

Conference Keynote Address

Representing the Acoustic World within the Brain: Normal and Abnormal Development of Frequency Maps in the Auditory System

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Introduction

This discourse is concerned with a fundamental way in which acoustical aspects of the outside world are represented within the brain. More specifically we consider the way in which spectral components of acoustic signals are represented by neural activity in tonotopically organized arrays.

The review will start with general notions about how a version of the world (outside of our heads) is recreated in the brain, using (limited) information from our various sensory organs. The process involves both the coding of stimuli at the level of the sensory epithelia, *and* the faithful transmission of information from the periphery to the cerebral cortex. We will look briefly at these concepts in visual and somatosensory systems before considering the equivalent organization in the auditory system, namely cochleotopic or tonotopic mapping.

We will discuss the normal development of central tonotopic maps and then the abnormal development of these representations. We will consider the plasticity of the developing system, as revealed by studies that show a reorganization of central tonotopic maps after experimental manipulations of the sensory (auditory) input. We will explore some differences between the tonotopic map plasticity of the developing auditory system and that of the adult animal. Finally we will discuss some clinical implications which arise from this and related work. Be it known here that the references provided are but a small sample of representative work; no attempt is made to provide an exhaustive list. For further,

original sources one might consult the reference lists from those papers cited.

Representation of the External World in the Brain

One of the earliest theories that a version of the external world is reproduced within our brain is to be found in the work of Rene Descartes. This concept is beautifully illustrated in figure 1 taken from the work of the 17th century philosopher. The world in which we live is really an illusion. We believe that there are objects and sounds around us, but in reality these percepts are all within our brain. What we see and hear and feel are actually portrayals of the outside world within the cerebral cortex. These representations are only as good as the ability of our sensory organs to transduce the external stimuli *and* the ability to transfer this sensory information to cerebral cortex. We only “see” an image that impinges on the retina, produces a pattern of neural activity at the level of the photo-receptors, and is faithfully transmitted to visual cortex. Similarly, we only “hear” those acoustic signals that activate the sensory epithelium of the cochlea, and which produce a pattern of neural activity that is faithfully transmitted to central auditory areas.

It is clear that the basic organization of the auditory system is very similar to other sensory systems. As shown in figures 2 and 3, images coded on the retina are faithfully transmitted through the thalamus to primary visual cortex in a systematic way such that we talk about retinotopic projections. This is essentially a spatially organized or topographic projection system. Thus as shown in figure 3 we see how

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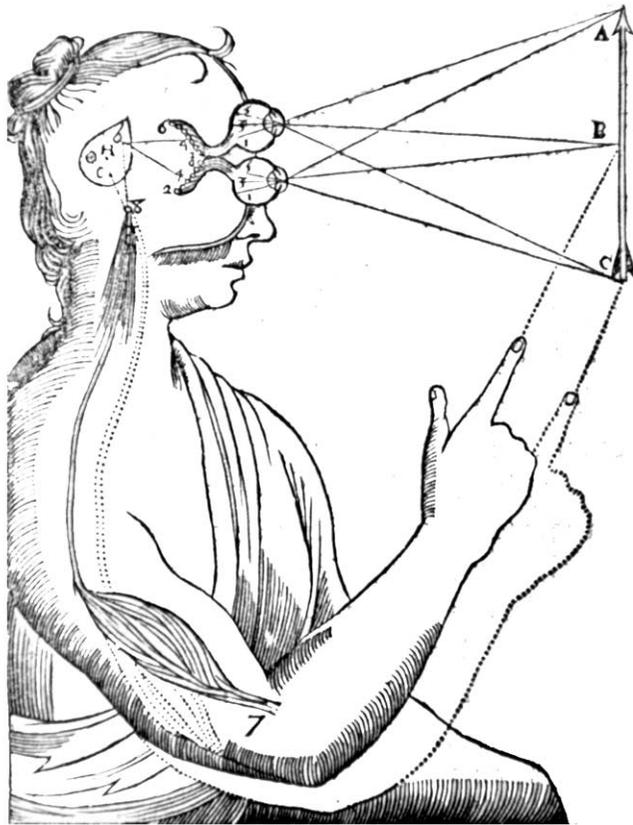


Figure 1. Representation of the outside world, as visualised by Rene Descartes.

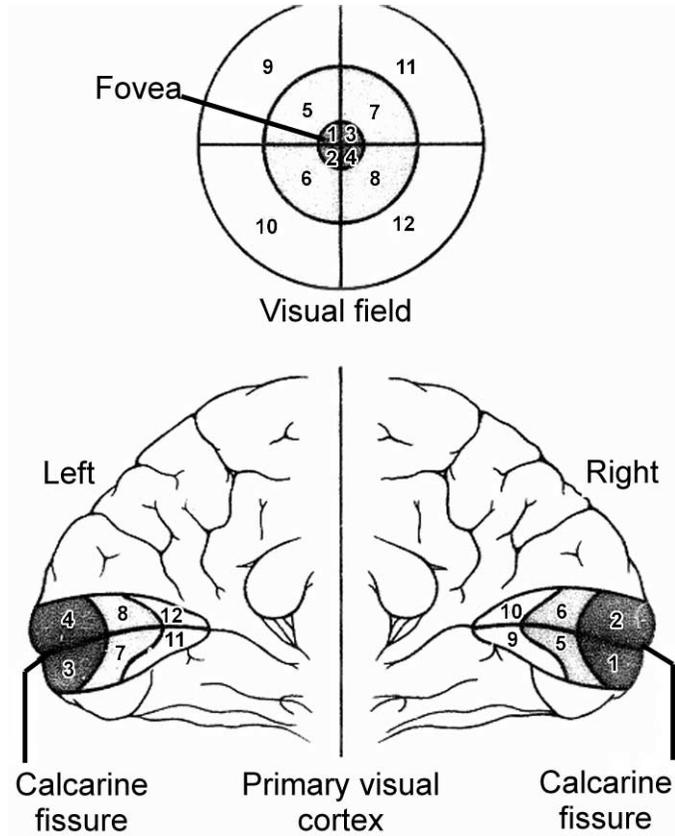


Figure 3. The retinotopic organisation of primary visual cortex.

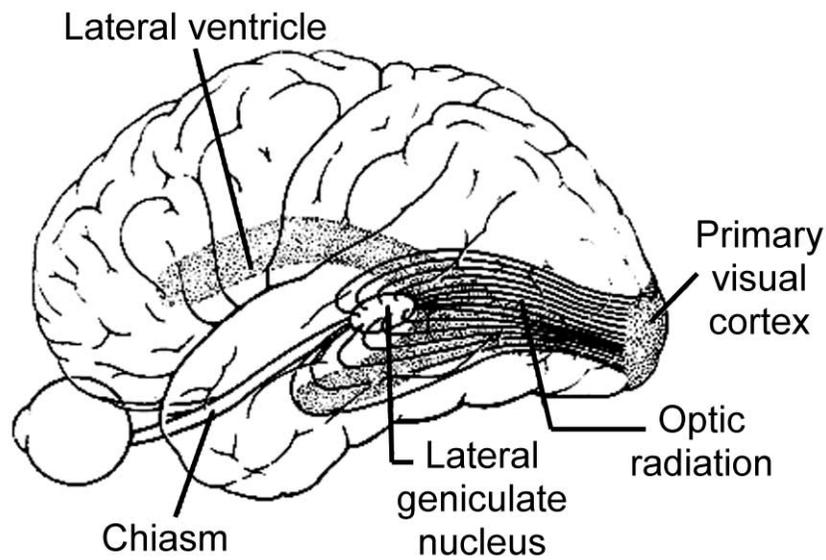


Figure 2. Ordered projections from the retina to cortex in the visual system.

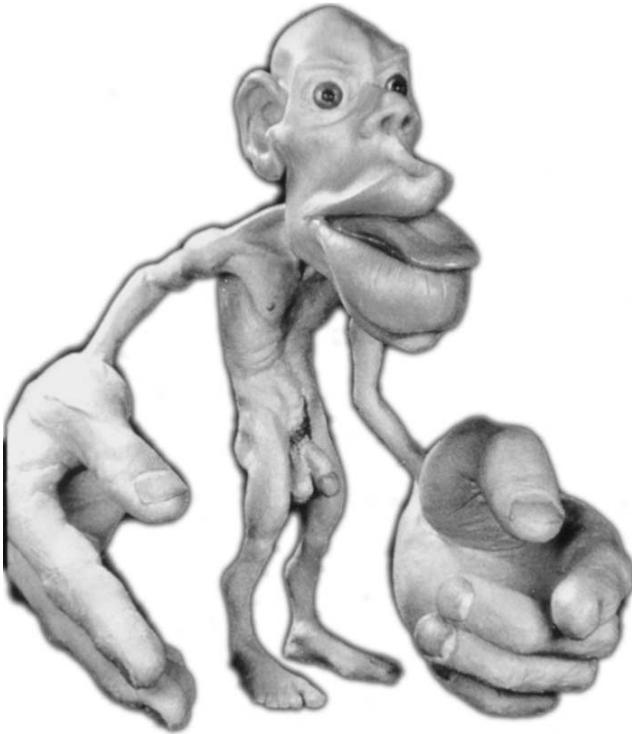


Figure 4. The sensory homunculus; how somatosensory cortex proportionally represents the sensory epithelium of the body surface.



Figure 6. Sensory epithelium of the cochlea.

