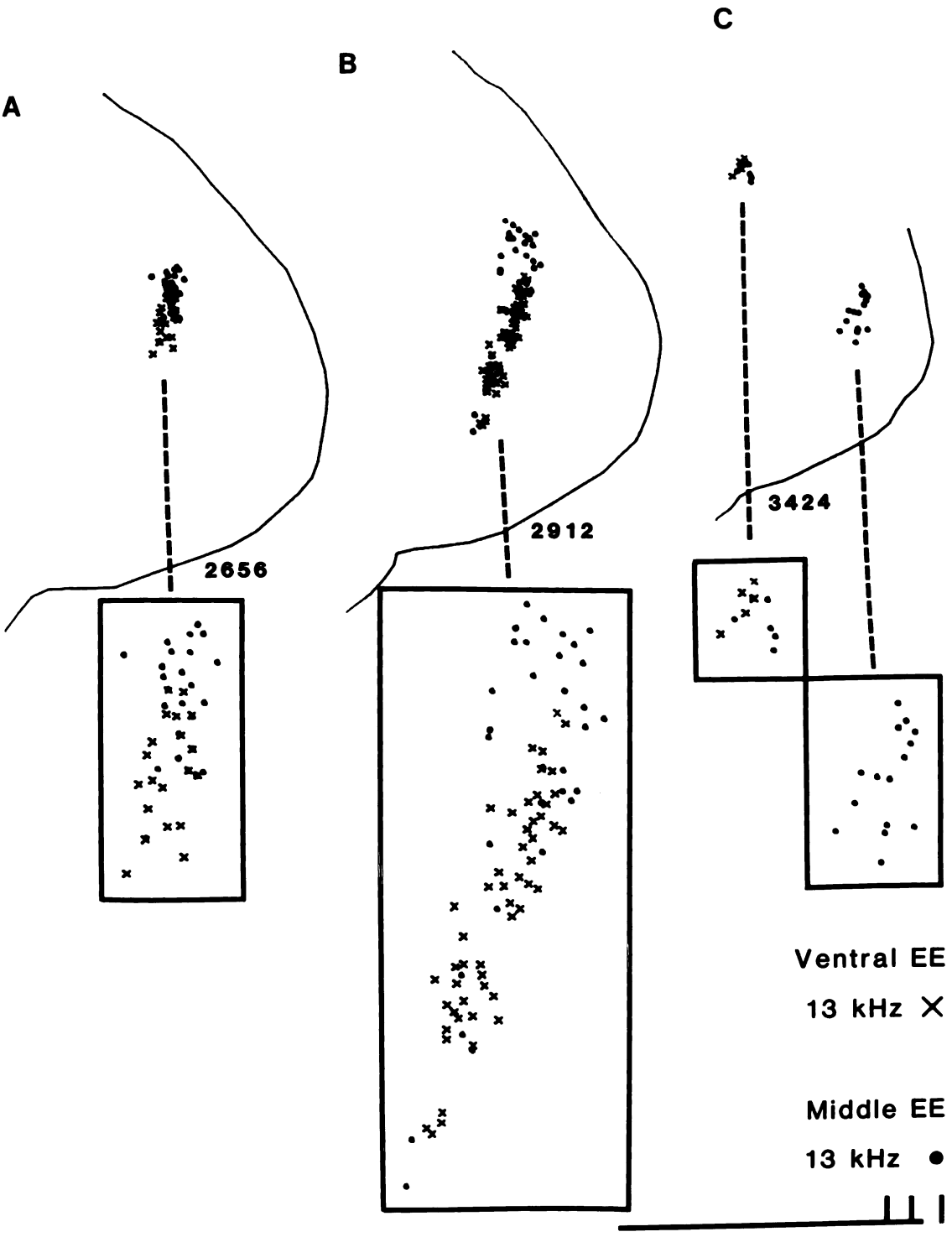

B
A
2900
Middle EE
10 kHz
2100

Figure 11. Pattern of labelled cells in the thalamus resulting from 2 injections along a 13 kHz isofrequency contour: NY in a middle EE band and PI in the ventral EE band. Case 81-80. The ventral EE projection in this case was unlike any of the 5 other ventral EE projections studied. A, Both projections were restricted to Vdc. B, Both projections lay within a lamina in the rostral pole of Vl, with the PI (ventral EE) projection centered ventral to the center of the NY (middle EE) projection. C, NY-labelled cells were found in Vl and POl, while PI cells are restricted to POl. Further as details in fig. 3.


A
B
C
2656
2912
3424
Ventral EE
13 kHz ×
Middle EE
13 kHz ●

unlike the projections that were demonstrated with five injections in four other cases (described above). Caudally (fig. 11A), the projection occupied a cluster in Vdc. This cluster overlapped extensively with the middle EE projection, although it was centered slightly more ventral. Some doubly labeled cells were observed (indicated with crosses superimposed in filled circles) although cells singly labeled with PI or NY were much more numerous. Like the middle EE projection, the ventral EE projection occupied a dorsoventrally oriented lamina at rostral levels (fig. 11B), although once again the center of the ventral EE projection lay further ventral. Each of these injections produced a cluster of labeled cells in POl (fig. 11C). Neither injection resulted in any labeled cells in Vo.

The dorsal zone. In nine cases, microelectrode maps were continued to or beyond the dorsal margin of AI across a sector (the dorsal zone; DZ) in which responses differed in frequency specificity and/or in binaural response from those recorded elsewhere in AI. Although there was some variation in the responses that were recorded from this area, it will be treated here as a distinct cortical region, as: 1) responses that were recorded therein differed from those in EE or EI subdivisions as defined previously; 2) this area consistently occupied the dorsal margin of AI; and, 3) because there was a consistent pattern of label observed in

the thalamus in all cases in which retrograde tracers were injected into this region.

Although unit responses always differed from those recorded elsewhere in AI, no single functional feature was identified as exclusively and universally a characteristic of DZ neurons. In nearly all of the maps which included penetrations in this region, the responses recorded there were unequivocally more broadly tuned for frequency than elsewhere in AI (penetrations where broad tuning was encountered are indicated in fig. 1 with triangles). However, in some cases, broad tuning was encountered only in some penetrations, while responses at nearby penetration sites were sharply tuned (indicated with circles). In several cases in which tuning was sharp enough for CF's to be determined in DZ, isofrequency contours appeared to turn caudally as they entered DZ, and the representation of high frequencies appeared to be disproportionately large. In other cases, frequency tuning was so broad that CF's could not be measured reliably, but in all penetrations units were encountered that were sensitive to sound stimulation across a broad range of high frequencies. Regardless of the breadth of tuning, there was in all cases at least a general trend of increasing best frequency associated with increasing rostral position.

