Cortical mechanisms in hearing

Malcolm N Semple* and Brian H Scott†

Current understanding of neural processing in the auditory cortex has been shaped by a variety of experimental approaches in animals and humans. It remains a daunting challenge to reconcile data as diverse as synaptic properties recorded in a rodent brain slice and functional images of auditory cortex in a behaving human. Nevertheless, the gaps are narrowing through a renewed focus on humans and other primates, a continuing interest in evidence for functional pathways, a broader application of modern imaging techniques, a growing awareness of cortical sensitivity to dynamic features of sounds, and an improved understanding of auditory cortical circuitry.

Addresses
Center for Neural Science, New York University, 4 Washington Place, Room 809, New York, NY 10003, USA
*e-mail: mal.semple@nyu.edu
†e-mail: brian@cns.nyu.edu

Current Opinion in Neurobiology 2003, **13**:167–173

This review comes from a themed issue on
Cognitive neuroscience
Edited by Brain Wandell and Anthony Movshon

0959-4388/03/$ – see front matter
© 2003 Elsevier Science Ltd. All rights reserved.

DOI 10.1016/S0959-4388(03)00048-5

Abbreviations
AI primary auditory cortex

Introduction

Although for decades the cat has reigned as the dominant species for auditory cortical research, the focus has now clearly shifted to non-human primates. One attraction of this shift has been the adoption of an animal model whose auditory cortical mechanisms closely match those in humans, particularly as researchers move beyond the primary sensory areas. Recent evidence suggests that although the subcortical auditory systems of monkeys and non-primates are similar, there are important differences in cortical organization [1]. Some of these apparent differences may reflect historic choices in experimental emphasis rather than substantive differences in mechanisms, and in any case there are many advantages of a comparative approach to the study of the auditory cortex. Nevertheless, the current convergence of opinion on the cortical mechanisms for hearing in monkeys and humans is energizing the field and influencing experimental objectives.

Recent progress in studies of the cortical mechanisms for hearing covers an extensive range of questions and techniques, and is beyond the scope of this review. Here, we therefore choose to focus particularly on recent studies in humans and monkeys, supplemented by selected examples from other species. Other recent reviews [2–9] collectively provide a more balanced illustration of the considerable progress being made in studies over a wide range of species.

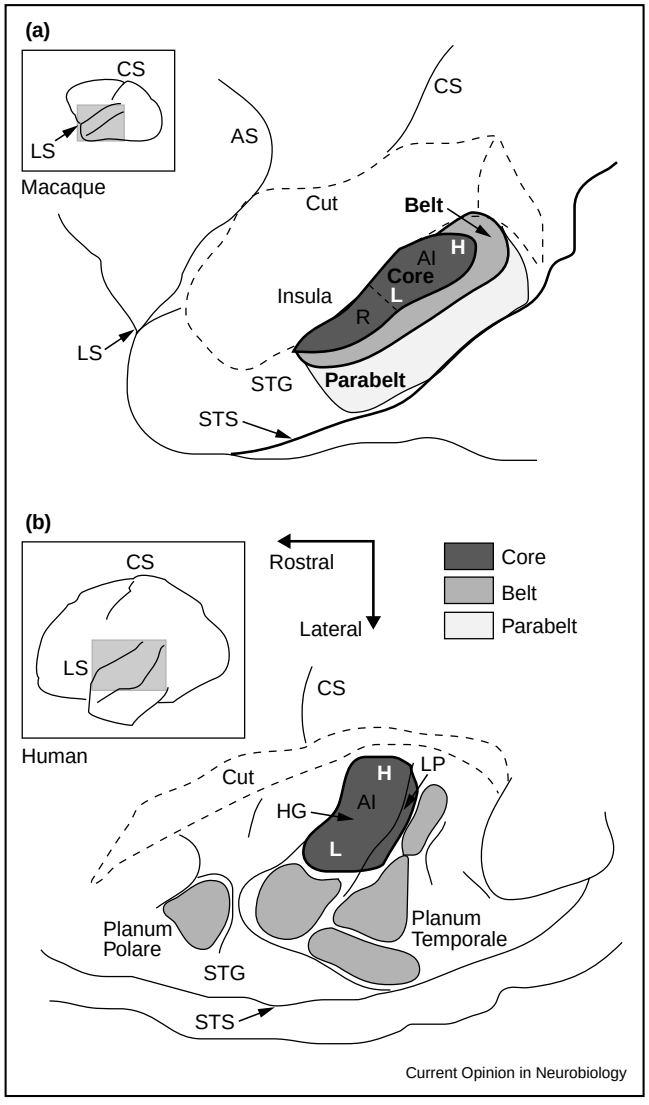
Organizational principles of the primate auditory cortex

On the basis of anatomical and physiological characteristics, the auditory cortex in macaque monkeys is now thought to include: a central core region of two or three subdivisions (including the primary auditory cortex [AI], a rostral field, and possibly an additional rostrotemporal field), a surrounding belt of seven or eight divisions, and a lateral parabelt region comprised of at least two fields [10–21]. In macaque monkeys, the core is characterized by sharp frequency tuning and tonotopic organization (a topographic gradient of tuned frequencies across the surface of the tissue). A general framework of a tonotopic core surrounded by a belt of tissue that is less clearly tonotopic, flanked further by auditory areas that show no evidence of tonotopy, is likely to be shared by a broad range of species. For example, the guinea pig auditory cortex has recently been described as consisting of a central core of two tonotopic fields, partially surrounded by six belt areas [22].

