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The Effects of Neonatal Auditory Cortical Lesions on
Minimum Audible Angles for Sound Localization by
the Ferret (*Mustela putorius*)

by

Bryan J. Rooney, E.Sc., M.Sc.

A thesis submitted to
the Faculty of Graduate Studies and Research
in partial fulfilment of
the requirements for the degree of
Doctor of Philosophy

Department of Psychology

Carleton University

Ottawa, Canada

August, 1994

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Minimum Audible Angles for Sound Localization by
the Ferret (*Mustela putorius*)

submitted by

Bryan J. Rooney, B.Sc., M.Sc.

in partial fulfilment of the requirements
for the degree of Doctor of Philosophy

Chair, Department of Psychology

Thesis Supervisor

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ABSTRACT

In adult ferrets, unilateral lesions of the auditory cortex produce severe deficits in sound localization in the contralateral hemifield. Damage restricted to just primary auditory cortex (AI), results in profound contralateral impairments. There is, however, no evidence regarding the effects on sound localization of auditory cortical lesions sustained during early development. Indeed, there is only one published report that describes any effects of early cortical ablation on auditory function. In the young cat, large bilateral lesions of auditory cortex fail to produce impairments in tone duration discrimination whereas lesions in adults do, a result that indicates sparing of function following early brain damage (Scharlock, Tucker and Strominger, 1963). In the present study, sound localization was used to examine the effects of early unilateral auditory cortex lesions. For adult ferrets, unilateral ablation of auditory cortex resulted in a severe contralateral sound localization deficit, although acuity around midline and in the sound field ipsilateral to the lesion were unaffected. In contrast, adult ferrets that had unilateral ablations of presumptive auditory cortex at post-natal day 6, did not show a contralateral deficit. The results of this study support the idea of functional sparing following early damage, since all the neonatally-operated animals had contralateral performance that was significantly better than

the adult-operated ferrets. Behavioral sparing did not occur, however, in neonatally-operated ferrets that had all, or most, of the cerebral hemisphere ablated. Retrograde fluorescent dyes injected into specific frequency regions of primary auditory cortex yielded useful information on the tonotopic organization of the ferret medial geniculate nucleus but failed to provide evidence of anatomical reorganization. This study is the first to examine the effects of early auditory cortex damage on sound localization.

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For My Father
Ronald James Rooney
1929 - 1982

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INTRODUCTION

The effects of auditory cortical lesions have been investigated in a number of mammalian species over the past several decades using a variety of discrimination tasks. It is clear from these studies that auditory cortex is not essential for "hearing" since it is possible to establish conditioned responses to sounds of various intensities and frequencies following bilateral lesions (Butler, Diamond and Neff, 1957; Goldberg and Neff, 1961; Heffner, 1978; Massopust, Wolin and Frost, 1971; Masterton and Diamond, 1978; Neff, Diamond and Casseday, 1975; Raab and Ades, 1940). In contrast, bilateral, or even unilateral ablation of auditory cortex is sufficient to disrupt the ability to localize the source of a sound in space (Jenkins and Masterton, 1982; Kavanagh and Kelly, 1987).

Given the number of studies that have investigated the effects of auditory cortical damage, it is surprising that only one has examined the outcome of damage in a young animal (Scharlock, et al., 1963). Scharlock and colleagues found that cats that had undergone large bilateral temporal cortex ablations as neonates, showed complete sparing of function on tasks requiring discrimination of tone durations or recognition of sound patterns. This study will examine sound localization ability in animals that have sustained early cortical damage. A sound localization task was chosen

since it has been clearly demonstrated, by many investigations of various species, that auditory cortical damage in the adult reliably produces a deficit in sound localization (Heffner, 1978; Heffner and Masterton, 1975; Jenkins and Masterton, 1982; Neff, 1968; Neff, Arnott and Fisher, 1950; Neff, et al., 1975; Neff, Fisher, Diamond and Yela, 1956; Strominger, 1969a, 1969b; Wegener, 1964). It therefore provides a reliable and sensitive measure of functional sparing.

Definition of Auditory Cortex

The first studies to localize the auditory cortex were performed over a hundred years ago. Ferrier (1876) studied a number of species (including monkey, dog, cat and rat) and showed that electrical stimulation of the temporal region of cerebral cortex evoked pricking of the opposite ear and turning movements to the opposite side. Since those primitive studies, the locus and extent of auditory cortex has been charted with greater precision and in a greater number of species anatomically, on the basis of cytoarchitecture, thalamic projections, and electrophysiologically, by evoked responses and microelectrode recordings. It should be noted at the outset of this review that much of our understanding of the auditory system is based on studies of the cat. Therefore, a large proportion of the evidence presented here will come from studies of the cat. Both the cat and ferret are

carnivores, and all the available anatomical, physiological and behavioral research has shown that the main features of their auditory systems are comparable.

Cytoarchitecture. The foundation for the localization and parcellation of auditory cortex can be placed on Rose's (1949) cytoarchitectural study of cat cortex. Studying cellular morphology in Nissl stained tissue and defining regions based on similar cellular characteristics, he divided auditory cortex into three distinct areas: primary auditory cortex (AI), secondary auditory cortex (AII) and an area in the posterior ectosylvian gyrus. Primary auditory cortex is cytoarchitecturally similar to other primary sensory cortical areas, it has six layers and a high density of pyramidal and granular cells in layers II, III and IV, with a cell-sparse layer V. Since this early work, auditory cortex has been defined cytoarchitecturally in a number of other mammalian species including human (Galaburda and Sanides, 1980).

Thalamocortical projections. Studies of thalamocortical projections have expanded the anatomical boundaries of auditory cortex and further subdivided those regions which were previously defined by cytoarchitectural criteria. Rose and Woolsey (1958) studied the pattern of thalamic degeneration following cortical ablation and found

that the secondary somatosensory area and the insulo-temporal area (I-T) were also auditory regions (see Fig. 1) since damage to these regions produces degeneration in the medial geniculate. Their results also showed that AI is the main recipient of projections from the ventral division of the medial geniculate, the main ascending auditory thalamic relay. This finding has since been confirmed in a number of other degeneration studies (Aitkin, 1976; Niimi and Naito, 1974; Sousa-Pinto, 1973) and in later tracing studies which looked at retrograde transport of HRP injected in auditory cortical regions (Anderson, Knight and Merzenich, 1980; Niimi and Matsuoka, 1979; Raczkowski, Diamond and Winer, 1975; Winer, Diamond and Raczkowski, 1977). In general, the cat's primary auditory cortex (AI) receives ascending projections from the ventral division of the medial geniculate nucleus, whereas the surrounding, secondary areas receive input mainly from either the medial or dorsal divisions (Niimi and Matsuoka, 1979; Raczkowski, Diamond and Winer, 1975; Ravizza and Belmore, 1978; Winer, Diamond and Raczkowski, 1977).

Auditory cortex in the ferret has been defined by both HRP labelling and retrograde degeneration. Kavanagh and Kelly (1987) found that following HRP injections into the middle ectosylvian gyrus, cells were labelled in the ventral division of the medial geniculate nucleus in a pattern similar to that previously described for the cat. Moreover, following lesions of the middle ectosylvian gyrus (MEG),

retrograde degeneration was found in the ventral division of the medial geniculate and the posterior thalamic nucleus. This pattern of degeneration was found in other studies of the cat and indicates that primary auditory cortex (AI) is located in the MEG. Lesions that were restricted to the MEG did not result in degeneration of all divisions of the entire medial geniculate nucleus. However, complete degeneration of the medial geniculate did result following large lesions that included the anterior and posterior ectosylvian gyrus. This indicated that these are secondary auditory regions in the ferret. A diagram based on this anatomical evidence is presented in Fig. 2.

Electrophysiological mapping. Auditory cortex has also been defined on the basis of electrophysiological recordings. Early studies explored the boundaries of auditory cortex by recording slow-wave "evoked potentials" that were elicited, not by sound, but by electrical stimulation of auditory nerve fibers at various distances along the length of the cochlea (Tunturi, 1944; Woolsey and Walzl, 1942). These studies identified a number of responsive regions whose spatial extents were consistent with the earlier cytoarchitectonic analysis (Rose, 1949). In addition to providing a parcellation of auditory cortex based on physiology, these studies showed a point-to-point correspondence between different stimulation positions, and positions on the surface of cortex. This is the same as the

point-to-point representation between the sensory epithelium and cortex that is found in other sensory modalities, such as the retinotopic representation found in visual cortex or the representation of the surface of the body in somatosensory cortex. However, since different positions along the cochlea are associated with different frequencies of sound, this topographic organization came to be regarded as 'tonotopic'.

Direct evidence that cortex possessed a tonotopic organization awaited studies which presented tones and used microelectrodes to record single unit activity. These studies involved "mapping" the surface of auditory cortex by determining the "characteristic", or "best" frequency for single units recorded at multiple sites across cortex. Characteristic frequency (CF) is the frequency for which a unit has the lowest threshold of excitation. At high intensities a unit may respond to a wide range of frequencies but as the intensity of a pure tone is reduced, a unit will tend to respond to a more restricted frequency range. The CF is determined then, by successively lowering the intensity and scanning across frequencies until a single frequency is found to which the unit is most sensitive. Initial attempts to map the frequency organization of auditory cortex with tones were characterized by vague and inconsistent reports of tonotopicity (Erulkar, Rose and Davies, 1956; Evans, 1950; Evans and Whitfield, 1964; Goldstein, Ables, Daly and McIntosh, 1970; Hind, Rose,

Davies, Woolsey, Benjamin, Welkes and Thompson, 1960).

Common to these early studies was the method of superimposing data from a number of individual animals onto one 'standard' reference with different parts of cortex mapped in different animals and the results combined. Merzenich and his colleagues (Merzenich, Knight and Roth, 1975) attributed the failure of earlier studies to resolve an organized tonotopic map to this practise of collapsing data over individual animals. They observed that the location of physiologically defined AI is variable with respect to the position of the suprasylvian sulcus. Thus the procedure of combining data from many animals obscures the tonotopic organization. By identifying the characteristic frequency of single neurons, or clusters of neurons, they recorded from many more sites than earlier single unit experiments, and constructed entire frequency maps for individual cats. They found an orderly frequency representation which was consistent with the cochlear place maps derived by Woolsey and Walzl (1942) from their earlier evoked potential studies. That is, a pure tone that stimulates a single point in the cochlea, is represented as a strip of cells in the auditory cortex, with high frequencies represented rostrally and low frequencies caudally. Although the axis of orientation of these "isofrequency contours" may differ across species, an orderly tonotopic organization has been observed and mapped in primary auditory cortex of a number of other animals (see

page 238 in Clarey, Barone and Imig, 1992) including the ferret (Kelly, Judge and Phillips, 1986; Phillips, Judge and Kelly, 1988).