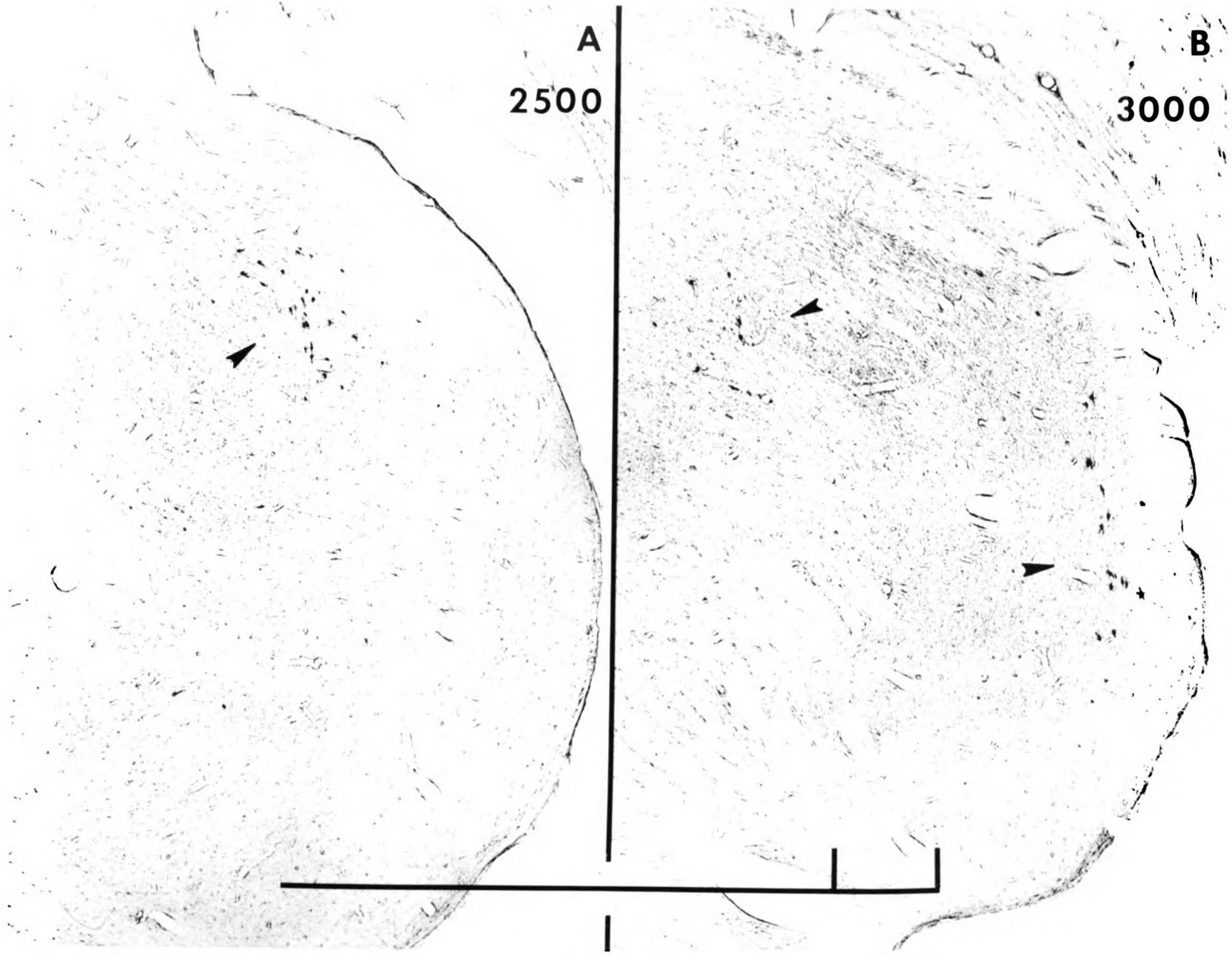
In most penetrations into DZ, unit clusters could

not be driven with monaural stimuli, although vigorous responses were elicited at low threshold for stimuli presented binaurally. Thus, this responsive zone almost certainly was not included in the "AI" defined exclusively with use of monaural stimuli (e.g., see Merzenich et al., '75). In a much smaller number of penetrations located well within this broadly tuned zone, EI responses were recorded.

The dorsal margin of DZ was explored in only a few cases, so its exact dimensions cannot be stated confidently. However, DZ is at least 1 mm wide in the dorsoventral dimension and is bordered dorsally by a region in which no responses could be elicited with the tonal stimuli (and under the state of anesthesia) that were employed in these studies.

Injections of retrograde tracers were introduced into DZ in four successful cases. Although the response properties of unit clusters in DZ varied somewhat among these cases, the pattern of retrograde label in the thalamus displayed common features. In a representative experiment, illustrated in figure 12, an injection of HRP was placed at a site in DZ where unit clusters were tuned somewhat more broadly than is typical of AI, but had best frequencies around 10 kHz. As was true of all DZ injection cases, the region of dense labeling in the projection in V was restricted in its rostrocaudal extent to the rostral half of

Figure 12. Retrogradely labeled cells in the thalamus resulting from an injection of HRP into the DZ at 10 kHz. A, The arrowhead indicates a cluster of labeled cells in Vdc. B, Arrowheads indicate a lateral lamina of cells in Vl and a more medial cluster of cells in POl. Scale as in figure 3.


A
2500
B
3000

the domain of ventral EI neuronal projections at comparable frequencies. The caudal pole of the projection consisted of a dense cluster in the "dorsal cap" of V (Vdc; fig. 12A; Morest, '65). This cluster of cells lay immediately lateral to the auditory radiation in the dorsal aspect of V. The caudal aspect of the projection appeared in the same coronal plane as the rostral pole of Vo. At more rostral levels in all DZ injection cases (fig. 12B), labeled cells in V were found further ventral and lateral, occupying a lamina oriented parasagittally. This lamina was similar in form and location to that labeled by ventral EE injections, although in some cases it appeared that labeled cells in rostral Vl were distributed somewhat more diffusely in the mediolateral dimension than was observed following comparably sized injections in the ventral EE band. All DZ injections produced a cluster of labeled cells in M and a single column of labeled cells in Dd that could be followed rostrally into POl (fig. 12B).

In addition to the dense cluster of labeled cells in Vdc, many sections in DZ injection cases contained a few cells scattered throughout the caudal levels of Vl and Vt. These cells might be the sources of input to the few sites in DZ at which EI responses were recorded. No more than a few cells were found in Vo in any DZ injection case. The pattern of label in V found in the case illustrated in

Figure 13. Three dimensional reconstruction of the pattern of label resulting from an injection of HRP in DZ at 10 kHz. Cases 81-44 (same as fig. 12). Note the limited rostrocaudal extent of this projection. Further details as in fig. 4.

