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Editors

The Auditory Cortex

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Chapter 13

Spectral Processing in Auditory Cortex

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Abbreviations

AAF	anterior auditory field
ADF	anterior dorsal field
AI	primary auditory cortex
AII	second auditory cortical field
AL	antero-lateral field
BF	best frequency
BW	bandwidth
CF	characteristic frequency
CL	caudolateral field
CM	caudal medial field
DC	dorsal-caudal field
DCB	dorsocaudal belt
DRB	dorsorostral belt
DZ	dorsal zone
EP	ectosylvian fields
FRA	frequency response area
FSU	fast-spiking unit
FTC	frequency tuning curve
GABA	gamma-aminobutyric acid
MGB	medial geniculate body
MI	mutual information
MID	maximally informative dimension
ML	medial-lateral field
MM	middle medial field
MTF	modulation transfer function
P	postnatal day
PAF	posterior auditory field
PDF	posterior dorsal field
PPF	posterior pseudosylvian field
PSF	posterior suprasylvian field
Q	quality factor
R	rostral field
RF	receptive field
RM	rostro-medial field
RSS	random spectral stimulus
RSU	regular-spiking unit
RT	rostro-temporal field
SRAF	suprarhinal auditory field
STA	spike-triggered average
STRF	spectro-temporal receptive field
TORC	temporally orthogonal ripple combinations
VCB	ventrocaudal belt
VPAF	ventroposterior auditory field
VRB	ventrorostral belt

1 Introduction

Historically, the main purpose of the auditory system has been interpreted as a frequency analyzer (Ohm 1843; von Helmholtz 1863) that provides a faithful spectral representation of the received acoustic waveform. Analysis and characterization of spectral processing, beginning with the principle of parallel signal processing in narrow, partially overlapping frequency channels in the cochlea, has provided a framework for all subsequent stages of computation, information extraction and encoding in the auditory system, including the auditory cortex. This still evolving bottom-up characterization around the concept of a set of parallel frequency filters has been significantly enhanced by including temporal or dynamic and nonlinear aspects of spectral processing. Quantitative and rigorous systems and information analysis approaches have resulted in more complete characterizations of spectral encoding and decoding abilities throughout the auditory system.

However, the view of the ear as a mere frequency analyzer, even a nonlinear, dynamic one, is an incomplete characterization of the auditory system, especially when it comes to more central stations, including the auditory cortex. Firstly, the ability to process complex, natural acoustic environments, including transmission of communication sounds in the presence of background noise or competing signals in a

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complex or reverberant auditory environment, is likely to require special mechanisms that may not be apparent using simple spectral analysis methods.

Secondly, and perhaps more importantly, our experience of the world around us is not simply an accurate reflection of its physical features. Determining the meaning of stimuli, and generating behaviors that lead us to successfully and efficiently achieve our immediate and long-term goals, is an inherent aspect of sensory processing. Consequently, sensory stimuli often need to be grouped according to their category membership in behaviorally equivalent classes of sounds. For interpretational purposes, sound classes require a grouping process into categories along various dimensions that can be perceptual, in that stimuli share perceivable attributes, or interpretational, in that stimuli share a behavioral response. A purely spectrally based solution to this problem seems unlikely.

Conceptually, cortical stimulus representations must employ mechanisms to compensate for natural variations in stimuli, such as intensity, timing, vocal tract length, noise interference and speed of presentation, that otherwise may hamper if not preclude efficient and robust sound classification and categorization tasks essential for speech perception (King and Nelken 2009; Winkler et al. 2009). Potential auditory cortical stimulus encoding principles that differ from subcortical stations have been proposed: (i) shifts from temporal coding to rate-coding (Wang et al. 2008); (ii) non-isomorphic transformations of acoustic features (Barbour and Wang 2003b; Wang 2007); (iii) emphasis of natural sound statistics (David et al. 2009; Mesgarani et al. 2009; Nagel and Doupe 2008; Sen et al. 2001; Theunissen and Shaevitz 2006; Woolley et al. 2006); (iv) creation of feature combinations toward an "object"-based representation (Bar-Yosef and Nelken 2007; King and Nelken 2009); and (v) creation of representational invariances, e.g., for intensity (Billimoria et al. 2008; Sadagopan and Wang 2009), background noise robustness (Mesgarani et al. 2009; Nagarajan et al. 2002), or sound source properties (Grana et al. 2009; Margoliash and Fortune 1992; Theunissen and Shaevitz 2006). These cortical processes may include stimulus transformations into internal representations that may no longer be faithful to their physical structure (Wang 2007) and have to reflect influences from behavioral states, such as attention and vigilance, in the context of optimal behavioral task performance (Edeline 2003; Fritz et al. 2007a, b).

While spectral analysis aspects alone may seem inadequate in addressing these issues, new estimation methods of dynamic spectral processing (Atencio et al. 2008, 2009; Bruno and Simons 2002) indicate that emergent processing aspects do exist in auditory cortex and that they may contribute to some of these proposed encoding principles of auditory stimuli.

The types and spatial distribution of physiological response properties have provided crucial information for deciphering principles and mechanisms underlying processing in cat and primate visual cortex (Callaway 1998; Henry 1991; Hirsch 2003; Lund 1990). Similarly, in auditory cortex, non-uniform spatial distributions of functional properties have been found for many basic response properties reflecting regional specializations.

Expansion of the central auditory representation of a given frequency from a point in the cochlea to many neurons tuned to the same frequency in cortex introduces the ability to treat many different aspects of required multiple analyses in parallel. This is further reflected in a reduction of redundancy between different stations: cortical neurons are less redundant than subcortical neurons suggesting that different cortical neurons, even when tuned to the same frequency, can convey different perceptual or interpretational aspects of stimuli (Chechik et al. 2006; Nelken and Bar-Yosef 2008).

Spectral processing in the auditory forebrain appears to undergo major transformations relative to the initial coding of acoustic information in the cochlea and compared to various principles that shape brainstem processing. However, our knowledge of the nature, purpose and mechanisms of these cortical transformations, especially in light of the dual purpose of stimulus representation and stimulus interpretation, is still rather rudimentary. The need for profound changes in the way spectral information must be processed becomes evident from the very diverse roles that auditory cortex has to play. In the following sections, we review some of the emerging and emergent properties of auditory cortical processing following a largely historical development in the sophistication of the employed spectral analysis methods. The focus is on more recent accomplishments. Several recent reviews (Escabí and Read 2003; Escabí and Read 2005; Schreiner et al. 2000; Sutter 2005; Young 2008) and other chapters in this book complement and often expand on aspects of spectral auditory cortical processing. If data are available, we consider spectral processing at different structural levels of cortical organization, such as cell types, cortical layers, and cortical fields and subfields, especially within the framework of general divisions such as primary and non-primary areas or auditory core, belt and parabelt areas – connectionally differentiated by thalamic input sources and cortico-cortical projection patterns (Hackett 2008; Hackett and Schroeder 2009; Kaas and Hackett 2000).

2 Spectral Analysis of Tonal Stimuli

2.1 Frequency Specificity

The most basic approach to characterize the excitatory spectral response of auditory neurons has been to present single tones of different frequencies and intensities to the

ear and record the evoked neuronal responses. From the responses, different response profiles, such as the frequency tuning curve (FTC), frequency response area (FRA), or iso-intensity frequency profile of excitatory responses can be reconstructed. Two main aspects of response characterization commonly have been extracted. The first is the frequency preference or sensitivity of a neuron as captured by the characteristic frequency (CF), the tone that produces a response at the lowest intensity of any tested frequency, or the best frequency (BF), the tone that produces the strongest response for a given sound intensity. The second is the frequency selectivity or sharpness of tuning, often expressed as the bandwidth (BW) or range of frequencies, at a given sound intensity, that produce an excitatory response. Alternatively, a relative measure of sharpness of tuning, the Q-factor, is used which is defined as CF/BW and stated for a given sound intensity above minimum response threshold, such as Q10, Q20, or Q40.

Areal Organization: Many neurons in early auditory cortical stations, such as primary auditory cortex (AI), appear to have fairly simple, often V-shaped FRAs (Fig. 13.1), especially in various anesthetized preparations (e.g., rats: Gaese and Ostwald 2001; Sally and Kelly 1988; cats: Brugge and Reale 1985; Phillips and Irvine 1981; monkeys: Merzenich and Brugge 1973; Recanzone et al. 2000). Frequency specificity of cortical neurons, i.e., the presence of frequency-specific channels, is reflected in a wide range of CFs for many cortical fields and is largely independent of the particular cell type such as excitatory pyramidal cells or inhibitory interneurons (Atencio and Schreiner 2008). For many cortical areas, the full range of CFs, corresponding to the species-specific cochlear frequency extent, is present.

Convergent frequency information from the two ears is usually matched in auditory cortex, resulting in similar CFs for the two inputs. CFs derived from contralateral stimulation can be, on average, slightly higher (0.06 octave;
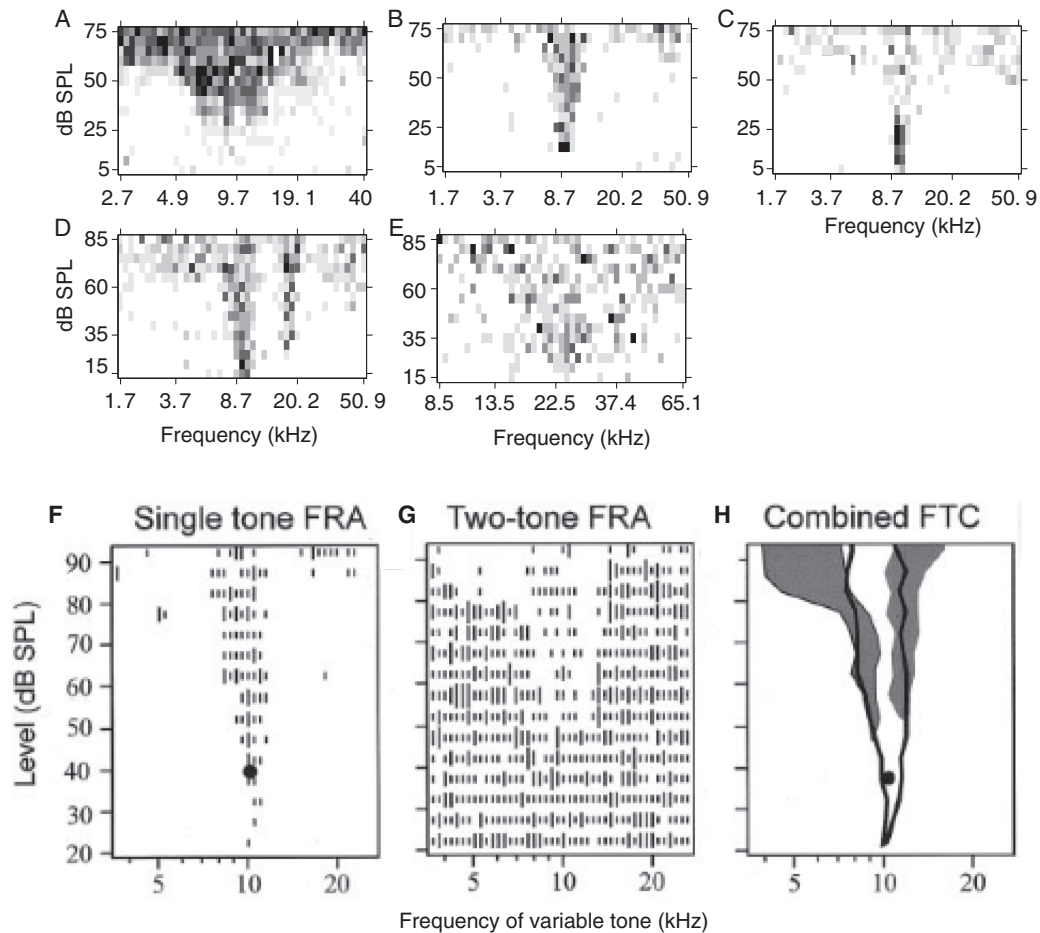