As discussed above, the auditory cortex has different frequencies organized in strips of tissue that span the length of the primary auditory cortex. This represents a major departure from the organizational scheme of the visual or somatosensory cortex which have a two dimensional mapping of their respective sensory epithelium projected onto the cortical surface (Hubel and Weisel, 1963; Mountcastle, 1957). This difference reflects the fact that the cochlea is a one-dimensional receptor surface while vision and somesthesia have a two-dimensional receptor epithelia. Tunturi (1952) recognized this, and was the first to speculate that the isofrequency contours of the auditory cortex contained neurons which varied in their response to some dimension of acoustic stimulation other than frequency. This hypothesis has since been substantiated by studies which have shown that the second dimension of primary auditory cortex is organized on the basis of binaural response type. Some cells are excited by stimulation of either ear and show a response facilitation when both ears are simultaneously stimulated while others are excited by stimulation of the contralateral ear only, and are strongly inhibited by stimulation of both ears. Cells of each type are grouped together to form regions in cortex that are organized roughly orthogonal to the isofrequency contours

(Imig and Adrian, 1977; Imig and Brugge, 1978; Imig and Reale, 1981; Middlebrooks, Dykes and Merzenich, 1980; Middlebrooks and Zook, 1983; Reale and Kettner, 1986). A discussion of this property will be presented later in the context of the role auditory cortex plays in binaural processing. Below I will summarize the importance of binaural hearing for the localization of sounds.

Binaural Hearing and Sound Localization

In vision and somesthesia, spatial information is readily available to higher centres by virtue of a one to one correspondence between the site of activation on the sensory surface, and the location of a stimulus in the sensory domain. In these modalities, a topographic representation of space is already present in the ascending fibers. On the other hand, the auditory receptor is not capable of directly coding the spatial location of a sound source. In the ear, tones of differing frequencies displace the basilar membrane maximally at different locations along the length of the cochlea. High frequencies stimulate the basal end of the cochlea, while low frequencies stimulate the apical end, with the amount of the displacement proportional to the intensity of the sound. The acoustic signal is thus coded with respect to intensity and frequency, but not spatial position. Instead, the auditory system must derive the location of the sound, in part, by a comparison of the physical energy present at the two ears

(Mills, 1972). As first stated by Lord Rayleigh (1907) in the Sidgwick lecture given at Cambridge, England, low frequency sound sources are localized on the basis of interaural temporal differences, while high frequency sources are localized on the basis of interaural intensity differences. This is the so-called "duplex theory" of sound localization.

Interaural time difference. A sound pressure wave emanating from a position on the horizontal plane other than the midline will arrive at the ears at slightly different times. This temporal disparity is referred to as the interaural time difference (ITD) and is a consequence of the difference in the length of the sound path from the source to each ear. For example, a sound presented in the right hemifield will reach the right ear first because of the additional time required for the sound to travel around the head to the left ear, about 29.4 μ sec for every centimeter it must travel (Mills, 1972; Woodworth, 1938). Thus, the magnitude of the ITD is directly related to stimulus location and, of course, differs between animals with different head sizes. For example, for humans, a sound located directly to one side (90 degrees azimuth) will lead to an ITD of 660 μ sec, whereas for a ferret the same location would produce an ITD between 150 and 200 μ sec.

The above discussion of ITDs is most appropriate when applied to transient sounds such as the interaural time

disparity for the arrival of a sound onset or a brief sound such as a click. For sustained, low frequency sounds, the ITD also produces an ongoing interaural phase difference that can be used for localization. A pure tone signal presented to the right ear will be phase delayed by the time the sound reaches the left ear. The phase difference between the sounds at each ear can indicate the location, since the ear farthest from the sound will be receiving the wave at a delayed phase angle compared to the near ear. The cue becomes ambiguous, however, when the wave length of the tone is less than the diameter of the listener's head (Haftner, 1984; Mills, 1972; Yost, 1974, 1981). For high frequency tones, with wavelength shorter than the interaural distance, the phase angle of sounds arriving at the two ears may be greater than 360 degrees, which would lead to an ambiguous localization of the sound source. Moreover, at high frequencies the auditory system is unable to maintain the synchronous phase-locked activity required for analysis of phase disparities (Johnston, 1980). It should be noted that the importance of interaural phase difference in the localization of sounds is debatable since in the natural environment sounds always have a beginning and an end. Moreover, environmental sounds are not sinusoids but are complex, and often contain transient signals with sharp onsets and offsets, any of which can be analyzed for interaural time differences.

Interaural intensity difference. The interaural intensity difference (IID) is highly dependent on the frequency of the source. The IID arises from the sound shadow produced by the head and is only appreciable for frequencies with wave lengths that are small relative to the interaural distance (Calford, Moore and Hutchings, 1986; Feddersen, Sandel, Teas and Jeffress, 1957; Mills, 1972). Thus, for low frequencies where the wavelength is large, the head is essentially sound transparent whereas high frequencies can produce a large IID. The IID resulting from the shadow of the head can be augmented by the pinnae which, at high frequencies, can act as directional amplifiers to increase the intensity at the ear nearest the source (Aitkin and Semple, 1982; Calford and Pettigrew, 1984; Phillips, Calford, Pettigrew, Aitkin, and Semple, 1982). As was the case for ITDs, the IID varies as a function of sound position: the more lateralized the sound source, the greater the IID. For example, in humans a sound originating from 90 degree azimuth, will produce an IID of 20 dB for frequencies above 6000 Hz (Feddersen, et al., 1957).

The Role of Auditory Cortex in Sound Localization

The earliest indication that auditory cortex might be involved in sound localization comes from the studies of Ferrier (1876). Ferrier found that when the temporal cortex was stimulated electrically, animals responded by pricking their ears and turning their head away from the stimulated

side. Since that early study, numerous electrophysiological investigations have shown that cortical cells are responsive to binaural stimulation. However, it was behavior/lesion studies that demonstrated the necessity of auditory cortex for sound localization. Below I will present a brief review of the electrophysiological and behavioral evidence that identifies the role that auditory cortex plays in the localization of sound.

Binaural physiology. The importance of auditory cortex for sound localization is suggested by numerous single unit electrophysiology studies that have employed sealed headphone systems to presented stimuli dichotically. These studies have shown that the responses of cortical neurons are influenced by the very binaural parameters that are important for sound localization namely, ITD and IID (Brugge, Dubrovsky, Aitkin and Anderson, 1969; Brugge and Merzenich, 1973; Kitzes, Wrege and Cassady, 1980; Phillips and Irvine, 1983). In the case of ITDs, the firing rate of cortical units can be either facilitated or inhibited depending on the interaural delay of the stimulus. For example, after determining the characteristic frequency of a cortical neuron, Brugge and colleagues (1969) measured the number of unit spikes with the CF tone presented to each ear at various interaural delays. They found that histograms of the unit spike counts formed periodic functions that corresponded to the period of the stimulating tone, thus

indicating that the units were sensitive to the interaural phase disparities. Many of these cells were sensitive to ITDs ranging from 0-400 μ sec which corresponds to the ITDs that the cat would experience in nature. Moreover, the cells had CFs less than 2400 Hz, which is consistent with the psychophysical data that indicate interaural phase differences are only useful indicators of sound location for low frequencies. As indicated earlier, ITDs of transient signals can be used as a reliable indicator of sound location irrespective of the frequency. Indeed, some cortical cells have been found to exhibit a "characteristic delay" sensitivity that is independent of the stimulus frequency. Therefore, the cell will respond maximally to a specific ITD regardless of tonal frequency (Brugge and Merzenich, 1973). Kitzes, et al. (1980) also observed cortical neurons that showed a suppression of an excitatory response over a wide frequency range. The interaural delay over which the suppression occurred was very large, several milliseconds. The magnitude of this interaural delay exceeds any ITD that could result from the physical distance between the ears, but it does correspond to latency differences that may arise from IIDs. Some units have been identified that respond poorly to monaural stimulation of either ear, but respond vigorously to binaural stimulation with very small ITDs (Kitzes, et al., 1980; Phillips and Irvine, 1983). These units, termed predominantly binaural, likely code for midline sound sources.

A number of studies have also shown that cortical neurons are sensitive to IIDs (Brugge, Dubrovsky and Rose, 1964; Brugge et al., 1969; Phillips and Irvine, 1981, 1983). The majority of cortical units are excited by stimulation of the contralateral ear and respond to increases in ipsilateral stimulation with either a suppression or facilitation of responding. Phillips and Irvine (1981) investigated the effects of varying IIDs within the range that would occur naturally by the sound shadow cast by the animal's head. Measuring unit activity in relation to interaural intensity, they found that most cells were maximally sensitive to IIDs which correspond to a range of azimuth within the contralateral sound hemifield, suggesting these units code for contralateral space. Indeed, studies of azimuth preference employing free-field stimulation have found that many azimuth-sensitive cells are responsive to contralaterally located sound sources (Eisenman, 1974; Imig, Irons and Samson, 1990; Middlebrooks and Pettigrew, 1981; Rajan, Aitkin and Irvine, 1990).

As mentioned earlier in the context of the organization of auditory cortex, there is growing evidence that cortical cells of similar binaural response type are grouped together in strip-like assemblies that run across the isofrequency contours (Imig and Adrian, 1977; Imig and Brugge, 1978; Imig and Reale, 1981; Middlebrooks, et al., 1980; Middlebrooks and Zook, 1983; Reale and Kettner, 1986; Kelly and Judge, 1993). Imig & Adrian (1977) found that cortical cells which

displayed a summation or a suppression response to binaural stimulation were grouped separately in bands or patches. They mapped a band of suppression cells that was 4 mm long and oriented orthogonal to the isofrequency contours such that it intersected frequencies from 4.9 Hz to 22.7 kHz. By passing a recording electrode tangential to the cortical surface, Middlebrooks, et al. (1980) were able to record units along a single isofrequency contour. They found that regions with the same binaural response type, were clearly segregated from one another - summation or suppression as the electrode advanced along the isofrequency contour. Moreover, they presented evidence that the binaural bands and isofrequency contours crossed each other. Recently, a similar organization of binaural response regions has been reported for the ferret auditory cortex (Kelly and Judge, 1993).