The core of the auditory cortex in the macaque monkey is clearly revealed by its dense immunoreactivity in layer IV for parvalbumin (a calcium-binding protein abundant in thalamic projection neurons). This dense layer of staining is surrounded by a more lightly stained belt, and then flanked in turn by a very sparsely stained parabelt [14,15,23]. Parvalbumin immunoreactivity is also successful as a selective marker of the core auditory cortex in humans [24,25]. When the results obtained when staining for Nissl substance, myelin, acetylcholinesterase, and cytochrome oxidase are also considered, a convincing case is established for a common auditory cortical arrangement in macaque monkeys, chimpanzees and humans [26••].

The apparent homology of the auditory cortex in non-human and human primates helps to clarify the extent to which auditory cortical processing in non-human primates might reasonably be extrapolated to human hearing, and it also helps to reconcile the nomenclature adopted independently for animal and human studies. Primary auditory cortex in humans is located within the transverse temporal (Heschel's) gyrus, sitting on the supratemporal plane of the superior temporal gyrus. A recent study [27]

Figure 1



In macaques and humans the auditory cortices lie on the superior temporal plane, mostly within the lateral sulcus. Insets (left) highlight these areas on a lateral view of the macaque (a) and human brain (b). In these schematic illustrations, dashed lines indicate where overlying parietal cortex has been 'cut away' to reveal the superior temporal plane. The superior temporal gyrus (STG) lies between the superior temporal sulcus (STS) and lateral sulcus (LS). The auditory core (darkest shading) in human lies on the transverse gyrus (Heschl's gyrus [HG]) and is thought to include at least two fields: primary auditory cortex (AI) in both species, as well as the lateroposterior (LP) area in humans and the rostral field (R) in macaques. The direction of the tonotopic gradient in AI is defined by high frequencies caudo-medially, and low frequencies rostro-laterally (H and L, in white). Lighter shading marks the belt, or secondary, fields in both species, and the lightest shading marks the tertiary parabelt fields in macaque. Abbreviations: CS, central sulcus; AS, arcuate sulcus. Adapted from [1,27].

reports that Heschel's gyrus contains two core fields, partially surrounded by at least six belt fields that lie mostly on the superior temporal gyrus (Figure 1). The core auditory cortex in macaque monkey also lies on the supratemporal plane, and it has sometimes been observed that AI coincides with a small bump that is reminiscent of Heschel's gyrus (e.g. [14]). In the auditory cortex of humans [28•] and other primates [18], increased stimulus complexity is associated with increased activation throughout the auditory cortical core and surrounding auditory regions; however, the efficacy of tonal stimuli is largely restricted to the core. There is also recent evidence for a transformation of spectral and temporal response properties between the core and belt regions of guinea pig auditory cortex [29].

The macaque auditory cortical core, belt and parabelt collectively occupy a vast extent of the superior temporal gyrus. Surface recordings and other physiological measures suggest that the core and 'association' auditory cortex in humans lies within the posterior two-thirds of this gyrus (e.g. [30]). Nevertheless, there is evidence under some conditions for the additional involvement of the anterior extreme of the superior temporal gyrus in auditory processing. For example, in macaques, new evidence suggests that this largely unexplored area of auditory cortex may be organized into alternating columns of ipsilateral and contralateral inputs [31••].

Auditory cortical processing streams

Cortical mechanisms for hearing include anatomically and functionally distributed pathways that have been interpreted as evidence of different streams of information processing (for recent reviews see [1,20]). The thalamocortical auditory projections in monkeys provide a basis for hierarchical transformation, as the auditory signal is processed sequentially through core, belt and parabelt regions. Subsequently, the signal is distributed to multimodal areas of the temporal, parietal and frontal lobes. It is noteworthy that the belt is never bypassed as information is relayed from the core to higher brain levels. Consistent with our expectations of a hierarchy, responses in belt areas are to some extent transformations of the properties of the core. Within this framework there is also a clear basis for parallel processing. Parallel processing begins with the parallel projection from the primary auditory thalamus to multiple core cortical fields. It culminates with parabelt projections within temporal and parietal areas near the superior temporal plane, and also to frontal lobe targets that are implicated in visual gaze, working memory and multimodal stimulus recognition. The physiological evidence shows that different fields within the same level of the processing hierarchy (e.g. AI and the rostral field, or different lateral belt fields) process information at least partly in parallel, and with some specialization.