The motor and sensory areas of the cerebral cortex

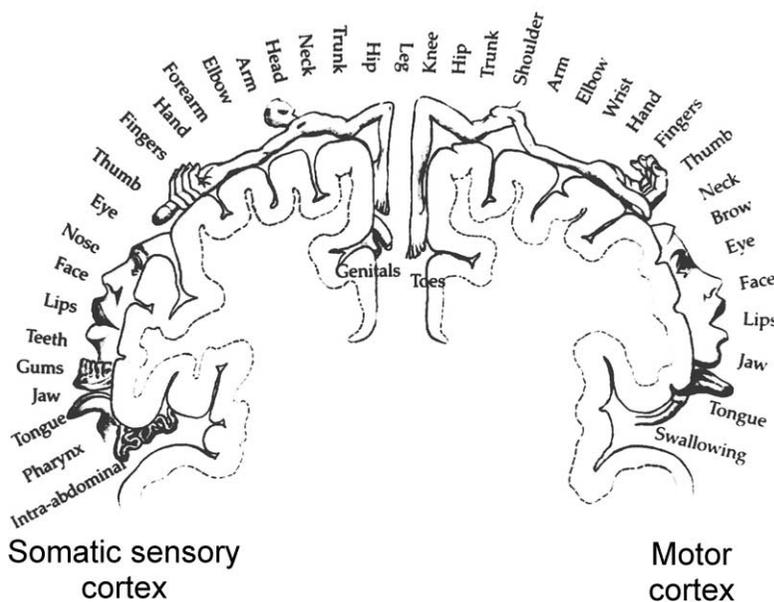


Figure 5. Original illustration of the sensory homunculus by Wilder Penfield.

the representation of the retinal activity (including that in foveal and extra-foveal areas) is systematically re-represented at the level of primary visual cortex. Similarly for the somatosensory system, as shown in figure 4, the body surface (more specifically activity from the sensory epithelium of the skin) is re-represented in somatosensory cortex. A more familiar representation of the sensory homunculus is illustrated in figure 5 (Penfield 1958).

Sound Frequency Maps in the Auditory System

In the auditory system we have exactly the same type of “main-line” organization as in other sensory systems. Neural activity patterns generated along the sensory epithelium of the cochlea (figure 6) are re-represented at all levels within the auditory pathway up to and including primary auditory cortex and areas

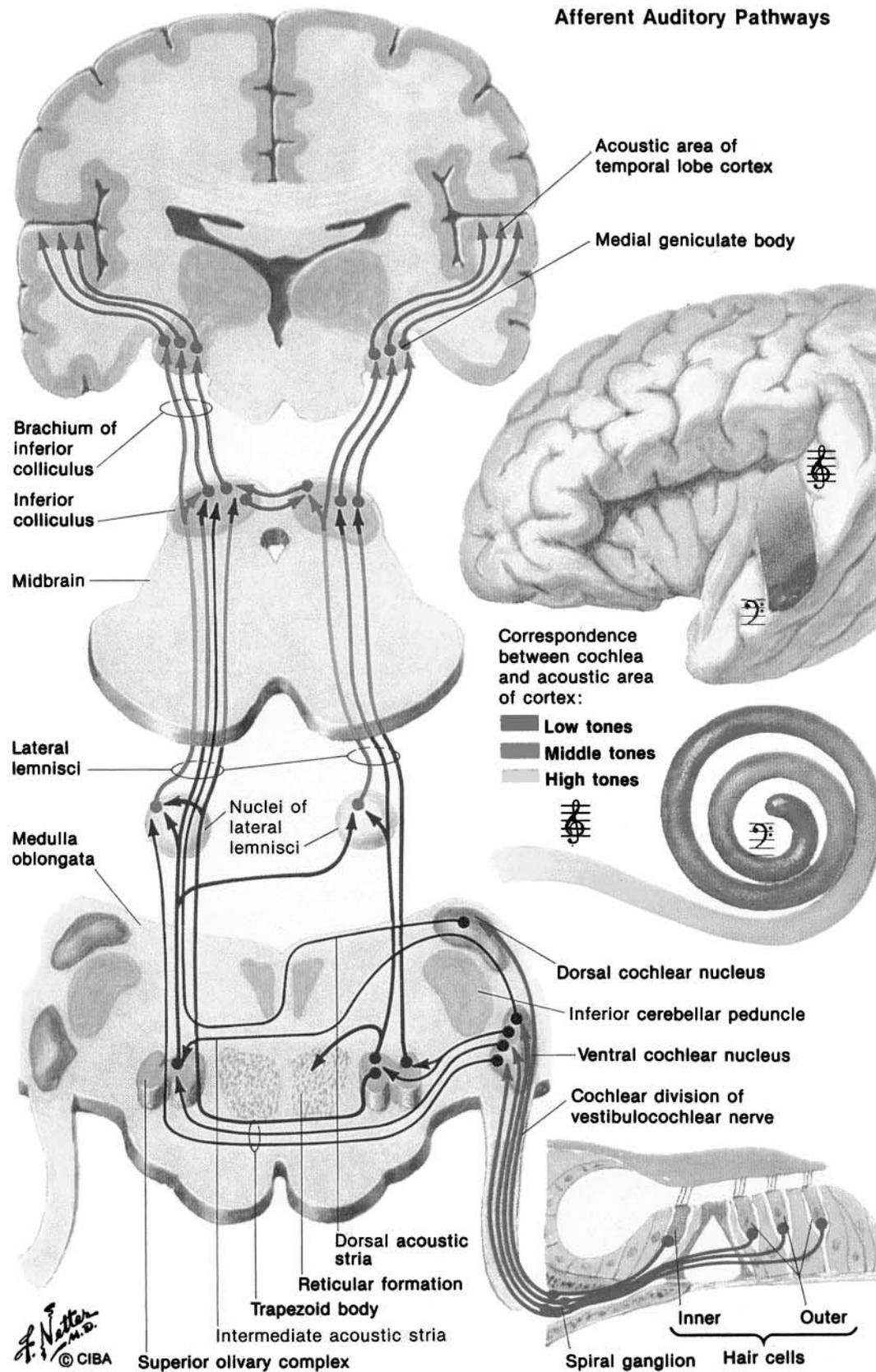


Figure 7. Central projections in auditory system as illustrated by Netter.

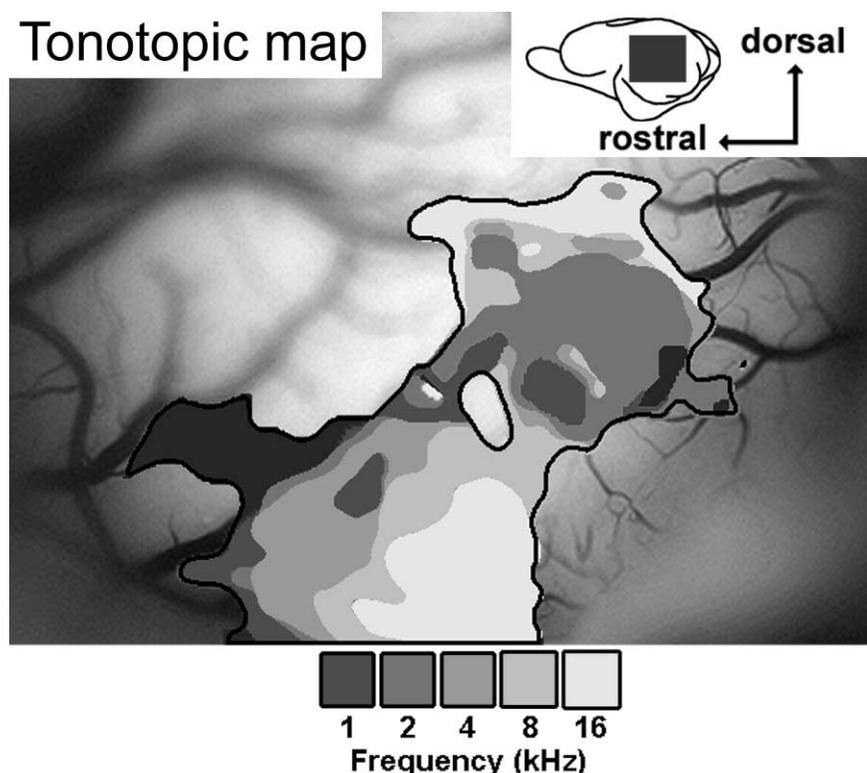
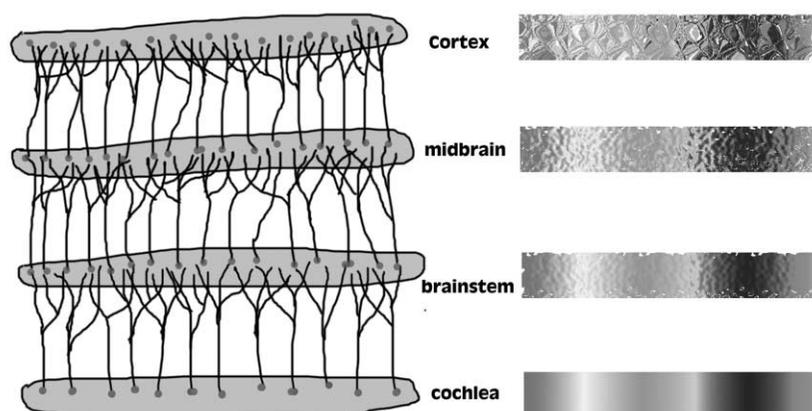


Figure 10. Chinchilla cortical tonotopic map revealed by optical imaging of hemodynamic changes that result from acoustically driven neural activity.

COCHLEOTOPIC PROJECTIONS



EARLY DEVELOPMENT: MORE DIVERGENT INNERVATION

Figure 11. Simple conceptualisation of central auditory projections during early development.

stimulation at different frequencies (as shown by the gray scale key).