As indicated earlier in the context of the thalamic input, a number of secondary auditory fields have been found outside of primary auditory cortex (Knight, 1977; Merzenich, Knight and Roth, 1975; Reale and Imig, 1980). In the cat, several of these regions have been shown to possess a tonotopic representation and respond to binaural stimulation (for reviews, see Brugge and Reale, 1985; Winer, 1992). For example, the anterior auditory field (see Fig. 1) has a frequency representation that mirrors that found in adjacent AI (Knight, 1977), the cells are sharply tuned to frequency and are binaurally sensitive to both time and intensity

disparities (Phillips and Irvine, 1982). Another region, field P, located in the caudal bank of the posterior ectosylvian sulcus, also has a frequency organization (Reale and Imig, 1980). Like cells in both AI and A, field P cells display binaural sensitivity to interaural time and intensity, but unlike the other regions they show nonmonotonic rate-intensity functions and thus respond over a restricted range of stimulus intensity (Phillips and Orman, 1984). Although secondary auditory fields outside of AI have not been extensively studied in the ferret, Kowalski, Versnel and Shamma (1993) have identified an anterior field on the basis of electrophysiological mapping data. In addition, the pattern of thalamic degeneration following large cortical lesions indicates that at least some secondary regions are located in the anterior and posterior ectosylvian gyrus. Nevertheless, lesion studies that are described in the following section provide evidence that these secondary auditory fields are not necessary for sound localization while primary auditory cortex is essential.

Behavioral studies. The importance of auditory cortex in sound localization has been best demonstrated by behavioral studies of the effects of brain lesions on auditory spatial responses. While the role auditory cortex plays in simple intensity or frequency discriminations is unclear (intensity & no deficit: Kryter and Ades, 1943; Neff

et al., 1975; intensity & deficit: Heffner and Heffner, 1986; frequency & no deficit: Elliot and Trahiotis, 1970; Neff et al., 1975; Thompson, 1960; frequency & deficit: Allen, 1945; Meyer and Woolsey, 1952), it has been reliably shown that auditory cortical damage produces deficits in sound localization (Heffner, 1978; Heffner and Masterton, 1975; Jenkins and Masterton, 1982; Neff et al., 1956; Neff, 1968; Strominger, 1969a, 1969b). The earliest evidence that cortex may be important for sound localization can be traced to Ferrier's (1876) experiments. He found that lesions of the temporal lobe led to a hemi-neglect, that is, animals would not orient their pinna or head to sounds contralateral to the lesion.

Since that early work, numerous studies have found deficits in sound localization following auditory cortical ablation (Heffner, 1978; Heffner and Masterton, 1975; Neff, et al., 1950; Neff, et al., 1975; Neff, et al., 1956; Strominger, 1969a, 1969b, Wegener, 1964). For instance, Neff et al. (1950) trained cats on a left versus right, 2-choice task in which the animal was required to approach a food reward box behind which a buzzer had sounded. They found that normal cats could discriminate sound sources separated by as little as 5 degrees, however, following large bilateral lesions (included AI, AII, Ep, I-T, SII) similar levels of performance required 40 degrees separation. Using a similar task, Strominger (1969b) produced restricted bilateral lesions in various

subdivisions of auditory cortex. He found that area AI was particularly important for sound localization since animals with lesions which spared AI but included the surrounding auditory regions were unimpaired, while animals with lesions that were confined to AI showed a deficit. It is clear from these studies that primary auditory cortex, in particular, is necessary for sound localization.

While bilateral auditory cortical lesions produced large impairments, unilateral lesions, even large unilateral lesions, appeared to have no effect on sound localization when animals were tested using the left versus right, 2-choice task (Neff et al., 1950, 1956). However, Strominger (1969a) tested with smaller angles of sound source separation and noticed that unilateral lesions produced small impairments that resulted from errors in detecting sounds contralateral to the lesion. Later studies used a more sensitive, 7-choice sound localization task which required that the animal localize sounds originating from one of seven speakers spaced at 30-degree intervals around a semicircular apparatus. This test clearly demonstrated the contralateral deficit that Strominger (1969a) had observed earlier (Jenkins, 1983; Jenkins and Masterton, 1982; Jenkins and Merzenich, 1984; Kavanagh and Kelly, 1983; Thompson and Cortez, 1983). For example, Jenkins and Masterton (1982) found that unilateral lesions produced a severe deficit in localizing sounds in the contralateral hemifield while performance was unaffected ipsilateral to the lesion. In

the ferret, an exclusively contralateral deficit following unilateral damage has also been demonstrated using a 7-choice task (Kavanagh and Kelly, 1983).

As discussed previously, different frequencies are represented in cortex along discrete strips of tissue or isofrequency contours. In a remarkable study, Jenkins and Merzenich (1984) combined microelectrode electrophysiological recording and behavioral testing. They produced unilateral lesions restricted to physiologically defined isofrequency contours and tested their animals in a 7-choice situation using tone pips. Not only did they find a deficit limited to the contralateral hemifield, but the deficit was confined only to the tonal frequencies corresponding to the ablated isofrequency contour. Conversely, in another case, Jenkins and Merzenich produced a large unilateral lesion that included all the auditory cortical fields sparing only a restricted isofrequency region in AI. This animal showed no sound localization deficit when tested with noise or tone pips of frequencies represented in the spared AI tissue. However, when tested with frequencies higher or lower than those represented in the remaining AI tissue, the animal showed a severe contralateral deficit. This study provides strong evidence that AI is required for sound localization and suggests that the processing of binaural information necessary for sound localization is coded in a frequency specific way.

While the 7-choice task is useful for quickly testing sound localization performance at different locations in space, measures of minimum audible angle provide a more precise test of sound localization acuity. The minimum audible angle (MAA) is defined as the "smallest detectable difference between the azimuths of two identical sound sources" (Mills, 1958). Kavanagh and Kelly (1987) measured MAAs in their investigation of the effects of auditory cortex lesions on sound localization in the ferret. They used a 2-choice test with speakers centered around 0 degrees azimuth (midline test), +60 and -60 degrees (right and left test, respectively). In this way they determined the MAA independently in the midline and each hemifield. Following large unilateral lesions that destroyed all auditory cortex in one hemisphere, the animals were unable to localize sounds in the contralateral hemifield. In contrast, performance at midline and in the ipsilateral hemifield were unaffected. Moreover unilateral lesions restricted to AI produced the same pattern of deficit. It is clear from both this work and the previous studies of the cat, that primary auditory cortex (AI) is necessary for localization of sounds in the contralateral hemifield.

Early Lesions of Auditory Cortex

Over three decades ago Scharlock, Tucker and Strominger (1963) examined the effects produced by large bilateral auditory cortical lesions in adult and neonatal cats. They

found that lesions in the adult resulted in a severe impairment in the ability to discriminate durations of pure tones. In contrast, neonatally operated cats showed normal performance. They concluded that early damage to the auditory system does not result in the impairment that follows from damage sustained at maturity. This study is the only investigation to examine the effects of early auditory cortical damage and will be described in detail in the discussion.

Present Study

Advantage of using the ferret. The ferret (*Mustela putorius*) has been used for auditory studies of anatomy (Henkel and Brunso-Bechtold, 1993; Moore, 1988), electrophysiology (King and Carlile, 1993; King and Hutchings, 1987; Kelly and Judge, 1993; Kelly, et al., 1986; Moore, Semple and Addison, 1983; Phillips, et al., 1988; Shamma, Fleshman, Wiser and Versnel, 1993) and behavior (Kavanagh and Kelly, 1983, 1987, 1992; Kelly, Kavanagh and Dalton, 1986). One of the main advantages of the ferret is in studies of early development, since the ferret is born in a very immature state (altrical) relative to other commonly used mammals. The onset of hearing in the ferret does not occur until about 32 days postnatally, compared to a cat which hears at 6 days (Moore, 1982; Morey and Carlile, 1990). In the visual system it has been found that the developmental time course of the ferret lateral geniculate

nucleus is similar to that of the cat if conception is taken as the beginning of development (Linden, Guillery and Cucchiaro, 1981). Therefore, it has been suggested that the difference in the postnatal timing of events arises from the much shorter gestation period of only 42 days for the ferret as compared to 64 days for the cat. Evidence from work in the auditory system is consistent with this argument since both the cat and ferret show acoustic responses to sound at about the same age after conception (cat: Aitkin and Moore, 1975; Moore and Irvine, 1979, ferret: Moore, 1982). The ferret, therefore, is an especially suitable species for studies of mammalian central auditory development.

Purpose of the present study. In this investigation the effects of early damage to auditory cortex on sound localization in the ferret were examined. This research offers valuable insight into the functional sparing or recovery that can occur in the auditory system of young mammals. This is only the second study designed to address the issue of behavioral sparing following early damage to auditory cortex and it is the first study to examine the effects of early damage restricted to one hemisphere. This is possible since unilateral cortical ablation produces a reliable deficit in the adult ferret which is limited to the hemifield contralateral to the lesion (Kavanagh and Kelly, 1987). By employing a testing procedure that allows for independent assessment of midline and lateral hemifield

sound localization capabilities, the animals' performance on the midline and ipsilateral to the damage can be used as a control for any extraneous variables which might affect sound localization ability.

METHOD

Subjects

Neonatal ferrets (*Mustela putorius*) used in this study were born at Carleton University from pregnant females obtained from Marshall Research Labs of North Rose, New York. The pregnant ferrets were immunized against canine distemper prior to importation, and the neonates were immunized when approximately 6 months old. Animals with sable coats were used to avoid any sensory abnormalities associated with albinism (Moore and Kowalchuk, 1988). Except during behavioral testing, animals were housed in groups of 2-4 and provided with food and water *ad libitum*. During behavioral testing the animals were individually housed and water deprived.

Lesion Method

Unilateral destruction of auditory cortex in the adult, or presumptive auditory cortex in the neonate, was achieved by subpial aspiration.

Neonatal Cases

Anesthesia. Neonatal ferrets were initially induced to a surgical level of anesthesia with halothane (Fluothane) in oxygen, delivered by an Ohmeda VMC anesthesia machine. After induction, the subjects were packed in crushed ice and maintained in a state of areflexia by combining 2% Fluothane and hypothermia.

Surgical procedures. Surgery on the neonates was performed when the subjects were 6 days old, and clean (aseptic) procedures were observed. Once the neonate was anesthetized, a midline incision was made in the scalp and the skin retracted. The bone overlying presumptive auditory cortex was cut with a #11 scalpel and the bone flap reflected to expose cortex. The cortical ablation was produced by vacuum aspiration using a glass pipette. Following surgery the wound was closed with 4-0 silk suture and the head rinsed with sterile saline. The neonates were slowly warmed and returned to the mother once they were mobile.

I have previously determined the location of presumptive auditory cortex by injecting rhodamine labelled Latex microspheres (Molecular Probes) in the neocortex at postnatal day 6 and subsequently locating the injection site when the animal matured. This was possible since the microspheres are stable over a long period and diffuse very little. In the adult brain, the injections that were made at 6 days of age were found restricted to the crown of the middle ectosylvian gyrus (Fig. 3).