Current opinion supports the notion of two major cortical streams, popularly known as 'what' and 'where' pathways

[20]. The 'where' (dorsal) pathway is thought to link AI via the caudomedial belt to frontal eye field and parietal targets that are implicated in spatial processing. The 'what' (ventral) pathway is thought to represent a pattern (or object) information stream that originates in the anterior core and belt areas and influences targets within the temporal lobe. This what/where distinction has gained support not only from animal studies [17,21,32,33•,34] but also more recently in human studies [28•,35].

Despite the attractive simplicity of the dual-streams hypothesis, there is abundant evidence for more complexity. A fundamental concern is that localization and pattern processing are not necessarily independent auditory tasks: spatial information is one of the key factors contributing to the 'determination' (or recognition) of sound sources [36], and sound localization is greatly influenced by the spectral and temporal structure of sounds. Moreover, a growing body of evidence suggests that spatial information is carried in temporal discharge patterns and encoded in the ensemble activity distributed throughout auditory cortex (e.g. [37•,38]).

Recent evidence from human imaging studies [39–43] is generally consistent with the basic dual-pathway hypothesis, but reveals some caveats. On the one hand, evidence shows that the processing of various auditory stimuli that are thought to be representative of 'what' tasks (e.g. pitch, working memory, and phonemes) predominantly activate auditory cortex and inferior prefrontal lobe, whereas spatial processing is associated with the activation of posterior temporal areas, parietal cortex and superior frontal sulcus [35]. On the other hand, the imaging studies offer some fresh insights. For example, Zatorre and co-workers [44••] have shown that the 'where' pathway might be involved in tasks such as sensorimotor integration and the disambiguation of overlapping sound sources, and that spatial sensitivity is linked to spectro-temporal features [45••]. Alain and co-workers [35] reported a significant correlation between the temporal and parietal cortex during pitch and localization tasks, revealing the possibility of considerable cross-talk between the streams.

Such complexities are consistent with the detailed anatomy of the auditory cortex in macaque monkeys [1]. The core fields are heavily interconnected and must influence each other considerably, and the core regions of each hemisphere are heavily interconnected via the corpus callosum. The connections of the belt fields provide the basis for considerable cross-talk within the belt, and feedback to the core, in addition to projections to the parabelt. Although the parabelt gets no direct input from core auditory cortex, it does receive input from several non-primary thalamic nuclei. Thus, auditory cortex has a structural framework suited to the partial segregation of processing tasks, but with the capacity at each hierarchical level for extensive sharing of processed data.

Auditory cortical response properties

Decades of physiological investigation have provided many details of functional topography within the auditory cortex. The core auditory cortices (including the primary auditory cortex [AI]) of many species are characterized by their tonotopic organization of individual neurons that are narrowly tuned for frequency. Although lesion data have often been interpreted as indicating that frequency discrimination does not depend on the integrity of the frequency array, a recent study in humans suggests that fine-grained frequency perception does indeed depend on neuronal frequency selectivity in the cortex [46•].

Several response properties other than frequency tuning show some degree of organization along the isofrequency axis (e.g. [47]), but many aspects of these topographies — including their functional interrelationships and their generality across species — remain to be clarified. One complication is the indirect relation between the acoustic stimulus and some of the mapped response properties (e.g. the relation between discharge-rate and sound pressure level, or the balance of binaural excitation and inhibition).

Evidence for the organization of response properties within the tonotopic array is largely derived from recordings in the middle layers of the auditory cortex, where responses in anaesthetized animals are most robust. Even when researchers are not constrained by the time pressure of characterizing responses across a large tonotopic field, discharge properties have rarely been studied in any detail as a function of laminar depth within a cortical column [48]. This recording bias towards the middle cortical layers has the consequence of obscuring the diversity of mechanisms that are known to exist across laminae, and gives more weight to properties expressed in the thalamocortical input. For example, GABAergic inhibitory circuits in the gerbil AI are reportedly abundant in superficial and deep layers, but rare in the middle layers [49]. In human [24] and macaque [14] AI, different calcium-binding proteins are expressed by different neuronal types and have different distributions throughout the neuropil: parvalbumin and calbindin are associated with almost complementary laminar distributions. Evidence that functional maps in the cortex may arise from subcortical organization comes from a recent study using tract tracing and physiological mapping in the rabbit to reveal a clear relation between thalamocortical patches and the topography of the auditory cortical response [50]. Cortical recordings in alert animals offer the prospect of broad sampling across layers if recording depths can be identified with sufficient precision.