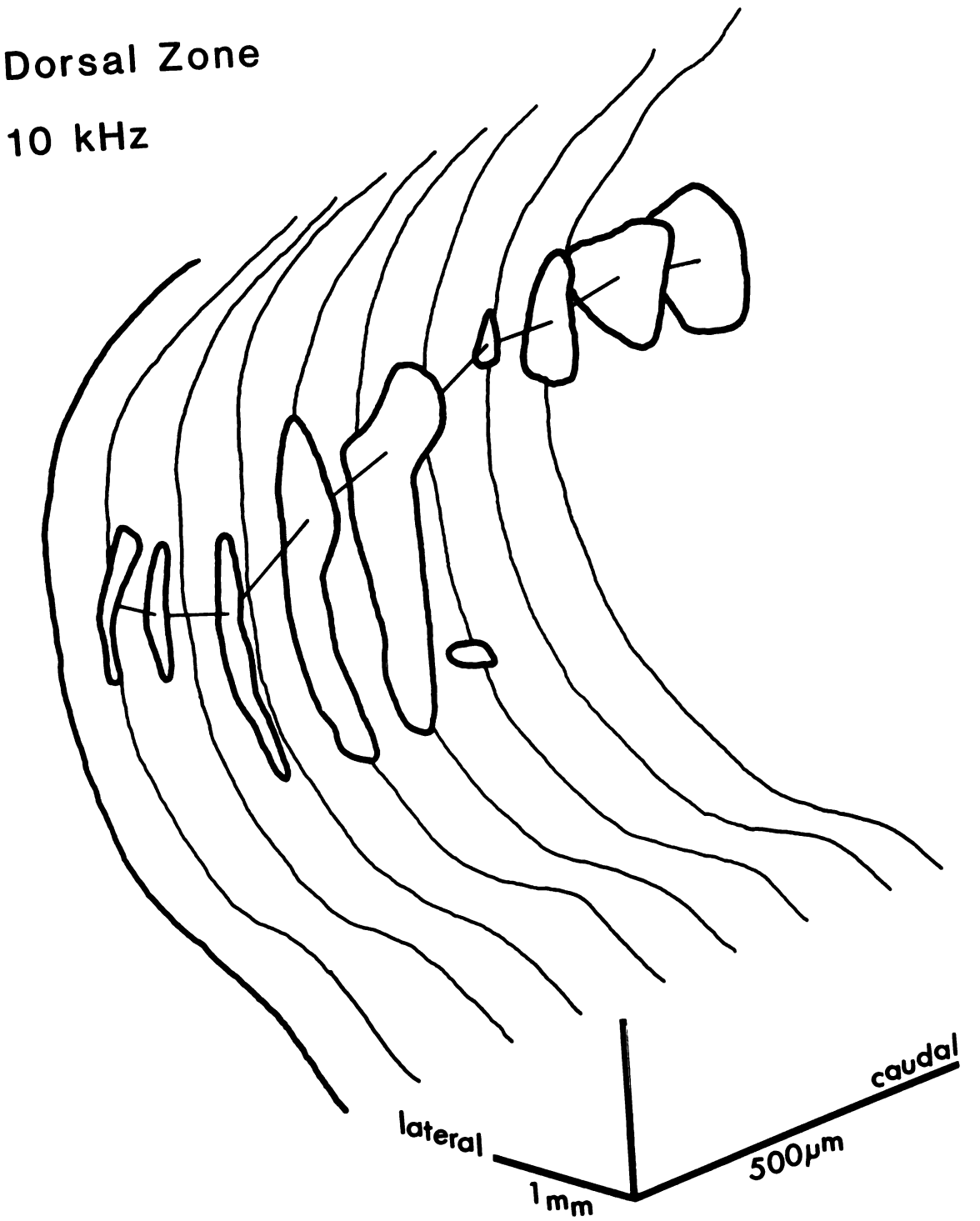

Dorsal Zone
10 kHz
lateral
1mm
caudal
500μm

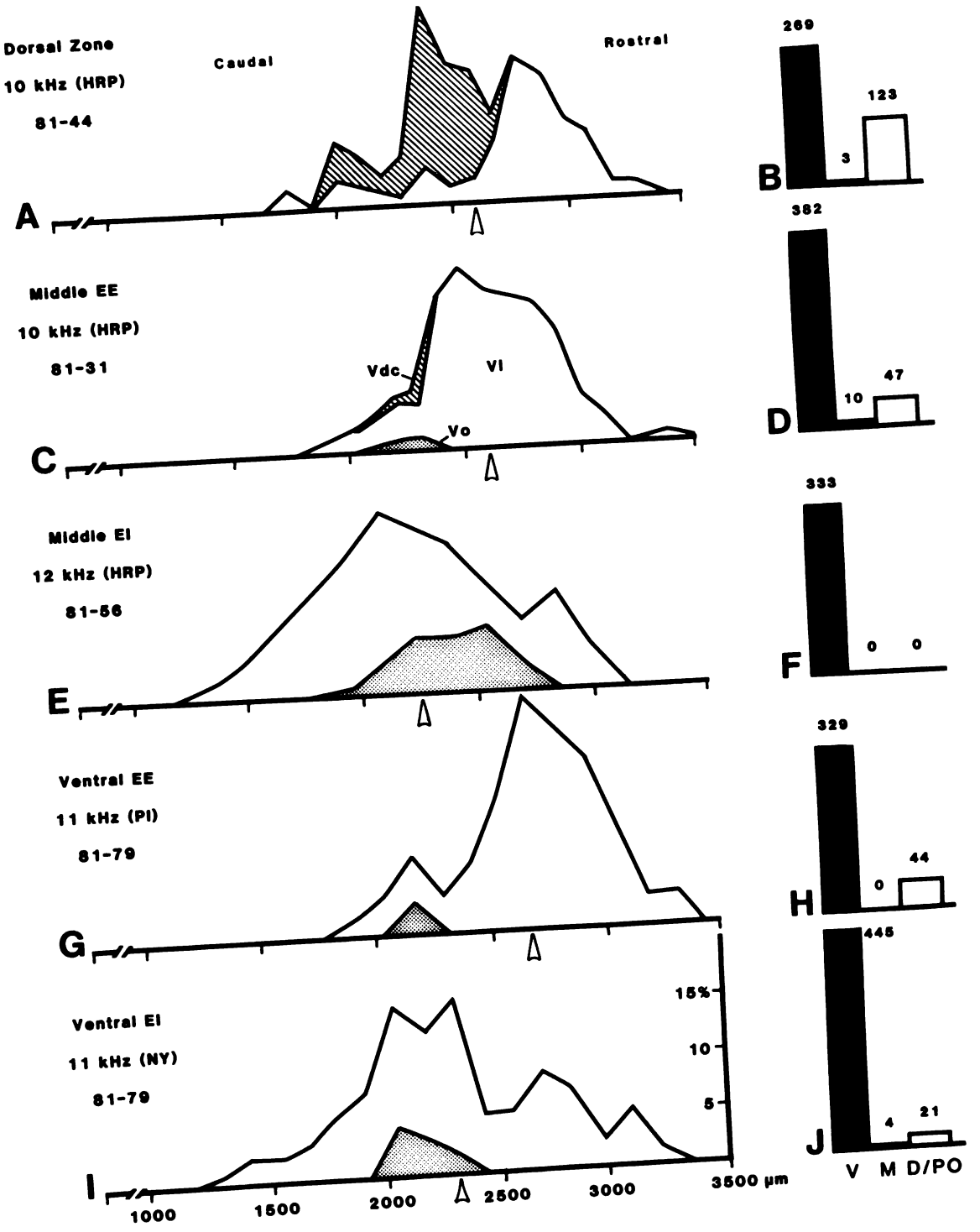
figure 12 is reconstructed in three dimensions in figure 13. The areas of dense labeling are indicated with outlining. The limited rostrocaudal extent of this projection pattern was typical of DZ projections.

Differences in the thalamic distribution of neurons that project to different binaural response-specific regions.

The graphs shown in figures 14A, C, E, G, and I illustrate the distribution of cells among subdivisions of V as a function of rostrocaudal position within the MGB for five representative cases. The abscissa represents the locations of labeled neurons relative to the caudal tip of the MGB. The ordinant represents the number of cells found in each section, expressed as a percentage of the total number of cells found in V for each case. The open arrowhead along the abscissa of each graph indicates the position of the section which contains the median cell number in that case. These graphs illustrate that the caudal pole of the projection from V to AI is occupied by cells that project to EI bands, while the rostral pole is occupied more predominantly by neurons which project to EE bands. The neuronal arrays that project to EE bands and to DZ are centered rostral to those that project to EI bands.

The absolute numbers of labeled cells found in V, M, and Dd/POl in these cases are plotted in figures 14B, D, F,

Figure 15. Summary of the distribution in the thalamus of cells projecting to identified binaural bands. Examples of the projections to DZ and middle and ventral EE and EI bands. A, C, E, G, and I, Normalized number of cells in Vo, Vl, and Vdc as a function of rostrocaudal position. Arrowheads indicate the sections containing the median cell number for each case. B, D, F, H, and J, Absolute numbers of labelled cells found in major divisions of the auditory thalamus. Counts for Dd and POl have been combined. Counts for case 81-44 based on 1 in 2 50 um sections; Case 81-31, 1 in 2 50 um; Case 81-56, 1 in 2 50 um; Case 81-79, 1 in 4 32 um.


Dorsal Zone
10 kHz (HRP)
81-44
Caudal
Rostral
A
269
123
3
B
Middle EE
10 kHz (HRP)
81-31
Vdc
VI
Vo
C
382
47
10
D
Middle EI
12 kHz (HRP)
81-56
E
333
0
0
F
Ventral EE
11 kHz (PI)
81-79
G
329
44
0
H
Ventral EI
11 kHz (NY)
81-79
15%
10
5
I
445
21
4
J
1000
1500
2000
2500
3000
3500 µm
V
M
D/PO

H, and J. These graphs demonstrate: 1) The principal projection (in terms of cell numbers) to <u>any</u> site in AI is from V. 2) The projection from M, although identified in most cases by a few scattered cells, never constitutes more than a minor fraction of the total population of projecting neurons. 3) Neurons that project from Dd/POl can account for nearly half of the input to a site in AI in some cases. The numbers of Dd/POl neurons projecting to AI sites varied considerably between the cases. No consistent relationship between the binaural band that was injected and the resulting pattern of label in Dd/POl has yet been identified.

DISCUSSION

Previous studies of the thalamic projections to the auditory cortex (AI) of the cat have demonstrated a systematic, tonotopic organization in the projection from the ventral division (V) of the medial geniculate body (MGB). The AI sites of representation of successively higher frequencies derive input from successively more medial folded sheets of neurons which cross all of the subdivisions of V (Colwell, '75; Colwell and Merzenich, '75, '82; Winer et al, '77; Andersen, '79; Andersen et al., '80b; Merzenich et al., '82). In the current study, retrograde tracers, introduced in relation to physiologically identified boundaries of binaural bands in AI, were used to define the organization of the projection from V to AI in the orthogonal, isofrequency dimension of the representation. These experiments reveal a complex yet orderly relationship between thalamic subdivisions defined by their cortical projections and the functionally defined binaural bands of AI.