Adult Cases

Anesthesia. Adult ferrets were anesthetized with pentobarbital sodium (Somnotol; 35 mg/kg, males; 25 mg/kg,

females, i.p.) after premedication with atropine sulfate (1 mg, i.p.) to inhibit respiratory tract secretions.

Surgical procedures. Following pre-operative sound localization testing (see below), the adult ferrets underwent unilateral auditory cortical ablation. Surgical procedures for the adult ferrets followed sterile surgical protocols. Therefore, once an animal was anesthetized, the head was shaved, fixed in a head holding device, scrubbed with a solution of providone-iodine (Betadine) and covered with sterile drapes. A midline incision was made in the scalp, the skin was reflected and the temporal muscle was blunt dissected from dorso-caudal to ventro-rostral and retracted to expose the skull. A hole was drilled in the bone overlying auditory cortex. This location is clearly identifiable as a slight elevation in the skull surface. The craniotomy was enlarged with a rongeur, the dura mater incised and reflected, and auditory cortex ablated by subpial aspiration. The temporal muscle and perimysium were sutured with 2-0 absorbable suture (PDS II) and finally the skin was closed with 3-0 nylon sutures (Dermalon). The animal was administered penicillin G (Derapen; 0.15 ml, s.c.) and allowed to recover. Sutures were removed 2 weeks after surgery and postoperative testing was begun after a 4 week recovery period.

Behavioral Task

Subjects. Twenty-four hours prior to training, the ferrets were water deprived and subsequently received all their required water during daily sessions in the test apparatus. The condition of the external ear canals was monitored by regular otoscopic examination and the tympanum and middle ear were examined by postmortem dissection.

Overview of procedure. Three independent 2-choice sound localization tests were used to evaluate the effects of auditory cortical lesions on minimum audible angles around 0 degrees azimuth (Midline Test), -60 degrees azimuth (Left Hemifield Test), and +60 degrees azimuth (Right Hemifield Test). Performance curves were generated for each test based on the percentage of correct responses at each angle of speaker separation. A threshold for sound localization was set at the speaker separation at which the animals obtained 75% correct performance; this value was interpolated from the performance curves. Changes in this threshold angle following lesions were used as a measure of the extent of impairment. Performance of each animal was also evaluated against chance, with confidence limits determined by the binomial distribution with an alpha level of $p = .01$ (Hays, 1988).

Apparatus. Animals were trained and tested in a semicircular apparatus (92 cm radius) built by Carleton

University's Science and Technology Center (Fig. 4) which is similar to one used previously (Kavanagh and Kelly, 1987, 1992). The floor was constructed of plastic coated plywood, and the walls and ceiling were made of 1 cm. stainless steel mesh. A raised platform, located at the back of the apparatus, served as a start area from which animals initiated trials. The middle third of the start area was covered by a wire tunnel 17 cm in diameter and the surface of the back quarter was covered with a moistened cloth held by a steel mesh cover. A stainless steel spout raised 11 cm above the floor was mounted 9 cm in front of the start area. For an animal to initiate a trial it was required to stretch forward through the wire tunnel and touch its nose to the center spout while at the same time keeping its hind feet in contact with the damp cloth. A high impedance circuit designed by the author signaled contact with the centre spout to the computer system. The start area was designed so that an animal had to face directly forward with its head situated at the geometric centre of the apparatus in order to initiate a trial.

Loudspeakers suspended around the outside perimeter of the apparatus at a height of 14 cm were moved to different positions to permit midline and lateral field tests of sound localization. Solenoid-operated water spouts were mounted in the wall of the apparatus, 6 cm above the floor. For the midline test, water spouts were located at -30 and $+30$ degrees azimuth. For testing in the left hemifield, they

were located at -90 and -30 degrees, and for testing in the right hemifield they were fitted at +30 and +90 degrees. Contact between the water spout and a stainless steel plate (25 cm wide) located on the floor around the perimeter of the apparatus, provided the electrical signal necessary for delivery of water.

The test apparatus was located within a soundproof chamber (Eckel Industries) in a room separate from the experimenter and the sound-generating equipment. To reduce reflected sound, the walls and ceiling of the chamber were insulated with fiberglass batting. A closed-circuit television camera (RCA model BW 003) mounted above the test cage was used to monitor the animals' behavior during testing. Stimulus presentation, water delivery, and response tabulation were controlled by an IBM compatible computer. The control program, written in Turbo Pascal (Borland International), and an optically isolated parallel interface, were prepared and assembled by the author.

Training procedure. Training took place in two stages designed to condition the animals to initiate trials from the center spout. During the initial stage of training, loudspeakers and response spouts were located at -30 and +30 azimuth, and the stimulus was a continuous train of 45 msec noise bursts presented at a rate of 2/sec. Water deprived ferrets were allowed to move freely in the apparatus while the stimulus was presented automatically

from one of two loudspeakers. Ferrets were required to contact the response spout below the active speaker to obtain a water reward (0.2-0.4 ml). This stage of training served to familiarize the animals with the basic stimulus-response contingencies and was continued for approximately 100 reinforcements.

In the second stage of training, stimulus presentation was controlled by the experimenter, and the ferrets' behavior was shaped by successive approximation to enter the start area, initiate the stimulus by contacting the center spout, and respond to the appropriate water spout. In the case of a correct response, i.e., contact with the response spout below the active loudspeaker, water reinforcement was delivered immediately and the stimulus was discontinued. The position of the stimulus on the next trial was then selected by the computer according to a pseudorandom sequence (Gellermann, 1933). In the case of an incorrect response, the stimulus was discontinued and no reinforcement was delivered. On subsequent trials, the stimulus was presented from the same location until a correct response was made. This 'correction procedure' served to prevent animals from forming a position preference for one spout or the other. Testing commenced when an animal reliably initiated its own trials from the start area.

Test procedure. For the training procedures the stimulus was a noise burst presented 2/sec, however, during

the test procedure the stimulus was a single 45 msec noise burst. Thresholds for minimum audible angles were determined separately for the midline and each lateral field by the method of limits, using a descending series of angles. Thus, in the case of midline testing, with the speakers centered around 0 degrees azimuth, the animals were tested first, with the speakers separated by 60 degrees, followed by successively smaller angles of separation (40, 20, 10, 6, and 0 degrees). The same procedure was followed for lateral field testing where the speakers were centered at +60 and -60 degrees for the right and left tests, respectively. Prior to testing in the lateral fields, animals were given the opportunity to localize 2/sec stimuli in order to familiarize them with the placement of the response/water spouts.

Data acquisition and analysis. An animal's performance at any given speaker separation was obtained from the average percent correct for at least three blocks of 50 trials. A maximum allowable range in performance of 10% was permitted at each speaker separation. If after 3 blocks of trials the range was greater than 10%, the lowest data point was discarded and the animal was tested for an additional block of 50 trials before proceeding to the next smaller angle.

Details of the Stimulus

The acoustic stimulus was a 45 msec noise burst of 75-85 dB SPL (re: 20 μ Pa) as measured at the initiate area with an impulse sound level meter (Brüel and Kjær 2209) and 0.5 in. microphone (Brüel and Kjær 4134). Measurements of the noise burst show that the predominant energy was between 500 Hz and 20 kHz and that the duration was just slightly longer than 45 msec due to a slight reverberation in the test apparatus (Fig. 5). The stimulus was produced from continuous noise from a Coulbourn noise generator (model S81-02), was bandpass filtered from 0.1-15 kHz by a Krohn-Hite active filter (model 3550), and split to two Coulbourn Instruments gates (model S84-04). The switching of the gates was computer controlled using a TTL (transistor-transistor logic) pulse of 45 msec to produce the noise burst. An Aiwa DC stereo amplifier (model P30) delivered the noise burst to one of two Philips loudspeakers (model ADO 160/T8). The details of the stimulus are shown in Fig. 5.

The frequency response characteristics for loudspeakers used in this study were matched in intensity within 5 dB for one-third octave frequency bands between 100 and 40,000 Hz (see spectrogram in Figure 5). Nevertheless, as an additional control for any possible intensity differences between the speakers, the noise was amplitude modulated prior to being gated so that the intensity of the noise burst varied from one trial to the next. A modulation of 10

dB was produced by a Coulbourn amplitude modulator (model S77-05) operated by a 0.1 Hz sine wave from a Hewlett-Packard function generator (model 3312a). This procedure ensured that the stimulus could not be distinguished on the basis of subtle intensity differences between the two speakers. As a safeguard against any differences in speaker quality, the speakers were frequently exchanged, left for right, and the animals carefully observed for disruption of their performance.

Anatomical Tract Tracing and Electrophysiology

To examine possible anatomical reorganization of auditory cortex following neonatal ablation, injections of retrograde tracers were made in primary auditory cortex opposite the lesion and the cortical tissue surrounding the lesion was examined for transcallosal labelling. For seven ferrets, pressure injections of horseradish peroxidase (HRP, 0.2 μ l of 30% Sigma Type VI) were made into the middle ectosylvian gyrus. Following a 2-day post-injection survival period, the animals were deeply anesthetized with pentobarbital sodium and perfused through the left ventricle of the heart. The brains were removed, embedded in gelatin and frozen sectioned at 40 μ m on a sliding microtome. The tissue was TMB-reacted using the procedure of Mesulam (1978).

The tonotopic frequency organization of auditory cortex was mapped in the spared hemisphere of eight ferrets, by

conventional microelectrode recording techniques (for a detailed description of methods see, Kelly, Judge and Phillips, 1986). Briefly, anesthesia was induced with a combination of halothane and pentobarbital sodium and halothane was used to maintain a state of areflexia throughout the recording session. The middle ectosylvian gyrus was surgically exposed using sterile techniques. The ferret was located in a sound-attenuating room (Eckel Industries) and 100 msec tone pulses were delivered by KEF high frequency (Type SP1032) and mid-range (Type AD5060) loudspeakers with a crossover network (KEF, Type SP1015). The responses of single neurons or neuron clusters were recorded extra-cellularly using insulated tungsten microelectrodes (1.2-1.5 M Ω at 1 kHz). Frequency mapping was accomplished by determining the CF (characteristic frequency: the tone frequency for which the neural elements had their lowest excitatory SPL) of neurons or neuron clusters at positions across the cortical surface. Once a frequency map was complete, the fluorescent retrograde dyes, Fluoro-Gold (10% Fluoro-Gold, Fluorochrome) and Fluoro-Ruby (10% dextran, tetramethylrhodamine, Molecular Probes), were pressure injected at specific frequency regions. The incision was sutured closed, the ferret was administered penicillin G (Derapen; 0.15 ml, s.c.) and allowed to recover. After a post-injection survival time of one week the animals were deeply anesthetized and perfused, the brains were removed, embedded in gelatin and frozen

sectioned. The sections were mounted on slides and cover slipped with D.P.X. (Aldrich) for fluorescence microscopy.