Fig. 13.1 Examples of cortical frequency response areas (FRAs; cat AI). The firing rate during the presentation of tones of different frequency and intensity are displayed. **a** Broadly tuned V-shaped FRA. **b** Narrowly tuned, I-shaped FRA. **c** Non-monotonic, O-shaped FRA. **d** Multipeaked FRA. **e** Diffuse FRA. **f** Single-tone FRA. **g**, **h** Two-tone FRAs. One tone is varied in frequency and intensity, similar to the single-tone FRAs in **a–e**. A second, constant tone at CF and at moderate to low levels (*black dot*) is presented conjointly with the varying tone to create an increase in baseline activity. This allows distinction of excitatory regions (firing rate above baseline) and suppressive regions (firing rate below baseline, *gray area* in H). Adapted from Sutter et al. (1999)

squirrel monkey (Cheung et al. 2009)). The significance of interaural CF asymmetry in normal hearing animals, however, is unlikely to be physiologically meaningful. Aurally asymmetric hearing loss can result in mismatch of convergent frequency information in cortical neurons with potential perceptual consequences (Cheung et al. 2009).

Stimulus information is distributed across a wide range of cortical neuron types, laminae, and areas. Knowledge of the spatial layout of information processing is important because it can provide crucial insights into the local functional tasks and algorithms (Eggermont 2001; Schreiner and Winer 2007). In primary/core cortical areas, neighboring neurons often have similar CF values. Spatial analysis of cortical frequency distributions obtained with extracellular, action potential-based mapping reveals that local clustering of similar functional properties, i.e., exceeding the expectations from random parameter distributions, is a general feature of many response and receptive field parameters (Schreiner and Winer 2007). Only few parameters, however, show a systematic spatial gradient across an entire cortical field. For CF, such functional gradients have been shown for many auditory cortical areas across many different species (e.g., Table 13.1). For classifying the degree of local clustering and global CF gradients, little quantitative information is available although precise measures have been used (Imaizumi et al. 2010; Bandyopadhyay et al. 2010; Rothschild et al. 2010). A coarse classification can, however, be derived for some of the more completely assessed animal models based on general descriptions of their CF organization in primary/core and non-primary/belt areas. Fields can be considered to have "strong" tonotopy if they show both local and global frequency organization, commensurate with a smooth CF gradient across most of the cochlear frequency range (e.g., cat AI, Merzenich et al. 1975; Fig. 13.2). "Weak" tonotopic fields are considered to have considerable variability in local clustering and neighborhood relationships but show evidence of a global gradient (e.g., cat PAF; Loftus and Sutter 2001; Reale and Imig 1980). "Non-tonotopic" areas may still

Table 13.1 Tonotopy and spectral bandwidth properties across cortical fields in six species. Classification of the fields into primary/core and non-primary/belt regions was based on a survey of several studies

Species	Field	Field class	Tonotopy	Spectral tuning	Species	Field	Field class	Tonotopy	Spectral tuning
Carnivores									
Cat					*Ferret*				
	AI	P	Strong	Narrow		AI	P	Strong	Narrow
	AAF	P	Strong	Medium		AAF	*Np*	Strong	Medium
	PAF	*P*	Weak	Medium		ADF	Np	No	Medium
	VPAF	*P*	Weak	Medium		PPF	Np	Weak	Medium
	DZ	Np	No	Broad		PSF	Np	Weak	Medium
	AII	Np	No	Broad		PDF	Np	No	Medium
	EP	Np	No	Broad					
Rodents									
Rat					*Guinea Pig*				
	AI	P	Strong	Narrow		AI	P	Strong	Narrow
	AAF	P	Weak	Medium		DC	P	Strong	Narrow
	PAF	*P*	Weak	Medium		DRB	Np	No	Medium
	VAF	Np	Weak	Broad		VRB	Np	No	Broad
	SRAF	Np	Weak	Medium		DCB	Np	No	Broad
						VCB	Np	No	Broad
Primates									
Macaque					*Marmoset*				
	AI	P	Strong	Narrow		AI	P	Strong	Narrow
	R	P	Strong	Narrow		R	P	Strong	Narrow
	RT	P	Weak	Medium		RT	P	Strong	Narrow
	CL	Np	Weak	Broad		CM	Np	Weak	Medium
	ML	Np	Weak	Broad					
	AL	Np	Weak	Medium					
	CM	Np	Weak	Broad					
	MM	Np	Weak	Broad					
	RM	Np	Weak	Medium					

Areas with some uncertainty regarding this classification are indicated in italic. Classification of tonotopy and spectral tuning was based largely on verbal description of these properties, since uniform quantitative measures (see text) are rare beyond primary fields. Among the studies that were surveyed are: Bendor and Wang (2008), Bizley et al. (2005), Imaizumi et al. (2004), Hackett et al. (1998), Hackett (2008, 2010), Kajikawa et al. (2008), Kowalski et al. (1995), Kusmierek and Rauschecker (2009), Loftus and Sutter (2001), Merzenich and Brugge (1973), Nishimura et al. (2007), Polley et al. (2007), Rauschecker and Tian (2004), Recanzone (2000, 2008), Rutkowski et al. (2002), Sally and Kelly (1988), Schreiner and Cynader (1984), and Tian and Rauschecker (2004).

Fig. 13.2 Spatial distribution of CF and sharpness of tuning (Q) across cat AI and AAF. **a** Schematic view of cat auditory cortex. Recording locations of example maps are superimposed on AI and AAF, respectively. **b** Cat AI CF map. **c** Cat AI Q40 map. **d** Cat AAF CF map. **e** Cat AAF Q40 map. **f** Cumulative cortical area as a function of CF. *Solid lines* (*gray*, *purple*; no data symbols) are two cat AI cumulative area functions for two AI maps. The area functions with data symbols are from four cat AAF maps. Adapted from Imaizumi et al. (2004)
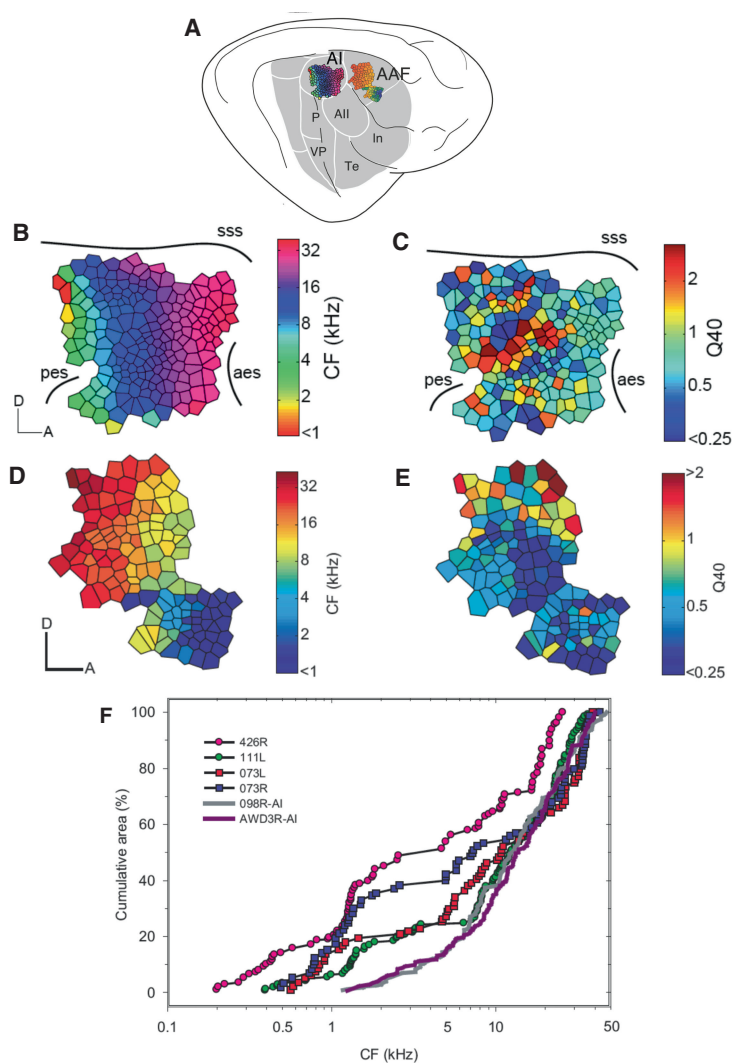
contain some local CF clustering but show no indication of a single spatial gradient covering significant portions of the cochlear frequency range (e.g., cat AII; Reale and Imig 1980; Schreiner and Cynader 1984). For two primates, two carnivores, and two rodents, with fairly advanced characterizations of several cortical fields, 11 of 16 (70%, Table 13.1) primary/core fields exhibit strong tonotopy while only 1 of 21 (5%) non-primary/belt areas show this trait. Conversely, none of the primary/core fields lacks tonotopy whereas 9 of 21 (43%, Table 13.1) non-primary/belt areas are non-tonotopic. Differences in map structure may reflect differences in underlying intracortical circuits, related to differences in input statistics, local algorithms, or in behavioral tasks requirements (Chklovskii and Koulakov 2004; Schreiner and Winer 2007).

Even in primary/core areas, the frequency representation of sounds, as reflected in the distribution of CFs, is not a faithful replica of the cochlear frequency map. Fine-grain electrophysiological cortical frequency mapping usually shows a clear CF gradient in cat AI (Fig.13.2). The mean gradient changes as a function of CF with the steepest slope below 5 kHz and differs from the cochlear frequency gradient. The steep section corresponds to a smaller magnification factor and a relative under-representation of those frequencies (Merzenich et al. 1975). However, the AI tonotopic gradient is relatively smooth compared to that in other primary fields, such as the anterior auditory field (AAF). Cat, gerbil, and ferret AAF all express gross local distortions and apparent omissions in their CF representations that appear to be unique to each individual animal and species (Bizley et al. 2005; Imaizumi et al. 2004; Thomas et al. 1993; Fig. 13.2). The functional implications of these uneven frequency representations remain unclear but likely reflect specific environmental or task-specific adaptations of cortical or subcortical processing that benefit from non-uniform spectral emphasis.

A further reduction or even elimination of tonotopy is often connected to a loss of neuronal frequency

selectivity near response threshold. This is the main cause for the virtual absence of frequency organization in cat auditory field AII (Schreiner and Cynader 1984) and ferret anterior dorsal field (Bizley et al. 2005) and is suggestive of different types of information transformation between cortical stations. The computational goals and advantage of these variations and their proper functional interpretation are difficult to assess without clear hypotheses about the implemented perceptually and behaviorally relevant tasks.