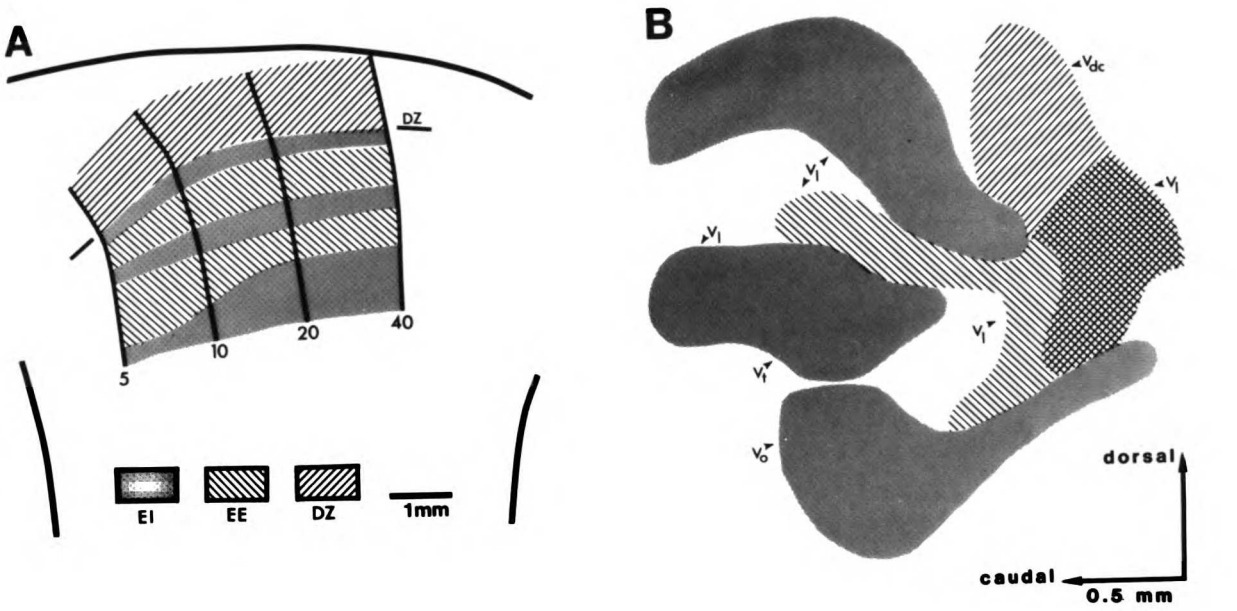
Specifically, the results indicate that: 1) The ventral division of the MGB also is functionally subdivisible, at least in the sense that the sources of input to the functionally defined subdivisions of AI occupy regional subdivisions in V. 2) Restricted segments of EI bands in AI derive their principal inputs from three

discrete columns of neurons. Two such columns pass across Vl; one crosses from Vl into Vo. 3) Restricted sites along EE bands in AI derive their input from a continuous, branched sheet of neurons in the dorsal cap (Vdc) and the lateral part (Vl) of V. 4) Binaural bands in AI of the same functional class appear to derive their input from the same restricted sectors of V. 5) The ovoidal part of V projects heavily to EI bands, but provides little input to EE bands, suggesting that it might be predominantly an EI nucleus. 6) Arrays of neurons that project to loci in EE bands are centered further rostralward within V than are those that project to loci in EI bands. 7) The pattern of retrogradely labeled cells that resulted from an injection centered on an EE/EI border was indistinguishable from the sum of the patterns resulting from two similar sized injections that were centered within an EE and an EI band. Thus, common EE and EI projections must diverge to fill the dorsoventral extent of individual respective EE and EI bands. 8) A dorsal zone (DZ) of AI with special response characteristics was identified in a number of cases. Marked by relatively broad frequency tuning and, commonly, by insensitivity to monaural stimulation (yet driven strongly by binaural stimulation) its thalamic neuronal sources overlapped those of EE regions which displayed more conventional response properties.

The basic organization within the isofrequency dimensions of AI and V is illustrated schematically in figure 15. The EI, EE, and DZ subdivisions in AI and the sources of input to these regions from V are indicated, respectively, with shading and cross-hatching at two orientations. The organization within V is represented by a lateral view of one unfolded high frequency (11 kHz) lamina in figure 16B. Of course, these subdivisions are extended in the dimension orthogonal to that drawing, i.e., these projection sources constitute large slabs of projecting neurons, each sending projections to the representation in AI of at least the three highest octaves of the audible range. The extension of these large functional subunits to frequencies below 3 to 5 kHz is questionable, as is discussed below.

Relation to earlier anatomical studies. The results of these tracing studies are largely consistent with recent descriptions of the basic patterns of projections of the MGB to AI. In addition, by distinguishing the arrays of neurons that project to binaural bands, these results show some of the complex, hitherto unrevealed organization that is contained within the isofrequency dimension of the V to AI projection. onto the isofrequency axis of AI. This more detailed information also provides a basis of understanding of some of the apparent discrepancies in the existing

Figure 15. Schematic of the topography of the projection from V to AI. A, Idealized binaural and tonotopic map of the portion of AI representing 5-40 kHz. EI and EE bands and DZ are indicated with shading and two types of cross hatching, respectively. Lines with numbers indicate isofrequency contours with CF's specified in kHz. B, An 11 kHz isofrequency lamina flattened into the plane of the paper. Shading and two types of cross hatching indicate regions from which cells project to EI, EE, and DZ regions of AI. Areas of the EE and DZ sources overlap in the rostral pole of Vl. The approximate locations of Vo, Vl, Vt, and Vdc are indicated.


A
DZ
5
10
20
40
EI
EE
DZ
1mm
B
V_{dc}
V_1
V_1
V_1
V_1
V_1
V_o
dorsal
caudal
0.5 mm

literature in descriptions of the thalamic sources to AI.

Studies that relied on anterograde or retrograde degeneration techniques for neuroanatomical tracing identified the "principal division" (the ventral division and deep part of the dorsal division of Morest, '64) of the MGB as the major thalamic source of input to AI. A more diffuse input originating from within the magnocellular division (from Morest's medial division, M) also was identified (e.g., Rose and Woolsey, '49; Neff et al., '56; Wilson and Cragg, '69; Niimi and Naito, '74). No projection from PO to AI was demonstrated with degeneration techniques, even though studies revealed ascending inputs from the inferior colliculus to POl (Moore and Goldberg, 1963) and descending inputs to POl from the auditory cortex (Jones and Powell, '71).

The thalamic projection to AI has been defined in several earlier studies in which HRP was used as the retrograde tracer. The basic AI projection was first described by Colwell and Merzenich, who introduced injections of HRP at known best frequency sites located well within the physiologically defined borders of AI (Colwell, '75; Colwell and Merzenich, '75, '82). They found that an intermediate sized HRP injection placed in AI resulted in a continuously labeled sheet of neurons in V, with an additional column of cells labeled in the deep part of the

dorsal division (Dd) and the lateral part of the posterior thalamic group (POl) and a pocket of cells labeled in M. They also demonstrated the basic topography of interconnection across the tonotopic axes of AI, V, and Dd. Winer and colleagues ('77) and Andersen and colleagues (Andersen, '79; Andersen et al., '80b) described similar arrays, the latter group also using functional mapping techniques to characterize injection loci in regard to tonotopic organization. Winer, et al. ('77) illustrated the result of one relatively dorsal injection that was quite different from cases illustrated in other studies. In that cat, the labeled MGB cells were located rostrally in V, with a dense cluster of labeled neurons in (what we take to be) Vdc and a rostral parasagittal sheet of neurons. Indeed, the present experiments indicate that this array almost certainly resulted from a DZ injection.

Niimi and Matsuoka ('79) also used HRP as a retrograde tracer in an attempt to demonstrate the thalamic projections to AI. Their results were consistent with the fundamental tonotopic organization observed in the current study. However, they found that dorsal injections in AI tended to result in projections located dorsally in V, while more ventral AI injections tended to result in more ventral projections. They concluded that the dorsoventral dimension might be represented in the cortex as a continuous gradient

in the dorsomedial to ventrolateral dimension of AI. In our results, the projections resulting from some dorsal injections were located further dorsal in V than the projections resulting from other more ventral injections (e.g., the DZ projections compared to the ventral EE projections). However, the results of other injections (e.g., the ventral or middle EI injections) are incompatable with the existence of any single continuum in the thalamocortical topography of that dimension.