Assessment of Damage

The extent of cortical damage was illustrated by projecting coronal sections onto graph paper and plotting the borders of the lesion. These maps were then transferred to standard drawings of the sulcal pattern of the ferret cortical surface. The extent of the lesion was also determined by examining thalamic degeneration. The extent of cell loss was judged by two trained observers and illustrated on standard drawings of frontal sections.

Summary of Research Design

The study consists of two main subject groups: neonatally-operated and adult-operated ferrets. The results are based on 18 neonatally operated ferrets which were divided into five groups on the basis of lesion size. In addition, there were 10 adult ferrets; 6 were used for normative sound localization data and 4 served as adult-lesion cases. The performance of each animal was plotted against speaker separation for midline and lateral field tests of sound localization with the level of chance responding indicated with a dashed line. Thresholds for minimum audible angle and performance at 60 degrees speaker separation were used for comparisons between the neonatal and adult groups.

RESULTS

Sound Localization in the Ferret. Before examining the effects of auditory cortex lesions in the adult and neonate, sound localization ability of normal adult animals will be presented. Sound localization performance for six normal ferrets is shown in Figure 6. A psychophysical function was found for each animal, with high performance at large angles of speaker separation and performance near 50% at smaller angles. Differences between midline and lateral field performance were apparent in most cases. The performance was superior and the psychophysical curves had a steeper drop-off for midline sound localization than for the lateral fields. Indeed, mean thresholds for minimum audible angles were 9 degrees for midline and 24 degrees for the lateral fields. Figure 7 shows the psychophysical curve for the midline and lateral field tests averaged across animals. While some ferrets showed performance that was slightly better in one hemifield, this was neither a large nor a reliable effect.

Behavioral testing verified that the animals could not distinguish the noise bursts on the basis of stimulus quality or 'speaker signature', but relied exclusively on sound source position. As the speaker separation was decreased it was consistently found that the animals' performance dropped to levels that were no better than what would be expected by chance. Moreover, at larger angles of

speaker separation exchanging individual loudspeakers had no effect on the animals' performance. Therefore, it was clear that the ferrets performed the task only on the basis of sound source location.

- Adult Lesions -

Adult lesions - anatomy. Of the four ferrets that received lesions as adults, two (F407 and F417) had damage that was restricted to the middle ectosylvian gyrus with little or no damage to surrounding cortical regions. The other two animals (F414 and F418) had larger lesions that included the middle ectosylvian gyrus, part of the anterior and posterior ectosylvian gyrus and some of the posterior suprasylvian gyrus (see Fig. 8). In every case, serial reconstructions of the posterior thalamus showed severe degeneration throughout the ventral division of the medial geniculate ipsilateral to the lesion. The extent of thalamic degeneration ranged from restricted, as in the case of F407 with damage limited solely to the ventral division of the medial geniculate, to severe, as in F418 where damage included the caudal, ventral and posterior divisions of the medial geniculate, as well as portions of the magnocellular division. F418 also showed degeneration throughout most of the posterior nucleus, with some damage more rostrally in the lateral geniculate and caudal aspect of both the ventroposterior and lateral posterior nuclei (see Fig. 9).

Adult lesions - behavior. The pre- and post-operative sound localization curves for the adult lesion cases are shown in Figure 10. Animals F407 and F417 sustained auditory cortical ablations of the right hemisphere, while F414 and F418 had lesions in the left hemisphere. By comparing the pre- and post-operative performance it is evident that the lesion had little effect on midline performance. Although the midline performance for three animals (F407, F414 and F417) was poorer postoperatively, the effect was small. Sound localization performance in the hemifield ipsilateral to the lesion was either unaffected (F414 and F418) or showed only a slight drop in performance (F407 and F417). In contrast, every animal showed a large drop in postoperative performance in the hemifield contralateral to the lesion. Indeed, only one case (F407) performed substantially better than the level expected by chance, and that was achieved only at the largest speaker separation. Thus, in spite of variations in performance across animals and variations in lesion size, all the adult operated ferrets showed a large contralateral deficit.

Repeated postoperative testing showed little evidence of improvement for any animal. One ferret (F407) showed some improvement in contralateral performance from 4 to 16 weeks postoperatively, however, there was no evidence of further gains at 26 weeks. It is important to note that the contralateral deficit in sound localization can not be

attributed to a general motor deficit or spatial neglect since performance levels greater than 90% were observed in every animal when continuous 2/sec burst trains were used instead of a single sound burst.

Animals in the adult lesion group are the only ones that afford a comparison between preoperative and postoperative performance, since preoperative testing was clearly impossible in cases with neonatal lesions. For the neonatally ablated animals, comparisons were made against normal performance.

Within-subject comparisons between performance in each hemifield were possible since the deficit was so strongly lateralized. Following unilateral ablation of the middle ectosylvian gyrus in the adult, sound localization performance in both midline and in the hemifield ipsilateral to the lesion was relatively unaffected (Fig. 11). In contrast, animals were either severely impaired or completely unable to localize brief sounds only in the contralateral sound field ($t(3) = 8.91$, $p < .01$). This clearly lateralized effect is ideal for assessing the effects of early lesions because deficits are evident from within subject comparisons between performance in each lateral sound field.

Neonatal Lesions. The ferrets that received ablations as neonates are organized into five groups on the

basis of the extent of damage. The anatomical and behavioral results are presented together for each group.

- Hemidecorticates -

Hemidecorticate - anatomy. Two ferrets (F324 and F327) had extensive neocortical damage that included virtually the entire hemisphere (see Fig. 12). Both cases had massive cell loss throughout the entire posterior thalamus ipsilateral to the lesion (see Fig. 13), the contralateral thalamus appeared normal. In both ferrets the dorsal hippocampus was also destroyed ipsilateral to the ablation.

Hemidecorticate - behavior. The hemidecorticate animals (F324 and F327) showed poor performance in the sound field contralateral to the ablated hemisphere. Their contralateral performance never reached 75%, even at the widest speaker separation (see Fig. 14). Indeed, at 60 degrees speaker separation they performed just slightly above the level expected by chance (69% for F324 and 68% for F327). Nevertheless, both ferrets had good midline performance with psychophysical curves that look essentially normal. The performance differed between the two animals on tests of the ipsilateral field. F327 had performance that was exceptionally good relative to normal animals, while the ipsilateral performance for F324 was good at 60 degrees speaker separation but dropped sharply to near chance levels at 40 degrees.

- Massive Lesions -

Massive lesions - anatomy. The cortical damage in this group, though not a complete hemispherectomy, went well beyond the ectosylvian gyrus. The lesions were extensive, with only F319 having any spared posterior cortex (see Fig. 15). Rostrally, the lesions encompassed all, or a large part, of the suprasylvian gyrus. The damage extended dorsally to include the splenocruciate and cingulate gyri and was bounded ventrally by the rhinal sulcus. Two animals also had complete destruction of the hippocampus (F323 and F326).

The thalamic degeneration in these animals was as widespread as that seen in the hemidecorticate animals. Degeneration extended throughout the entire posterior thalamus with only a small amount of sparing in the lateral posterior nucleus found in F319 and F323 (see Fig 16).

Massive lesions - behavior. The psychophysical curves for this second group of neonatally ablated animals (F319, F323, F326 and F331) is shown in Figure 17. The psychophysical curves for midline and the sound field ipsilateral to the lesion are comparable to normal data with the exception of F331 which showed poor ipsilateral performance.

All of these ferrets had contralateral sound localization deficits. For each animal, the performance in the hemifield contralateral to the lesion was worse than the

ipsilateral performance. F331 showed contralateral performance that was only marginally better than chance, while F323 and F326 were unable to perform the task even at the largest speaker separation. Nevertheless, all animals were capable of high performance levels when continuous trains were substituted for the single noise burst. The contralateral performance of F319 was considerably better than the other cases. This animal had some sparing of the posterior ectosylvian gyrus and ventral posterior cortex and had the greatest thalamic sparing of the four cases.

The results of the animals with massive cortical damage are combined with the hemidecorticate ferrets and summarized in Figure 18. The graph shows each animal's performance ipsilateral and contralateral to the lesion as well as the mean performance for the group. Since only one animal had contralateral performance that reached 75%, threshold minimum audible angles are not presented, instead the graph presents performance data at the largest speaker separation. It is readily apparent from Figure 18 that, relative to their ipsilateral performance, these animals were severely impaired in their ability to localize sounds contralateral to the lesion ($t(5) = 3.74$, $p < .01$).

- Large Lesions -

Large lesions - anatomy. This group had lesions that encompassed all the middle ectosylvian gyrus and most of the anterior and posterior ectosylvian gyrus (see Fig. 19). In

the normal ferret this lesion would comprise all of the primary auditory cortex, localized in the middle ectosylvian gyrus, and most, if not all, secondary auditory areas which are situated in the anterior and posterior ectosylvian gyrus. Damage in these animals also involved the surrounding suprasylvian gyrus, however, all the animals had some sparing of the ventral edge of the anterior ectosylvian gyrus and one animal (F321) had the ventral aspect of both the anterior and posterior ectosylvian gyrus preserved. Both F434 and F435 had some damage to the dorsal hippocampus.

Thalamic degeneration was extensive in all cases and correlated well with the extent of cortical damage (see Fig. 20). For example, F321 had the smallest cortical lesion and showed the least thalamic damage, whereas F329 had the largest cortical lesion and also the most widespread thalamic degeneration. (In fact, F435 had the most cortical damage, but histological analysis of the thalamus was not possible for F435.) The cases with the smaller cortical lesions (F320 and F321) showed thalamic degeneration restricted to the ventral division of the medial geniculate and the ventral two thirds of the lateral geniculate nucleus. The other two cases (F329 and F434) showed degeneration that encompassed the entire medial geniculate nucleus, the caudal extent of the lateroposterior nucleus of the thalamus, a majority of the lateral geniculate nucleus and part of the ventroposterior nucleus.

Large lesions - behavior. The psychophysical curves for the animals in this group are shown in Figure 21. In spite of the cortical damage, all these animals were able to localize in the contralateral hemifield. In all but one animal (F321), however, performance was worse in the hemifield contralateral to the lesion relative to their ipsilateral performance. As with the other groups, the psychophysical curves obtained from tests of midline and ipsilateral sound localization performance did not differ from the performance of normal ferrets.

