PLASTICITY IN THE ADULT CENTRAL AUDITORY SYSTEM

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The central auditory system retains into adulthood a remarkable capacity for plastic changes in the response characteristics of single neurons and the functional organization of groups of neurons. The most dramatic examples of this plasticity are provided by changes in frequency selectivity and organization as a consequence of either partial hearing loss or procedures that alter the significance of particular frequencies for the organism. Changes in temporal resolution are also seen as a consequence of altered experience. These forms of plasticity are likely to contribute to the improvements exhibited by cochlear implant users in the post-implantation period.

1. INTRODUCTION

One of the most exciting discoveries of the last forty or so years in sensory neuroscience has been the extent to which the stimulus selectivity of neurons in, and the functional organization of, sensory cortical and subcortical structures are modifiable by experience (i.e., exhibit plasticity). The first reports of such plasticity were of changes that were maximal within restricted "critical periods" during early development [1], when neuronal pathways and connections were being formed. It was therefore believed for many years that such changes occurred only during development, and that sensory processing mechanisms were stable features of the adult brain. More recently, however, it has been demonstrated that these mechanisms can in fact be modified in adults as a consequence of altered patterns of input or of procedures that change the significance of particular sensory inputs. Kaas and Florence [2] provide a comprehensive review of such plasticity in a number of sensory systems.

It should be emphasised that not all changes in neural responsiveness and organization as a consequence of altered input are reflections of plasticity. Some changes are explicable as direct, or passive, consequences of the altered input. For example, in the auditory system, destruction of the outer hair cells results in immediate and marked changes in the frequency tuning of auditory nerve (AN) fibres [3], and of neurons throughout the auditory pathway. These changes are a direct consequence of the elimination of the cochlear amplifier [4], rather than of plastic processes. Although plasticity can be broadly characterized as involving some form of active or dynamic modification of neural properties that is triggered by the changed input, it is not always a simple matter to distinguish between plastic and non-plastic changes [5,6].

In the case of the auditory system, much of the evidence for adult plasticity has been obtained from neurophysiological studies of frequency selectivity and organization in animal models. There is additional evidence for adult plasticity from a number of studies of the temporal characteristics of responses to acoustic and intra-cochlear electrical stimulation. The animal data are also complemented by a growing body of evidence from functional imaging and psychophysical studies in adult humans. This evidence will be briefly reviewed in this paper.

2. PLASTICITY OF FREQUENCY PROCESSING MECHANISMS

2.1 Frequency tuning and tonotopicity

The majority of neurons at all levels of the auditory system are sharply tuned for frequency, commonly having V-shaped frequency tuning curves (plots of threshold as a function of frequency), with lowest threshold at the neuron's characteristic frequency (CF). At the level of the AN, the tuning curve of a single fibre reflects that of the inner hair cell (IHC) from which its input is derived, and thus the mechanical tuning of the point on the basilar membrane where that IHC is located. AN fibres innervating adjacent points on the basilar membrane project to adjacent points in auditory brainstem structures, with the consequence that these central projections are organized topographically with respect to the cochlea (i.e., are cochleotopically organized). Because adjacent points on the cochlea are tuned to different frequencies, this anatomical cochleotopy results in a functional organization with respect to frequency tuning (i.e., tonotopy). The tonotopic organization of primary auditory cortex (AI), as derived from determining the CFs of neurons across the surface of AI, is illustrated in Figure 1, A and B. So-called iso-frequency contours (more correctly, iso-CF contours) separate strips of cortex in which neurons with CFs within narrow frequency ranges are located.

Although the cochleotopic organization of anatomical projections is the basic substrate of central tonotopy, it should be emphasised that the frequency tuning of central neurons is not determined solely by these patterns of anatomical connectivity. Rather, there is a good deal of convergence of input derived from different regions of the cochlea (i.e., from different frequency channels) onto single neurons in central auditory structures, and the sharp tuning of central neurons is derived and maintained computationally by the integration of these convergent (excitatory and inhibitory) inputs. It is largely as a consequence of changes in the relative strengths of these convergent inputs and in the processes by which they are integrated that central plasticity of frequency selectivity is possible.