Systematic degradations in the fidelity of auditory cortex tonotopy across areas seem related to other hierarchical area classifications, such as in the core, belt, and parabelt scheme (Rauschecker 1998). However, tonotopy alone cannot serve as the single functional parameter to classify fields regarding their status as primary/core of non-primary or belt, which requires additional information based on source and target connectivity of its projections (e.g., Hackett 2010; Hackett et al. 1998; Kaas and Hackett 1999).

Anatomical studies of auditory cortex have revealed that all extrinsic areal connections, whether tonotopic, nontonotopic, multisensory, or limbic, show a high degree of connectional topography (Lee and Winer 2005; Schreiner and Winer 2007). Local topographies in convergent inputs create distinct conditions for functional processing and it is not surprising to see topographic principles expressed by several functional aspects in auditory cortex. It is conceivable that spatial orders similar to the CF organization are present in areas outside the primary/core areas although it is not clear, at this time, what the functional parameters are that may be organized and where they fall along a spatial order hierarchy.

Laminar Organization: Evidence in support of a precise anatomical lamination of auditory cortex is manifold and compelling (Kelly and Wong 1981; Mitani and Shimokouchi 1985; Mitani et al. 1985; Winer 1984a, c; Winguth and Winer 1986). Laminar borders, defined by cell structure, connections, or chemical anatomy, are precise to within a few micrometers, as is the spatial segregation of afferents (Winer 1992). Each layer differs in its neuronal architecture and cytoarchitecture, GABAergic organization, thalamic input, commissural input and output, cortico-cortical input and output, and corticofugal projections to the telencephalon and brainstem (Winer 1992; see Chapter 2).

In AI, cells are vertically arranged in a more conspicuous manner than in other sensory systems (Jones 2000; Winer 1984b). This vertical arrangement is accompanied by highly specific interlaminar connections (Barbour and Callaway 2008; Mitani and Shimokouchi 1985; Mitani et al. 1985; Wallace et al. 1991). This vertical microcircuitry has been considered a key element of cortical processing (Mountcastle 1997). Thus, the connections between layers follow a precise and characteristic pattern that offers the opportunity to compare the function of specific components of the cortical microcircuit (Martinez et al. 2005). Functionally defined columns may not be a fundamental (canonical) building block or provide a transcendent principle given their variability in presence and appearance in some species (Horton and Adams 2005). However, the vertical circuit – influenced by horizontal inputs and feedbacks – does provide a more robust organizational principle that may contain the key to understanding the local transformations and output patterns that emerge from every point in the horizontal sheet of cortical cells (Atencio and Schreiner 2010a,b; Atencio et al. 2009).

A basic feature of sensory cortex is that certain response parameters are conserved across cortical depth, especially with regard to the location of the receptor surface (Linden and Schreiner 2003). In auditory cortex, the evidence is compelling that this is also the case for frequency sensitivity. Vertical electrode penetrations across all cortical layers often show a clear and moderately tight alignment and correspondence of CFs, supporting a strong columnar organization principle, at least in primary/core areas (Abeles and Goldstein 1970; Phillips and Irvine 1981; Shen et al. 1999; Wallace and Palmer 2008; Atencio and Schreiner 2010a,b; Atencio et al. 2009). Similar studies in non-primary/belt areas are still lacking. In some subregions of cat AI, e.g., in the central narrowly tuned section, the average deviation of CFs in an orthogonal penetration across all cortical layers is only 0.1–0.2 octaves (Fig. 13.3) (Abeles and Goldstein 1970; Atencio and Schreiner 2010a,b). CF variations of similar magnitude across depth have been observed in unanesthesized mice (Shen et al. 1999). Other regions in cat AI proper, such as near the ventral or dorsal borders, can show a larger CF scatter across layers with some CFs within a penetration deviating by as much as 1 octave (Abeles and Goldstein 1970; Schreiner and Sutter 1992; Phillips and Irvine 1981; Atencio and Schreiner 2010a). This indicates that a strict columnar frequency organization, preserving close functional neighborhood relations across different layers, may be common, especially in cortical core areas, but is not a universal principle of auditory cortex organization. In fact, recent studies of the fidelity of the tonotopic organization in mouse AI, using two-photon calcium imaging techniques, have revealed evidence for a highly fractured local frequency organization in the horizontal domain of the upper cortical layers (Bandyopadhyay et al. 2010; Rothschild et al. 2010). At a fine spatial scale, local CFs differed by up to an octave creating a highly diffuse local frequency organization, while maintaining a rather coarse tonotopic gradient on a global scale. By contrast, mapping in the thalamic input layers has demonstrated a reasonably strong tonotopic organization in mouse AI (Stiebler et al. 1997). These discrepancies in the observed fine and global frequency organization, such as tight alignment across layers in some cases and large local CF scatter within a cortical layer in other cases, require further attention because it has profound consequences on

Fig. 13.3 Laminar distribution of spectral response properties. **a, b** *Vertical* electrode penetrations in cat AI with low and high variability in the CF distribution. **c,d** Depth profile of spectral tuning width (Q; high values correspond to more narrow tuning) for the same penetrations shown in (**a**) and (**b**). **e, f** Laminar profile of best spectral modulation frequency distribution for the same penetrations shown in (**a, c**) and (**b, d**), respectively. Data based on Atencio and Schreiner (2010b) and unpublished observations by Atencio and Schreiner
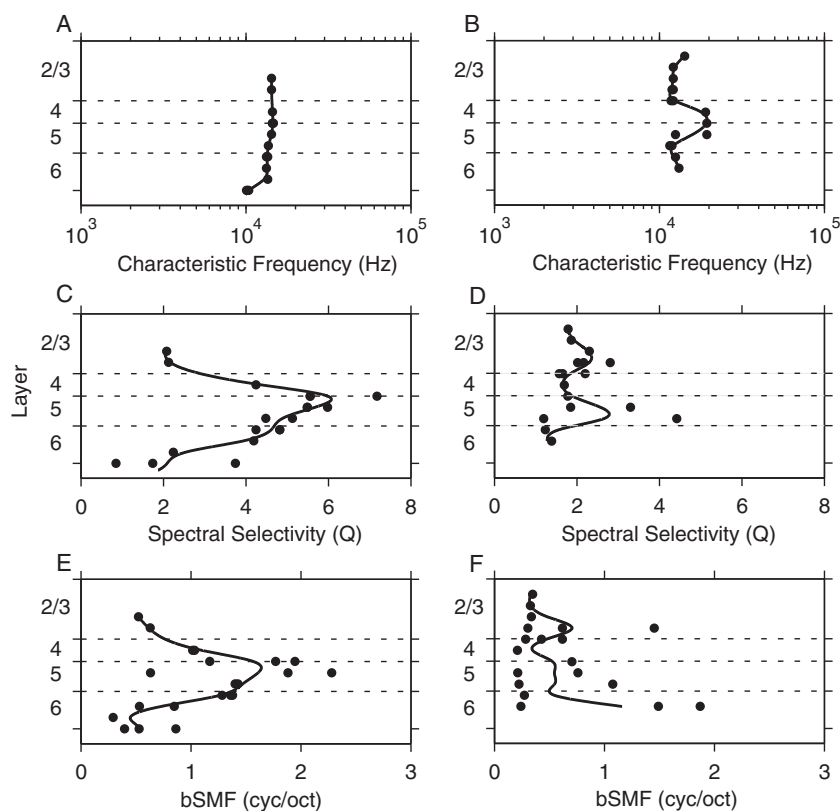
our understanding of cortical processing principles. Issues that certainly play a significant role in accounting for these differences are related to methodologically determined selectivity biases toward cell types, spatial integration, and anesthesia influences. Further biases arise from uncertainties regarding developmental stage, environmental properties and demands, and species-specific organization and processing principles. Species-, areal-, laminar-, and cell-specific computational tasks are not stereotypic but likely involve many different algorithms and serve different goals. The main limitation in interpreting any of the auditory cortex organizational features is, for many species, a lack in understanding the purposes served by individual processing steps. Together, these points emphasize the need for thorough comparative studies and highlight the limits of interpretational generalizations.

2.2 Frequency Selectivity

For tonotopy, quite precise maps can be derived from near-threshold pure-tone responses, especially in primary/core areas, but the validity of an interpretation of the frequency sensitivity for suprathreshold stimuli is limited without considering other aspects of stimulus parameter covariations, such as the spread of excitation across the receptor surface with sound intensity and systematic changes in filter bandwidth in the cochlea and in subcortical processing stations, as well as behavioral task relevance. Thus, frequency specificity does not reflect the actual frequency selectivity of neurons and, consequently, is a poor substrate for understanding spectral processing, especially of broad-band sounds.

Areal Organization: Excitatory bandwidths of neurons have generally been assessed by varying pure-tone stimuli over a large range of frequencies and intensities (Fig. 13.1). For many cortical neurons this results in a single, circumscribed frequency/intensity region of elevated activity. The differences in upper and lower frequency limits of the excitatory region serve as a measure of excitatory bandwidth, although one has to take into consideration that the range can strongly depend on sound intensity. As a consequence, frequency selectivity measures are often expressed with reference to a specific stimulus intensity, such as 10 or 40 dB above minimum response threshold. In primary/core areas, many neurons show a fairly narrow excitatory range, especially in the anesthetized preparation. Other fields show low frequency selectivity for all neurons and across all stimulus intensities. Even in primary/core areas, the range of Q and BW values can span 1–1.5 orders of magnitude (Phillips and Irvine 1981; Schreiner and Sutter 1992; Cheung et al. 2001a; Kowalski et al. 1995; Recanzone et al. 1999). This means

that the range of potential spectral integration – as reflected in the neurons output – can be as narrow as one tenth of an octave or wider than five octaves.

At least in primary/core fields, there is a tendency for Q to increase as a function of CF indicating that excitatory FRAs are relatively narrower (on a logarithmic frequency scale) at high frequencies (Aitkin 1976; Batzri-Izraeli and Wollberg 1992; Cheung et al. 2001a; Pelleg-Toiba and Wollberg 1989; Phillips and Irvine 1981; Recanzone et al. 1999).

While a quantitative description of the frequency selectivity of neurons across many auditory fields and species is still not possible due to lack of sufficient data, a coarse classification can be attempted for some of the more completely assessed animal models based on general descriptions of their frequency tuning properties in primary/core and non-primary/belt areas. Fields can be classified according to narrow, medium, or broad frequency tuning/selectivity. For our purpose, this corresponds for highly selective neurons to bandwidth values below ~0.5 and ~1.5 octaves at sound intensities 10 and 40 dB above threshold, respectively, and for low selectivity neurons to bandwidths above ~1.5 and ~4 octaves, respectively. Among the six model species (Table 13.1), ~60% of the primary/core fields can be classified as highly frequency selective (narrow), while none were found to have low selectivity (broad). Conversely, 52% of the non-primary/belt areas have low frequency selectivity (broad) and none were classified as highly selective. Similar to the classification based on tonotopy, frequency selectivity alone does not provide a functional differentiation of fields that accurately corresponds to that based on anatomical/connectivity aspects. Relating frequency selectivity to tonotopy estimates strengthens the global field classification. All ten narrowly tuned fields (Table 13.1) are primary/core areas and have strong tonotopy. Conversely, all eleven broadly tuned areas are non-primary/belt and 55% of these show no evidence of a tonotopic gradient. Eleven areas with weak tonotopy and medium frequency selectivity split nearly evenly between primary/core and non-primary/belt regions underscoring that basic frequency processing aspects alone cannot align functional and anatomical cortical field classifications.