In a study by Colwell and Merzenich ('75, '82; Colwell, '75), microelectrode mapping was used to position injections of HRP in known relation to the tonotopic organization of AI, as in the current study. Single, moderate sized injections of tracers introduced into AI produced single, continuously labeled isofrequency laminae in V. Injections placed at two loci along the tonotopic axis in AI produced two such laminae in V. Two or more injections centered at different points along the isofrequency axis in AI resulted in no significant change in the labeled isofrequency contour. These results suggested that projections from all across isofrequency laminae in V converge onto restricted segments of isofrequency contours in AI and, conversely, that restricted loci in V send projections that diverge to sites distributed all along isofrequency contours. Single small injections placed at

high frequency loci sometimes resulted in a discontinuous, banded pattern of label in V. Colwell and Merzenich ('75, '82; also see Merzenich et al., '82) interpreted that result to indicate that there was some sort of repeating subunit within the AI projection from V that was smaller than the effective spread of their moderate size injections. Andersen et al. ('80) also found that single small injections of HRP sometimes labeled multiple, discrete, rostrocaudally oriented columns of cells in V. Merzenich et al. ('82) suggested that the discontinuous columns labeled by small injections placed in the high frequency area of AI might be regions of V that project to single binaural interaction bands in AI. That hypothesis has been confirmed in the current experiments in which injections were introduced in known relation to single binaural bands.

Relationship to physiological studies of the auditory thalamus. Neurons in the MGB exhibit binaural responses that are similar to those recorded in AI (Aitkin and Webster, '72; deRibaupierre et al., '75; Calford and Webster, '81). However, physiological studies of the MGB have failed to demonstrate any segregation of EE- and EI-responding neurons that is comparable to the functional subdivision of V that is suggested by the current results. Aitkin and Webster ('72) reported no systematic distribution within Vl of binaural responses. The proportion of EE to EI

neurons encountered in Vl and Vo was approximately equal, contrary to the prediction from the current anatomical results that most of the units in Vo should display EI or monaural responses. However, the large proportion of EE responses recorded in Vo might have resulted from the apparent over-sampling of units in Vo tuned to low frequencies (most of the reported EI units in the MGB have high CF's; Aitkin and Webster, '72). The discrepancy also may lie with the definition of Vo itself. Physiologically controlled projection studies of Colwell and Merzenich ('75, '82) strongly indicated that Vo was predominantly a high frequency nucleus, consistent with the present results and contrary to the physiological results of Aitkin and Webster.

deRibaupierre et al. ('75) concluded that binaural response properties apparently were distributed randomly in Vl. In contrast, Calford and Webster ('81) reported that units with different binaural properties were segregated in many microelectrode tracks across the MGB (they restricted attention to the caudal part of the dorsal division and to V), but saw no indication of rostrocaudally oriented binaural columns. In the case in which binaural responses are illustrated along reconstructed electrode tracks, no clear conclusions about segregation of classes of binaural units can be drawn.

The failure of physiological studies to demonstrate

a layered separation of EE and EI units in the MGB could be interpreted in the light of the present results in several ways. First, the complex folded structure of isofrequency laminae in V, particularly in the caudal aspect (in which it appears that most electrode tracks have passed), would confound any attempt to demonstrate the binaural organization within such a lamina. Second, the demonstration of a segregation of input sources in the thalamus based upon a functional distinction in the cortex may not be reflected by a correspondence in responses in V. Thus, for example, a population of EE-responding neurons in Vo might project only to cortical sites outside of AI, or there might be EE-responding units in Vo that provide an inhibitory or otherwise masked projection to cortical EI bands.

The existence of functional subdivisions in the MGB is strongly supported by the demonstration by Andersen et al. ('80a) that restricted injections of anterograde tracer into response-specific regions of the central nucleus of the inferior colliculus result in discontinuous labeling in the MGB. Taken with these cortical projection studies, it would appear likely, then, that the physiological mapping studies in the MGB simply have not been refined enough to demonstrate the complex three dimensional distribution of binaural neurons in V.

Toros et al. ('79) described a systematic variation in the number of cells receiving excitatory ipsilateral input associated with position along the rostrocaudal axis of Vl. Those authors classified units as 'contralateral dominant' or 'ipsilateral dominant' and found that the percentage of the sampled population displaying ipsilateral dominance rose to a maximum in the anterior pole of the middle third of Vl. This observation might correspond to our finding that the array of cells that project to EE bands is centered rostral to the center of the EI projection.

It should be noted that the low frequency segment of AI (especially the area representing frequencies below about 2.5 kHz) is largely EE in response character. Correspondingly, Colwell and Merzenich ('75; '82) and Andersen and colleagues ('80b) observed discontinuous thalamic arrays resulting from high frequency but <u>not</u> from low frequency AI injections. The current description of a layered ventral division almost certainly applies only to the higher frequency (more medial) aspect of V.

In most penetrations in DZ, the units that were encountered were broadly tuned for frequency. Might this broad tuning in DZ be accounted for by a projection from a population of broadly tuned EE units in the thalamus? The major sources of thalamic input to DZ are Vdc and the rostral pole of Vl. There has been no significant

population of broadly tuned neurons described in V, although judging from the illustrated electrode tracks (Aitkin and Webster, '72; Calford and Webster, '81), there have been few or no recordings made from Vdc. It is unlikely that a large percentage of the cells in Vdc or the rostral pole of Vl are broadly tuned, since cells in both of these areas also constitute a major part of the projection to the ventral and middle EE bands in which units are sharply tuned. It appears more probable that the broad tuning in DZ results from a convergence of input from a population of sharply tuned neurons whose CF's vary within the population. This hypothesis is consistent with the observation that the sheet of labeled cells in the rostral pole of Vl tended to be thicker and more diffusely labeled than that resulting from comparably sized injections in other EE subdivisions.

Topography of projections along isofrequency contours within AI subdivisions. Historically, Tunturi ('50; '52) hypothesized that there might be a single systematic binaural representation within AI, constituting the probable basis of a map of sound location. A map of target location and other systematic auditory cortical maps recently have been described within the auditory cortex of the mustache bat (e.g., Suga et al., '79; Suga and O'Neill, 80). The current studies demonstrate that there is no single, continuous binaural representation in the higher

frequency sector of AI, nor is there a systematic "map" explicit in the projection from V to the isofrequency dimension of AI. They also bring into question whether or not there is an orderly topographic pattern of projection within the isofrequency dimension of the subunits of AI. For example, an injection deliberately positioned on the border between the ventral EE and EI bands resulted in a retrogradely labeled array in V that was indistinguishable from the sum of the two arrays that resulted from injections centered within each band. Such observations are limited in number, but they strongly indicate that there is no dramatic spatial ordering of projections from sites within EE or EI thalamic projecting zones to sites along the isofrequency dimension of EE or EI cortical subdivisions.

All cortical EI injections resulted in labeling in arrays in V which comprised the same three subunits: two columns in Vl and a column passing from Vo to rostral Vl. Although we cannot rule out the possibility of variation in the extent of labeling within each thalamic subunit, the same set of subunits always was labeled regardless of the particular EI band that was injected. In contrast, there was more variation in the EE- and DZ-projecting arrays. All EE and DZ sites derive their input from regions of the same continuous sheet in Vl and Vdc, yet the relative amount of label that was found in each area of the sheet depended on

the particular band containing the injection site. All EE and DZ injections resulted in labeling in the same part of the rostral pole of Vl. However, Vdc was labeled by all DZ injections and to a varying extent by middle EE injections, but almost never by ventral EE injections. Conversely, the lamina of cells in Vl which formed the most caudal part of the EE projecting sheet was labeled after all but one of the ventral EE injections, some of the middle EE injections, and none of the DZ injections. This somewhat systematic variation in labeling is consistent with the suggestion from pysiological studies of a segregation in AI of different subclasses of EE units within different AI subdivisions (Imig and Adrian, '77; Merzenich et al., '79; Kitzes et al., '80; the current results). It is likely that some of the areas left unlabeled in the schematic drawing (fig. 15), especially in the rostral part, are EE sources to more dorsal EE regions in AI. (The schematic was based largely on injections in the ventral bands and DZ.)

The relationship of the dorsal zone to AI. The dorsal zone would appear to be a part of AI, as 1) it appears to fall within the cytoarchitectonic boundaries of AI (Rose, '49; Rose and Woolsey, '49; Sousa-Pinto, '73); and 2) its thalamic sources of input coincide with those of other predominantly EE regions within which neurons are sharply tuned. It probably was not included in "AI" as

defined by Merzenich and colleagues ('75) who used contralateral monaural stimulation. Neurons within DZ usually cannot be driven effectively by monaural stimulation. The dorsal zone apparently was excluded from AI in the mapping experiments of Reale and Imig ('80) because of the broad tuning of neurons and because of its apparent discrepancy with the tonotopic organization in "AI"; it was termed by them the "dorsoposterior region of the peripheral auditory belt". If our interpretation is correct, the basic frequency organization described for "AI" in the latter two studies applies to all but DZ. That is, there is a significant area within AI in which tuning is broad and characteristic frequencies are difficult to measure reliably. Perhaps this discrepancy in frequency specificity between DZ and the balance of AI has contributed to historical descriptions of "AI" as lacking tonotopic organization (Evans et al., '65; Oonishi and Katsuki, '65; Goldstein et al., '70). Indeed, most of the area <u>is</u> strictly tonotopically organized, but over this significant dorsal sector, such order would be difficult to demonstrate.