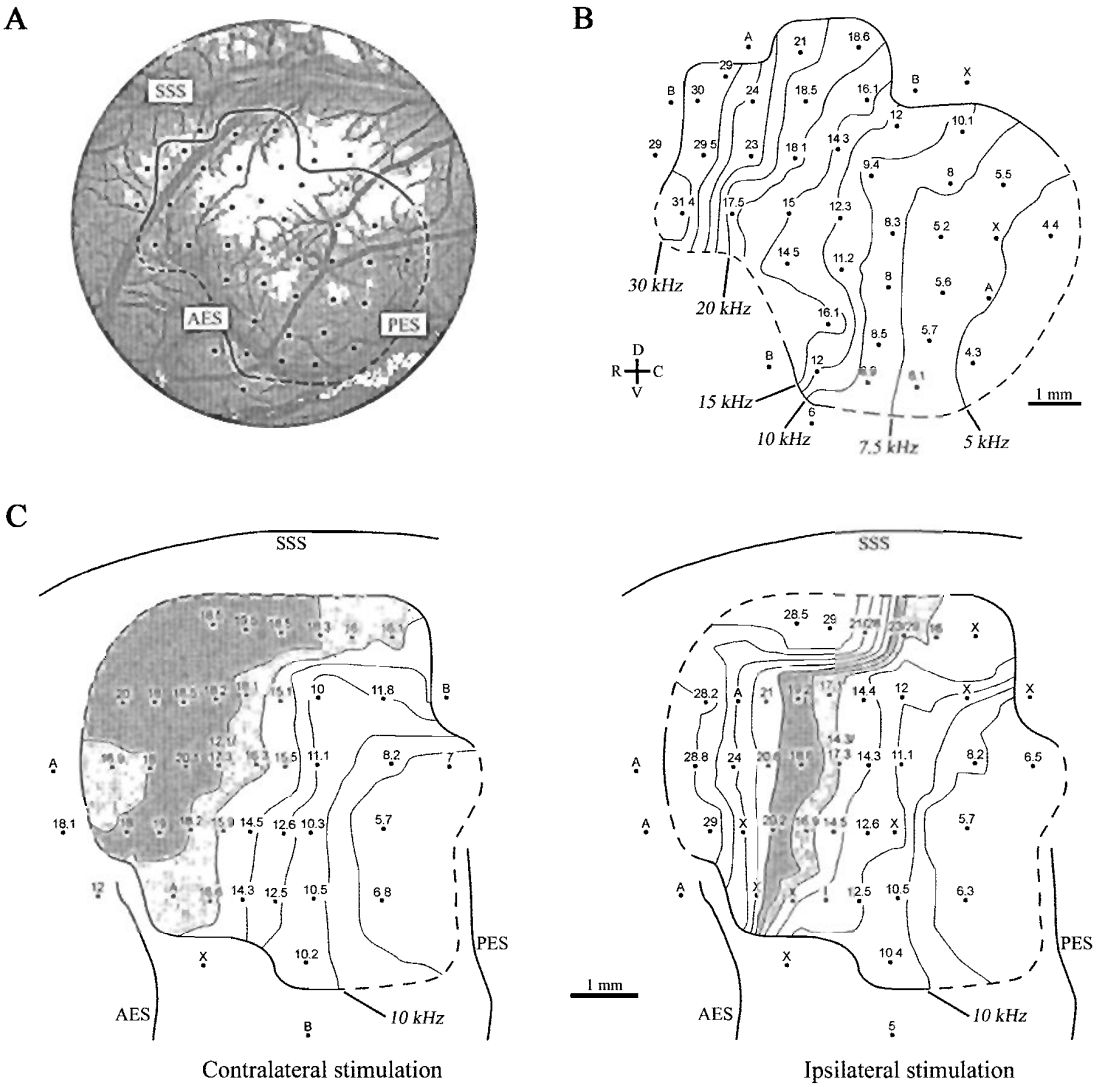

Figure 1. A Digital photograph of the exposed cortical surface of a cat with normal hearing. Dots indicate the sites at which microelectrode penetrations were made, and the solid black line indicates the physiological boundary of AI as defined from the data shown in B. Abbreviations: AES: anterior ectosylvian sulcus; PES: posterior ectosylvian sulcus; SSS: suprasylvian sulcus. **B.** Frequency map derived from matrix of penetrations shown in A. The CF of the neuron cluster recorded in each penetration is indicated above the dot; other penetrations are labelled 'X' (no response to acoustic stimulation), A (acoustically responsive, but CF could not be determined), B (broadly tuned) or I (inhibitory response). The line defining the physiological boundary of AI is broken where this boundary was not determined unequivocally. Thin lines indicate iso-CF contours (CF identified by figures at lower boundary of AI) fitted to the data at 2.5 kHz intervals using an inverse-distance smoothing function. R, C, D, and V indicate rostral, caudal, dorsal, and ventral directions, respectively. **C.** Frequency maps of AI in the hemisphere contralateral to a unilateral cochlear lesion for stimulation of the contralateral (lesioned) ear and the ipsilateral (normal) ear in a chronically lesioned cat. Conventions as in A and B. Light and dark shaded bands indicate the area of cortex containing neurons with CFs in the range 16–18 kHz and 18–20 kHz, respectively. Panels B and C reproduced from Reference [8], copyright 2005, with permission from Elsevier.

2.2 Lesion-induced plasticity of frequency processing mechanisms

Evidence for adult plasticity of frequency processing mechanisms has been derived from two major experimental paradigms. One has been to determine the effects of a restricted cochlear lesion, which eliminates output from the cochlea over a particular frequency range, on the frequency organization of central structures (i.e., lesion-induced plasticity). The second has been to determine the effects of behavioural conditioning procedures, in which a tone of particular frequency comes to have behavioural significance for the animal, on the frequency tuning of central auditory neurons (learning-related plasticity). Detailed accounts of this evidence have been given elsewhere [5], and it will be only briefly summarised here.