The hemifield performance for this group of animals is summarized in Figure 22. Minimum audible angles are not presented because two animals (F320 and F329) had contralateral performance that never attained 75%. Instead, performance data at the largest speaker separation is presented. It is apparent that contralateral performance was inferior to the ipsilateral performance ($t(4) = 3.43$, $p < .05$), but the effect was small and the contralateral performance was well above chance level.

- Middle Ectosylvian Lesions -

Middle ectosylvian lesions - anatomy. The animals of this group had lesions that included the entire middle ectosylvian gyrus. This tissue corresponds to the primary auditory cortex of the ferret. Two animals (F433 and F436) had damage that was confined to the middle ectosylvian gyrus, whereas one animal (F430) had damage that extended

dorsally to include part of the suprasylvian gyrus (see Fig. 23). Although these animals had lesions that were similar to the adult-ablated animals in both size and location, their pattern of thalamic degeneration was remarkably different. Whereas the adults showed extensive thalamic degeneration, two of these neonatally ablated ferrets (F433 and F436) had no distinguishable cell loss, and the remaining case (F430) had only partial degeneration restricted exclusively to the ventral division of the medial geniculate (see Fig. 24).

Middle ectosylvian lesions - behavior. Figure 25 shows the sound localization performance for the three animals in this group. In striking contrast to the adult-ablated animals which showed a contralateral disability, all the animals in this group showed good performance in the contralateral sound field. Indeed, the contralateral performance was as good as in normal ferrets. Although the performance of F430 was not as high in the hemifield contralateral to the lesion compared to the ipsilateral performance, the levels of performance were high in both hemifields and the psychophysical functions did not differ noticeably from normal ferret performance. The contralateral performance of F433 was virtually identical to the performance of F430 and, likewise, its performance was similar to that seen for lateral field localization by normal ferrets. On the other hand, the midline and ipsilateral performance of F433 was peculiar. This animal

was completely unable to localize sounds *ipsilateral* to the lesion. Clearly, none of these early-ablated animals showed the severe *contralateral* impairment shown by the adult-ablated animals.

The lateral field performance for this group is summarized in Figure 26. Performance is shown at 60 degrees speaker separation. This group clearly indicates a sparing of function with early damage. The graph shows no reliable difference between the hemifield performance *ipsilateral* and *contralateral* to the lesion.

- Small Lesions -

Small lesions - anatomy. This group of animals had lesions that damaged only part of the middle ectosylvian gyrus and some portion of the suprasylvian gyrus (see Fig. 27). Since the primary auditory cortex of the ferret is situated in the middle ectosylvian gyrus, it is clear that these animals have at least some damage to AI.

Of the four animals in this group, only one (F431) had any discernible thalamic cell loss (see Fig. 28). The normal appearance of thalamus is surprising since adults with similar cortical damage would have certainly shown some thalamic degeneration. Oddly, the only animal that showed thalamic cell loss, F431, had a cortical lesion which was smaller than F316, a case that exhibited no thalamic cell loss.

Small lesions - behavior. All the animals in this group showed good midline and ipsilateral sound localization performance and only one (F431) had poor contralateral performance (see Fig. 29). This same animal was the only ferret to show cell loss in the thalamus. The hemifield performance for this group is summarized in Figure 30. The figure presents the performance at 60 degrees speaker separation. It is clear from the graph that these lesions did not produce a contralateral deficit.

Neonatal Lesion Versus Adult Lesion: Comparison of Sound Localization Performance

The main result of this study is presented in Figure 31. The mean performance for tests of the hemifield contralateral to the lesion is shown for each group. The data are for performance at 60 degrees speaker separation. Since their performance did not differ, the data from the two hemidecorticate ferrets were combined with the results for the massive lesion group. It is readily apparent that, with the exception of the massive lesion group, all the neonatally operated groups performed significantly better than the adult lesion group. Therefore, the neonatal lesion animals were spared the profound contralateral sound localization deficit that follows auditory cortical lesions in the adult. However, sparing of function did not occur with early lesions that included almost the entire hemisphere.

All the ferrets in the large lesion group had cortical damage that was considerably larger than the adult lesion cases and yet their contralateral sound localization ability was significantly better than the adult lesion cases ($t(7) = 2.38$, $p < .05$). As shown earlier, three of the four adult-lesion animals had performance that never surpassed the level expected by chance (see Fig. 10), whereas all the animals in the large-lesion group showed some sound localization ability. Indeed, three animals (F321, F434 and F435) had psychophysical curves that were not unlike normal animals.

The animals in the MEG-lesion and small-lesion groups were also spared the contralateral sound localization deficit observed in adult ablated ferrets (MEG-lesion: $t(5) = 3.17$, $p < .05$, small-lesion: $t(6) = 2.48$, $p < .05$). Both groups had slightly more sparing than the neonates with large lesions. Nevertheless, the ferrets of the MEG-lesion group had lesions that were of similar size to the lesions that resulted in a severe deficit for adult ablated animals.

Tract Tracing

Thalamic labelling. Injections of HRP or fluorescent dyes into the crown of the middle ectosylvian gyrus retrogradely labelled cells in the ipsilateral medial geniculate nucleus. Cells that project to primary auditory cortex were found in the ventral and medial division of the medial geniculate, and dorsally in the posterior nucleus. The general pattern

of labelling is consistent with earlier studies of the normal ferret (Kavanagh and Kelly, 1937; Pallas, Roe and Sur, 1990) and cat (Imig and Reale, 1981; Imig and Morel, 1985a; Imig and Morel, 1985b; Winer, Diamond and Raczowski, 1977). Figure 32 shows the mapped tonotopic organization of primary auditory cortex and the dye injection sites for four animals. These cases had limited injections that illustrate the topographic organization of the thalamic projections. The electrophysiological mapping confirmed that the primary auditory cortex of the ferret is organized tonotopically, with high frequencies represented dorsally and low frequencies ventrally. No clear topographic organization was evident in the rostral part of the ventral division of the medial geniculate but the caudal portion had a simple organization. Dorsomedial cells project to the ventral, low frequency regions of AI, while the ventrolateral cells project to the dorsal, high frequency regions. This topographic organization is the reverse of the organization found in the cat (Imig and Reale, 1981; Imig and Morel, 1985a; Imig and Morel, 1985b; Winer, Diamond and Raczowski, 1977). The labelling in the medial division of the medial geniculate was too sparse to determine an organization.

Transcallosal labelling. The transcallosal labelling that results from a primary auditory cortex injection is shown in Figure 33. This normal ferret had a fluorescent dye injected into the high frequency region of AI.

Retrograde labelling was present in large pyramidal cells in the opposite cortex. The distribution of these cells was largely restricted to a homotopic region contralateral to the dye injection. Of the 15 ablated ferrets that had cortical injections of either HRP or fluorescent dyes not a single case showed labelled cells anywhere in contralateral cortex, neither directly adjacent to the lesion, nor at distal sites.

Summary of Results. The results of the present study indicate that early auditory cortical damage results in some sparing of function but sparing does not occur with massive lesions. The minimum audible angles for sound localization are summarized in Table I. Unilateral auditory cortical lesions in the adult, result in a profound sound localization deficit restricted to the sound field contralateral to the lesion. It was not possible to determine the minimum audible angles for three of the adult-ablated animals because their performance did not reach the 75% level. This was also the situation for the neonatally ablated ferrets with extensive cortical damage. In contrast, many of the neonatally ablated animals with lesions that were at least as large as the adult-ablated cases, did not show the deficit typical of the adult animals. These animals were able to localize sound sources in the contralateral hemifield and many had a level of performance that was like normal animals.

While there is clear sparing of function in the neonatally ablated animals, the transcallosal tracing provided no evidence of anatomical reorganization. That is, there was no evidence of anomalous projections from cortical regions surrounding the lesion, to AI in the opposite hemisphere.

DISCUSSION

Scharlock, Tucker and Strominger (1963) were the first to find sparing of function after auditory cortex lesions. In their study, cats were trained to avoid an electric shock by discriminating tone pulses of 1 second duration from 4 second pulses. Performance was measured as the number of trials required to perform the task to a criterion level. In adult animals, large bilateral cortical ablations that removed both primary and secondary auditory areas as well as the posterior regions (see Fig. 1), produced a deficit in 4 of their 7 adult ablated animals. That is, the animals were unable to learn the task within the investigator's criterion limit of 500 trials. The 3 other adult-ablated cats learned the task in about the same number of trials as normal animals (i.e. less than 150 trials). Five of their 9 infant operated animals had cortical damage that was as large as the adult operated animals. In contrast to the adult-lesion group, their infant operated animals were all able to learn the task in about the same number of trials as normal animals.

The present study is the first to investigate the effects of early auditory cortex lesions on sound localization. Sound localization has been found to be very sensitive to cortical damage. Numerous investigators, using different species in various localization tasks, have shown

that damage to auditory cortex reliably produces a profound deficit in sound localization (see introduction). Furthermore, unilateral cortical damage that is restricted to primary auditory cortex has been demonstrated to produce a complete inability to localize sound sources located in the hemifield contralateral to the lesion. This deficit is specifically limited to the contralateral sound field and little or no impairment is found about the midline or in the hemifield ipsilateral to the lesion. In concurrence with previous work, it was demonstrated that in adult animals unilateral ablation of auditory cortex, or primary auditory cortex alone, results in a severe sound localization deficit in the contralateral sound field.

This study is the first to show sparing of sound localization following lesions of auditory cortex. Unilateral lesions of auditory cortex, produced by ablation of presumptive auditory cortex in the neonate, do not result in the severe sound localization deficit observed in ferrets that are ablated as adults. Indeed, with the exception of the animals with massive cortical damage, all the neonatally operated animals had sound localization performance that surpassed the adult-ablated animals. This was the case even though the magnitude of cortical damage for the animals in the "large" and "MEG" lesion groups was greater or as extensive as the damage in the adult-operated ferrets.

The results of the present study support the concept that functional sparing in the auditory system is possible

when the damage occurs early in development. However, it is also evident that lesion size can impose a limit on the extent of sparing. For example, the animals of the large-lesion group showed behavioral sparing, as determined by their superior contralateral sound localization performance relative to the adult-ablated animals. However, their performance contralateral to the lesion was not as good as their ipsilateral performance. That is, they showed a partial sparing of function. With cortical lesions that were larger still, virtually no sparing of function occurred. This was observed for both the hemidecorticate and massive-lesion group; neither showed sparing of function. Instead, both groups had contralateral sound localization deficits that were as severe as the adult-lesion group.