In some primary/core fields, clusters of neurons sharply or broadly tuned to frequency are segregated along the iso-frequency axis of the tonotopic map. Cortico-cortical connectivity in cat AI finds that broad or narrow spectral bandwidth clusters predominantly are connected with other clusters of the same property (Imaizumi et al. 2004; Read et al. 2001), thus creating a functional and connectional mosaic of interconnected, interleaved modules of different spectral integration. This topographic arrangement can be interpreted as an iterated map of spectral integration (Schreiner et al. 2000) that is independent of, or orthogonal to, the frequency decomposition domain of the receptor surface. A clear functional, task-directed interpretation of these modules is still elusive but they may enhance processing of spectral shape as in the determination of vocal tract properties (Calhoun and Schreiner 1998; Versnel and Shamma 1998). Functional significance, however, needs to be established related to particular steps in a sequence of transformations and integrations rather than as an isolated, disassociated phenomenon.

Non-uniform distributions of spectral integration properties are also seen in other primary fields, such as cat AAF (Imaizumi et al. 2004), and in other species, such as the ferret (Shamma et al. 1993; Bizley et al. 2005), owl monkey (Recanzone et al. 1999), and squirrel monkey (Cheung et al. 2001a). However, in awake preparations, evidence of spectral integration topography has not been unambiguous (Recanzone et al. 2000).

The systematic change in spectral selectivity across AI is significant for understanding the cortical representation and processing of spectrally complex signals, like species-specific vocalizations, speech, music, and ambient noise. These topographies suggest that any incoming signal is simultaneously processed through many filters with different center frequencies and a broad range of bandwidths. Spectral information in AI is extracted and represented by multiple modules for frequency resolution along the iso-frequency domain, and the center frequency of each bandwidth module is aligned to the "frequency decomposition" or tonotopic axis. Parallel analysis by multiple bandwidths results in an iterative, multi-resolution representation of information within each iso-frequency domain differentially weighted by filter width. This parallel analysis may aid in the extraction and evaluation of complex spectral shapes, e.g., formant structure of vowels, and establish multiple, parallel output streams for further processing (Mesgarani et al. 2008; Schreiner and Calhoun 1994; Shamma et al. 1993; Sutter 2005; Wang and Shamma 1995)

The heterogeneity of spectral integration properties across primary and non-primary fields is in contrast to psychophysically determined spectral integration that is relatively constant at a "critical bandwidth" of ~1/3 octave throughout the cat hearing range (Ehret and Schreiner 1997; Nienhuys and Clark 1979; Pickles 1975). The module-like spatial organization of Q values across CFs in AI and AAF may be related to peripheral and thalamocortical mechanisms as well as to the RF construction in auditory cortex (Miller et al. 2001; Suga 1995; Sutter et al. 1999; Cheung et al. 2001a). Spectral bandwidth is already influenced by cochlear tuning properties (Liberman 1978; Narayan et al. 1998) and is reflected in subsequent processing stations. However, spectral integration differences in different frequency regions likely reflect higher-order processing principles, perhaps reflecting specific behavioral tasks (e.g., Razak et al. 2007; Suga 1995) or

neuroanatomical arrangements (Prieto et al. 1994a, b; Read et al. 2002).

Anesthesia strongly affects the responses of neurons in the central auditory pathway, from the dorsal cochlear nucleus (Young and Brownell 1976) to the auditory cortex (Gaese and Ostwald 2001; Sally and Kelly 1988; Schreiner and Sutter 1992; Sutter and Schreiner 1991, 1995). In particular, the frequency selectivity in barbiturate- or higher dose isoflurane-anesthetized animals (Sutter and Schreiner 1991, 1995; Cheung et al. 2001b) appears to be generally narrower than in other anesthetic regimens, such as under halothane (Moshitch et al. 2006), or in awake animals. For example, awake rats and cats can show a 3–4 times wider bandwidth of excitatory tuning curves than under barbiturate (Gaese and Ostwald 2001; Qin et al. 2003). However, similarly highly frequency selective and unselective neurons can be encountered in both awake and anesthetized models (e.g., Abeles and Goldstein 1970; Moshitch et al. 2006; Schreiner and Sutter 1992, 1995; Kadia and Wang 2003). The shift toward higher frequency selectivity under certain anesthetic regimens may be due to an increase in the effectiveness of inhibition in the cortex. The consequences of bandwidth differences due to anesthesia for the emergence and functional interpretation of the wide range of spectral integration properties in auditory cortex and their relationship to behavior remain to be fully evaluated.

Laminar Organization: Laminar differences in frequency tuning bandwidths have been seen in several studies of cat, bat, and rodent auditory cortex (Dear et al. 1993; Eggermont 1996; Norena and Eggermont 2002; Sugimoto et al. 1997; Wallace and Palmer 2008; Atencio and Schreiner 2010a, b). The tuning bandwidth was generally broader for single neurons in the deep layers (IV to VI) compared to layers I to III of the Guinea pig (Wallace and Palmer 2008) and was sharpest for layers III and IV in the Mongolian gerbil (Sugimoto et al. 1997). In AI of ketamine-anesthetized cats, layer-specific frequency selectivity was also present; however, sites with fairly constant BW values across depth were also encountered (Fig. 13.1d). On average, the cat data also reflect a lower frequency selectivity for infragranular layers (Atencio and Schreiner 2010a, b). This indicates that strict columnar invariance in frequency selectivity is not the rule. In addition to layer-specific differences, pyramidal cells appear to have slightly higher frequency selectivity than putative inhibitory interneurons when they are recorded from within the same layer (Atencio and Schreiner 2008).

Overall, auditory cortex shows a wide range of frequency specificity and selectivity. However, to adequately appreciate this broad and varied repertoire of frequency filters and its impact for signal analysis, other aspects of cortical signal encoding need to be taken into consideration (see below) and, foremost, a better understanding of local and global processing goals and algorithms has to be developed (e.g., Griffiths et al. 2004; King and Nelken 2009).

2.3 Shape of Frequency Response Areas

In primary auditory cortical fields, most extensively observed in AI of various species, many frequency/intensity response areas have a rather uniform V-shape under anesthesia, i.e., the frequency selectivity decreases with increasing intensity (Brugge and Reale 1985; Sally and Kelly 1988; Phillips and Irvine 1981). However, a substantial proportion of neurons have quite different FRA shapes, including intensity-independent frequency tuning (I-shape), and circumscribed FRAs with no or substantially reduced responses at higher sound intensities (O-shape) (e.g., Abeles and Goldstein 1972; deCharms et al. 1998; Goldstein and Abeles 1975; Pelleg-Toiba and Wollberg 1989). Some neurons have multiple, non-continuous response areas (multipeaked) (Abeles and Goldstein 1972; Sutter and Schreiner 1991, Kadia and Wang 2003; He and Hashikawa 1998) or diffuse/patchy response areas composed out of many local intensity/frequency combinations without a clear, joint appearance that fits into standard classification schemes (Moshitch et al. 2006; Sadagopan and Wang 2009). A higher incident of complexly shaped response patterns can be found in unanesthetized and halothane preparations (Abeles and Goldstein 1972; deCharms et al. 1998; Pelleg-Toiba and Wollberg 1989; Kadia and Wang 2003; Moshitch et al. 2006; Sadagopan and Wang 2009).

A large diversity of FRA shapes, including some with very broad frequency tuning and some with multiple distinct excitatory frequency ranges, are also seen in other cortical fields, especially in non-primary areas (e.g., cat PAF; Loftus and Sutter 2001; Horseshoe bat; Radtke-Schuller and Schuller 1995). However, more quantitative studies of non-primary FRAs are needed to fully assess systematic filter-shape differences between most cortical fields.

Under anesthesia, most AI neurons have a single peaked FRA (Phillips and Irvine 1981), i.e., they have a single region of low-intensity responses centered at the CF. However, multipeaked tuning curves with two or three distinct low-threshold peaks have been described (Abeles and Goldstein 1972; Sutter and Schreiner 1991, Kadia and Wang 2003; Fitzpatrick et al. 1998; He and Hashikawa 1998; Oonishi and Katsuki 1965; Wenstrup and Grose 1995). In AI of awake marmosets, 20% of neurons have multipeaked FRAs. In both cats and marmosets, the excitatory spectral peaks in the multipeaked FRAs are often harmonically related (Kadia and Wang 2003; Sutter and Schreiner 1991). Stimuli presented at the spectral peaks of the multipeaked FRA can

result in a facilitated response compared to either component presented in isolation. This suggests that sounds containing multiple, prominent spectral components may be processed by different classes of neurons (Kadia and Wang 2003).

Relating the position of single neurons with multipeaked tuning curves to the excitatory bandwidth distribution in cat AI reveals a distinct spatial distribution of these neurons (Sutter and Schreiner 1991). Multipeaked tuning curves are primarily found in the dorsal third of AI, whereas the rest of AI shows little evidence of single neurons with multiple FRAs. Multipeaked tuning curves are also characteristic for the Dorsal Zone, a non-primary area located adjacent and dorsal to AI (He and Hashikawa 1998). This subpopulation of cortical neurons may be sensitive to specific spectro-temporal combinations in the acoustic input (Sutter and Schreiner 1991; He et al. 1997). The spatial clustering of these specialized multipeaked neurons implies a functional segregation. Spatial and functional segregation of spectral analysis appears to be a general organizing principle of AI.

In the auditory cortex of awake animals, a substantial number of neurons do not respond to pure tones (Sadagopan and Wang 2009; Bandyopadhyay et al. 2010; Rothschild et al. 2010). At least some of these "unresponsive" neurons are likely to be selective for complex sound features with highly nonlinear combination-sensitive responses (Sadagopan and Wang 2009). Specific combinations of several tones with appropriate spectral and timing relationships can elicit strong responses whereas each component alone fails to produce an excitatory response (Sadagopan and Wang 2009), highly reminiscent of combination-sensitive neurons in echolocating bats (Suga 1984). Characterizing cortical neurons with more complex, broad-band spectra, including naturally occurring sounds, may reveal more appropriate response classifications that transcend the diversity of pure-tone FRA shapes.

2.4 Temporal Dependence of Pure-Tone Tuning

Frequency specificity (e.g., BF) and frequency selectivity (e.g., BW) are usually determined by integrating spikes over the entire duration of a tone stimulus for the construction of FRAs. This procedure masks three potential changes in frequency tuning during the time course of the response: (i) response latency differences for different intensities and for frequencies near the margins of the FRA, (ii) response duration differences, such as phasic versus sustained responses, and (iii) occurrence of "off" responses, i.e., excitatory activity following the end of tones.