A mechanical lesion damaging the basal region of one cochlea eliminates output from that cochlea over a restricted range of high frequencies, producing deafness in that ear over the affected frequency range. If AI contralateral to the lesioned cochlea is examined some weeks after the lesion, the (high-

frequency) region of cortex deprived of its normal input by the cochlear lesion is not silent, but is occupied by an expansion of the area containing neurons with CF at frequencies represented at the edge of the cochlear lesion [7,8]. This pattern of results is illustrated in Figure 1C, which shows the frequency organization in AI in the left cerebral hemisphere of a chronically lesioned cat for stimulation of the lesioned right ear (i.e., contralateral stimulation) and of the normal left ear (i.e., ipsilateral stimulation). In normal animals, the frequency maps for stimulation of the two ears are in register, such that neurons at any given point have the same CF for stimulation of the contralateral and ipsilateral ears. The cochlear lesion in the cat for which data are presented in Figure 1C eliminated output from the right cochlea at frequencies above 17-19 kHz. Neurons with CF at these "lesion edge" frequencies occupy narrow strips of cortex in the frequency map derived from stimulation of the normal ipsilateral ear (see shading), and that map is indistinguishable from normal maps. In contrast, the area occupied by neurons with CF at lesion-edge frequencies in the map derived from stimulation of the lesioned contralateral ear is massively enlarged, and occupies the area of cortex in which the higher CFs would normally have been represented. Frequency map plasticity of this sort has been described in a range of species (including non-human primates), and as a consequence of cochlear lesions produced in different ways (e.g., noise trauma; ototoxic injections) [5]. Although changes in cortical frequency maps would be expected to occur as a passive consequence of cochlear lesions, the thresholds and other response characteristics of neurons in the enlarged areas of representation of lesion-edge frequencies indicate that they reflect plastic changes [7,8].