While the studies of early damage to auditory cortex have been limited in number, there have been numerous investigations of early lesions in other cortical regions. In the discussion to follow I will describe some of this literature as it relates to the present study. In general, the evidence supports the view that sparing of function with early lesions is a general characteristic, and not limited to any single region of cortex. Broad anatomical reorganization, that can follow early damage, may be responsible for behavioral sparing. The evidence that anatomical reorganization may have occurred in the present

study will be discussed briefly. Finally, I will conclude by outlining directions for future research.

Early Cortical Lesions and Sparing of Function

The idea that brain damage sustained by a young animal results in fewer and less severe deficits than a comparable lesion in an adult animal has become known as the "Kennard principle", after the early work of Margaret Kennard (Finger and Almli, 1988). She produced lesions of the motor and premotor cortical areas in neonatal monkeys and found that they showed far more recovery of function than if the damage was produced in adulthood (Kennard, 1936, 1938). In adults, unilateral lesions of motor and premotor cortex result in severe loss of motor ability in the extremities contralateral, and to some degree, ipsilateral to the lesion. In contrast, Kennard found that a neonatal monkey which had a unilateral ablation at 10 days of age showed dramatic recovery. Within 24 hours after surgery the animal walked quadrupedally with only a slight lag on the side contralateral to the damage. Although the animal initially showed preferential use of the fingers and toes ipsilateral to the lesion, this was no longer evident after 10 days. The sparing of function is dramatic following early lesions of frontal cortex, but is this also the case in sensory cortex?

Sparing of function following early lesions has been observed in the visual system. Animals that sustain

bilateral visual cortical damage as adults lose their ability to discriminate between patterns such as horizontal versus vertical stripes, and only eventually does pattern discrimination eventually recover (Spear, 1979; 1985). On the other hand, adult cats that received visual cortex damage early in life are able to learn pattern discriminations much more rapidly than cats that sustain similar damage as adults (Cornwell and Payne, 1989; Cornwell, Herbein, Corso, Eskew, Warren and Payne, 1989). Moreover, animals with neonatal visual cortex damage develop virtually normal visual acuity (Belleville and Wilkinson, 1987; Wilkinson, 1990), whereas acuity never returns to normal following damage in the adult (Berkley and Sprague, 1979; Iehmkuhle, Kratz and Sherman 1982). These results parallel the present findings, which show acuity for sound localization (MAA) to be good for the early operated ferrets, though the performance of the adult operated animals is severely impaired and shows no signs of recovery.

In a recent study of the effects of early visual cortex lesions, Shupert, Cornwell and Payne (1993) compared the performance of neonatal versus adult operated cats on a visual task that is directly analogous to the auditory task of the present study. Cats were trained in a semicircular apparatus to localize a food reward visually. A trial began when a cat, restrained in the center of the apparatus, was presented chow directly at midline. When the cat was fixating on the chow, the experimenter presented a high-

incentive food (eg. pork kidney, tuna, moist commercial cat food) through one of twelve peripheral openings situated at various azimuths. Simultaneously, the cat was released from the center area. A rapid, accurate turning of the head and body toward the high-incentive food constituted a correct response. They found that cats with lesions of visual cortex as neonates performed reliably better than the adult-operated cats at all azimuths. This finding is analogous to the sparing observed here for sound localization and indicates that both auditory and visual cortices may respond to early damage in a similar manner.

The results presented in this report indicate that behavioral sparing can result when cortical damage occurs in young animals but that the behavioral sparing does not occur if the lesion is extensive. Shupert and colleagues (1993) described a similar result in their study. When their lesions included damage to visual cortical areas 17, 18 and 19 they observed sparing in neonatally operated cats but found no evidence of sparing in animals with lesions that included surrounding cortical tissue. They speculate that this tissue, which is critical for the sparing of function, may be functionally reorganized to take over the functions of the damaged visual cortex. This may also be the case in the present study, since functional sparing did not occur when the lesion involved a substantial amount of cortex. Anatomical reorganization that may enable functional sparing is discussed below.

Early Cortical Lesions and Anatomical Re-organization

The present study demonstrates that dyes injected into primary auditory cortex of a normal ferret, label cells in AI of the opposite hemisphere. There is a homotopic organization, that is, the region with the greatest density of labelled cells directly corresponds to the location of the injection site in the contralateral hemisphere. In both the adult and neonatally ablated animals, dye injections into primary auditory cortex failed to label cells in the region around the lesion in the contralateral hemisphere. The examination of interhemispheric projections in the present study was prompted by findings of ectopic transcallosal projections in monkey prefrontal cortex following early ablations. Goldman-Rakic (1981) found that the typical homotopic projection of cortex was radically rewired in animals that sustained early unilateral ablations. By injecting dyes into the prefrontal cortex contralateral to the lesion, she found that fibers which normally innervate the resected cortex, by-passed the damaged region and became redistributed in the cortex dorsal and medial to the lesion. Similar reorganization was not detected in the present study. However, this does not preclude the occurrence of some other anatomical reorganization that may underlie, or contribute to, the observed sparing of function. The idea that cortical tissue ipsilateral to the lesion may be involved in functional

sparing is supported by the present finding that sparing was not observed when the ablation included all, or almost all, cortex of one hemisphere. Patterns of thalamic degeneration in adult ferrets, indicate that auditory thalamus projects to the anterior and posterior ectosylvian gyri in addition to primary auditory cortex. One might expect then, that anatomical reorganization would likely involve an increased thalamic projection to these regions, if they were not included in the early ablation. Moreover, it would also be likely that the inclusion of any secondary auditory fields in the early lesion might result in less, or a complete lack of, behavioral sparing. The results presented here clearly show that massive lesions prevent behavioral sparing, but any finer analysis would require evidence on the specific location of secondary auditory fields in ferret cortex and the inclusion of cases with neonatal lesions that both destroyed and spared these secondary fields.

In addition to cortex ipsilateral to the lesion, a likely structure for anatomical reorganization is the auditory thalamus. Dramatic reorganization of thalamus has been previously observed in neonatally operated ferrets (Pallas and Sur, 1993; Roe, Garraghty, Esguerra, Sur, 1993; Sur, Garraghty and Roe, 1988). This research describes retinal ganglion fibers that re-route to innervate the medial geniculate nucleus after ablation of their target nucleus, the dorsal lateral geniculate. Moreover, it has been found that thalamic neurons of the visual system

(lateral posterior/pulvinar complex) can send anomalous projections to auditory cortex (Pallas, Roe and Sur, 1990). The results of the present study show that the medial geniculate nucleus, and especially the ventral division which projects directly to AI, degenerates in animals that are ablated as adults. In contrast, some of the neonatally ablated ferrets had very little or no detectable cell loss. This sparing of thalamus has also been reported to occur to a lesser extent in the lateral geniculate nucleus following lesions of visual cortex in neonatal cats (Murphy, Mize and Schechter, 1975). On the other hand, the auditory investigation of Scharlock and colleagues (1963) found no difference in thalamic degeneration between adult and neonatally operated cats with auditory cortex lesions - both groups had extensive thalamic degeneration. It is not known whether the thalamic sparing observed in the present study is responsible for the behavioral sparing. However, it is apparent that preservation of the thalamus is not a necessary requirement for functional sparing, since some of the neonatally ablated animals that clearly displayed functional sparing ("large" lesion group), also had thalamic cell loss that was as severe as that observed in the adult-ablated ferrets.

Retrograde labelling of thalamic cells following injections of dyes in primary auditory cortex showed no evidence of anatomical reorganization. The labelling in the thalamus ipsilateral to the injection, however, did provide

information on the tonotopic organization of the ferret medial geniculate nucleus. The general organization of thalamocortical projections corresponds to the recent work of Pallas and colleagues (1990). The highest concentration of labelled cells was in the ventral division of the medial geniculate, cells were also evident in the medial division and also dorsally in the posterior division (PO). The use of electrophysiological mapping of the frequency organization of AI enabled the dye injections to be placed in specific frequency regions. Thus, the basic tonotopic organization of the ferret medial geniculate could be discerned. The rostral portion of the medial geniculate appeared to lack any clear tonotopic organization. However, the caudal aspect of the medial geniculate showed evidence for clear tonotopicity. The topographic organization from thalamus to cortex is opposite to the pattern observed in the cat (Imig and Morel, 1984; Imig and Morel, 1985a).

Considerations for Future Studies

This study has been the first to examine the effects of early auditory cortical lesions on a behavioral task that requires sound localization. The ability to locate a sound source in space is lost following auditory cortex ablations in adult animals. The results presented here indicate that sound localization ability is preserved in animals that sustain focal damage to auditory cortex as neonates. In addition, evidence is provided that behavioral sparing in

the neonatally operated animal is related to the size of the lesion, since sparing is not observed in ferrets with massive cortical damage.

A group of animals in the present study had complete damage of the middle ectosylvian gyrus and yet showed little or no cell loss in the thalamus. It is possible that these animals had re-wired thalamocortical projections. All the ferrets in this study were ablated at 6 days of age. In cats, the thalamocortical axons begin to accumulate beneath cortex before birth and do not begin to invade cortex until after birth (Shatz and Luskin, 1986). If the ferret and cat have similar developmental timetables. Then for the ferret, the thalamocortical axons should arrive and wait at the cortical plate between 0 and 10 days after birth and not invade cortex until at least 20 days postnatally. This means that when ablations were performed on the 6 day old ferrets the thalamic axons had either just started to arrive at the cortical plate or had yet to arrive. With the removal of presumptive auditory cortex before the arrival of the thalamocortical fibers, it is possible that these fibers, now devoid of their normal target, may have grown past the lesion to invade another cortical area (Ghosh, Antonini, McConnell and Shatz, 1990). It would have been informative to inject an anterograde tracer into the thalamus of these animals to determine their cortical projections if indeed there were any.

The results of the present study show that, while functional sparing can occur with early auditory cortical lesions, the sparing is a function of lesion size. Animals with little or no remaining cortex showed no evidence of behavioral sparing. This indicates that the cortical tissue remaining in the damaged hemisphere may be important for sparing of function. If this is the case, future research should be directed towards determining if this preserved cortex is responsive to auditory stimulation. To this end measures of auditory evoked responses or a survey of single unit activity across cortex might indicate regions that are functionally auditory. In addition, a second cortical ablation of tissue adjacent to the neonatally acquired lesion should result in a sound localization deficit in animals showing functional sparing.

Table I. Minimum audible angles in degrees azimuth.