Neurons with phasic response profiles predominate in anesthetized animals, and account for up to 50% of responses in awake animals (DeWeese et al. 2003; Evans and Whitfield 1964; Wang et al. 2005). In these neurons, frequency specificity strongly depends on the time relative to the stimulus onset (Schreiner et al. 2006). Early, short latency responses account for the high-intensity, broadly tuned region of most V-shaped FRAs (Fig. 13.4). Slightly longer latency responses provide lower intensity, near BF regions of the FRA. The longest latency phasic responses supply the off-CF regions of the FRA margins. Therefore, frequency specificity, including sensitivity and selectivity, for single neurons and for the neuronal population evolves rapidly over the course of the first ~40 ms after stimulus onset.

This is also the case for the phasic portion of neurons with sustained responses, however, the impact on the global tuning is diminished by the sustained portion of the activity. Yet, the frequency specificity of sustained neurons also undergoes a clear temporal evolution. FRAs of phasic (<30 ms) and early-sustained responses (<100 ms) were found to be highly similar, with BF differences of < 1/4 octaves (awake macaque; Fishman and Steinschneider 2009). In contrast, FRAs based on phasic and late-sustained (>100 ms) response portions differed considerably (BF differences: 2/3 octaves).

Fig. 13.4 Tuning curve shape as a function of time. The shape of a pure-tone FRA is plotted in 2 ms time intervals relative to tone-onset. *Shaded boxes* correspond to firing rate strength for different frequency-intensity combinations (*darker squares* correspond to higher firing rates). The *solid lines* indicate the lowest threshold across all time intervals, indicating the traditional frequency tuning curve that is customarily integrated across the total stimulus duration. Modified from Schreiner et al. (2006)
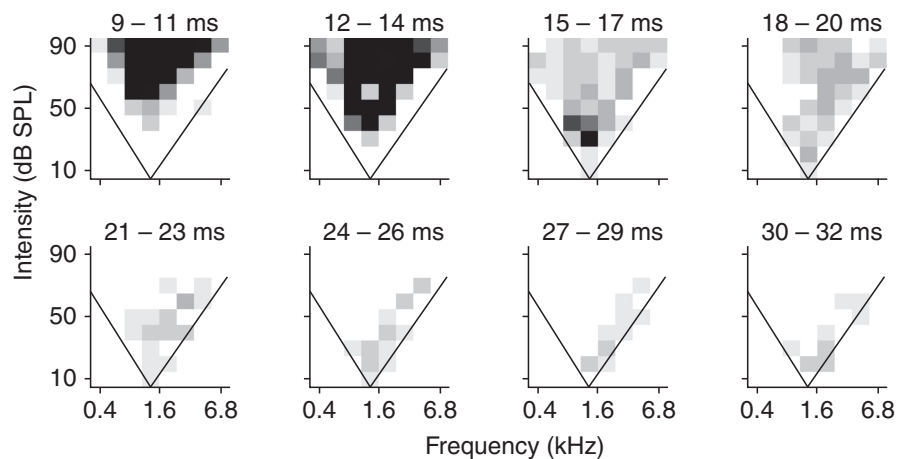
Many neurons with strong phasic or phasic/sustained response profiles also exhibit offset responses, especially in awake preparations (Fishman and Steinschneider 2009; Qin et al. 2007; Recanzone 2000). Prevalence of off-responsive neurons are about 30% in awake monkey (Recanzone 2000) and ketamine- or halothane-anesthetized cat (Volkov and Galazjuk 1991; Moshitch et al. 2006), and roughly 60% in awake cat (Qin et al. 2007). The frequency-filtering property of the off-responses differs from that of the phasic and sustained portions. Off-response FRAs usually are non-overlapping with or inversely related to that of the on-responses. Frequency tuning of off-responses is often ~1–2 octaves above that of on-responses in the awake macaque (Fishman and Steinschneider 2009; Pelleg-Toiba and Wollberg 1989). However, in awake cats, a similarly consistent relationship was not found (Qin et al. 2007). The different frequency tuning and excitatory–inhibitory compositions underlying on- and off-responses strongly suggest that they are driven by largely non-overlapping sets of synapses (Scholl et al. 2010). Frequency tuning of population responses may vary considerably over the course of the response to a tone, demonstrating a strong temporal dependence of the cortical spectral representation of sounds (Fishman and Steinschneider 2009).

2.5 Inhibitory Response Areas

Processing properties of cortical neurons are shaped by the convergence and interaction of excitatory thalamocortical and cortico-cortical inputs and inhibitory projections (see Section 13.6 and Chapter 2). Stimulus components outside of the excitatory FRA can exert strong suppressive effects on responses. If sufficient spontaneous activity is present, as is often the case in awake animals, suppressive effects from single tones can be observed (Qin and Sato 2004). Phasic neurons in awake cats showed that tone-evoked suppression and excitation temporally alternated and spectrally co-occurred, restricting excitatory spike-responses within narrow temporal limits but not setting the spectral limits. By contrast, sustained neurons showed that the suppression and excitation spectrally alternated and temporally co-occurred, restricting excitatory frequency tuning but not setting the time limits (Qin and Sato 2004). These observations hint at complex interactions of excitatory and inhibitory forces.

Many neurons, especially in anesthetized preparations, do not have sufficient spontaneous activity to observe suppressive effects at the level of extracellular recordings of spiking activity. By eliciting a mildly excitatory response, for example by a soft CF tone, suppressive effects of an additional tone can be observed. Application of this two-tone interaction paradigm has revealed a high incidence of neurons

(>90%) with suppressive response regions outside the excitatory (one tone) FRA. A wide variety in the structure of these "inhibitory bands" has been observed ranging from a single V- or I-shaped band to more than four distinct suppressive regions (e.g., Sutter et al. 1999; Loftus and Sutter 2001) (Fig. 13.1). The most common arrangement of suppressive bands (~35%) in the anesthetized cat, ferret, and gerbil AI is a single suppressive band on either side of the excitatory FRA (Loftus and Sutter 2001; Sutter et al. 1999; Shamma et al. 1993; Foeller et al. 2001). Regional differences in the distribution of suppressive regions across AI have also been reported (Loftus and Sutter 2001; Kowalski et al. 1995). In cat dorsal AI, only 16% of the neurons had one suppressive band on either side of the FRA whereas 50% of ventral AI neurons had this organization. Regional organizational differences, thus, are also present when considering suppressive areas of the spectral filters that may be part of functionally distinct auditory cortical processing streams (Sutter et al. 1999). No laminar differences in strength of inhibition were observed (Foeller et al. 2001), although the distribution and density of different interneuron classes varies across lamina (Prieto et al. 1994a,b).

Suppressive interactions can also play a role in shaping the response magnitude within the excitatory FRA such as in the generation of O-shaped, circumscribed FRAs (Fig. 13.1). In extracellular (Sutter and Loftus 2003) and intracellular recordings (Tan et al. 2007), the intensity tuning of excitatory and inhibitory/suppressive components can be negatively correlated, supporting the hypothesis that cortical inhibition can contribute to intensity tuning within the excitatory domain.

Most studies of inhibitory cortical properties in the auditory system have been limited to AI. Studies in cat PAF revealed a higher incident of complexly shaped inhibitory FRAs, such as with more than 2 suppressive regions (Loftus and Sutter 2001). It is likely that more complex suppressive frequency bands indicate an analysis of greater spectral complexity. However, detailed studies at the synaptic level are needed to clearly establish the role of inhibitory/excitatory interactions in the shaping of spectral filter properties and the generation of excitatory and suppressive FRA regions throughout auditory cortex (see Section 13.6).

3 Cortical Frequency Channels

Psychophysical experiments in humans and animals have demonstrated that auditory processing makes use of a set of frequency channels with well-defined bandwidth for the processing and resolution of complex stimuli. The components of such a filter bank with intensity-tolerant and

frequency-dependent bandwidth are known as critical bands (e.g., Greenwood 1974).

Speech recognition in humans requires relatively coarse spectral information, provided sufficiently resolved temporal information is available (Shannon et al. 1998, 2004). As little as four independent frequency channels may suffice for some basic speech identification. More channels, 16–64, can provide sufficient clues for nearly full speech perception, even in noise (Shannon 2005; Shannon et al. 1998, 2004; Smith et al. 2002). Music processing requires even higher spectral resolution (Shannon 2005). In addition to integration across relatively narrow frequency bands, for example for loudness formation and discrimination between different frequency components in a complex sound, integration across wider frequency regions is also perceptually utilized such as in co-modulation masking release and profile analysis (Bregman 1990; Hall and Grose 1988).

Although the spectral RFs of auditory cortical neurons derived from tones are useful for estimating properties of spectral integration, a more direct measure of the effective auditory filter bandwidth is necessary to establish the relationship between psychophysics and neuronal behavior. Methods analogous to psychophysical measurements of critical bands applied to single neuron responses, such as suppression of a tone response by noises of different bandwidths or by flanking noise-bands at different frequency separations, are useful to establish a neural-perceptual correspondence (Ehret and Merzenich 1985, 1988; Ehret and Schreiner 1997; Fishman and Steinschneider 2006). By repeating this measurement for different tone intensities, the level dependence of the neural critical bandwidth can be assessed.

A majority of neurons in anesthetized cat AI show spectral integration properties that remain relatively constant across intensity. However, the critical bandwidth of many intensity-tolerant neurons is broader than predicted from behavioral measurements of the critical band. Neurons that are intensity tolerant and have critical bandwidths similar to the behaviorally known values for cats (Pickles 1975; Nienhuys and Clark 1979) are less common but cluster in the central, narrow-band region of cat AI (Ehret and Schreiner 1997). Only in a subgroup of neurons does the spectral integration width estimated from pure-tone responses match that derived from noise masking with clear discrepancies between the two measures in the remaining neurons (Ehret and Schreiner 1997). Consequently, the actual spectral integration properties depend on the specific stimulus conditions and pure-tone excitatory measures are not sufficient to fully explain broad-band spectral integration behavior (Schreiner et al. 2000).

Using a two-noise masking paradigm, the spectral resolution of neural populations in AI of awake macaques also was found to parallel results of psychoacoustic studies in both monkeys and humans. The best fit of auditory filter shapes in psychoacoustic and these neural studies of frequency resolution was found in cortical layers IV and lower layer III compared to lower quality fits for more superficial cortical layers (Fishman and Steinschneider 2006). Evidence for physiological correlates of perceptual critical bands was also found in human auditory cortex using magneto-encephalographic measures (Soeta and Nakagawa 2006). These studies indicate that a cortical representation of perceptual frequency resolution is available, at least at the level of AI.

Evidence of a correspondence between psychophysical and neural spectral integration properties in non-primary/belt areas is still lacking. Broader pure-tone tuning in many non-primary fields may indicate that such a correspondence may be less likely than for narrowly tuned cortical fields and wider frequency integration may be emphasized at those later levels of analysis. Neurons in non-primary areas, especially in awake preparations, have been shown to respond often better to noise than to tonal stimuli (Recanzone 2000; Rauschecker and Tian 2004). However, the consequences of such observations for the formation of perceptual attributes, in particular for spectral integration and resolution, remain unclear.