Plasticity indistinguishable from that seen in AI is observed in the major auditory thalamic nucleus (the ventral division of the medial geniculate body) after mechanical cochlear lesions [9]. However, such plasticity either does not occur, or occurs only to a limited extent, in the major auditory midbrain nucleus, the inferior colliculus (IC) after such lesions[10]. It therefore appears that the capacity for this form of plasticity is a characteristic of the thalamo-cortico-thalamic system, although the primary site of plastic change has not yet been established [5,9].

In most of these studies, the auditory cortex was mapped some weeks or months after the cochlear lesion, and the time course of the changes in cortical frequency organization is therefore not known. In the somatosensory system, in which analogous plasticity in cortical maps of the body surface is seen as a consequence of peripheral lesions (digit amputation or nerve section), some of the changes contributing to cortical reorganization occur immediately after the peripheral lesion, while others take place more gradually [6]. It is likely that lesion-induced auditory cortical plasticity involves similar short-term and longer-term changes.

2.3 Possible perceptual consequences of lesion-induced auditory cortical plasticity

Although it is tempting to think of plastic changes following damage to the cochlea in terms of a central nervous system compensation for the peripheral loss, it should be noted that the organism remains deaf in the frequency range affected by the lesion. It seems likely that this form of plasticity should be viewed as a manifestation of the brain's *capacity* for plastic change in response to altered patterns of input, rather than as a compensatory adaptation. However, the dramatic changes in the cortical patterns of activity evoked by lesion-edge frequencies would be expected to have perceptual consequences. This expectation is apparently confirmed by the finding that humans with hearing losses of the sort shown to produce cortical reorganization in animal studies show enhanced frequency discrimination ability at lesion-edge frequencies [11,12]. It seems likely that this enhanced discriminative capacity reflects plastic changes in the cortex, although this has not yet been directly established by demonstrating changed cortical frequency maps in the human participants in the psychophysical studies.

2.4 Learning-related plasticity of frequency processing mechanisms

The effects of learning on auditory frequency selectivity have been investigated using a number of paradigms [5]. The most common has been classical conditioning, using a tonal conditioned stimulus (CS) at a frequency within the frequency response area of a neuron (or multi-unit cluster) but differing from its best frequency (BF; the frequency evoking the largest response). Although there is some disagreement (see [5] for review), the most commonly reported result in such studies has been an increase in the strength of the response evoked by the CS frequency and a decrease in response at the pre-training BF and at other frequencies, such that the CS frequency becomes the post-training BF [13,14]. Similar changes in the spectro-temporal receptive fields of auditory cortical neurons have recently been described in ferrets trained to detect a target tone of a particular frequency embedded in a sequence of broad-band noise-like stimuli [15]. The changes in neuronal frequency selectivity observed in these studies can occur within a single training session, confirming the contribution of short-term changes in the nervous system (probably changes in "synaptic weights", i.e., the strength of particular excitatory and inhibitory inputs to the neurons) to auditory cortical plasticity. The short- and long-term mechanisms responsible for auditory cortical plasticity are discussed in more detail elsewhere [5].

3. PLASTICITY OF TEMPORAL PROCESSING MECHANISMS

3.1 Temporal resolution: Latency and frequency-following

Information encoded in the fine temporal structure of an acoustic signal cannot be encoded by the frequency processing mechanisms described above. Therefore, such information must be encoded in the temporal structure of the firing patterns of neurons within the auditory system. There are two main limits on the ability of the auditory system to encode temporal information. One is jitter in the response of each neuron, which includes variations in both the timing of the initiation of action potentials and the time for action potentials to propagate along axons. The second is the maximum firing rate of each neuron, which is related to the refractory period of the neuron (the

period within which the neuron is incapable of firing another action potential). At all levels of the auditory system, temporal resolution is poorest for near-threshold stimuli, and improves to a saturating limit as stimulus intensity is increased.