The response properties of the auditory cortex reflect not only thalamocortical and intrinsic cortical processing but also the accumulated transformations occurring at lower levels of the auditory system. Although this greatly

complicates the task of understanding cortical mechanisms in hearing, two recent studies show how the brain-slice recording technique is currently being applied to investigate auditory cortical and subcortical influences [51•,52••]. One study focused on the evidence for intrinsic cortical mechanisms underlying different response phenotypes: the postsynaptic events of two populations were interpreted as reflecting distinct mechanisms for discerning transient from stationary acoustic features [51•]. A second study used recordings from brain slices to investigate the role of thalamocortical circuitry in transforming responses at the auditory cortex [52••]. Stimulation of the intact ventral division of the medial geniculate (primary auditory thalamus) was found to initiate monosynaptic, disynaptic and polysynaptic responses in auditory cortical middle layers, whereas stimulation of nonprimary thalamus gave rise to rapid activation of cortical layer I, followed by intracortical activity [52••].

This complex picture of excitatory and inhibitory thalamocortical mechanisms is not apparent under conventional direct stimulation of cortical columns, but is consistent with accumulating evidence for the considerable transformation of responses to certain features of acoustic stimuli. For example, simultaneous recordings in the cat primary auditory thalamus and AI [53•,54] reveal extensive thalamocortical modification of tuning to spectral and temporal modulation parameters, with minimal transformation of other properties.

The approach taken to demonstrate this transformation — documenting the linear dynamics of responses to complex sounds in the form of 'spectro-temporal' receptive fields — has been employed in numerous recent studies. The term 'spectro-temporal' has been widely adopted to describe the concurrent selectivity of a neuron for the frequency content and temporal envelope of a sound. Any spectro-temporal envelope can be expressed as a sum of sinusoidal envelopes, often called 'ripples'. Characterization of a neuron's responses to a family of ripples therefore permits a prediction of its sensitivity to any complex sound. Spectro-temporal receptive fields have frequently been generated from responses to ripples. Nevertheless, other approaches may be preferable for characterizing brain areas in which discharge rates are very low [29] or for estimating spectro-temporal tuning more directly from responses to auditory vocalizations or other arbitrary stimuli [55]. Furthermore, non-linearities in cortical responses are often reported [51•,56•,57•,58••,59,60] and must be considered. For example, the spectro-temporal transfer function of a typical neuron in the ferret AI can not be completely separated into purely temporal and purely spectral components [59]. This is because of differences in sensitivity to upward and downward spectral (rather than temporal) cross-sections. It is worth noting that directional sensitivity in AI has previously been found in response to various forms of frequency-modulated sweeps [60].

There is a continuing interest in the use of repetitive transients and temporal modulations of tones and noise as tools for exploring auditory cortical function. For example, a recent study of the auditory cortical physiology of the marmoset employed sinusoidal modulation of amplitude and frequency to investigate temporal coding [57•]. The authors concluded that dynamic acoustic features are represented for high and low modulation frequencies by rate and synchrony codes, respectively. Eggermont [56•] used a battery of repetitive transient stimuli to find that cat cortical neurons typically prefer signals such as clicks or gamma tones. Despite differences in responsiveness to the various test stimuli, temporal transfer functions were often very similar, suggesting that cortical responses to a diverse range of time-varying acoustic stimuli are shaped by a common temporal filtering process — perhaps synaptic depression and facilitation. This process is probably also one of the factors underlying the context dependence of cortical responses to binaural stimuli that vary with time. For example, firing rates follow slow modulations over long time courses, providing a basis for a contrast-gain mechanism in which adaptation enhances the representation of dynamic events [58••].

Significant recent progress is also evident in studies of human cortical processing of complex sounds. Consistent with the results from animal physiological recordings, human neuroimaging data reveal that activation within the auditory cortex is enhanced when stimuli are spectro-temporally complex [61]. It is also increasingly apparent that auditory cortical subregions can be readily differentiated on the basis of their spectro-temporal sensitivity. For example, Zatorre and Belin [45••] reported that the core auditory cortex was influenced predominantly by temporal variation, whereas the spectral manipulations were more effective in superior anterior temporal (belt) areas. Combining neuroimaging and acoustic stimulation to study the human auditory cortex, Seifritz and co-workers [62] reported concurrent, and possibly independent, onset and sustained patterns of activity, indicating that the auditory system can use multiple time scales to encode information about a single stimulus event.

Modern views of the auditory cortical discharge rate and temporal pattern are now more consistent with those held in other sensory systems. Although few would disagree that auditory cortex has the capacity for encoding information in terms of firing rate and spike timing, it has nevertheless been widely accepted that the responses of AI neurons are relatively weak and transient compared with those in other primary sensory cortices. This view has undoubtedly been influenced by the use of relatively deep (typically barbiturate) anaesthesia in most studies of auditory cortical physiology over several decades. Current research in alert animals (e.g. [32,57•,58••,63,64]) reveals a broad range of discharge rates and a variety of temporal discharge patterns. It has been suggested that different

tonal discharge patterns may reflect different roles in the processing of static and dynamic acoustic signals [65]. Considerable responsiveness has also been documented in the cat AI using an anaesthetic regime that is minimally depressing to cortical activity [53•,54]. Even in anesthetized animals, it has been shown that spike timing in the auditory cortex carries significant information about the location of the sound source [37•,38,66]. Maintained firing, which is most evident in the absence of anaesthesia, illustrates how information may be carried both in the discharge rate and in the temporal component of the discharge pattern [57•,58••].