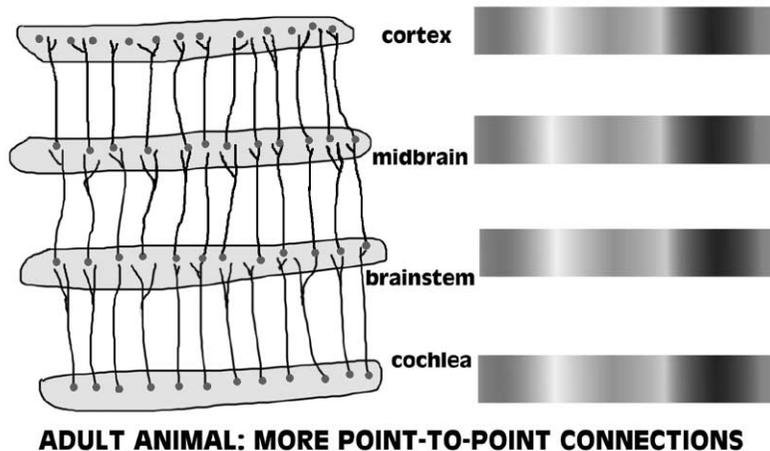
Development and Plasticity of Tonotopic Maps

Central (cortical) tonotopic maps are almost certainly not present at birth or during early stages of development. Whilst the human cochlea is completely functional at birth (as well as the middle ear, give or take a drop or two of fluid), the central auditory brain is very immature. During infancy and adolescence there is a continuing maturation of the central auditory pathways as revealed, for example, by the change in properties of the auditory evoked potentials (e.g. Eggermont 1985, 1988). Auditory brain stem evoked responses (ABRs) take up to five years to “mature”. Middle latency responses (MLR) and other potentials from auditory cortex are not “adult-like” for 12–15 years. Much of this maturation is paralleled by anatomical developments of cerebral cortex.

Figure 11 illustrates schematically the projections from the cochlea to auditory cortex. During early development it is known that the projections from one level to the next are not direct point-to-point connections, but rather there is considerable divergence of the connections at all levels. Under these conditions then, patterns of neural activity that represent sounds at the level of the cochlea will not be perfectly transmitted from the sensory epithelium to the cortex.

However, in the adult animal as modeled in figure 12, we see that the divergent connections

COCHLEOTOPIC PROJECTIONS



ADULT ANIMAL: MORE POINT-TO-POINT CONNECTIONS

Figure 12. Cochlea and cortex connected up with good point-to-point linkages.

have become much more direct. Now, with a precise point-to-point projection system, neural activity patterns that represent sound frequencies at the level of the cochlea are faithfully transmitted to the cortex.

There are various mechanisms whereby the organization of the pathways becomes more ordered, i.e. changes from that in figure 11 to that of figure 12. For example, some lateral (divergent) connections die out, by mechanisms not clearly understood. More direct connections remain or are made because they “win out” in the competition to make synapses on the target cell soma. The rules of the “competition” are likely to be very complex, based, for example, on physical space available at target sites, as well as complex chemical signaling mechanisms for axonal and synaptic growth. The synapses which become part of the most direct pathway are strengthened compared with those in less direct connections, perhaps because of Hebbian type processes which favor connections between cells which have highly correlated activity (Hebb 1949). In respect to Hebbian strengthening it is worth mentioning that acoustically driven activity will be a more influential stimulation than (randomly distributed) spontaneous activity. Various mechanisms for synaptic strengthening including, for example “long term potentiation” have been explored at the membrane level including the now well known activity-driven modifications to NMDA post synaptic receptor channels. Space does not permit any detailed review, but suffice to say that a host of mechanisms

probably contribute to the early development of point-to-point connectivity, and to the strengthening of active pathways.

Experiments Exploring the Developmental Plasticity of Tonotopic Maps

Let us now turn our attention to ways in which these tonotopic maps can become reorganized, or fail to organize correctly. Under discussion here is the plasticity of the auditory system, i.e. the inherent ability of the auditory system to modify or reorganize. There are many ways in which the plasticity of the auditory system has

been investigated. Some of the very earliest experiments were anatomical studies (e.g. Levi-Montalcini 1949; Webster and Webster 1979; Parks 1979; Rubel 1985) in which the developing auditory system was lesioned and the anatomical changes to neural pathways were investigated (e.g. making cell counts or looking at how axonal pathways are changed). There have been physiological studies in which the development of the auditory system has been monitored using auditory evoked potentials (e.g. Eggermont 1985, 1988). Another way of investigating the plasticity of the auditory system is to carry out behavioral studies. Anyone who does a psychophysical study (including clinicians measuring an audiogram) and repeats that study over a number of days or weeks and sees changing results may be revealing the plasticity of the auditory system.

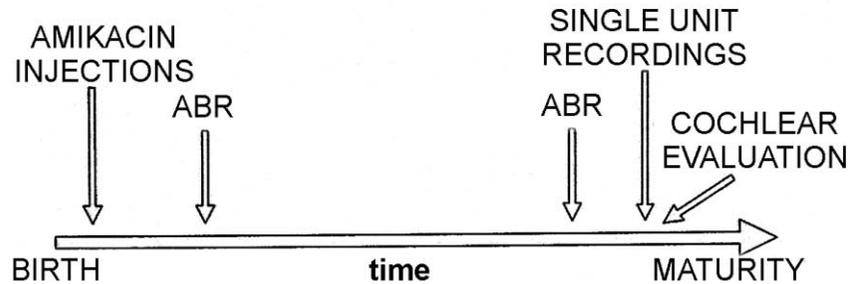
Here, I want to focus on data from single unit electrophysiological mapping studies that show some aspects of the developmental plasticity of the auditory system, particularly in tonotopic map development. Essentially these studies have measured tonotopic maps at various levels in the auditory system after changing the input to the system by making lesions to the cochlea or by inducing other abnormal patterns of activity at the level of the cochlea.

It is important here to draw your attention to the difference between developmental plasticity, and adult plasticity. There are a number of experimental plasticity studies that have been carried out in the

mature subject. In fact, the first studies to look at tonotopic map changes in auditory cortex resulting from lesions to the cochlea were done in the adult animal (Robertson and Irvine 1989; Rajan, Irvine, Wise and Heil 1993; Rajan and Irvine 1996, 1998b; Kakigi, Hirakawa, Harel, Mount and Harrison 2000). However, the data that I show here is related to developmental plasticity, where changes to the input to the system (e.g. by lesioning the cochlea), are made during early development. In this case, the animal experiences an abnormal input to the system during important early developmental periods (e.g. Willott 1984; Harrison, Nagasawa, Smith, Stanton and Mount 1991; Harrison, Smith, Nagasawa, Stanton and Mount 1992; Harrison, Ibrahim, Stanton and Mount 1996a; Stanton and Harrison 1996, 2000).

Figure 13 shows the general protocol for a typical developmental plasticity experiment. It depicts the time course of the subject from birth to maturity. In these studies we are changing the condition of the cochlea at birth using amikacin injections to cause cochlear hair cell loss. Amikacin is an aminoglycoside antibiotic that, in high concentration, is ototoxic. It primarily causes damage to the basal (high-frequency) region of the cochlea. After making a cochlear lesion, the animal is allowed to mature and then we carry out various functional and anatomical studies.

The first experiments that I review here were made in the cat. If we do nothing to the newborn kitten, i.e. if it matures normally, then we will record a normal frequency map in primary auditory cortex as is illustrated in figure 14. We can suppose that in this



EXPERIMENTAL PROTOCOL

Figure 13. General protocol for experiments on developmental plasticity.

Threshold based tonotopic map in primary auditory cortex of normal cat

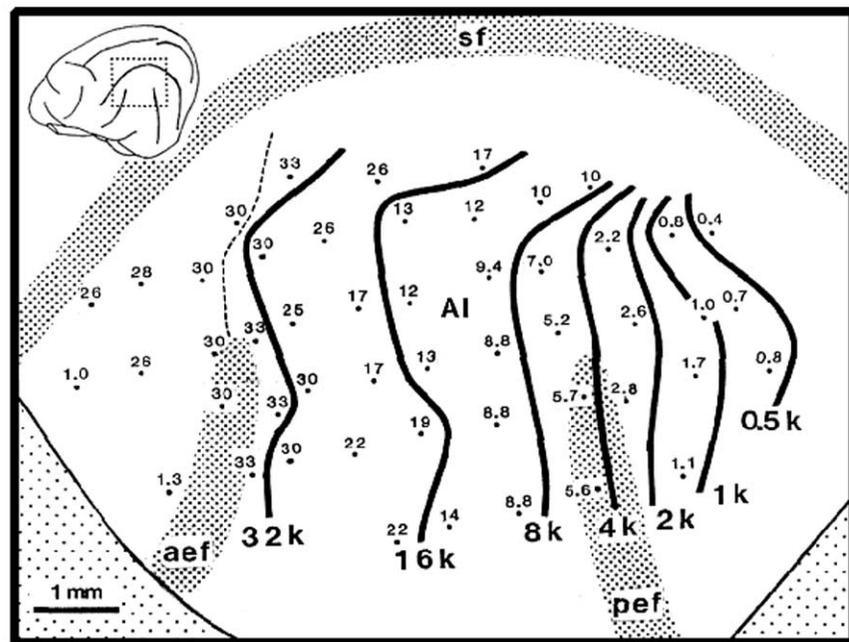


Figure 14. Tonotopic map in normal cat cortex based on single unit electrophysiological responses.