4 Static Spectral Profile Analysis

Given that naturally occurring sounds are usually neither tone- nor noise-like, the discrepancies between spectral response characterization between pure-tone and noise stimuli indicated in the previous section become even more relevant. Spectral profiles of environmental sounds, and in particular of communication sounds, typically are composed of distinct spectral peaks and troughs distributed over a wide frequency range. Examples are the formant structure of vowels, a fundamental spectral feature of the vocal tract expressed in speech and animal vocalization sounds, and the spectral notches and peaks introduced by head shadows and outer-ear resonance utilized for sound localization processing.

Sensitivity and selectivity of neurons for more natural, complex spectral profiles can be assessed with broad-band stimuli using various methods. Random spectrum stimulus (RSS) sets, i.e., time-invariant broad-band stimuli with complex spectral envelopes, have been used to estimate the spectral weighting function that a neuron applies to sound energy across frequency. A linear frequency weighting function can be deduced by presenting stimuli with many different predetermined spectral shapes, by recording the observed discharge rates, and by subsequent superposition of the profiles proportional to their evoked activity. The resulting function is a rate-code based, normalized and
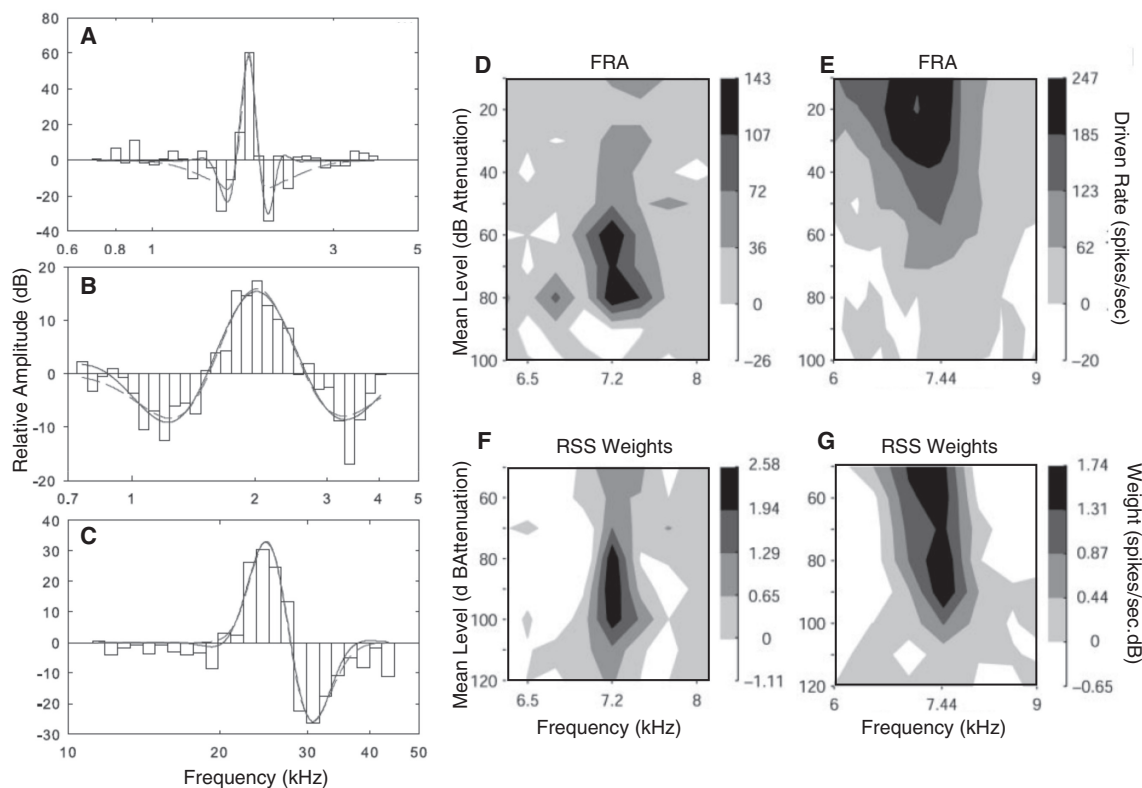
Fig. 13.5 Static spectral profiles determined with random sequence stimuli (RSS). **a–c** Three examples of spectral profiles indicating excitatory regions (activity above mean firing rate) and suppressive regions (activity below mean firing rate) (macaque monkey; adapted from O'Connor et al. 2005). **d, e** Two frequency response areas determined with pure tones (marmoset monkey; adapted from Barbour and Wang 2003a). **f, g** Two frequency response areas reconstructed from RSS obtained at different mean intensity levels for the same neurons as shown in (**d, e**)

weighted average spectral profile and corresponds to the spectral receptive field (Fig. 13.5; Barbour and Wang 2003a; Yu and Young 2000). Function values above the mean correspond to frequencies at which stimulus energy addition increases the driven rate of a neuron. Values below the mean are frequencies at which energy elimination increases the driven rate (Fig. 13.5a–c).

Similar estimates of neuronal spectral profile preference can be derived with adaptive stimulus optimization (Nelken et al. 1994a; O'Connor et al. 2005) by using variations of a static spectral stimulus profile to iteratively reach a maximum in the response rate. The resulting preferred stimulus profile also is a robust estimate of the neuron's actual spectral tuning, effectively representing properties found in natural sounds. While spectral profile estimations are not identical between the different methods, similarities exist revealing linear and nonlinear aspects of spectral integration properties (Sutter 2005).

RSS produced significant firing rate changes in 60–80% of neurons encountered in AI of awake marmoset and rhesus monkeys (Barbour and Wang 2003a; O'Connor et al. 2005) most of them showing sustained spiking. The resulting shapes of preferred spectral profiles (Fig. 13.5) showed

a range of appearances with narrow or broad excitatory maxima and various suppressive/inhibitory troughs on either side, described as circumscribed, multi-lobed antagonistic structures (O'Connor et al. 2005). When obtained for a range of different mean stimulus intensities, the shape of the estimate function closely resembled two-tone FRAs (Fig. 13.5d–g). In contrast to typical V-shaped FRAs, they remained relatively constant throughout the stimulus interval and across the stimulus properties of mean sound level (Fig. 13.5f, g), spectral density, and spectral contrast (Barbour and Wang 2003b; O'Connor et al. 2005). Similarities to FRAs include the occurrence of multiple excitatory bands, their shape and bandwidth, and the position of suppressive sidebands. However, it is highly likely that many auditory cortex neurons behave in a substantially nonlinear manner in response to complex spectral input (Barbour and Wang 2003a; Calhoun and Schreiner 1998; Linden et al. 2003; Machens et al. 2004; Nelken et al. 1994b; Sahani and Linden 2003). This should result in distinct differences between narrow- and broad-band estimates of spectral processing. This is emphasized by the observation that even linear predictions of rate responses from preferred spectral profiles for other RSSs yielded poor results, again implying

that auditory cortex neurons integrate information across frequency nonlinearly (Barbour and Wang 2003a).

Several other techniques have been used for characterizing the structure of auditory receptive fields. Auditory gratings or ripple spectra, i.e., broad-band stimuli with sinusoidal spectral envelopes (linear spacing along the logarithmic frequency axis) that resemble the formant structure of vowels, can be used to obtain the spectral modulation spectrum or spectral gain function of a neuron (Escabí and Schreiner 2002; Klein et al. 2000; Miller et al. 2002; Schreiner and Calhoun 1994; Shamma et al. 1995; Versnel and Shamma 1998). The main variables of the modulation spectrum are the spectral envelope periodicity or modulation frequency and the magnitude and the phase of each modulation component. The preferred spectral profile and the modulation spectrum are directly related and can be translated into each other via Fourier transform. The usefulness of the modulation spectrum approach as a descriptor is in its straightforward parametric space. The relevance of spectral modulation information for communication sound processing becomes evident when considering how challenging it is for listeners to discriminate speech with a degraded spectral envelope (Dreisbach et al. 2005; Leek et al. 1987; Shannon et al. 1998; Smith et al. 2002).

Cat and ferret cortical neurons respond preferentially to a limited range of spectral envelope frequencies (Calhoun and Schreiner 1998; Klein et al. 2000; Kowalski et al. 1996a, b; Schreiner and Calhoun 1994; Shamma et al. 1995). For these static ripple stimuli, preferred ripple frequencies for AI range between 0.2 and 4 cycles/octave (Schreiner and Calhoun 1994; Keeling et al. 2008; Shamma et al. 1995) with mean frequencies of ~1.0 cycles/octave. This range corresponds well to the best sine-profile frequencies that can be fit to the preferred spectral profiles obtained with RSS which range between 0.2 and 3 cycles/octave with a mean of 1.17 in the awake rhesus monkey (O'Connor et al. 2005). As with preferred spectral profiles, the relative response to different spectral modulation/ripple frequencies remains fairly constant with changes in the intensity and the spectral density of the broad-band carrier signal. However, variations of spectral modulation depth or contrast can result in nonlinear behaviors of the spectral modulation spectrum (Calhoun and Schreiner 1998). There is only sparse experimental evidence for a spatial organization or clustering of ripple transfer functions (Shamma et al. 1995; Kowalski et al. 1996a, b).

Studies in ferret AI find that ripple responses allow reasonable predictions of responses to pure tones and to spectrally complex natural sounds (Shamma et al. 1995; Versnel and Shamma 1998; Klein et al. 2000; David et al. 2009), suggesting that AI neurons analyze the shape of acoustic spectra in a substantially linear manner.

Details of the spectral shape of natural broad-band sounds, such as sharpness of formants or attributes of spectral edges, contribute to the perceived sound quality. Different types of preferred spectral profiles and their relationship to the distribution of excitatory and inhibitory subregions in AI neurons can help in an effective representation of these properties. The relative pattern of excitatory and inhibitory portions of the preferred spectral profile contributes to this process. For example, a response preference for steep slopes of formants or edges seems associated with a shift of processing balance toward inhibitory regions of the receptive field, whereas a preference for gentle slopes emphasizes engagement of excitatory spectral regions (Qin et al. 2004).

Laminar Organization: Significant differences exist between the expression of spectral modulation preferences in granular, supragranular, and infragranular neurons in cat AI (Atencio and Schreiner 2010a, b). Simultaneous recordings from 8 to 20 single neurons across cortical layers revealed that CFs show only small laminar variations. By contrast, clear laminar differences were evident for spectral modulation preferences, and equivalently, of preferred spectral profiles (Fig. 13.3f). Only ~30% of penetrations showed consistent spectral modulation preferences across layers, indicative of functional laminar diversity or specialization. Compared to layer IV, spectral modulation spectra were broader on average, and their upper cut-off frequencies higher, in layers V and VI. This suggests a higher representational fidelity of sharp edges in the spectral profile in the infragranular layers. Ensembles of auditory neurons that are tuned to different auditory features enhance the acoustic differences between classes of natural sounds and their distribution may reflect high informational regions in the environmental sound statistics (Woolley et al. 2005). Functional layer differences, reflecting different pre-processing for their respective projection targets, suggest then specific sensitivities to spectral profiles that need to be understood based on the goals and algorithms at each point in the circuit.