	Midline	Left	Right
<u>NORMALS</u>			
F304	15	35	60
F305	6	22	14
F325	15	26	18
F403	8	24	29
F405	7	10	32
F422	5	6	10
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	Midline	Ipsi	Contra
<u>Adult Lesion, Post-Op</u> ~~~~~			
F407	10	44	56
F414	12	42	**
F417	9	51	**
F418	23	41	**
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<u>Neonatal Lesion</u> ~~~~~			
<u>Hemidecorticate</u>			
F324	10	53	**
F327	14	16	**
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<u>Massive Lesion</u>			
F319	8	22	56
F323	29	34	**
F326	29	38	**
F331	12	**	**
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<u>Large Lesion</u>			
F320	12	16	**
F321	29	46	30
F329	9	44	**
F434	15	25	36
F435	11	26	40
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<u>MEG Lesion</u>			
F430	12	25	51
F433	32	**	46
F436	8	27	20
<hr/>			
<u>Small Lesion</u>			
F316	14	16	24
F322	20	30	15
F431	9	25	**
F432	5	30	33

** Performance was too low (i.e. less than 75%) to determine a minimum audible angle.

Figure 1. Lateral view of the left cerebral hemisphere of the cat. **Top:** Anatomical location of the middle ectosylvian gyrus (**MEG**), anterior ectosylvian gyrus (**AEG**), the posterior ectosylvian gyrus (**PEG**), insular cortex (**I**), and temporal cortex (**T**). **Bottom:** The physiological parcellation of auditory cortex showing primary (**AI**) and secondary (**AII**) auditory cortex, the anterior auditory area (**A**), posterior auditory area (**P**) and ventral posterior auditory area (**VP**). (Redrawn from: Imig and Reale; 1983).

Figure 2. Lateral view of the left cerebral hemisphere of the ferret. Shading indicates the location of primary auditory cortex within the middle ectosylvian gyrus (**MEG**). Vertical stripes denote secondary regions within the anterior and posterior ectosylvian gyrus (**PEG**). Also shown: suprasylvian gyrus, **SG**; suprasylvian sulcus, **SS**; pseudosylvian sulcus, **SS**. (From Kavanagh and Kelly, 1987).

Figure 3. Craniotomy of a ferret at postnatal-day 6. The location of presumptive auditory cortex (indicated by a dot) is based on Rhodamine labelled latex microsphere injections.

Figure 4. A schematic view of the test apparatus and the location of the loudspeakers for tests of left hemifield, midline, and right hemifield. The loudspeakers are shown separated by 60 degrees. In each test situation the separation was decreased to determine the minimum audible angle. In all 3 tests of sound localization, trials were initiated from a central start area consisting of a raised platform and a centrally positioned contact spout. The apparatus has a radius of 92 cm. (From Kavanagh and Kelly, 1988).

Figure 5. Frequency spectra of the sound burst from 4 of the loudspeakers used in this study. Impulse sound pressure measurements were obtained at 1/3 octave intervals from 100 to 40,000 Hz. Inset shows an oscilloscope trace of the unfiltered output of the sound level meter. The duration of the burst was slightly longer than 45 msec due to small reverberations in the test chamber.

Figure 6. Midline and hemifield performance for normal ferrets. **M** indicates midline performance, **L** indicates performance in the left hemifield and **R** indicates performance in the right hemifield. The dashed lines designate the upper confidence limits around chance ($P=0.01$).

F304

F305

F325

F403

F405

F422

Figure 7. Average performance for normal ferrets ($\pm$ S.D.)
Circles indicate midline performance, triangles indicate
right, and squares left hemifield performance. The dashed
line designates the upper confidence limit around chance
($P=0.01$)

Normals

Figure 8. Lateral reconstructions showing the extent of cortical damage in the adult-ablated group. In every case the damage includes the middle ectosylvian gyrus.

— F407 —

— F414 —

— F417 —

— F418 —

Figure 9. Representative frontal sections through the posterior thalamus showing the extent of thalamic degeneration in the adult-ablated cases. Sections proceed from rostral to caudal. Shading indicates complete cell loss. **C**, caudal division of the medial geniculate nucleus; **GL**, lateral geniculate nucleus; **LP**, lateral posterior nucleus; **M**, medial division of the medial geniculate nucleus; **PO**, posterior nucleus; **SC**, superior colliculus; **V**, ventral division of the medial geniculate nucleus; **VP**, ventral posterior nucleus.

— F407 —

— F414 —

PM-1 3½"x4" PHOTOGRAPHIC MICROCOPY TARGET
NBS 1010a ANSI/ISO #2 EQUIVALENT

PRECISIONSM RESOLUTION TARGETS

— F417 —

— F418 —

Figure 10. Left hemifield, midline, and right hemifield performance for adult-ablated ferrets. Psychophysical curves are shown for preoperative (filled circles) and postoperatively at 4 weeks (hollow circles), 16 weeks (hollow triangles), and 26 weeks (hollow squares). Asterisks indicate hemifield contralateral to the lesion. The dashed lines indicate the upper confidence limits around chance ($P=0.01$).

Figure 11. Performance at 60 degrees speaker separation for midline and the hemifields ipsilateral and contralateral to the lesions for the adult-ablated ferrets. Preoperative (filled bars) and postoperative (hatched bars) are shown for each animal. Postoperative values are from tests at the longest survival time. The dashed line indicates the upper confidence limit around chance ($P=0.01$).

Figure 12. Lateral reconstructions showing the extent of cortical damage in the neonatally ablated hemidecorticate group.

— F324 —

— F327 —

Figure 13. Representative frontal sections through the posterior thalamus showing the extent of thalamic degeneration in the hemidecorticate neonatally ablated cases.

— F324 —

— F327 —

Figure 14. Midline and hemifield performance for the hemidecorticate neonatally ablated ferrets. **M** indicates midline performance, **I** and **C** indicates performance in the hemifield ipsilateral and contralateral to the lesion. The dashed lines designate the upper confidence limits around chance ($P=0.01$).

F324

F327

Figure 15. Lateral reconstructions showing the extent of cortical damage in the neonatally ablated cases with massive lesions.

— F319 —

— F323 —

— F331 —

— F326 —

Figure 16. Representative frontal sections through the posterior thalamus showing the extent of thalamic degeneration in the neonatally ablated cases with massive cortical lesions.

— F319 —

— F323 —

— F326 —

— F331 —

Figure 17. Midline and hemifield performance for the neonatally ablated ferrets with massive cortical lesions. **M** indicates midline performance, **I** and **C** indicates performance in the hemifield ipsilateral and contralateral to the lesion. The dashed lines designate the upper confidence limits around chance ($P=0.01$).

F319

F323

F326

F331

Figure 18. Performance at 60 degrees speaker separation for the hemifield ipsilateral and contralateral to the lesion for neonatally ablated hemidecorticate (hatched bars), and animals with massive lesions (hollow bars), as well as mean performance (solid bars). The dashed line indicates the upper confidence limit around chance ($P=0.01$).

Hemidecorticate and
Massive Neonatal Lesions

Figure 19. Lateral reconstructions showing the extent of cortical damage in the neonatally ablated cases with large lesions.

— F320 —

— F321 —

— F329 —

— F434 —

— F435 —

Figure 20. Representative frontal sections through the posterior thalamus showing the extent of thalamic degeneration in the neonatally ablated cases with large lesions.

— F320 —

— F321 —

— F329 —

— F434 —

Figure 21. Midline and hemifield performance for the neonatally ablated ferrets with large cortical lesions. **M** indicates midline performance, **I** and **C** indicates performance in the hemifield ipsilateral and contralateral to the lesion. The dashed lines designate the upper confidence limits around chance ($P=0.01$).

F320

F321

F329

F434

F435

Figure 22. Performance at 60 degrees speaker separation for the hemifield ipsilateral and contralateral to the lesion for neonatally ablated ferrets with large cortical lesions. Performance is shown for each animal (hollow bars) and mean performance (solid bars). The dashed line indicates the upper confidence limit around chance ($P=0.01$).

Large Neonatal Lesions

Figure 23. Lateral reconstructions showing the extent of cortical damage in the neonatally ablated cases with lesions restricted to the middle ectosylvian gyrus.

— F430 —

— F433 —

— F436 —

Figure 24. Representative frontal sections through the posterior thalamus showing the extent of thalamic degeneration in the only ferret in the MEG-lesion group that had thalamic cell loss.

— F430 —

Figure 25. Midline and hemifield performance for the neonatally ablated ferrets with MEG lesions. **M** indicates midline performance, **I** and **C** indicates performance in the hemifield ipsilateral and contralateral to the lesion. The dashed lines designate the upper confidence limits around chance ($P=0.01$).

F430

F433

F436

Figure 26. Performance at 60 degrees speaker separation for the hemifield ipsilateral and contralateral to the lesion for neonatally ablated ferrets with MEG lesions.

Performance is shown for each animal (hollow bars) and mean performance (solid bars). The dashed line indicates the upper confidence limit around chance ($P=0.01$).

MEG Neonatal Lesions

Figure 27. Lateral reconstructions showing the extent of cortical damage in the neonatally ablated cases with small lesions.

- F316 -

- F322 -

- F431 -

- F432 -

Figure 28. Representative frontal sections through the posterior thalamus showing the extent of thalamic degeneration in the only ferret in the MEG-lesion group that had thalamic cell loss.

— F431 —

Figure 29. Midline and hemifield performance for the neonatally ablated ferrets with small cortical lesions. **M** indicates midline performance, **I** and **C** indicates performance in the hemifield ipsilateral and contralateral to the lesion. The dashed lines designate the upper confidence limits around chance ($P=0.01$).

F316

F322

F431

F432

Figure 30. Performance at 60 degrees speaker separation for the hemifield ipsilateral and contralateral to the lesion for neonatally ablated ferrets with small cortical lesions. Performance is shown for each animal (hollow bars) and mean performance (solid bars). The dashed line indicates the upper confidence limit around chance ($P=0.01$).

Small Neonatal Lesions

Figure 31. Performance at 60 degrees speaker separation for the hemifield contralateral to the lesion for the adult-ablated and the neonatally ablated groups. Mean performance ($\pm$ S.D.) is shown for each group. Note that all but the massive lesion group showed significant (asterisk indicates $p < .05$, compared to adult-ablated group) sparing of function.

Mean Contra Performance

Figure 32. **TOP:** Characteristic frequencies of neurons or neuron clusters, mapped onto primary auditory cortex of the ferret. Stars indicate injection sites of dextran rhodamine (solid star) and Fluoro-Gold (hollow star).

BOTTOM: Representative frontal sections through the posterior thalamus showing the extent and location of cells labelled with dextran rhodamine (dots) or Fluoro-Gold (dashes).

Figure 33. Transcallosal labelling shown in representative frontal sections through cortex. The injection site in right AI is shown on the right while sections of the left hemisphere are shown from caudal to rostral (top to bottom) on the left. Each dot is a single cell.

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