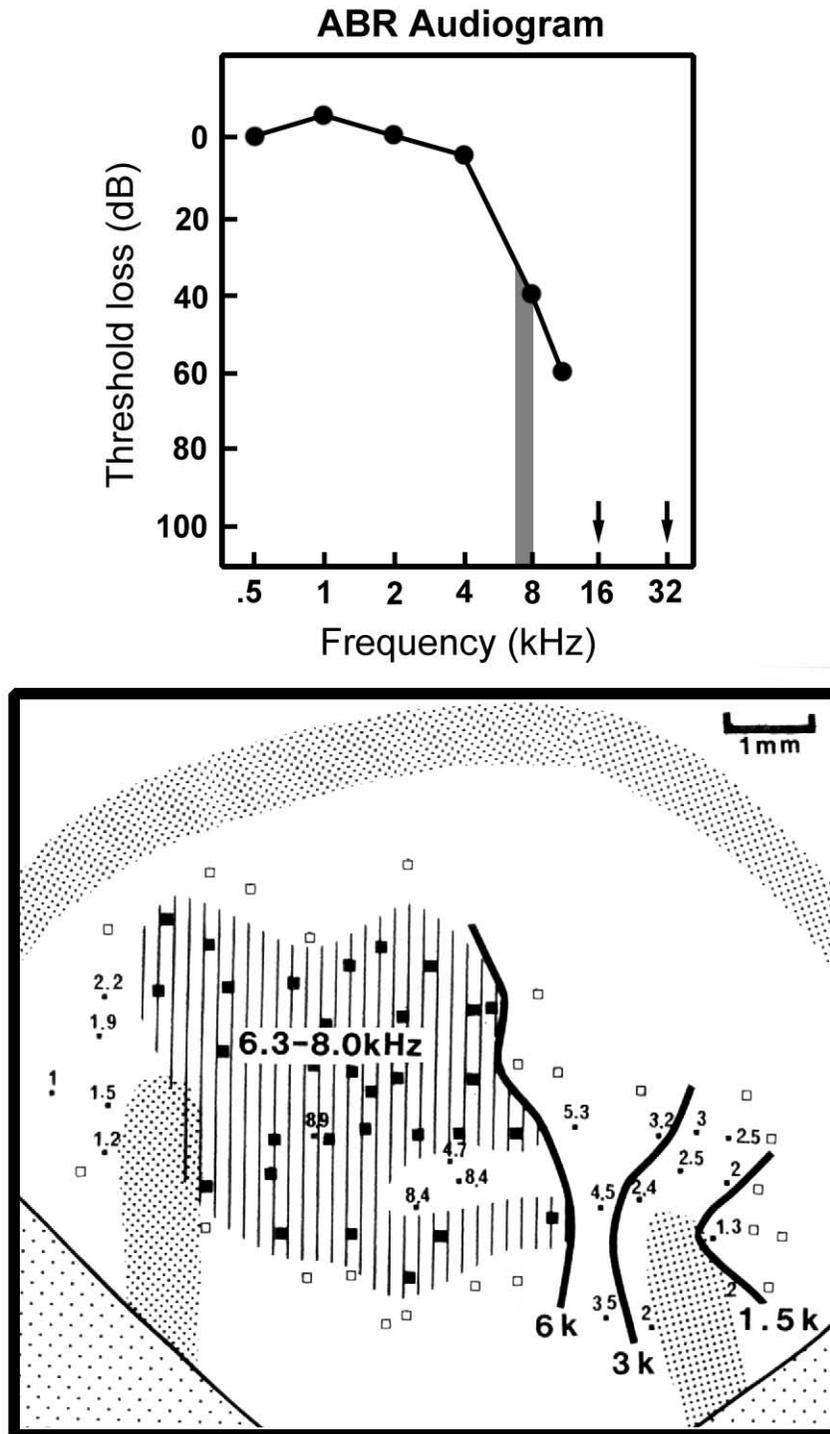


Figure 15. Tonotopic map in cat cortex after basal cochlear lesion induced during an early neonatal period.

subject there has been a good development of point to point projections such that in auditory cortex there is a very accurate representation of what is happening at the level of the cochlea (as depicted in the “model” of figure 12).

Figure 15 shows the results from an experimental animal in which we induced a basal cochlear lesion within a few days of birth. This cochlear damage results in a high frequency cochlear hearing loss as shown in the audiogram (derived from ABR thresholds to tone pips). We allow the cat to mature (for 6–9 months) and then make our cortical mapping study. We find a very abnormal tonotopic map in primary auditory cortex. First, note that the (low frequency) area of this tonotopic map, which corresponds to the normal (apical) region of the cochlea, is normal. For example this region has relatively normal separation of octave spaced iso-frequency contours. We can suppose that where there is a normal level of (driven) activity in cochlear afferent neurons there will be a normal cortical map. The big change in the frequency map of this experimental animal is in the de-afferented cortical region. Where normally there would be input from high-frequency regions of the cochlea, all of the neurons respond best to sounds around 6–8 kHz. In other words we have a very large cortical area which appears to connect up to one particular region of the cochlea. This cochlear location approximates to where there are surviving hair-cells on the border of the cochlear lesion.

A simple interpretation of these experimental findings is depicted in figure 16. We have damaged the base of the cochlea, and the associated cochlear

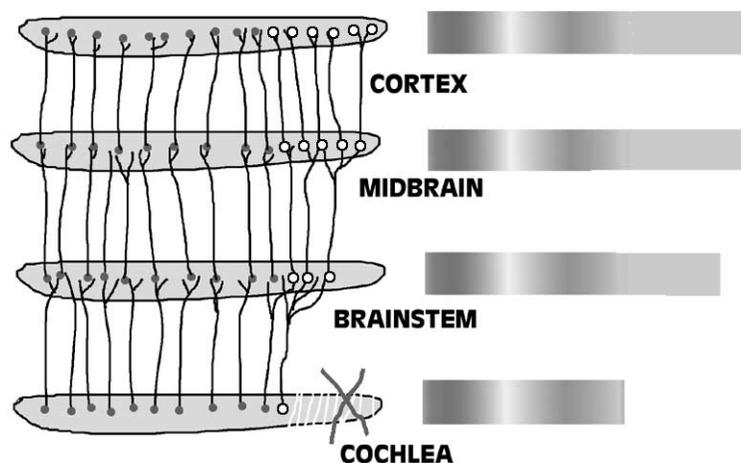
DEVELOPMENTAL PLASTICITY: basal cochlear lesion

Figure 16. Simple conceptual model of central projections after basal cochlear damage induced during an early post-natal period.

afferent neurons have degenerated. At the next level in the system (cochlear nucleus), the divergence which we find during normal early development is maintained because there is no competition from adjacent neurons to make or strengthen synaptic contacts. We could imagine this process occurring at all levels in the auditory system such that we end up with a large iso-frequency region of auditory cortex where all the neurons are essentially connected up from one point along the cochlear length, at the border of the experimental lesion.

Figure 17 shows data from another experiment. In this case, the lesion that we have made to the cochlea during early development is much more extensive, as reflected in the sloping ABR audiogram. Histological studies of this cochlea showed various degrees of haircell degeneration all the way up to the apex. In the cortical frequency map of this animal we note a large iso-frequency region in which all the neurons respond best to sound frequencies near to 6.6 kHz. We also see that there is another iso-frequency region where neurons respond best to about 0.6–0.7 kHz. In between these regions we see a very abnormal tonotopic map; the spacing of iso-frequency contours and their shape are clearly unusual. We can conclude from these data that the establishment of tonotopic maps in auditory cortex depends, in large part, on the pattern of activity coming from the periphery. If that

pattern of activity is abnormal, then an abnormal central representation develops.

The studies described so far have investigated the effects removing or reducing the input that comes from the cochlea during early development. What might happen to central frequency maps if we have an increased level of activity in certain cochlear regions? To address this question we have carried out a study in which, during an early postnatal period, an acoustic stimulus was used to constantly activate a particular region of the cochlea (Stanton and Harrison 1996). We reared kittens in an acoustic environment in which there was a constant 8 kHz tone which was modulated ± 1 kHz, at modulation rate of 1 Hz. We thus had a

stimulus that was frequency specific but also constantly changing so as to avoid both adaptation effects and acoustic trauma to the cochlea. This stimulus was presented such that at the kittens' ears it was approximately 60 dB SPL. Kittens were born into this acoustic environment and remained in it for 3 months. Six to nine months later, the mature cats were used in cortical mapping experiments.

Figure 18 shows the tonotopic map in cortex of a normal control animal (upper panel) compared with an experimental "augmented" animal (lower panel). On these maps, iso-frequency contours are spaced at one octave intervals. Note in particular the spacing of the 8–16 kHz region (cross-hatched area). The map from the subject which was reared in the environment containing that 8 kHz signal shows a significant increase in the amount of cortex which is coding, or representing frequencies at 8 kHz and above. Figure 19 shows pooled results from 3 experimental animals, versus 3 age-matched controls. The graph shows the percentage of auditory cortex that is devoted to particular sound stimulus frequencies. In the animals that were reared in an environment where there was the constant 8 kHz signal, we see a peak in the cortical representation for frequencies from 8–12 kHz. The over-representation extends above 8 kHz because of the suprathreshold level of the 8 kHz conditioning

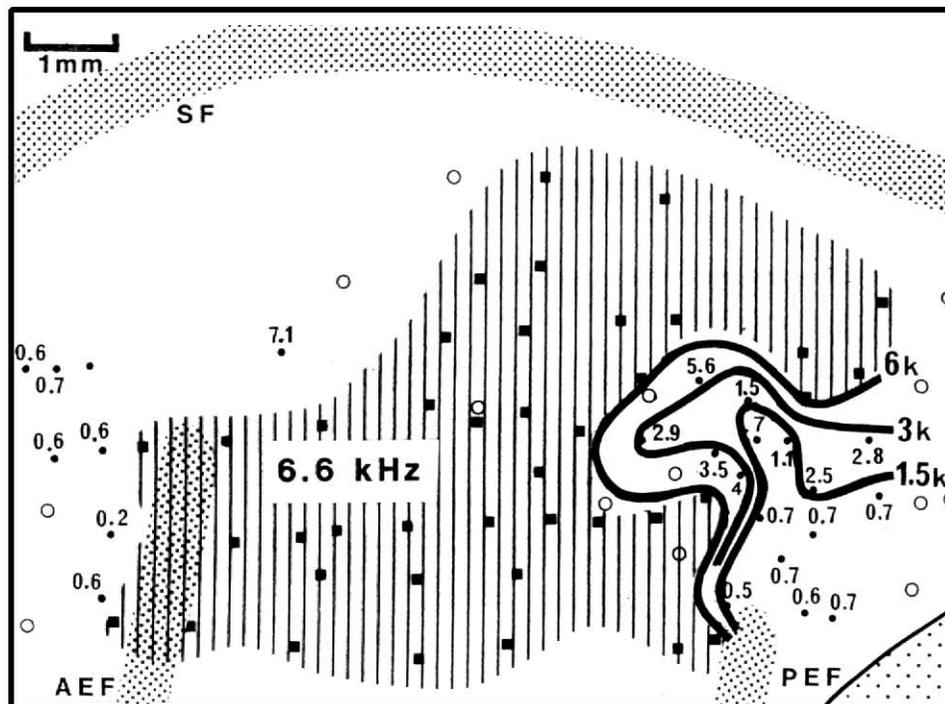
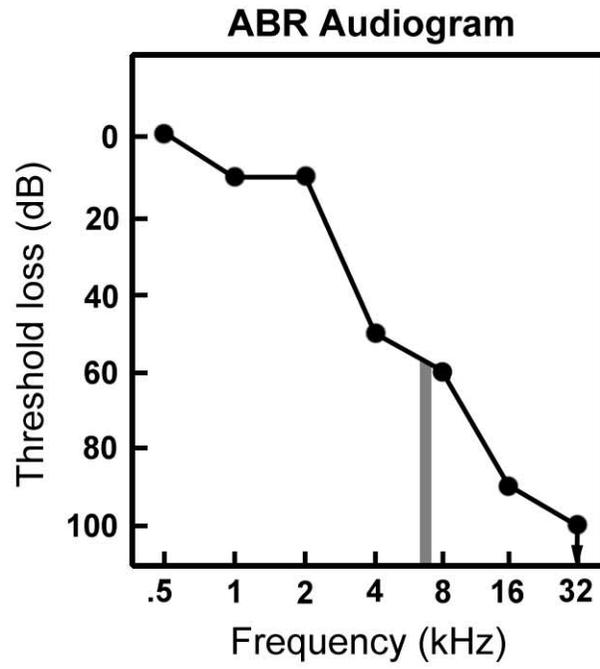


Figure 17. Effects of neonatal cochlear hearing loss on frequency mapping in cat auditory cortex.