5 Dynamic Spectro-Temporal Profile Analysis

5.1 Spectro-Temporal Receptive Fields

When the sensory functions and response characteristics of a neuron are unknown, it is preferable to make few assumptions and to explore a large set of stimulus attributes in an unbiased way. Reverse correlation or spike-triggered average (STA) techniques embody this principle. Synthetic, spectro-temporally complex stimuli, such as dynamic chord stimuli, dynamic ripples, ripple noise, and temporally orthogonal ripple combinations (TORCs) (Escabí and Schreiner 2002; Blake and Merzenich 2002; Klein et al. 2000), share many

properties with natural sounds and satisfy formal requirements for deriving spectro-temporal receptive fields (STRFs) through the STA. The STRF is a linear, time-frequency representation of neural stimulus preferences as shown by the excitatory and inhibitory STRF subregions (Aertsen and Johannesma 1981; Depireux et al. 2001; Eggermont et al. 1983; Gill et al. 2006). The two-dimensional Fourier transform of an STRF yields modulation transfer functions (MTFs) that characterize the neurons preferred spectral and temporal stimulus envelopes. The STRF and its relatives remain among the richest unbiased, linear descriptors of neuronal function. Compared to static spectral profiles, STRFs add a temporal axis that characterizes the temporal evolution or dynamics of the spectral influences. While informative, STRFs may be biased by stimulus correlations, may reflect nonlinear behavior in a very limited way, and do not characterize neural sensitivity to multiple stimulus dimensions. STRFs provide a versatile and integrated, spectral and temporal, functional characterization of neural responses (Klein et al. 2000, 2006). STRFs express a single feature dimension that captures the time-dependent behavior of stimulus

envelope processing in auditory neurons. This combined spectro-temporal processing is advantageous for encoding of natural sounds which are rarely static. It enables – at least partially – the basic reconstruction of the input signal (David et al. 2009; Mesgarani et al. 2009).

To extract additional feature dimensions and to account for nonlinear response rules, an alternative approach can be used that is based on maximizing the mutual information (MI) between the stimulus and the evoked spike train of a neuron (Atencio et al. 2008; Clifford et al. 2007; Sharpee 2007; Sharpee et al. 2006, 2008). The resulting maximally informative dimension (MID) can share many aspects with STRFs obtained through reverse correlation (Fig. 13.6) and has additional advantages, such as suitability for derivation with non-Gaussian signals and elimination of effects from stimulus correlations (Sharpee et al. 2004a, b).

Both MIDs and STAs can provide the linear component in a linear–nonlinear neuron model (Sharpee et al. 2008; Schwartz et al. 2006). In this model, spectro-temporal stimulus features, or linear filters, are combined with a static nonlinearity to compactly represent neural processing. This
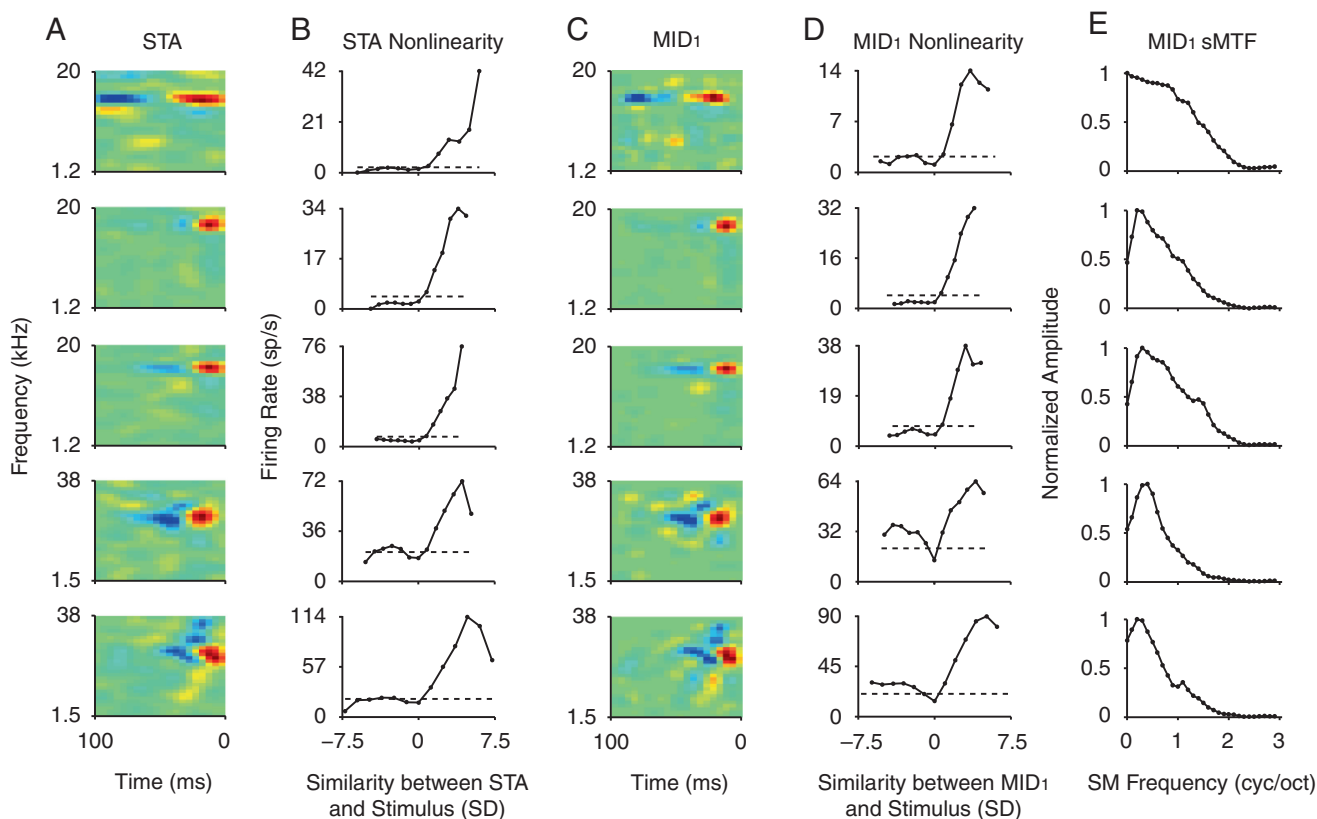

Fig. 13.6 Cortical spectro-temporal receptive fields (STRFs) and associated nonlinearities. **a** STRFs based on spike-triggered averaging (STA) in response to a 20 min dynamic moving ripple stimulus (*red*: excitatory regions; *blue* suppressive/inhibitory regions). **b** Associated nonlinearities. Nonlinearities express the firing rate as a function of the similarity between the stimulus and the STA or MID. **c** MID1.

Spectro-temporal response profile based on maximizing mutual information between stimulus and response. The MID1 and the STA are highly correlated (mean *r*=0.8) indicating that the two estimates of spectro-temporal processing are capturing highly similar aspects. **d** MID1 nonlinearity. MID1 and STA nonlinearity are highly correlated. **e** Spectral modulation transfer functions based on the MID1

linear–nonlinear model can account for features in stimulus space that best capture the variability in neuronal responses. The nonlinear input–output function, or nonlinearity, describes the firing probability of a neuron as the similarity, or correlation, between the stimulus and the STRF/MID changes (Fig. 13.6) and forms a fundamental component in linear/nonlinear cascade models of neuronal function (Chichilnisky 2001; Schwartz et al. 2006). Most STRF/MID nonlinearities in ketamine-anesthetized cat AI are asymmetric and sigmoidal in shape, representative of a thresholding and smoothing operation. Parameter ranges, such as slope and position of inflection point, of asymmetric nonlinearities provide a rich substrate for response differences in neurons with similar STRFs.

The main feature of STRFs is that they can capture temporal dependencies of spectral processing. Many neurons in cat and ferret AI have STRFs with "sloped" response maxima or minima, indicating that the frequency position of excitatory and/or inhibitory regions shift with time (Atencio and Schreiner 2008; Depireux et al. 2001). This means that spectral and temporal processes can interact and cannot be considered in isolation. This inseparability of spectral and temporal processing implies that the combined spectro-temporal transfer function of a cell cannot be written as the product of independent spectral and temporal transfer functions; i.e., the spectral tuning of a neuron changes over time. In cat and ferret AI, less than 10% of neurons were shown to be separable (Atencio and Schreiner 2008; Depireux et al. 2001). However, separability is a continuous variable and the degree of separability can vary substantially.

Areal Organization: Spectral modulation information derived from STRFs can undergo a transformation between thalamus and cortex (Miller et al. 2002). On average, spectral integration, as measured by excitatory bandwidth and spectral modulation preference, is similar across both stations (mean Q: thalamus = 5.8, cortex = 5.4; upper cut-off of spectral modulation transfer function: thalamus = 1.30 cycles/octave, cortex = 1.37 cycles/octave). However, modulation properties of cortical neurons are not strictly predictable from individual thalamic inputs to the cortical neuron (Miller et al. 2002) indicating the relevance of cortico-cortical interactions in shaping spectral modulation preferences.

STRFs in AI and the dorsal-caudal field (DC) of the guinea pig, both primary/core areas, revealed diversity in excitatory and inhibitory bandwidths but showed no clear field differences. The ventrorostral belt area also showed STRF types similar to those in AI and DC. However, the proportions of STRF types were significantly different, suggesting a difference in spectro-temporal processing between the ventrorostral belt and the core areas (Rutkowski et al. 2002).

Spectral properties of AI and AAF receptive fields in mice were largely similar, although STRF bandwidths were slightly broader in AI than in AAF. In both, AI and AAF, only a small proportion of STRFs were spectro-temporally inseparable, e.g., revealing slanted STRFs. This suggests still a fairly independent processing of temporal and spectral aspects in these core areas (Linden et al. 2003). In cat PAF, a higher hierarchy core area, about half of the neurons have non-separable STRFs (Loftus and Sutter 2001) indicating a potential increase in spectral–temporal interactions at later stages of the cortical pathways.

Attempts to derive STRFs in prefrontal cortex of awake macaque monkeys (Averbeck and Romanski 2006; Cohen et al. 2007) did not reveal significant internal structures despite the fact that neurons responded strongly to acoustic stimuli, especially if they were complex in structure, such as vocalizations. A faithful time-frequency representation appears to be less useful at this stage and other processing aspects, such as time-probability representations, may play a larger role (Romanski and Averbeck 2009).

Noninvasive imaging methods showed selective tuning to combined spectro-temporal modulations in the primary and secondary auditory cortex in humans. The overall low-pass modulation rate preference matched the modulation content of natural sounds. These results suggest that complex signals are decomposed and processed according to their modulation content, the same transformation used by the visual system (Langers et al. 2003; Schönwiesner and Zatorre 2009).

Laminar Organization: In cat AI STRFs show some systematic changes with cortical depth, although STRFs within several $100\,\mu\text{m}$ of each other are usually quite similar. Layer-dependent spectral modulation behavior includes single and multipeaked excitatory and suppressive regions, resulting in bandpass and lowpass filter shapes, and narrow-band and broad-band filter widths. The width of the excitatory area was broadest in infragranular layers. In infragranular layers, STRF structure was more varied especially with regard to the position and structure of inhibitory subfields (Atencio and Schreiner 2010b).