Langner [16] provides a comprehensive review of temporal processing in the auditory system, two aspects of which will be considered here. One is the latency with which neurons respond to the onset of a stimulus; the second is the precision with which neurons represent the temporal patterns of repetitive stimuli. The first-spike latencies of individual AN fibre responses are dependent on the mode of stimulation (e.g., acoustic vs electric), but minimum latencies to acoustic stimuli are in the order of 2 ms, with a jitter (standard deviation) of ± 0.2 ms. This precise timing in response to acoustic stimuli is maintained throughout the auditory system; individual units in AI respond with minimum latencies in the range of 10-20 ms (an increase reflecting the longer conduction distances and increased number of synapses in the multiple pathways over which input reaches AI), but without a marked increase in the jitter of the response [17]. Individual AN fibres are capable of phase locking to periodically modulated acoustic stimuli at modulation frequencies up to approximately 1 kHz. This level of temporal sensitivity is not maintained at higher levels; the ability of neurons in AI to follow complex periodic stimuli is an order of magnitude lower. The mechanisms responsible for this decrease in temporal processing are not clear, although inhibitory effects are thought to play a major role.

3.2 Deprivation- and activity-induced plasticity of temporal processing mechanisms

As with frequency processing mechanisms, deprivation of input to the auditory system, due to a sensorineural hearing loss, results in changes in some aspects of temporal processing. Interestingly, many of the changes in temporal response characteristics are only present in animals with a complete lack of auditory input (i.e. with bilateral profound deafness), as it appears that unilateral input is sufficient to maintain near normal temporal processing in the IC [18]. Studies of potential plastic changes in temporal processing mechanisms therefore commonly use intra-cochlear electrical stimulation, which by-passes the IHCs and directly excites the AN fibres, to activate the auditory system. Changes in temporal response characteristics as a result of the elimination of auditory input are then examined by comparison of responses to electrical stimulation in acutely and chronically deafened animals.

Long-term bilateral deafness does not significantly alter the temporal response characteristics of AN fibres when compared to acutely deafened controls [19]. However, at the level of the IC, long-term deafness sufficient to produce profound spiral ganglion cell (SGC) loss and demyelination of the remaining SGCs results in an increase in both the latency and jitter of responses of individual neurons to electrical stimulation, and a decrease in the maximum following rate [18]. It is unclear whether these changes in IC are simply passive consequences of the peripheral degenerative changes in SGCs produced by hair cell damage, or represent plasticity. Although the changes in IC would be expected to be reflected at higher levels, the temporal responsiveness of AI neurons does not appear to be significantly affected by long periods of deafness [20], suggesting the occurrence of plastic changes in cortex.

Subsequent to the changes consequent on hearing loss, reactivation of the auditory system via chronic electrical stimulation of the auditory nerve, similar to that delivered by a cochlear prosthesis, enhances its temporal processing capacity. Neurons in the IC of chronically stimulated animals respond with shorter latencies, and follow higher frequencies of electrical stimulation, than neurons in either chronically- or acutely-deafened animals [21,22].

3.3 Learning-related plasticity of temporal processing mechanisms

The temporal processing mechanisms of the auditory system are not only influenced by changes in activation at the periphery, but can also be altered by training. AI neurons in normal-hearing rats trained on a task in which the repetition rate of noise pulses increased with proximity to a target showed stronger phase locking and stronger responses to high-rate stimuli [23]. The mechanisms responsible for the increased temporal resolution are not clear, but are presumed to involve multiple neuromodulator systems.