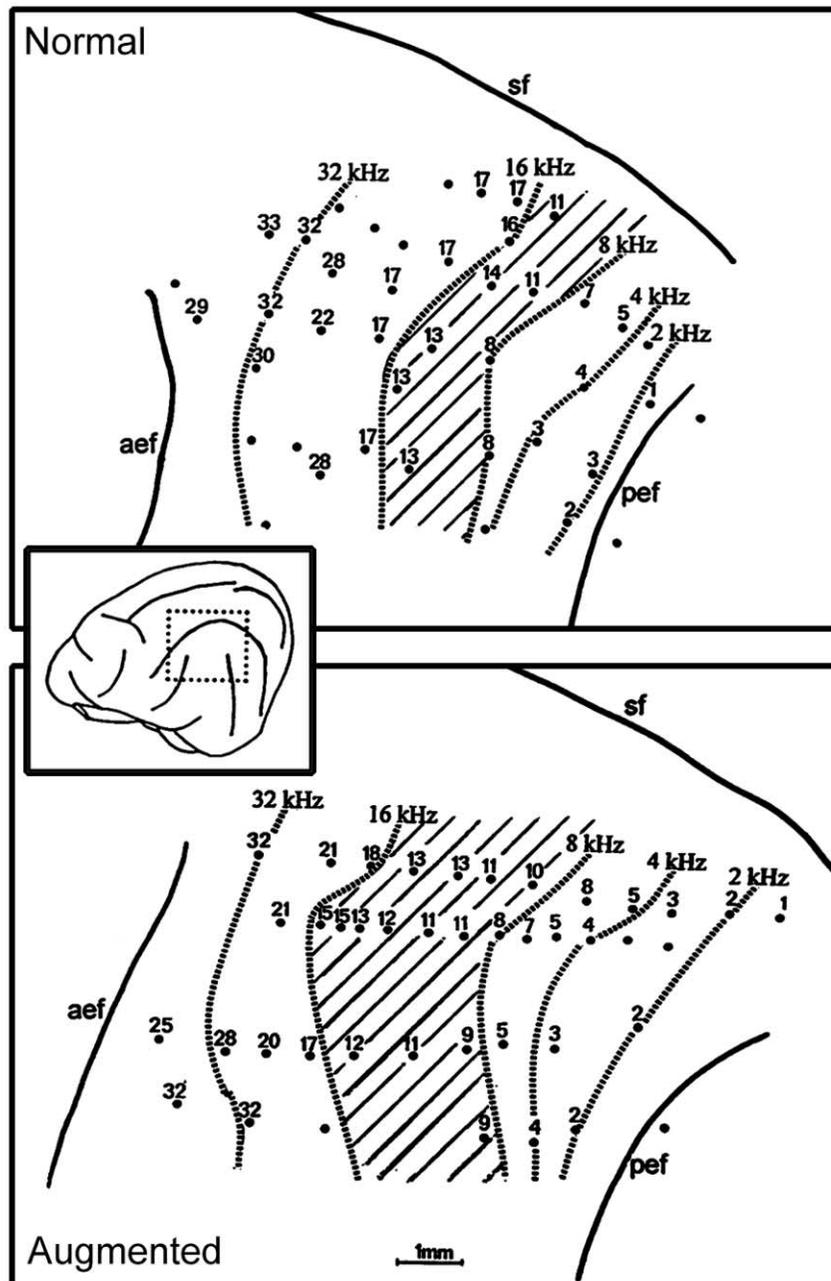


Figure 18. Lower panel: over representation of the 8–16 kHz region of cortical frequency map (cross-hatched) after rearing kitten in presence of a constant 8 kHz acoustic signal. Upper panel shows normal control data.

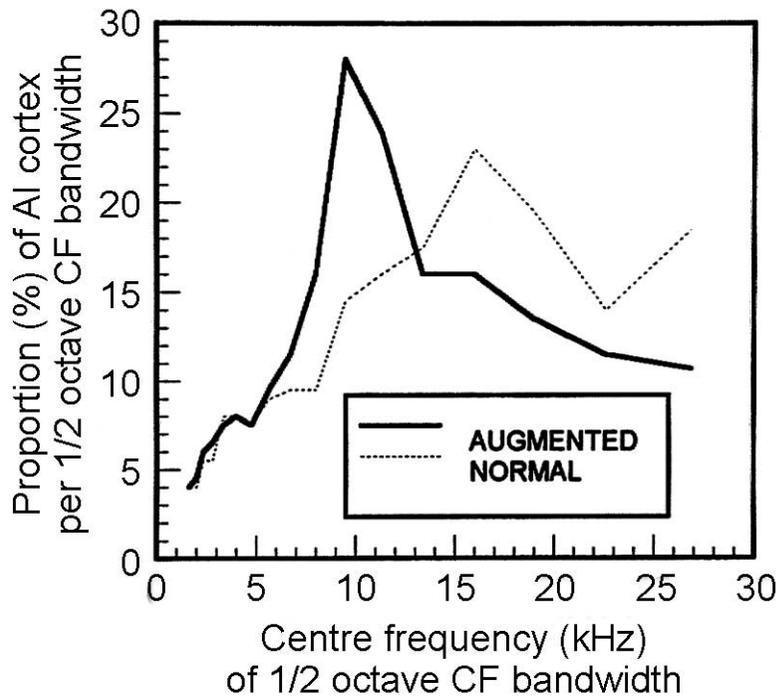


Figure 19. Amount of auditory cortex devoted to different sound frequencies in kittens ($n = 3$) reared in presence of a constant 8 kHz acoustic stimulus (continuous line). Dotted line shows data from three normal controls.

signal which produces a basal (higher frequency) spread of the activated cochlear region.

Our “model” to explain what might be happening is shown in figure 20. Because there is an over-stimulation of a certain region of the cochlea, we suppose that these more active neurons win in the competition to form synapses on target cells. The synapses associated with the active neurons will be more strengthened than less active surrounding neurons. This strengthening will involve Hebbian type mechanisms, and well as those known to mediate various types of long-term potentiation. Ultimately one can see how this could result in an over-representation at the level of cortex of one particular frequency region of the cochlea. These data are further evidence that central tonotopic maps do not result from some hard wiring process governed by a genetic blueprint, but rather they form, in large part, as a consequence of the pattern of activity that comes from the level of the cochlea during early development.

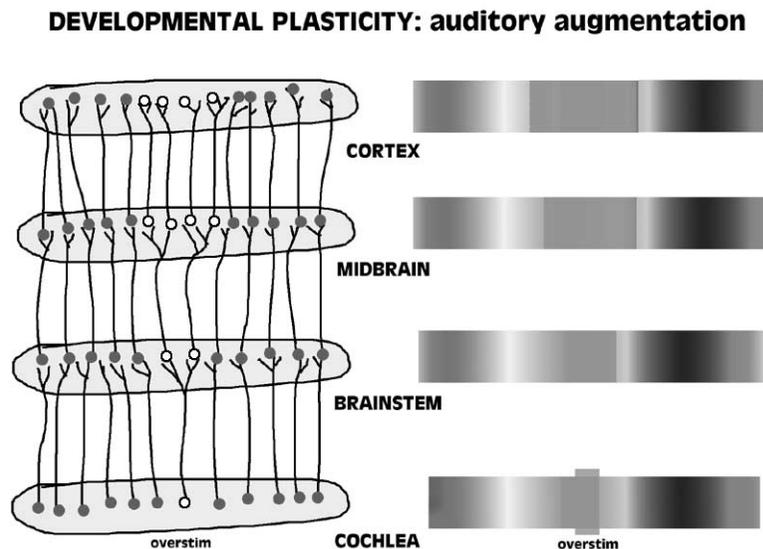


Figure 20. Simple schematic model suggesting the pattern of cochleotopic projections in kitten reared with an over activation of one cochlear region.

Plasticity of Sub-Cortical Frequency Maps

We next asked the question, are these reorganizations of cortical frequency maps just limited to cortex, or are there similar changes at lower levels in the auditory pathway? If the “models” of figures 16 or 20 are half accurate, one might predict sub-cortical changes. In the following set of experiments we have looked at changes to tonotopic maps at the level of the mid-brain, i.e. the central nucleus of inferior colliculus.