<u>How does the functional subdivision of AI reflect the organization of the ascending auditory neuraxis</u>? The current observations support the hypothesis that binaural bands represent elements of subsystems that are largely segregated from each other from the brainstem to at least

the level of AI. Restricted injections of anterograde tracer into the central nucleus of the inferior colliculus (ICC) resulted in labeling of banded arrays in V (Andersen et al., '80a). Those discontinuous patterns of label appear to correspond to the complex arrays that were labeled by intraband AI injections in this study. Restricted regions in the ICC receive their input from a limited number of the many brainstem nuclei that project to the colliculus (Roth et al., '78; Semple and Aitkin, '79). Together with the current observation of segregation of functionally distinguishable thalamocortical projections, these observations suggest that the inputs to different binaural bands in AI arise from different brainstem nuclei and ascend in parallel through the midbrain and thalamic levels to terminate in discrete bands in AI.

Segregation of ascending projections in auditory and visual systems. In the auditory system, binaural bands apparently are the targets of parallel projections that arise in different brainstem nuclei and are isolated from each other at several subcortical levels. In the visual system, projections from the two retinae are segregated within discrete laminae in the lateral geniculate nucleus (LGN), and the LGN laminae project to eye-specific ocular dominance columns in the primary visual cortex (see Hubel and Wiesel, '77). In the LGN, each lamina contains a

representation of most of the retina. Similarly, EE- and EI-projecting regions in V each appear to extend across isofrequency laminae to encompass the representation of all of at least the basal half of the cochlea. Within AI, it appears that the binaural bands of each class constitute complete representations of the basal cochlea. This is not the case for ocular dominance columns, but this discrepancy might be a necessary consequence of the difference between the one- and two- dimensional sensory epithelia of the auditory and visual systems.

Some functional implications. We have observed a systematic segregation of different classes of binaural neurons in AI and in their sources of input within V. What might be the functional significance of the complex intrinsic organization of this thalamocortical system?

Although we noted some quantitative differences between the responses of different EI units, at a superficial level of analysis there was no indication that the EI class could be subdivided. Conversely, differences in binaural responses within the EE class have been reported and, to some extent, associated with different binaural bands (Imig and Adrian, '77; Merzenich et al., '79; Kitzes et al., '80; this study). Consistent with those physiological observations, different EI bands have been found in this study to derive their input from apparently

coincident thalamic populations, but different EE bands derive input preferentially from different regions of a continuous EE projecting zone.

If all EI bands apparently derive input from the same complex thalamic projection array and display, qualitatively, indistinguishable response properties in AI, what is indicated by the presence of multiple discrete EI bands? Perhaps the true functional unit is an EI-EE band pair. In general, responses of EI neurons are implicated in the neural representation of higher frequency sounds. It is now evident that AI integrity is essential for the localization of brief sounds (Jenkins and Merzenich, '81;) which, at higher frequencies, almost undoubtedly are encoded by EI neuronal populations. Also, recent studies (Middlebrooks and Pettigrew, '81) have indicated that EI neurons are sensitive to the location of a sound relative to the position of the cat's mobile external ear. Conversely, many other aspects of sound analysis probably are carried out within EE systems. One might hypothesize, then, that the EI bands confer sound location-related information upon the products of each of several response-specific EE zones.

In the lower frequency sector of AI, EE and EI bands have not been found, and there, small injections of retrograde tracer result in labeling of very continuous neuronal arrays in V (Colwell, '75; Colwell and Merzenich,

'75; '82). What might be the meaning of a banded projection in AI and the MGB that is present at the higher frequency aspects and lacking at lower frequencies? One hypothesis might be that over the lower frequency range, binaural sound loaction and spectral information is processed within the same projection axis, while at higher frequencies it is processed within different subsystems. This is consistent with the fact that at lower frequencies, both location and spectral information are encoded in temporal cues, while at higher frequencies spectral analysis probably depends more on place coding and location sensitivity on intensive cues. In fact, it has been contended that sound spectrum decoding occurs largely within the line of projection of the medial superior olive (see Merzenich, '81; Loeb et al., '81), which is the principal nucleus implicated in the brainstem representation of the location of low frequency sounds. We hypothesize that, for whatever reason, sound location representation is embedded within the same low frequency system that accounts for analysis of other features of sound in AI and V, while a double (EE, EI) projection system applies for the higher frequency domain.

Binaural response-specific subdivisions as "cortical fields". While we have hypothesized that EI bands might interact closely with EE bands to confer sound location information on other aspects of sound feacture extraction,

it also is possible that EE and EI band classes each constitute discrete "representations". That is, individual bands or classes of bands could be operating largely independently of each other at or beyond AI in largely separate, parallel systems. Indeed, by the Rose and Woolsey criteria (Rose, '49; Rose and Woolsey, '49), it could be argued that the binaural band classes of "AI" each constitute a separate cortical field. As EE and EI subdivisions in the cat differ strikingly in their transcallosal projections (originating from large pyramidal cells in layer 3; Imig and Brugge, '78), they presumably are delimitable cytoarchitecturally. Although there has been no clear description of cytoarchitectonic boundaries within AI in the cat, structural subdivisions have been observed in the presumptive primary fields in man and other primates (Economo, '27; Bonin and Bailey, '47; Bailey and Bonin, '51; Pandya and Sanides, '73). There, the auditory granular cortex is interrupted by "bands and islets" of cortex that are characterized by the presence of large layer 3 pyramidal cells. The two other Rose and Woolsey criteria, field-specific functional characteristics and field-specific differences in connectivity, also are met by the binaural band subdivisions of AI. In fact, the binaural <u>bands</u> of AI are as distinguishable by these criteria as are the various identified cochleotopic <u>fields</u> of the auditory area in the cat!

A further question. The current results demonstrate a large degree of convergence and divergence within the thalamic projection to AI. Projections from three elongated columns of cells in V converge onto restricted loci in single EI bands in AI. Similarly, the entire extent of a lamina in the rostral part of V1 converges onto single loci in EE bands, and single loci in this lamina diverge to three EE bands. The significance of this convergent and divergent organization remains a central question in understanding this complex projection system.

REFERENCES

Abeles, M. and M.H. Goldstein, Jr. (1970): Functional architecture in cat primary auditory cortex. J.Neurophysiol. 33:172-187.

Adams, J. (1980): Stabilizing and rapid thionin staining of TMBbased HRP reaction product. Neurosci. Lett. 17:7-9.

Aitkin, L.M., and W.R. Webster (1972): Medial geniculate body of the cat: organization and responses to tonal stimuli of neurons in the ventral division. J. Neurophysiol. 35:365-380.

Andersen, R.A. ('79): Patterns of connectivity of the auditory forebrain of the cat. Doctoral Dissertation, Univ. Calif. San Francisco.

Andersen, R.A., G.L. Roth, L.M. Aitkin, and M.M. Merzenich (1980): The efferent projections of the central nucleus and the pericentral nucleus of the inferior colliculus in the cat. J. Comp. Neurol. 194:649-662. Calif. San Francisco.

Andersen, R.A., R.L. Snyder, and M.M. Merzenich (1980): The topographical organization of projections from physiologically identified loci in the AI, AII, and anterior auditory cortical fields of the cat. J. Comp. Neurol. 191:479-494.

Bailey, P., and G. von Bonin (1951): The isocortex of man. IN: Illinois Monographs in the Medical Sciences 6 (R.M. Allen, O.F. Kampmeier, I. Schour, and E.R. Serles, eds.), Univ. of Illinois Press, Unbana, Ill., pp. 1-301.

Bailey, P., G. von Bonin, and W.S. McCulloch (1950): The Isocortex of the Chimpanzee. Univ. of Illinois Press, Urbana, Ill.