Conclusions

Recent evidence reveals multiple interleaved stages of auditory cortical processing that give rise to functionally and structurally differentiated higher systems. The response properties of neurons in the auditory system show multiple levels of transformation, with higher levels emphasizing the representation of dynamic features of auditory signals. Auditory cortical research is gaining considerable momentum from a growing body of evidence that humans and non-human primates share common cortical mechanisms for hearing. This progress is likely to accelerate because our current understanding of cortical mechanisms for hearing now offers a more substantive basis for comparison with cortical mechanisms for vision. A recent study [31••] illustrates this promise, suggesting that the auditory 'where' pathways to parietal and frontal cortex are perhaps better understood as components of a multimodal (visual and auditory) system for processing location and motion, rather than as an intrinsically auditory system (see also [67•]). This explanation retains the essence of the 'what/where' pathway distinction, but also allows for the likely sharing of spatial information as a component of object recognition in the auditory cortex. It seems probable that the currently popular hypothesis of dual independent streams will be further refined as researchers attempt to reconcile notions of streams that are based on functionally distinct central pathways and streams of information derived from concurrent sound sources. The challenge is to understand how cortical mechanisms are engaged in the fundamental task of auditory scene analysis, in which sound sequences derived from different sources must be segregated perceptually. Evidence that the monkey AI contains ensemble activity that is largely consistent with the human psychophysics of auditory stream segregation [68] seems certain to stimulate future research.

Acknowledgements

We thank Brian J Malone for insightful discussions. Brian H Scott was supported by National Institute on Deafness and other Communication Disorders 05287-01.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Kaas JH, Hackett TA: **Subdivisions of auditory cortex and processing streams in primates**. *Proc Natl Acad Sci USA* 2000, **97**:11793-11799.
2. Suga N, Xiao Z, Ma X, Ji W: **Plasticity and corticofugal modulation for hearing in adult animals**. *Neuron* 2002, **36**:9-18.
3. Eggermont JJ, Ponton CW: **The neurophysiology of auditory perception: from single units to evoked potentials**. *Audiol Neurootol* 2002, **7**:71-99.
4. Kral A, Hartmann R, Tillein J, Heid S, Klinke R: **Delayed maturation and sensitive periods in the auditory cortex**. *Audiol Neurootol* 2001, **6**:346-362.
5. Read HL, Winer JA, Schreiner CE: **Functional architecture of auditory cortex**. *Curr Opin Neurobiol* 2002, **12**:433-440.
6. Palmer AR, Summerfield AQ: **Microelectrode and neuroimaging studies of central auditory function**. *Br Med Bull* 2002, **63**:95-105.
7. Irvine DR, Rajan R, Brown M: **Injury- and use-related plasticity in adult auditory cortex**. *Audiol Neurootol* 2001, **6**:192-195.
8. Gaese BH: **Population coding in the auditory cortex**. *Prog Brain Res* 2001, **130**:221-230.
9. Hall DA, Hart HC, Johnsrude IS: **Relationships between human auditory cortical structure and function**. *Audiol Neurootol* 2003, **8**:1-18.
10. Hackett TA, Stepniewska I, Kaas JH: **Thalamocortical connections of the parabelt auditory cortex in macaque monkeys**. *J Comp Neurol* 1998, **400**:271-286.
11. Hackett TA, Stepniewska I, Kaas JH: **Subdivisions of auditory cortex and ipsilateral cortical connections of the parabelt auditory cortex in macaque monkeys**. *J Comp Neurol* 1998, **394**:475-495.
12. Hackett TA, Stepniewska I, Kaas JH: **Callosal connections of the parabelt auditory cortex in macaque monkeys**. *Eur J Neurosci* 1999, **11**:856-866.
13. Hackett TA, Stepniewska I, Kaas JH: **Prefrontal connections of the parabelt auditory cortex in macaque monkeys**. *Brain Res* 1999, **817**:45-58.
14. Jones EG, Dell'Anna ME, Molinari M, Rausell E, Hashikawa T: **Subdivisions of macaque monkey auditory cortex revealed by calcium-binding protein immunoreactivity**. *J Comp Neurol* 1995, **362**:153-170.
15. Kosaki H, Hashikawa T, He J, Jones EG: **Tonotopic organization of auditory cortical fields delineated by parvalbumin immunoreactivity in macaque monkeys**. *J Comp Neurol* 1997, **386**:304-316.
16. Pandya DN: **Anatomy of the auditory cortex**. *Rev Neurol (Paris)* 1995, **151**:486-494.
17. Rauschecker JP, Tian B, Pons T, Mishkin M: **Serial and parallel processing in rhesus monkey auditory cortex**. *J Comp Neurol* 1997, **382**:89-103.
18. Rauschecker JP: **Cortical processing of complex sounds**. *Curr Opin Neurobiol* 1998, **8**:516-521.
19. Rauschecker JP: **Parallel processing in the auditory cortex of primates**. *Audiol Neurootol* 1998, **3**:86-103.
20. Rauschecker JP, Tian B: **Mechanisms and streams for processing of "what" and "where" in auditory cortex**. *Proc Natl Acad Sci USA* 2000, **97**:11800-11806.
21. Tian B, Reser D, Durham A, Kustov A, Rauschecker JP: **Functional specialization in rhesus monkey auditory cortex**. *Science* 2001, **292**:290-293.
22. Wallace MN, Rutkowski RG, Palmer AR: **Interconnections of auditory areas in the guinea pig neocortex**. *Exp Brain Res* 2002, **143**:106-119.