Tonotopic representation in normal chinchilla IC (central nucleus)

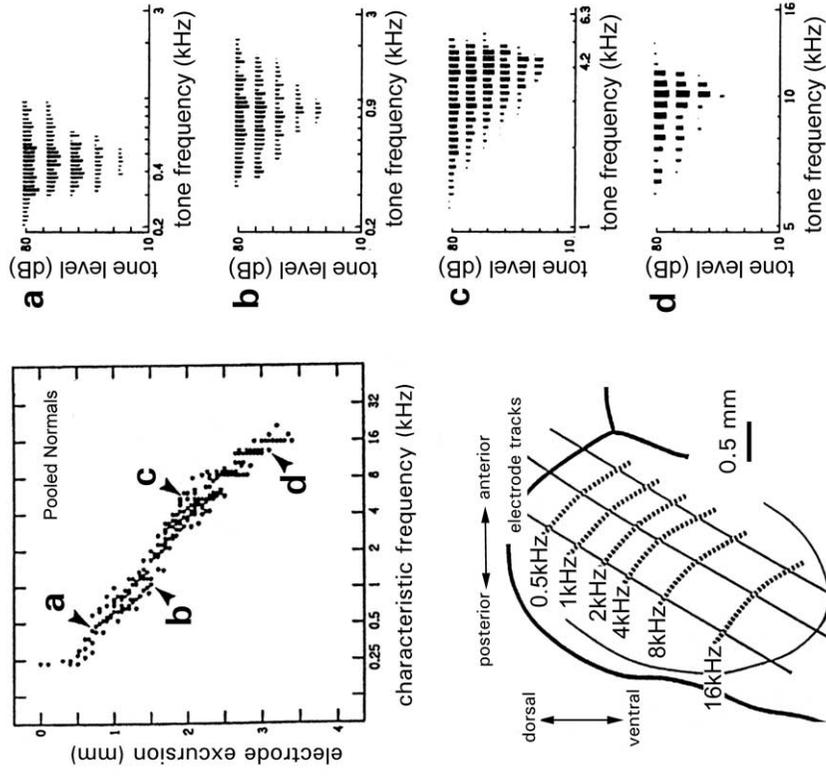


Figure 21. Normal frequency mapping in the inferior colliculus of the chinchilla.

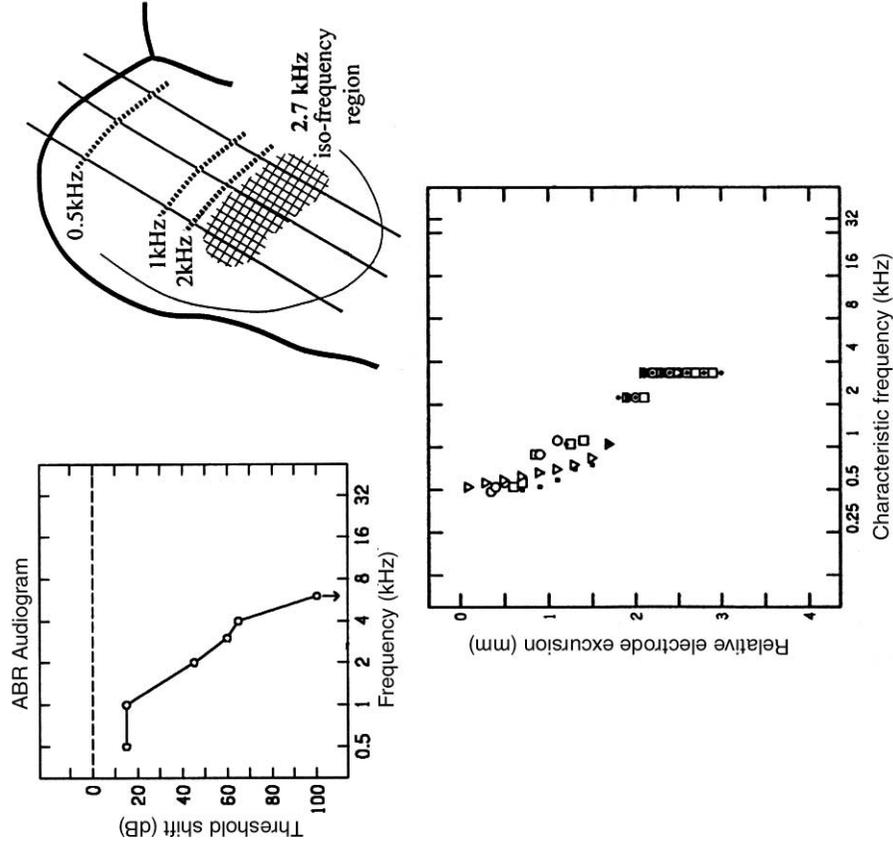


Figure 22. Tonotopic representation in auditory mid-brain of chinchilla after neonatal cochlear lesion.

The experimental protocol is similar to that outlined in figure 13. The animal (in this case the chinchilla) is born and then we immediately induce a lesion to the cochlea taking advantage of the ototoxic effects of the aminoglycoside amikacin. We allow the animal to mature (3 months) and then we investigate tonotopic mapping in inferior colliculus.

Figure 21 shows the tonotopic map in the inferior colliculus (central nucleus) of a normal chinchilla. As depicted in the lower left panel, an electrode introduced into the dorsal region will record from neurons responding best to low frequencies. As the electrode progresses ventrally, we encounter cells responding best to higher frequencies. The progression of best (or characteristic) frequency as a function of electrode excursion is clearly shown in the upper left plot. Note that in the normal animal, there is a very clear linear relationship between electrode position and characteristic frequency on a logarithmic frequency scale. As can be noted in the lower left panel, the octave interval iso-frequency contours are relatively evenly spaced.

Results from one experimental animal are shown in figure 22 (adapted from Harrison, Ibrahim and Mount 1998). In this chinchilla, as a neonate, we made a widespread cochlear lesion which started in the basal cochlear turn and extended apically. The functional consequences of this cochlear damage are reflected in the ABR audiogram. In this animal we can note (upper right panel) an iso-frequency region in the mid-brain tonotopic map at around 2.7 kHz. This matches up with the mid-point of the cut-off slope of the ABR audiogram, which in turn corresponds to the main border area of damage along the cochlear length. In many ways, the mid-brain tonotopic map changes are rather similar to what we found at the level of auditory cortex in our other experiments. In this chinchilla we also note that the tonotopic map for lower frequency regions is abnormal (compare with control animal of figure 21). We suppose that this is related to abnormal activity patterns arising from the damaged sensory epithelium of apical regions of the

cochlea. This again reflects what we have previously observed at the level of cortex in other experiments.

Therefore, in a *developmental model*, the reorganization of tonotopic maps is not exclusively cortical but is present at lower levels in the system. Indeed one might speculate that if there is abnormal sensory input during early development, some degree of reorganization is likely to be present wherever there are synapses to be modified.

As already pointed out, after the cochlea is lesioned in the mature animal one can see evidence of reorganization to cortical tonotopic maps (e.g. Robertson and Irvine 1989; Rajan et al. 1993; Kakigi et al. 2000). However at the mid brain level we have a different picture. Figure 23 shows results from two tonotopic mapping experiments in inferior colliculus

Tonotopic representation in IC after basal cochlear deafferentation

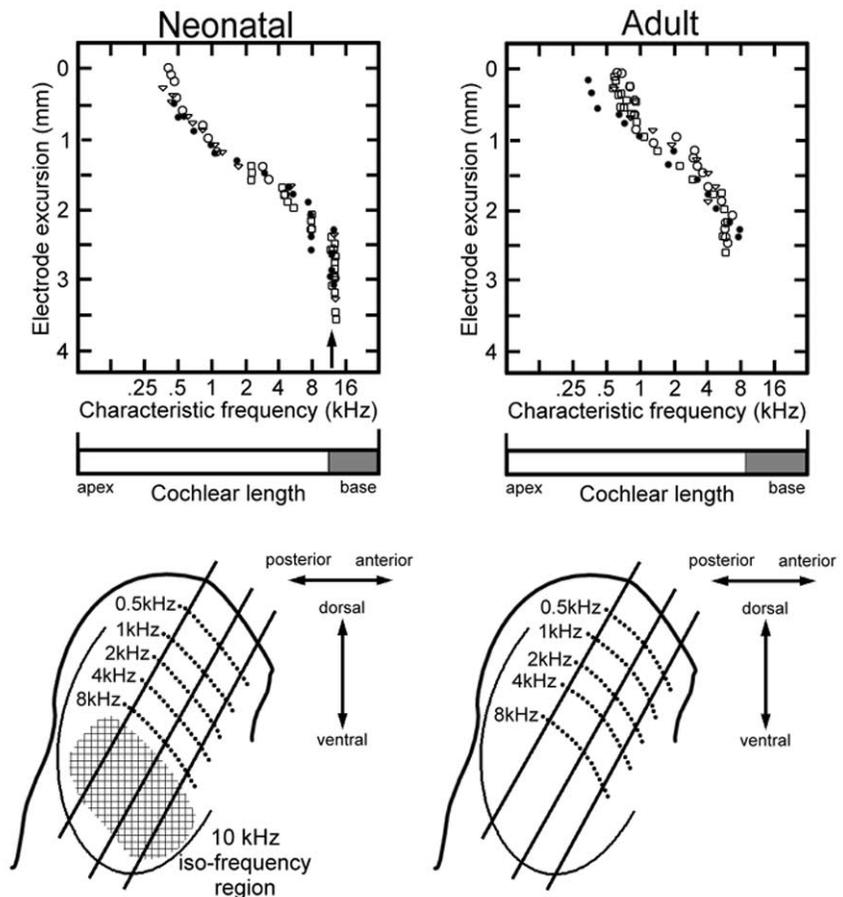


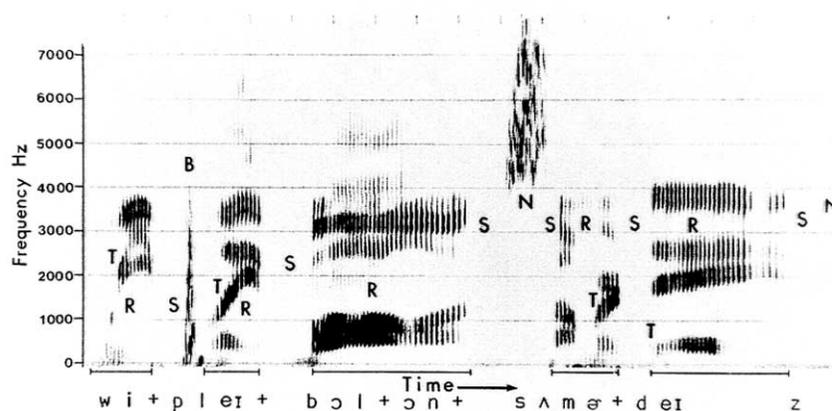
Figure 23. Tonotopic mapping at level of inferior colliculus in chinchilla after basal cochlear lesion induced in the neonatal animal (left-hand panels) versus in the adult subject (right-hand panels).

in which the cochlear lesion was made neonatally (left) compared with in the adult animal (right). After a neonatal cochlea lesion, we see evidence of map reorganization (e.g. the large iso-frequency region at 10 kHz). In contrast, for the subject lesioned as an adult there is no iso-frequency region or other evidence of map reorganization. To reiterate, at the level of the inferior colliculus, the reorganization of tonotopic maps shown in a developmental model (i.e. where the auditory system is interfered with during an early postnatal period) is not found in an adult plasticity model. A similar lack of plasticity in the adult animal has been previously reported at the level of the cochlear nucleus (Kaltenbach, Meleca and Falzarano 1996; Rajan and Irvine 1998a).