Bentivoglio, M., H. G. J. M. Kuypers, and C. E. Catsman-Berrevoets ('80): Retrograde neuronal labeling by means of bisbenzimide and Nuclear Yellow (Hoechst S769121). Measures to prevent diffusion of the tracers out of retrogradely labeled neurons. Neurosci. Lett. 18:19-24.

Bentivoglio, M., H. G. J. M. Kuypers, C. E. Catsman-Berrevoets, H. Loewe, and O. Dann ('80): Two new fluorescent retrograde neuronal tracers which are transported over long distances. Neurosci. Lett. 18:25-30.

Bishop, P.O., W.Kozak, and G.J. Vakkur (1962): Some quantitative aspects of the cat's eye: Axis and plane of reference, visual field coordinates, and optics. J.Physiol.(London) 163:466-502.

Bonin, G. von, and P. Bailey (1947): The neocortex of Macaca mulatta. IN: Illinois Monographs in the Medical Sciences (R.M. Allen, O.F. Kampmeier, I. Schour, and E.R. Serles, eds.) Univ. of Illinois Press, pp. 1-163.

Brodmann, K. (1909): Vergleichende Lokalizationslehre der Grosshirnrinde, Barth.

Brugge, J.F., N.A. Dubrovsky, L.M. Aitkin, and D.J. Anderson (1969): Sensitivity of single neurons in the auditory cortex of cat to binaural stimulation: Effects of varying interaural time and intensity. J.Neurophysiol. 32:1005-1024.

Brugge, J.F., and T.J. Imig (1978): Some relationships of binaural responses patterns of single neurons to cortical columns and interhemispheric connections of auditory area AI of cat cerebral cortex. IN: Evoked Electrical Activity in the Auditory Nervous System (R.F. Nauton, ed.) Academic Press, New York.

Calford, M.B., and W.R. Webster (1981): Auditory representation within principal division of cat medial geniculate body: an electrophysiological study. J. Neurophysiol. 45:10131028.

Campbell, A.W. (1905): Histological Studies on the Localization of Cerebral Function. Cambridge Press,

Cambridge.

Casseday, J.H. and W.D. Neff (1973): Localization of pure tones. J.Acoust.Soc.Am. 54:365-372.

Clarke, P.G.H., I.M.L. Donaldson, and D. Whitteridge (1976): Binocular visual mechanisms in cortical areas I and II of the sheep. J.Physiol.(Lond.) 256:509-526.

Colwell, S.A. (1977): Corticothalamic projections from physiologically defined loci within primary auditory cortex in the cat: reciprocal structure in the medial geniculate body. Doctoral Dissertation, Univ. Calif. San Francisco.

Colwell, S.A., and M.M. Merzenich ('75): Organization of thalamocortical and corticothalamic projections to and from physiologically defined loci within primary auditory cortex in the cat. Anat. Rec. 181:336.

Colwell, S.A., and M.M. Merzenich ('82): Corticothalamic projections from physiologically defined loci in AI in the cat. J. Comp. Neurol., in press.

Cooper, M.L., and J.D. Pettigrew (1979): A neurophysiological determination of the vertical horopter in the cat and owl. J.Comp.Neurol. 184:1-25.

Economo, C. von (1927): L'Architecture Cellulaire Normale de

L'Ecorce Cerebral. Masson, Paris.

Eisenman, J.M. (1974): Neural encoding of sound location: An electrophysiological study in auditory cortex (AI) of the cat using free field stimulation. Brain Res. 75:203-214.

Evans, E.F. (1968): Cortical representation. In A.V.S. de Reuck and J. Knight (Eds.). Hearing Mechanisms in Vertebrates, Churchill, London.

Evans, E.F., H.F. Ross, and I.C. Whitfield (1965): The spatial distribution of unit characteristic frequency in the primary auditory cortex of the cat. J. Physiol. 177:238-247.

Gilbert, C.D., and T.N. Wiesel (1979): Morphology and intracortical projections of functionally characterised neurones in

Goldberg, J.M., and P.B. Brown (1969): Responses of binaural neurons in dog superior olivary compled to dichotic tonal stimuli: some physiological mechanisms of sound localization. J. Physiol. (Lond.) 32:613-636.

Goldstein, M.H. Jr., M. Abeles, R.L. Daly, and J. McIntosh (1970): Functional architecture in cat primary auditory cortex: tonotopic organization. J. Neurophysiol. 33:188-197.

Hall, J.L. III and M.H. Goldstein, Jr. (1968): Representation of binaural stimuli by single units in primary auditory cortex of unanesthetized cats. J.Acoust.Soc.Am. 43:456-461.

Hebrank, J. and D. Wright (1974): Spectral cues used in the localization of sound sources on the medial plane. J.Acoust.Soc.Am. 56:1829-1834.

Hind, J.E. (1953): An electrophysiogical determination of tonotopic organizatin in auditory cortex of cat. J. Neurophysiol. 16:475-489.

Hind, J.E., J.E. Rose, P.W. Davies, C.N. Woolsey, R.M. Benjamin, W.S. Welkes, and R.F. Thompson (1960): Unit activity in the auditory cortex. IN: Neural Mechanisms of the Auditory and Vestibular Systems (G.L. Rasmussen and W.F. Windli, eds.), Thomas.

Hubel, D.H. and T.N. Wiesel (1962): Receptive fields, binocular interaction, and functional architecture in the cat's visual cortex. J.Physiol.(London) 160:106-154.

Hubel, D.H., and T.N. Wiesel (1977): Functional architecture of macaque monkey visual cortex. Proc. R. Soc. Lond. B. 198:1-59.

Imig, T.J. and H.O. Adrian (1977): Binaural columns in the

primary field (AI) of cat auditory cortex. Brain Res. 138:241-257.

Imig, T.J. and J.F. Brugge (1978): Sources and terminations of callosal axons related to binaural and frequency maps in primary auditory cortex of the cat. J.Comp.Neurol. 182:637-660.

Imig, T.J., and R.A. Reale ('81): Ipsilateral corticocortical projections related to binaural columns in cat primary auditory cortex. J. Comp. Neurol. 203:1-14.

Imig, T.J., M.A. Ruggero, L.M. Kitzes, E. Javel, and J.F. Brugge (1977): Organization of auditory cortex in the owl monkey. J. Comp. Neurol. 171: 111-128.

Jenkins, W.M. (1980): Sound localization: Effects of unilateral lesions in the central auditory system. Doctoral dissertation, Florida State University.

Jenkins, W.M., and M.M. Merzenich (1981): Lesions of restricted representation sectors within primary auditory cortex produce frequency dependent sound localization deficits. Neurosci. Abst. 7:392.

Jerger, J., N.J. Weikers, F.W. Sharbrough, and S. Jerger (1969): Bilateral lesions of the temporal lobe: a case study. Acto Otolaryngol. Suppl. 258.

Jones, E.G., and T.P.S. Powell (1971): An analysis of the posterior group of thalamic nuclei on the basis of its afferent connections. J. Comp. Neurol. 143:185-216.

Kitzes, L.M., K.S. Wrege, and J.M. Cassady (1980): Patterns of responses of cortical cells to binaural stimulation. J. Comp. Neurol. 192:455-472.

Knight, P.A. (1977): Representation of the cochlea within the anterior auditory field (AAF) of the cat. Brain Res. 130:447-467.

Knudsen, E.I. and M. Konishi (1978): Space and frequency are represented separately in auditory midbrain of the owl. J.Neurophysiol. 41:870-884.

Knudsen, E.I., M. Konishi, and J.D. Pettigrew (1977): Receptive fields of auditory neurons in the owl. Science 198:1278-1280.

Kuypers, H.G.J.M., M. Bentivoglio, D. van der Kooy, and C.E. Catsman-Berrevoets (1979): Retrograde transport of bisbenzimide and propidium iodide through axons to their parent cell bodies. Neurosci. Lett. 12:1-7.

Levick, W.R. (1972): Another tungsten microelectrode. Med.Electron.Biol.Engng. 10:510-513.

Loeb, G.E., M.W. White, and M.M. Merzenich (1981):

Mechanisms of auditory information processing pitch perception. Neurosci. Abstr. 7:56.

Manabe, T., N. Suga, and J. Ostwald (1978): Aural representation in the Doppler-shifted-CF processing area of the auditory cortex of the mustache bat. Science 200:339-342.

Merzenich, M.M., R.A. Andersen, and J.C. Middlebrooks (1979): Functional and topographic organization of the auditory cortex. Exp.Brain Res. Suppl 2:61-75.