23. Kaas JH, Hackett TA: **Subdivisions of auditory cortex and levels of processing in primates**. *Audiol Neurootol* 1998, **3**:73-85.

24. Chiry O, Tardif E, Magistretti PJ, Clarke S: **Patterns of calcium-binding proteins support parallel and hierarchical organization of human auditory areas**. *Eur J Neurosci* 2003, **17**:397-410.

25. Nakahara H, Yamada S, Mizutani T, Murayama S: **Identification of the primary auditory field in archival human brain tissue via immunocytochemistry of parvalbumin**. *Neurosci Lett* 2000, **286**:29-32.

26. •• Hackett TA, Preuss TM, Kaas JH: **Architectonic identification of the core region in auditory cortex of macaques, chimpanzees, and humans**. *J Comp Neurol* 2001, **441**:197-222.
Functional imaging studies of human auditory cortex often reference the core/belt/parabelt model that was developed in lower primates. This is the first anatomical study to compare directly the cytoarchitecture of auditory cortex in the monkey, ape, and human.

27. Wallace MN, Johnston PW, Palmer AR: **Histochemical identification of cortical areas in the auditory region of the human brain**. *Exp Brain Res* 2002, **143**:499-508.

28. • Wessinger CM, VanMeter J, Tian B, Van Lare J, Pekar J, Rauschecker JP: **Hierarchical organization of the human auditory cortex revealed by functional magnetic resonance imaging**. *J Cogn Neurosci* 2001, **13**:1-7.
In this study, functional magnetic resonance imaging (fMRI) of human auditory cortex reveals an organizational hierarchy previously observed in animal studies. That is, pure tones primarily activate the core, whereas more complex sounds are needed to activate belt areas.

29. Rutkowski RG, Shackleton TM, Schnupp JW, Wallace MN, Palmer AR: **Spectrotemporal receptive field properties of single units in the primary, dorsocaudal and ventrorostral auditory cortex of the guinea pig**. *Audiol Neurootol* 2002, **7**:214-227.

30. Howard MA, Volkov IO, Mirsky R, Garell PC, Noh MD, Granner M, Damasio H, Steinschneider M, Reale RA, Hind JE *et al.*: **Auditory cortex on the human posterior superior temporal gyrus**. *J Comp Neurol* 2000, **416**:79-92.

31. •• Poremba A, Saunders RC, Crane AM, Cook M, Sokoloff L, Mishkin M: **Functional mapping of the primate auditory system**. *Science* 2003, **299**:568-572.
In this study, the extent of the auditory cortical system was demonstrated by assessing glucose consumption in the brain of macaques that were passively listening to sound. Unilateral lesion of the ascending auditory pathway allowed each animal to serve as its own control. Comparison of the 'deaf' and 'hearing' hemispheres revealed not only strong signals in the core and belt region but also elevated levels across the entire superior temporal gyrus and large areas of parietal and prefrontal cortices in response to sound. Previous studies identified many of these areas as visual, confirming modal overlap in what has long been known as the 'association' cortex.

32. Recanzone GH: **Response profiles of auditory cortical neurons to tones and noise in behaving macaque monkeys**. *Hear Res* 2000, **150**:104-118.

33. • Romanski LM, Goldman-Rakic PS: **An auditory domain in primate prefrontal cortex**. *Nat Neurosci* 2002, **5**:15-16.
In this study, ventrolateral prefrontal cortex — previously shown to receive connections from auditory cortex — is shown to respond to complex sounds. An adjacent prefrontal region (dorsolateral PFC) has previously been investigated as a domain for spatial acoustic processing, and receives a distinct set of auditory inputs.

34. Romanski LM, Bates JF, Goldman-Rakic PS: **Auditory belt and parabelt projections to the prefrontal cortex in the rhesus monkey**. *J Comp Neurol* 1999, **403**:141-157.

35. Alain C, Arnott SR, Hevenor S, Graham S, Grady CL: **'What' and 'where' in the human auditory system**. *Proc Natl Acad Sci USA* 2001, **98**:12301-12306.

36. Yost WA: **Auditory image perception and analysis: the basis for hearing**. *Hear Res* 1991, **56**:8-18.

37. • Furukawa S, Middlebrooks JC: **Cortical representation of auditory space: information-bearing features of spike patterns**. *J Neurophysiol* 2002, **87**:1749-1762.
A neural network was trained to identify sound-source location from spike patterns elicited in anaesthetized cats. Features of the spike trains were systematically degraded to isolate the dependency of transmitted information on spike rate, timing, latency and average responses across trials.