One conclusion from these studies is that whilst the highest levels of the auditory system (cortex) can remain plastic in the adult animal, lower levels of the auditory system may only be plastic during certain early stages in development. In a sense we are saying that the plasticity of lower levels of the auditory system is age related and may even have some critical period of plasticity after which there is little possibility for reorganization.

What can Interfere with the Central Representation of Complex Signals?

In most of the studies reported here, there has been a radical change to the sensory input. In the cochlear lesion experiments the animals have the equivalent of a moderate to severe sensorineural hearing loss from birth, that clearly translates to very abnormal activity patterns arising from the cochlea. However, I want



A spectrographic display of the sentence
"We play ball on summer days."

Figure 24. A complex acoustic signal such as this speech utterance can be broken down, as shown here, into its spectral components.

Guinea pig cochlear fibre frequency threshold curves (FTCs):
Normal

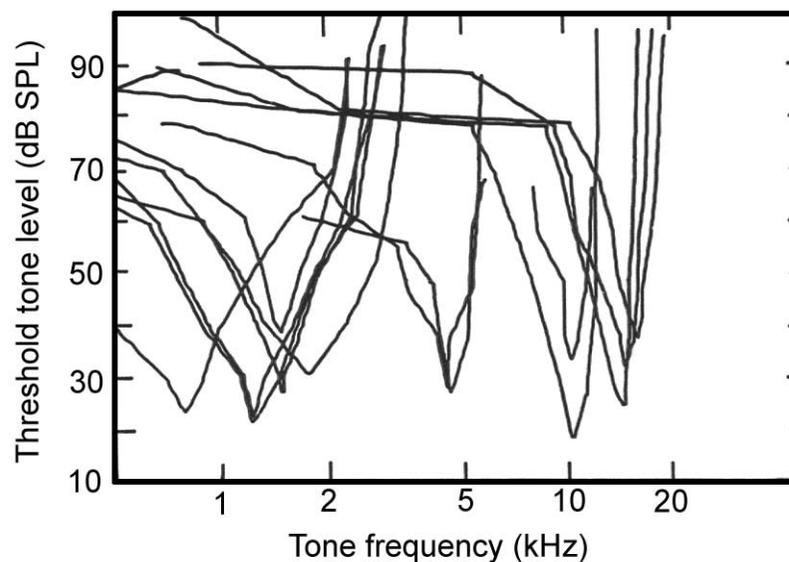


Figure 25. Part of the bank of narrow, overlapping band pass filters that constitute the peripheral hearing mechanism.

to suggest that much more subtle changes, which could occur not just at the level of the cochlea but at higher levels in the system, might potentially interfere with the development (and maintenance) of point-to-point projections.

Figure 24 serves to illustrate the task of the peripheral auditory system. This spectrogram shows how a complex speech signal (“we play ball on summer days”) can be analyzed into its frequency components, as a function of time. The cochlea carries out a similar operation. This image could easily represent the pattern of neural activity generated in the cochlear nerve in response to this speech signal. Imagine that the ordinate is not a frequency scale but rather the neural array from the apex to the base of the cochlea. (This transformation has been made in figures 26–29.) This pattern of neural activity is achieved by the narrow band-pass filtering elements of the cochlea. Figure 25 serves to remind us about the characteristics of the filtering elements at the level of the cochlea which are performing this frequency analysis. This diagram shows the frequency threshold curves or tuning curves from normal cochlear nerve fibers (recorded from the guinea pig).

The process of the initial cochlear frequency analysis is very important. We are all well aware that there are many pathological cochlear conditions that can degrade this analysis. For example all types of sensorineural hearing loss involving outer hair cell damage will reduce not just the sensitivity of the system, but also its ability to separate out frequency components (e.g. Kiang, Moxon and Levine 1970; Evans and Harrison 1976; Dallos and Harris 1977; Harrison and Evans 1977, 1979). However, the initial frequency analysis is only part of the whole process of getting patterns of neural activity faithfully transmitted to cerebral cortex. The point-to-point transmission system can be potentially degraded in many ways.

Figures 26–29 show, diagrammatically, some of the possible ways in which the projection system from cochlea to cortex might be degraded. The lower panel

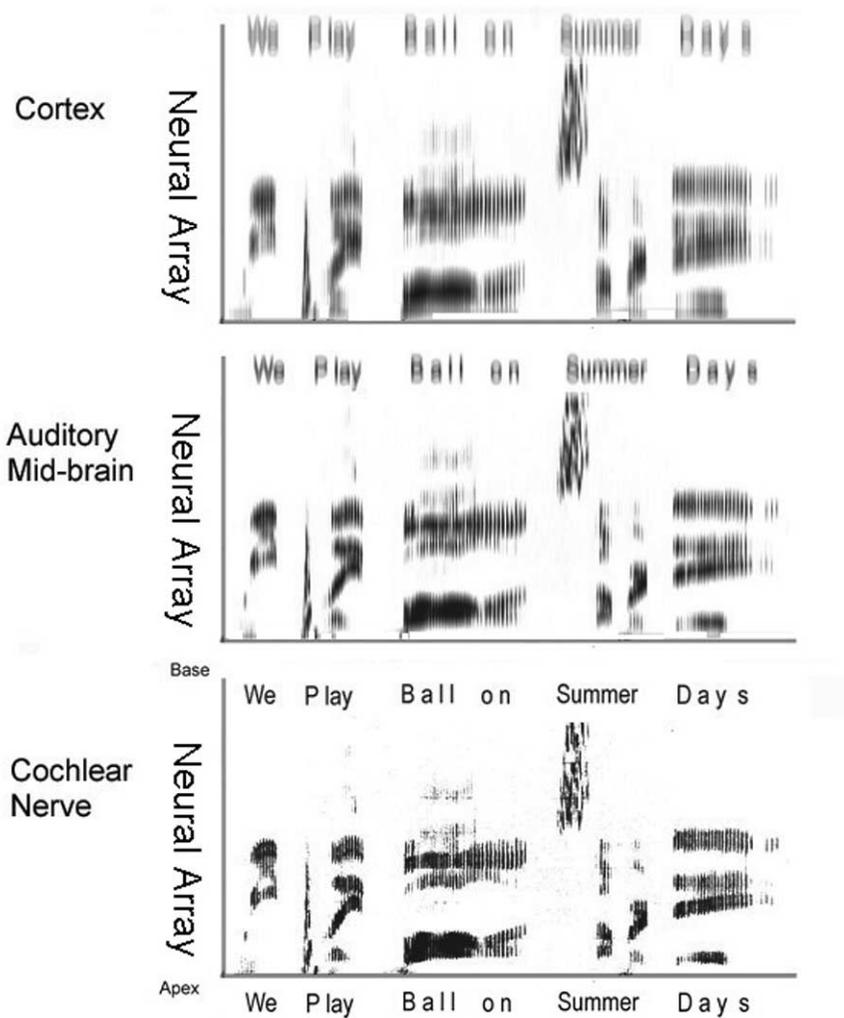


Figure 26. Schematic diagrams of the spatio-temporal patterns of neural activity representing a speech signal at three levels within the auditory system. Cumulative effect of a poor maintenance of spatial activity pattern across neural array (spatial “blur”).

of each figure represents the neural array of activity at the cochlear nerve level evoked by the speech signal “we play ball on summer days” (adapted from figure 24). The upper panels show (two) stages of progressive degradation of the signal. For illustrative purposes the clarity of the auditory percept is represented in each panel by the text. This is a sort of visual depiction of the degradation of the sound percept!

For figure 26 the small degradation is a “blur” in the clarity of representation of frequency across the neural array. This degradation in spectral frequency