4. IMAGING EVIDENCE FOR AUDITORY CORTICAL PLASTICITY IN HUMANS

Modern techniques for measuring brain activity in humans have provided evidence supportive of the animal evidence for plasticity of frequency processing mechanisms, although the bulk of this evidence relates to a different form of experience-related plasticity. In the only investigation of the organization of auditory cortex in humans with steeply-sloping hearing losses, Dietrich et al. [24] presented magnetoencephalographic (MEG) evidence for an expanded representation of lesion-edge frequencies of the type seen in animals with such losses. However, in the only study of the effects of classical conditioning in humans, Morris et al. [25] found that conditioning was associated with a decrease in response to the CS (as measured by positron emission topography). This result is at variance with the finding in the majority of animal studies, which implies an increase in the number of neurons responding most strongly to the CS frequency, although it is in agreement with a smaller number of animal studies (see [5] for discussion). The largest body of evidence for auditory cortical plasticity in humans is provided by a number of MEG studies that indicate larger responses to various pure and/or musical tones in musicians than in non-musicians. This correlation could reflect the fact that people with these characteristics are more likely to become musicians, rather than effects of musical training on neural processing mechanisms, but evidence from other studies indicates that at least in some cases the changes are training-specific [5, 26]

5. CONCLUSION

The predominantly neurophysiological evidence for central auditory system plasticity is complemented by a similar body of psychophysical evidence for plasticity in auditory perceptual processes [5]. There is no doubt that these forms of plasticity contribute to the plastic changes that underlie the remarkable

success of many humans with cochlear prostheses in achieving near-normal speech perception despite the abnormal (and in many ways impoverished) input provided by the prosthesis [27]. The evidence for central auditory plasticity is also matched by evidence for analogous plasticity in visual and somatosensory processing mechanisms [2]. This evidence has transformed our understanding of the nature of the processing of sensory information in the brain.