38. Mickey BJ, Middlebrooks JC: **Responses of auditory cortical neurons to pairs of sounds: correlates of fusion and localization**. *J Neurophysiol* 2001, **86**:1333-1350.

39. Maeder PP, Meuli RA, Adriani M, Bellmann A, Fornari E, Thiran JP, Pittet A, Clarke S: **Distinct pathways involved in sound recognition and localization: a human fMRI study**. *Neuroimage* 2001, **14**:802-816.

40. Clarke S, Bellmann Thiran A, Maeder P, Adriani M, Vernet O, Regli L, Cuisenaire O, Thiran JP: **What and where in human audition: selective deficits following focal hemispheric lesions**. *Exp Brain Res* 2002, **147**:8-15.

41. Bushara KO, Weeks RA, Ishii K, Catalan MJ, Tian B, Rauschecker JP, Hallett M: **Modality-specific frontal and parietal areas for auditory and visual spatial localization in humans**. *Nat Neurosci* 1999, **2**:759-766.

42. Griffiths TD, Green GG, Rees A, Rees G: **Human brain areas involved in the analysis of auditory movement**. *Hum Brain Mapp* 2000, **9**:72-80.

43. Wise RJ, Scott SK, Blank SC, Mummery CJ, Murphy K, Warburton EA: **Separate neural subsystems within 'Wernicke's area'**. *Brain* 2001, **124**:83-95.

44. •• Zatorre RJ, Bouffard M, Ahad P, Belin P: **Where is 'where' in the human auditory cortex?** *Nat Neurosci* 2002, **5**:905-909.
In this positron emission tomography (PET) study, a speaker array creates a 'free-field' presentation within the scanner. The authors provide evidence that may clarify the functions of certain brain areas that are implicated in 'where' processing. They report that posterior auditory cortex is involved in the disambiguation of overlapping auditory sources, whereas the right inferior parietal cortex is involved in sensorimotor integration and spatial transformation.

45. •• Zatorre RJ, Belin P: **Spectral and temporal processing in human auditory cortex**. *Cereb Cortex* 2001, **11**:946-953.
In this study, PET is used to compare cortical activation by tonal sequences, in which tone spacing or sequence alternation speed are manipulated. Core auditory cortex is influenced predominantly by temporal variation, whereas the spectral manipulations are more effective in superior anterior temporal (belt) areas. Moreover, temporal processing is more pronounced in the left core and spectral processing is weighted towards the right belt. The findings complement a growing literature devoted to hemispheric specialization in auditory processing.

46. • Tramo MJ, Shah GD, Braida LD: **Functional role of auditory cortex in frequency processing and pitch perception**. *J Neurophysiol* 2002, **87**:122-139.
A clinical psychophysical and anatomical study that addresses the contentious issue of whether auditory cortex is necessary for frequency discriminations. Among five patients with focal damage to auditory cortex, four unilateral and one bilateral, only bilateral damage predicted significant impairment in frequency discrimination relative to normal controls.

47. Schreiner CE: **Spatial distribution of responses to simple and complex sounds in the primary auditory cortex**. *Audiol Neurootol* 1998, **3**:104-122.

48. Linden J, Schreiner C: **Columnar transformations in auditory cortex? A comparison to visual and somatosensory cortices**. *Cereb Cortex* 2003, **13**:83-89.

49. Foeller E, Vater M, Kossl M: **Laminar analysis of inhibition in the gerbil primary auditory cortex**. *JARO* 2001, **2**:279-296.

50. Velenovsky DS, Cetas JS, Price RO, Sinex DG, McMullen NT: **Functional subregions in primary auditory cortex defined by thalamocortical terminal arbors: an electrophysiological and anterograde labeling study**. *J Neurosci* 2003, **23**:308-316.

51. • Atzori M, Lei S, Evans DI, Kanold PO, Phillips-Tansey E, McIntyre O, McBain CJ: **Differential synaptic processing separates stationary from transient inputs to the auditory cortex**. *Nat Neurosci* 2001, **4**:1230-1237.
The authors show that postsynaptic responses in layer II/III of AI slices fall into two discrete classes that differ in amplitude, failure rate, kinetics and short-term plasticity.

52. •• Cruikshank SJ, Rose HJ, Metherate R: **Auditory thalamocortical synaptic transmission *in vitro***. *J Neurophysiol* 2002, **87**:361-384.

In this study, a slice preparation is described that preserves the connections between the ventral division of the medial geniculate body and AI. The authors contend that maintaining the integrity of this input is essential to study the thalamocortical transform, as suggested by differences between its physiology and conventional slice studies using columnar stimulation.

53. Miller LM, Escabi MA, Read HL, Schreiner CE: **Functional**
• **convergence of response properties in the auditory thalamocortical system**. *Neuron* 2001, **32**:151-160.