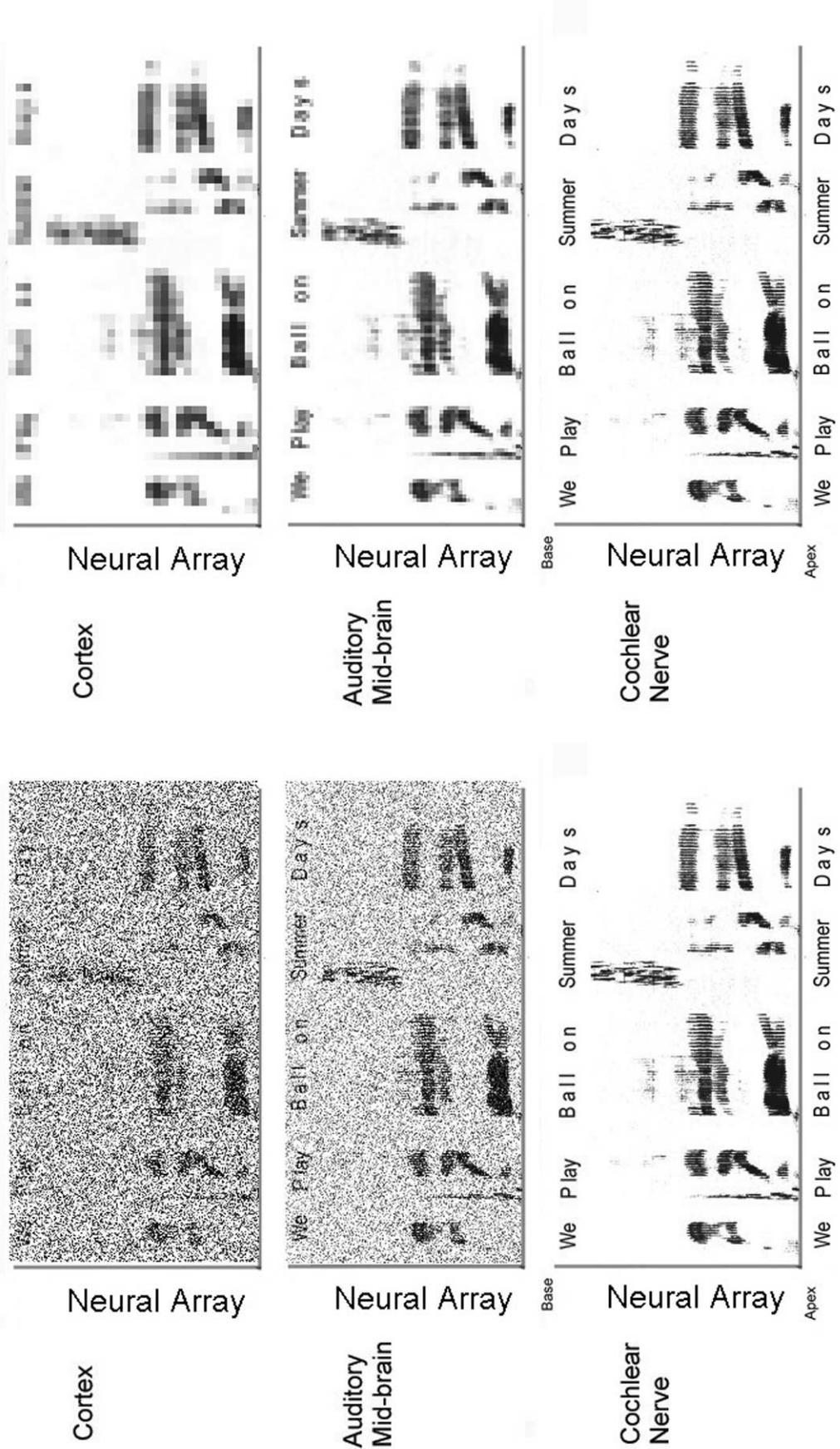


Figure 27. Schematic diagrams of the spatio-temporal patterns of neural activity representing a speech signal at three levels within the auditory system. Effect of abnormal noise levels.

Figure 28. Schematic diagrams of the spatio-temporal patterns of neural activity representing a speech signal at three levels within the auditory system. Effect of progressive reduction in number of information channels.

representation could initially be due to poor cochlear filtering as found in sensorineural hearing loss. It could also result from poor lateral inhibition in neurons throughout the central auditory system, or perhaps a de-synchronization of neurons due to myelination disorders. More importantly, it could result from a failure to establish good point-to-point projections during early development. In other words it could represent a failure of the projection system to change from its early divergent innervation pattern depicted in figure 11 to the more direct pattern shown in figure 12.

Another way in which we can degrade information reaching cortex from the cochlea is by adding noise, as illustrated in figure 27. Physiologically, such noise may result from a lack of inhibition in the neural systems involved. There may be pathological conditions that produce noise, e.g. too many “leaky” synapses, neuronal injury discharges. Perhaps there is a link here to tinnitus.

The next example of a potential source of degradation is depicted in figure 28, and relates to reducing the number of channels of information, which can carry neural representations of sound to cortex. This is the situation, for example, in subjects having a cochlear implant device in which the channel numbers are considerably reduced (down to the number of implanted electrodes). Auditory neuropathy might also result, in many cases, from a significant reduction in the number of channels bringing information from the cochlea to the cortex (see Harrison 1998 for further arguments).

The final example of information degradation is perhaps the one most likely to have a real biological basis. In figure 29, the “blur” occurs in the time domain. Anything that interferes with the transmission of action potentials or electrotonic conduction (e.g. various postsynaptic potentials) could smear the neural representation of a signal. One major design weakness of the cochlea-to-cortex projection system is that it involves multiple stages, each interrupted by

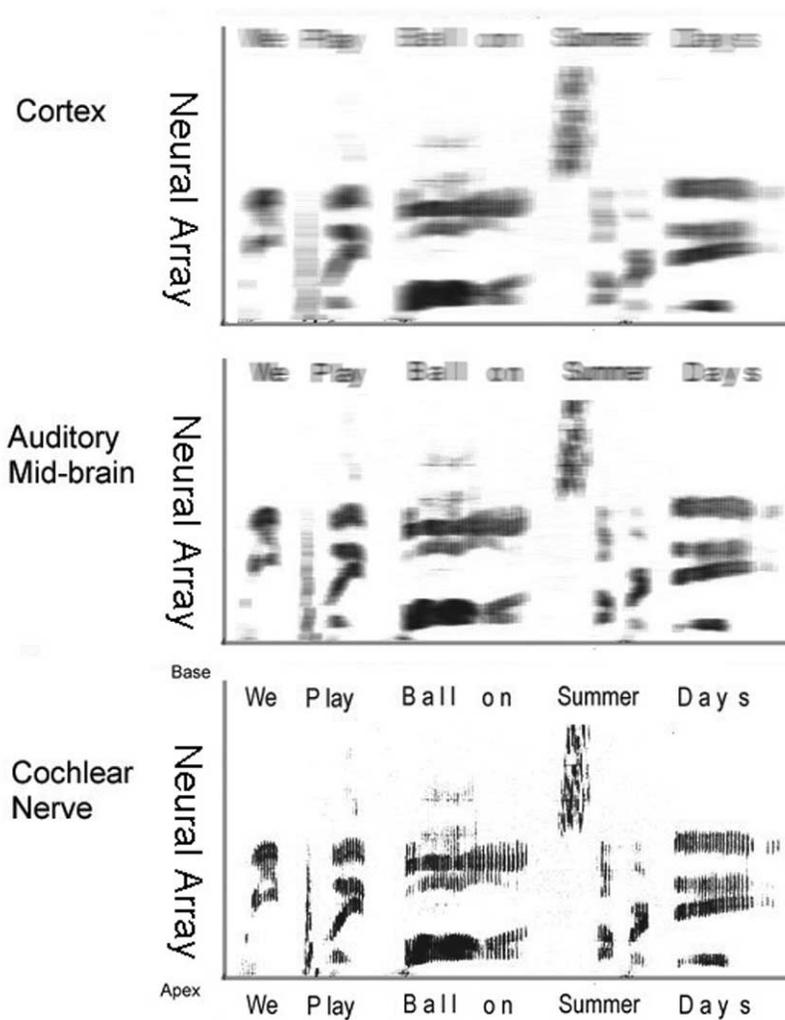


Figure 29. Schematic diagrams of the spatio-temporal patterns of neural activity representing a speech signal at three levels within the auditory system. Effect of increasing timing uncertainty (“temporal blur”).

synapses. There is always some timing uncertainty at synapses. There are many pathological conditions in which synaptic function might be impaired, leading to increased time jitter. More importantly a delay or failure to produce synaptic strengthening during early development might lead to a degraded system in the mature subject. Given that lower levels of the auditory pathways may only be “plastic” for a certain early time period, the adults system might be permanently impaired.

Clinical Implications

One of the main “take home messages” from the experimental animal studies is that during an early developmental period, activity patterns arising at the cochlear level are instrumental in establishing central tonotopic maps (as well as other central sound coding mechanisms). From a clinical perspective, any early conditions that might change cochlear activation patterns will possibly disrupt normal central development. These conditions could for example include chronic conductive hearing loss caused by repeated middle ear infection.

Another important message from the studies is that the plasticity of the auditory system appears to be much greater in the developing animal compared to the adult. Thus our studies (Harrison 2001) have indicated that at the level of the mid-brain, there is little evidence of plasticity in the adult animal compared with that found during early development. Therefore, when we consider the plasticity of the auditory system we have to bear in mind that different levels in the system have different degrees of plasticity. We have evidence that at the level of primary auditory cortex (and beyond) plasticity is present perhaps for life. This does not appear to be the case for the lower level “gateway”. At lower levels there is “age related plasticity” and perhaps some well-defined “critical periods”.

Clinically, if we are trying to ameliorate or compensate for congenital auditory deficits, for example with a hearing aid or a cochlear implant, the best results are going to be obtained when we do this in young infants. Indeed if they are not young enough at time of intervention, it may be too late. This imperative is, of course, driving the establishment of universal infant hearing screening programs. Practically, the early hearing screening is feasible, but then the greater challenge is to provide useful intervention very soon after. That issue was the main topic of the conference reported in this volume.

Important Summary Points

- Speech and other complex sounds are represented in the brain by activity patterns within large neural arrays.
- These activity patterns are established along the sensory epithelium of the cochlea by mechanisms that can separate out closely spaced frequency

components, and represent them at different places along the cochlea.

- These tonotopically mapped patterns have to be faithfully re-represented in auditory cortex, for further processing.
- Both the cochlear mechanisms and the transmission pathways to cortex can be disrupted such that central representations of sounds are abnormal.
- The central pathways develop, in part, as a result activity patterns from the cochlea, and can develop abnormally if there is cochlear dysfunction. Even very small changes to transmission in neural signals will result in poor representation of sound at cortex
- There appears to be considerable plasticity in whole pathway during early development, but in the adult subject plasticity at lower level (e.g., brainstem, midbrain) is considerably reduced, perhaps lost.
- Clinically these data indicate that the early post natal period is very important for the establishment of auditory pathways that can accurately represent complex sounds at the cortical level.
- There appears to be a critical period of plasticity, at least for the lower “gateway” pathways of the auditory system. Thus, every effort should be made to detect hearing problems early (e.g., with neonatal hearing screening programs).
- If infants need intervention (e.g., amplification, cochlear implant, auditory verbal therapy), it should be provided as soon as possible.

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