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REFERENCES

1. Hensch, T. K. (**2004**). "Critical period regulation," Annu. Rev. Neurosci. **27**, 549-579.
2. Kaas, J. H., and Florence, S. L. (2001), "Reorganization of sensory and motor systems in adult mammals after injury," in *The Mutable Brain,* edited by J. H. Kaas (Harwood Academic Publishers, Amsterdam), pp. 165-242.
3. Dallos, P., and Harris, D. (**1978**). "Properties of auditory nerve responses in absence of outer hair cells," J. Neurophysiol. **41**, 365-383.
4. Fettiplace, R., and Hackney, C. M. (**2006**). "The sensory and motor roles of auditory hair cells," Nature Rev. Neurosci. **7**, 19-29.
5. Irvine, D. R. F., and Wright, B. A. (2005), "Plasticity in spectral processing," in *Auditory Spectral Processing,* edited by M. Malmierca, and D. R. F. Irvine (Elsevier Academic, San Diego), pp. 435-472.
6. Calford, M. B. (**2002**). "Dynamic representational plasticity in sensory cortex," Neuroscience **111**, 709-738.
7. Rajan, R., Irvine, D. R. F., Wise, L. Z., and Heil, P. (**1993**). "Effect of unilateral partial cochlear lesions in adult cats on the representation of lesioned and unlesioned cochleas in primary auditory cortex," J. Comp. Neurol. **338**, 17-49.
8. Kamke, M. R., Brown, M., and Irvine, D. R. F. (**2005**). "Basal forebrain cholinergic input is not essential for lesion-induced plasticity in mature auditory cortex," Neuron **48**, 675-686.
9. Kamke, M. R., Brown, M., and Irvine, D. R. F. (**2003**). "Plasticity in the tonotopic organization of the medial geniculate body in adult cats following restricted unilateral cochlear lesions," J. Comp. Neurol. **459**, 355-367.
10. Irvine, D. R. F., Rajan, R., and Smith, S. (**2003**). "Effects of restricted cochlear lesions in adult cats on the frequency organization of the inferior colliculus," J. Comp. Neurol. **467**, 354-374.
11. McDermott, H. J., Lech, M., Kornblum, M. S., and Irvine, D. R. F. (**1998**). "Loudness perception and frequency discrimination in subjects with steeply sloping hearing loss: Possible correlates of neural plasticity," J. Acoust. Soc. Am. **104**, 2314-2325.
12. Thai-Van, H., Micheyl, C., Moore, B. C. J., and Collet, L. (**2003**). "Enhanced frequency discrimination near the hearing loss cut-off: A consequence of central auditory plasticity induced by cochlear damage?" Brain **126**, 2235-2245.
13. Weinberger, N. M. (**2004**). "Specific long-term memory traces in primary auditory cortex," Nature Rev. Neurosci. **5**, 279-290.
14. Ji, W. Q., Gao, E. Q., and Suga, N. B. (**2001**). "Effects of acetylcholine and atropine on plasticity of central auditory neurons caused by conditioning in bats," J. Neurophysiol. **86**, 211-225.
15. Fritz, J., Shamma, S., Elhilali, M., and Klein, D. (**2003**). "Rapid task-related plasticity of spectrotemporal receptive fields in primary auditory cortex," Nature Neurosci. **6**, 1216-1223.
16. Langner, G. (**1992**). "Periodicity coding in the auditory system," Hear. Res. **60**, 115-142.
17. Heil, P., and Irvine, D. R. F. (**1997**). "First-spike timing of auditory-nerve fibers and comparison with auditory cortex," J. Neurophysiol. **78**, 2438-2454.
18. Shepherd, R. K., Baxi, J. H., and Hardie, N. A. (**1999**). "Response of inferior colliculus neurons to electrical stimulation of the auditory nerve in neonatally deafened cats," J. Neurophysiol. **82**, 1363-1380.
19. Javel, E., and Shepherd, R. K. (**2000**). "Electrical stimulation of the auditory nerve: III. Response initiation sites and temporal fine structure," Hear. Res. **140**, 45-76.
20. Hartmann, R., Shepherd, R. K., Heid, S., and Klinke, R. (**1997**). "Response of the primary auditory cortex to electrical stimulation of the auditory nerve in the congenitally deaf white cat," Hear. Res. **112**, 115-133.
21. Vollmer, M., Snyder, R. L., Leake, P. A., Beitel, R. E., Moore, C. M., and Rebscher, S. J. (**1999**). "Temporal properties of chronic cochlear electrical stimulation determine temporal resolution of neurons in cat inferior colliculus," J Neurophysiol **82**, 2883-2902.
22. Snyder, R., Leake, P., Rebscher, S., and Beitel, R. (**1995**). "Temporal resolution of neurons in cat inferior colliculus to intracochlear electrical stimulation: Effects of neonatal deafening and chronic stimulation," J. Neurophysiol. **73**, 449-467.
23. Bao, S., Chang, E. F., Woods, J., and Merzenich, M. M. (**2004**). "Temporal plasticity in the primary auditory cortex induced by operant perceptual learning," Nature Neurosci. **7**, 974-981.
24. Dietrich, V., Nieschalk, M., Stoll, W., Rajan, R., and Pantev, C. (**2001**). "Cortical reorganization in patients with high frequency cochlear hearing loss," Hear. Res. **158**, 1-7.
25. Morris, J. S., Friston, K. J., and Dolan, R. J. (**1998**). "Experience-dependent modulation of tonotopic neural responses in human auditory cortex," Proc. Roy. Soc. Lond., Series B **265**, 649-657.
26. Pantev, C., Roberts, L. E., Schulz, M., Engelien, A., and Ross, B. (**2001**). "Timbre-specific enhancement of auditory cortical representations in musicians," NeuroReport **12**, 169-174.
27. McKay, C. M. (2005), "Spectral processing in cochlear implants," in *Auditory Spectral Processing,* edited by M. Malmierca, and D. R. F. Irvine (Elsevier Academic, San Diego), pp. 473-509.