The authors use a reverse-correlation technique to explore the thalamocortical transform. They recorded the receptive-field structure in functionally connected pairs of thalamic and cortical neurons in lightly anesthetized cats. On the basis of these data, they describe three mechanisms for creating cortical receptive fields from thalamic input. The spectrotemporal modulation selectivity of AI neurons may differ markedly from that of their inputs.

54. Miller LM, Escabi MA, Read HL, Schreiner CE: **Spectrotemporal receptive fields in the lemniscal auditory thalamus and cortex**. *J Neurophysiol* 2002, **87**:516-527.

55. Theunissen FE, David SV, Singh NC, Hsu A, Vinje WE, Gallant JL: **Estimating spatio-temporal receptive fields of auditory and visual neurons from their responses to natural stimuli**. *Network Comp Neural* 2001, **12**:289-316.

56. Eggermont JJ: **Temporal modulation transfer functions in cat**
• **primary auditory cortex: separating stimulus effects from neural mechanisms**. *J Neurophysiol* 2002, **87**:305-321.

The authors present a battery of modulated sounds to anesthetized cats, and find that these stimuli generate almost identical temporal transfer functions, consistent with a common low-pass temporal filter function with a 10Hz cutoff.

57. Liang L, Lu T, Wang X: **Neural representations of sinusoidal**
• **amplitude and frequency modulations in the primary auditory cortex of awake primates**. *J Neurophysiol* 2002, **87**:2237-2261.

In this study, cortical responses to amplitude and frequency modulation are surveyed in unanesthetized marmosets. The authors report that the best modulation frequencies are generally lower when measured in terms of synchrony than in terms of rate, but individual neurons show similar responsiveness to modulation of amplitude or frequency. This work has implications for the perception of fluctuating sounds and pitch.

58. Malone BJ, Scott BH, Semple MN: **Context-dependent adaptive**
•• **coding of interaural phase disparity in the auditory cortex of awake macaques**. *J Neurosci* 2002, **22**:4625-4638.

The authors demonstrate that the cortical representation of a binaural cue to sound source location is profoundly context-dependent. These findings suggest that the cortical processing of dynamic acoustic signals is dominated by an adaptive coding strategy that prioritizes the representation of stimulus changes over actual stimulus values. The authors show how cortical selectivity for motion direction in real space could emerge as a consequence of this general coding principle.

59. Depireux DA, Simon JZ, Klein DJ, Shamma SA: **Spectro-temporal response field characterization with dynamic ripples in ferret primary auditory cortex**. *J Neurophysiol* 2001, **85**:1220-1234.

60. Orduna I, Mercado E III, Gluck MA, Merzenich MM: **Spectrotemporal sensitivities in rat auditory cortical neurons**. *Hear Res* 2001, **160**:47-57.

61. Hall DA, Johnsrude IS, Haggard MP, Palmer AR, Akeroyd MA, Summerfield AQ: **Spectral and temporal processing in human auditory cortex**. *Cereb Cortex* 2002, **12**:140-149.

62. Seifritz E, Esposito F, Hennel F, Mustovic H, Neuhoff JG, Bilecen D, Tedeschi G, Scheffler K, Di Salle F: **Spatiotemporal pattern of neural processing in the human auditory cortex**. *Science* 2002, **297**:1706-1708.

63. Reser DH, Fishman YI, Arezzo JC, Steinschneider M: **Binaural interactions in primary auditory cortex of the awake macaque**. *Cereb Cortex* 2000, **10**:574-584.

64. Lu T, Liang L, Wang X: **Neural representations of temporally asymmetric stimuli in the auditory cortex of awake primates**. *J Neurophysiol* 2001, **85**:2364-2380.

65. Chimoto S, Kitama T, Qin L, Sakayori S, Sato Y: **Tonal response patterns of primary auditory cortex neurons in alert cats**. *Brain Res* 2002, **934**:34-42.

66. Furukawa S, Xu L, Middlebrooks JC: **Coding of sound-source location by ensembles of cortical neurons**. *J Neurosci* 2000, **20**:1216-1228.

67. Kohler E, Keysers C, Umilta MA, Fogassi L, Gallese V, Rizzolatti G:
• **Hearing sounds, understanding actions: action representation in mirror neurons**. *Science* 2002, **297**:846-848.

Reports of selective auditory projections to the prefrontal cortex are supported by this description of higher-level auditory sensitivity beyond the auditory cortex proper. 'Mirror neurons' in the premotor cortex fire when a monkey performs a certain action, views another monkey performing that action, or hears the associated sound. The relevant area of the premotor cortex is homologous to Broca's area in humans, suggesting a link between speech and the encoding of abstract features of actions.

68. Fishman YI, Reser DH, Arezzo JC, Steinschneider M: **Neural correlates of auditory stream segregation in primary auditory cortex of the awake monkey**. *Hear Res* 2001, **151**:167-187.