Merzenich, M.M., and J.F. Brugge (1973): Representation of the cochlear partition on the superior temporal plane of the macaque monkey. Brain Res. 50:275-296.

Merzenich, M.M., S.A. Colwell, and R.A. Andersen (1982): Thalamocortical and corticothalamic connections in the auditory system of the cat. IN: Cortical Sensory Organization III (C.N. Woolsey, ed.) Humana, Clifton, N.J., pp. 43-57.

Merzenich, M.M., P.L. Knight, and G.L. Roth (1975): Representation of the cochlea within the primary auditory cortex in the cat. J.Neurophysiol. 38:231-249.

Mesulam, M.-M. (1978): Tetramethyl benzidine for horseradish peroxidase neurohistochemistry. A non-carcinogenic

blue reaction-product with superior sensitivity for visualizing neural afferents and efferents. J. Histochem. Cytochem. 26:106-117.

Middlebrooks, J.C., R.W. Dykes, and M.M. Merzenich (1978): Binaural response-specific bands within AI in the cat: specialization within isofrequency contours. Neurosci. Abstr. 4.

Middlebrooks, J.C., R.W. Dykes, and M.M. Merzenich (1980): Binaural response-specific bands in primary auditory corex (AI) of the cat: Topographical organization orthogonal to isofrequency contours. Brain Res. 181:31-48.

Middlebrooks, J.C. and J.D. Pettigrew (1980): Functional classes of auditory cortical neurons distinguished by sensitivity to sound location. Neurosci.Absts. 6:333.

Middlebrooks, J.C., and J.D. Pettigrew (1980): Spatial receptive fields of neurons in the primary auditory cortex (AI) of the cat. J.Acoust.Soc.Am. Suppl. 68.

Middlebrooks, J.C., and J.D. Pettigrew (1981): Functional classes of neurons in primary auditory cortex of the cat distinguished by sensitivity to sound location. J. Neurosci. 1:107-120.

Middlebrooks, J.C., and J.M. Zook (1981): Thalamic

connections to and from binaural interaction bands in AI of the cat. Neurosci. Abst. 7.

Mills, A.W. (1960): Lateralization of high frequency tones. J. Acoust. Soc. Amer. 32:132-134.

Moore, R.Y., and J.M. Goldberg (1963): Ascending projections of the inferior colliculus in the cat. J. Comp. Neurol. 121:109-135.

Morest, D.K. (1964): The neuronal architecture of the medial geniculate body of the cat. J. Anat. 98:611-680.

Morest, D.K. (1965): The laminar structure of the medial geniculate body of the cat. J. Anat. 99:143-160.

Neff, W.D., G.P. Arnott, and J.D. Fisher (1950): Function of auditory cortex: localization of sound in space. Am. J. Physiol. 163:738.

Neff, W.D., I.T. Diamond, and J.H. Casseday (1975): Behavioral studies of auditory discrimination: central nervous system. In W.D. Keidel and W.D. Neff (Eds.), Handbook of Sensory Physiology, Vol. V/2:307-400. Springer, New York.

Neff, W.D., J.F. Fisher, I.T. Diamond, and M. Yela (1956): Role of auditory cortex in discrimination requiring localization of sound in space. J.Neurophysiol.

19:500-512.

Niimi, K., and H. Matsuoka (1979): Thalamocortical organization of the auditory system in the cat studied by retrograde axonal transport of horseradish peroxidase. Adv. Anat. Embryo. Cell Biol. 57.

Niimi, K., and F. Naito (1974): Cortical projections of the medial geniculate in the cat. Exp. Brain Res. 19:326-342.

Oonishi, S., and Y. Katsuki (1965): Functional organization and integrative mechanism in the auditory cortex of the cat. Jap. J. Physiol. 15:342-365.

Pandya, D.M., and F. Sanides (1973): Architectonic parcellation of the temporal operculum in Rhesus monkey and its projection pattern. Z. Anat. Entwichkl.-Gesch. 139:127-161.

Phillips, D.P. and Irvine, D.R.F. (1979): Methodological considerations in mapping auditory cortex: binaural

Reale, R.A., and T.J. Imig. (1977): An orderly frequency representation in the posterior ectosylvian sulcus of the cat. Neurosci. Abstr. 3:10. columns in AI of cat. Brain Res. 161:342-346.

Reale, R.A., and T.J. Imig. (1980): Tonotopic organzation in

auditory cortex of the cat. J. Comp. Neurol. 192:265-292.

deRibaupierre, F, A. Toros, and Y. deRibaupierre ('75): Acoustical responses of single units in the medial geniculate body of the cat. Exp. Brain Res. Suppl. 23:S98.

Riss, W. (1959): Effect of bilateral temporal cortical ablation on discrimination of sound direction. J.Neurophysiol. 22:374-384.

Rose, J.E. (1949): The cellular structure of the auditory region of the cat. J. Comp. Neurol. 91:409-440.

Rose, J.E., and C.N. Woolsey (1949): The relations of thalamic connections, cellular structure, and evocable activity in the auditory region of the cat. J. Comp. Neurol. 91: 441-466.

Roth, G.L., L.M. Aitkin, R.A. Andersen, and M.M. Merzenich (1978): Some features of the spatial organization of the central nucleus of the inferior colliculus of the cat. J. Comp. Neurol. 182:661-680.

Sanchez-Longo, L.P., and F.M. Forster (1958): Clinical significance of impairment of sound localization. Neurology (Minneap.) 8:119-125.

Semple, M.N., and L.M. Aitkin (1979): Representation of sound frequency and laterality by units in central nucleus of cat inferior colliculus. J. Neurophysiol. 42:1626-1639.

Shaw, E.A.G. (1965): Earcanal pressure generated by a free sound field. J.Acoust.Soc.Am. 39:465-470.

Sousa-Pinto, A. (1973): The structure of the first auditory cortex (AI) in the cat. I. Light microscopic observations on its organization. Arch. Ital. Biol. 111:112-137.

Sovijarvi, A.R.A., and J. Hyvarinen (1974): Auditory cortical neurons in the cat sensitive to the direction of sound source movement. Brain Res. 73:455-471.

Strominger, N.L. (1969): Localization of sound in space after unilateral and bilateral ablation of auditory cortex. Exp. Neurol. 25:521-533.

Suga, N. (1977): Amplitude spectrum representation in the Doppler-shifted-CF processing area of the auditory cortex of the mustache bat. Science 196:64-67.

Suga, N., and W.E. O'Neill (1980): Auditory processing of echos: representation of acoustic information from the environment in the bat cerebral cortex. IN: Animal Sonar Systems (R.-G. Busnel and J.F. Fish, eds.)

Plenum.

Suga, N., W.E. O'Neill, and T. Manabe ('79): Harmonic sensitive neurons in the auditoy cortex of the mustache bat. Science 203:270-274.

Toros, A., E. Rouiller, Y. deRibaupierre, C. Ivarsson, M. Holden, and F. deRibaupierre ('79): Changes of functional properties of medial geniculate body neurons along the rostro-caudal axis. Neurosci. Lett. Suppl. 3:S5.

Tunturi, A.R. (1950): Physiological determination of the arrangement of the afferent connections to the middle ectosylvian auditory area in the dog. Am. J. Physiol. 162:489-502.

Tunturi, A.R. (1952): A difference in the representation of auditory signals from the left and right ears in the isofrequency contours of the right middle ectosylvian auditory cortex of the dog. Am.J.Physiol. 168:712-727.

Wiener, F.M., R.R. Pfeiffer, and A.S.N. Backus (1966): On the sound pressure transformation by the head and auditory meatus of the cat. Acta Otolaryngol. 61:255-269.

Wilson, M.E., and B.G. Cragg (1969): Projection from the medial geniculate body to the cerebral cortex of the cat. Brain Res. 13:462-475.

Winer, J.A., I.T. Diamond, and D. Raczkowski (1977): Subdivision of the auditory cortex of the cat: the retrograde transport of horseradish peroxidase to the medial geniculate body and posterior thalamic nuclei. J. Comp. Neurol. 176:387-418.

Woolsey, C.N. (1961): Organization of cortical auditory system. IN: Sensory Communication (W.A. Rosenblith, ed.)

Woolsey, C.N., and E.M. Walzl (1942): Topical projection of nerve fibers from local regions of the cochlea in the cerebral cortex of the cat. Bull. Johns Hopk. Hosp. 71:315-344. M.I.T. Press., pp. 235-257.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