The layer-dependent behavior of spectral modulation processing is dissimilar to that of temporal modulations that have a stronger tendency for a columnar, layer-independent behavior (Atencio and Schreiner 2010b). Differences in the preferred spectral modulation range across cortical laminae are quite common. In about 70% of penetrations, significant interlaminar differences can be detected, whereas this is only true for ∼30% of penetrations for temporal modulations (Atencio and Schreiner 2010b). On average, layer V neurons have the highest preferred spectral modulation frequencies. Compared to layer IV, spectral MTFs are broader and their upper cut-off frequency higher in layers V and VI. This filter broadening and increase in preferred spectral modulation frequencies in infragranular layers can be accounted for by

the shift of the strength and location of inhibitory sidebands. Spectral integration appears to increase in infragranular layers (Wallace and Palmer 2008; Volkov and Galaziuk 1989; Atencio and Schreiner 2010b). Responsiveness of infragranular layers to higher modulations than in granular layers clearly requires additional inputs not provided by a simple columnar feedforward stream from the thalamo-recipient layers.

In cat AI, STRFs are less separable in supra- and infragranular layers, indicating that spectral and temporal processing aspects become more interdependent compared to the main thalamic input layer. In granular layers, the STRF nonlinearities were most asymmetric, revealing that in these layers responses are greatest for stimuli that are highly matched to the STRF. On average, the STRF nonlinearity of supragranular neurons showed the same degree of asymmetry as granular layer neurons. Infragranular neurons, however, had a clearly reduced asymmetry, suggestive of a processing manner less sensitive to the phase, or polarity, of the spectro-temporal envelope.

Receptive fields in the cortical input layers may be predominantly created via three general schemes: inheritance from thalamic inputs, constructive convergence of different narrow thalamic and cortical inputs, and/or by assembly convergence of combined, broader thalamic and cortical inputs (Miller et al. 2001). After this initial integration stage, further transformations occur related to the primary interlaminar flow of information from the thalamocortical input layers to the supragranular and then to infragranular output layers, by intralaminar cortico-cortical inputs as well as cortico-cortical feedforward and feedback connections (Wallace et al. 1991; Mitani and Shimokouchi 1985; Mitani et al. 1985; Winer 2006). The direction of STRF changes, however, is not strictly linked to a simple interlaminar flow pattern from thalamic input layers to supra- and infragranular output layers. Changes in modulation properties captured in STRFs make it feasible to dissect laminar-specific, module-specific, and field-specific variations in the cortical processing regime and can help to determine whether common functional patterns pertain to cortical or subcortical inputs, and how they reflect local, lamina-specific circuitry (Atencio and Schreiner 2010a, b).

5.2 STRF Differences Between Cell Classes

Excitatory pyramidal neurons and inhibitory interneurons constitute the main elements of the cortical circuitry and have distinctive morphologic and electrophysiological properties. Functional differences between these different neuronal classes have been found in mammalian cortex (Bartho et al. 2004; Bruno and Simons 2002; Hirsch 2003; Simons and Carvell 1989; Swadlow and Gusev 2002; Zhang and

Alloway 2004). Differences in spike duration and amplitude ratios are associated with specific classes of cortical neurons. "Regular-spiking" neurons (RSUs) have slow action potentials (initial negative wave >300 μs) and are presumably excitatory pyramidal cells, though some inhibitory interneurons also show this spike waveform (Bruno and Simons 2002; Kawaguchi and Kubota 1993; Swadlow 2003; Simons and Carvell 1989). "Fast-spiking" or "thin-spike" neurons (FSUs) have shorter action potentials (initial wave <200 μs) and are associated with inhibitory interneurons, although some excitatory neurons also show this spike waveform (Connors and Gutnick 1990; McCormick et al. 1985).

Excitatory sharpness of frequency tuning among simultaneously recorded fast-spiking and regular-spiking neurons differs despite the similarity of layer and local CF. Fast-spiking cells have slightly broader spectral tuning than RSUs. At a given intensity, fast-spiking inhibitory neurons exhibit less-selective frequency tuning than nearby excitatory neurons (Atencio and Schreiner 2008; Wu et al. 2008). A possible consequence of the wider FSU bandwidth is that the spike-based tuning of RSUs, the potential synaptic target of FSUs, is narrower than their synaptic inputs (Tan et al. 2004; Wu et al. 2008). No significant differences were found between FSUs and RSUs in relation to best spectral modulation frequency and spectral MTF width. Although the range of preferred spectral modulations values does not differ for the two cell distributions, the manner in which FSUs and RSUs respond to spectral and temporal envelope modulations does differ. A slightly higher proportion of RSUs show band-pass spectral modulation transfer functions (25%) as compared to FSUs (15%). Response latency was shorter for FSUs versus RSUs within a given cortical layer (Atencio and Schreiner 2008). This could enable them to transmit feedforward inhibition to nearby cells.

STRF structure differs between FSUs and RSUs. FSU STRFs are more separable, thus dissociating more fully spectral and temporal processing, since they can be approximated as the product of two independent functions. Whether this reflects different cortical connection patterns and/or different distributions and kinetic properties of GABAergic inputs to RSUs (Hefti and Smith 2003) is unknown, since detailed accounts of cortico-cortical inputs to inhibitory neurons are not yet available. The nonlinearities associated with the two cell classes revealed a stronger asymmetry for FSUs indicative of higher feature selectivity.

These global functional differences between RSUs and FSUs suggest clear distinctions between putative excitatory and inhibitory neurons that shape auditory cortical processing. FSUs have response characteristics more closely related to thalamic input properties than RSUs. Connected thalamocortical neuron pairs usually differ in most of their modulation properties (Miller et al. 2001). Intracortical

recurrent excitation appears to amplify the thalamocortical inputs to determine stimulus selectivity of cortical neurons (Wu et al. 2008). Cortical modulation likely is also shaped by local inhibitory mechanisms. The precise role of inhibition in determining modulation preferences is still unclear (Kurt et al. 2006) and contributing factors, such as convergence of different modulation ranges and synaptic depression/facilitation, play major roles in the modulation of cortical responses (Eggermont 2002; Wehr and Zador 2005).

Differences in STRFs of RSUs and FSUs provide a useful first step in the analysis of local circuits and laminar functional diversity and segregations within an auditory context. The extension of this approach to nonlinear, multi-feature receptive fields is required and will further delineate systematic processing differences between cell types.

5.3 Multi-filter Spectral Analysis

One of the advantages of the linear-nonlinear STRF/MID characterization is that it provides a rigorous framework to predict neuronal response behavior to novel sounds. Some success in STRF-based response prediction and stimulus reconstruction has been reported for auditory cortical neurons (e.g., Kowalski et al. 1996b; Versnel and Shamma 1998; Mesgarani et al. 2009). However, other studies have fallen short of successfully predicting responses to complex sounds, especially when test stimuli differ in their statistical properties from those sounds used to derive STRFs (e.g., Machens et al. 2004; Sahani and Linden 2003; Theunissen et al. 2000). One possible cause for low predictive power may be that standard STRFs/MIDs represent a single stimulus dimension that influences a neuron's response. In visual cortex it has been shown that an additional stimulus dimension may be necessary to provide a more complete depiction of the effective stimulus configurations (Rust et al. 2005). An extension of the information-based MID method has demonstrated that auditory cortical neurons as well are better characterized by at least two independent but interacting spectro-temporal filters (Atencio et al. 2008). In this method, two parametrically independent but jointly operating filters are iteratively adjusted until the mutual information between stimulus and response is maximized, resulting in two (or more) MIDs, and their associated nonlinearities. The first MID (MID1) maximizes the MI with respect to one STRF and the second MID (MID2) is an additional STRF that further maximizes the MI. The concurrent operation of these two MIDs in combination with their nonlinearities can capture a substantially larger proportion of the mutual information of cortical neurons than the STA or a single MID alone (Sharpee et al. 2004a, b; 2008).

The main observations (Atencio et al. 2008, 2009) from this approach include: (1) All neurons in cat AI with an STA/MID1 also have a significant although slightly less informative MID2, i.e., each neuron can be modeled as a combination of at least two stimulus dimensions (Fig. 13.7). The contribution of the MID2 to the combined mutual information is in the range of 20–40%. (2) MID1 and STA-based STRF and their nonlinearities are highly correlated, thus validating the use of spike-triggered averaging in previous studies to identify the strongest contributing filter (Fig. 13.7). (3) The nonlinearities of the two MIDs differ in character. The nonlinearity of the first STA/MID is asymmetric and sigmoidal, while the nonlinearity of the second MID is usually symmetrical. The asymmetric nonlinearity is typical for a feature detector. The symmetric nature of the MID2 nonlinearity shows that for this dimension the neuron has an increased probability of firing when a stimulus is either correlated or anti-correlated with the filter (Fig. 13.7). This type of nonlinearity is often seen in visual neurons that are envelope-phase insensitive or shift-invariant (Emerson et al. 1992; Dellen et al. 2009). The difference in the shape of the nonlinearities implies that a given AI neuron in this extended model contains functional subunits that both threshold (MID1) and square (MID2) the outputs of the individual filters. (4) Best frequencies of the two filters are usually closely matched. However, the shape of the two MIDs (i.e., the distribution and relationship of excitatory and inhibitory subregions) differs, reflecting their orthogonality and providing different constellations of spectral modulation preferences. The preferred spectral envelope modulation frequencies of a population of AI neurons span an equally wide range for both MIDs but are uncorrelated. As a consequence, spectral processing properties of cortical neurons reflect at least two differently tuned spectral filters (Fig. 13.7e). (5) The two MIDs cooperate in a nonlinear fashion, creating combination-sensitive, and sometimes synergistic, processing. On average, the combined applied filters account for 28% more information than the sum of each filter in isolation. This type of nonlinear combination-sensitivity differs from previously described combinations-sensitivity in subcortical and cortical auditory stations. It requires two interacting filters and cannot be explained by the shape and properties of a single, one-dimensional nonlinearity as is the case for combination-sensitivity described for tone-on-tone interactions, for example, in bats (Suga 1984), or in awake marmosets (Sadagopan and Wang 2009).

Of relevance is that the contributions of MID2s in subcortical stations, such as the central nucleus of the inferior colliculus or the ventral nucleus of the medial geniculate body, seem to be absent or significantly smaller than in AI (Atencio, Shih, Schreiner unpublished observation). This suggests that the generation of multiple STRFs/MIDs expressed in a single neuron is an emergent property of

Fig. 13.7 Auditory cortical responses are more fully characterized by two filters and their associated nonlinearities. **a** MID1 s of five single AI neurons (*red*: excitatory regions, *blue* suppressive/inhibitory regions). Same neurons as in Fig. 13.6. **b** MID2 for the same neurons. Note similar CFs but different distributions of excitatory and inhibitory subregions. **c** MID1 nonlinearities. MID1 nonlinearities are typically asymmetric, i.e., positive stimulus/MID correlation can result in increased firing rates, whereas negative correlations have little effect on firing rate. **d** MID2 nonlinearities. Note that the nonlinearities are mostly symmetric, i.e., either positive or negative stimulus/MID2 correlations can increase firing rate. **e** Distribution of the best spectral modulation frequency of MID1 and MID2 with marginal distribution histograms. The preferred spectral modulation frequency of the two filters is essentially uncorrelated
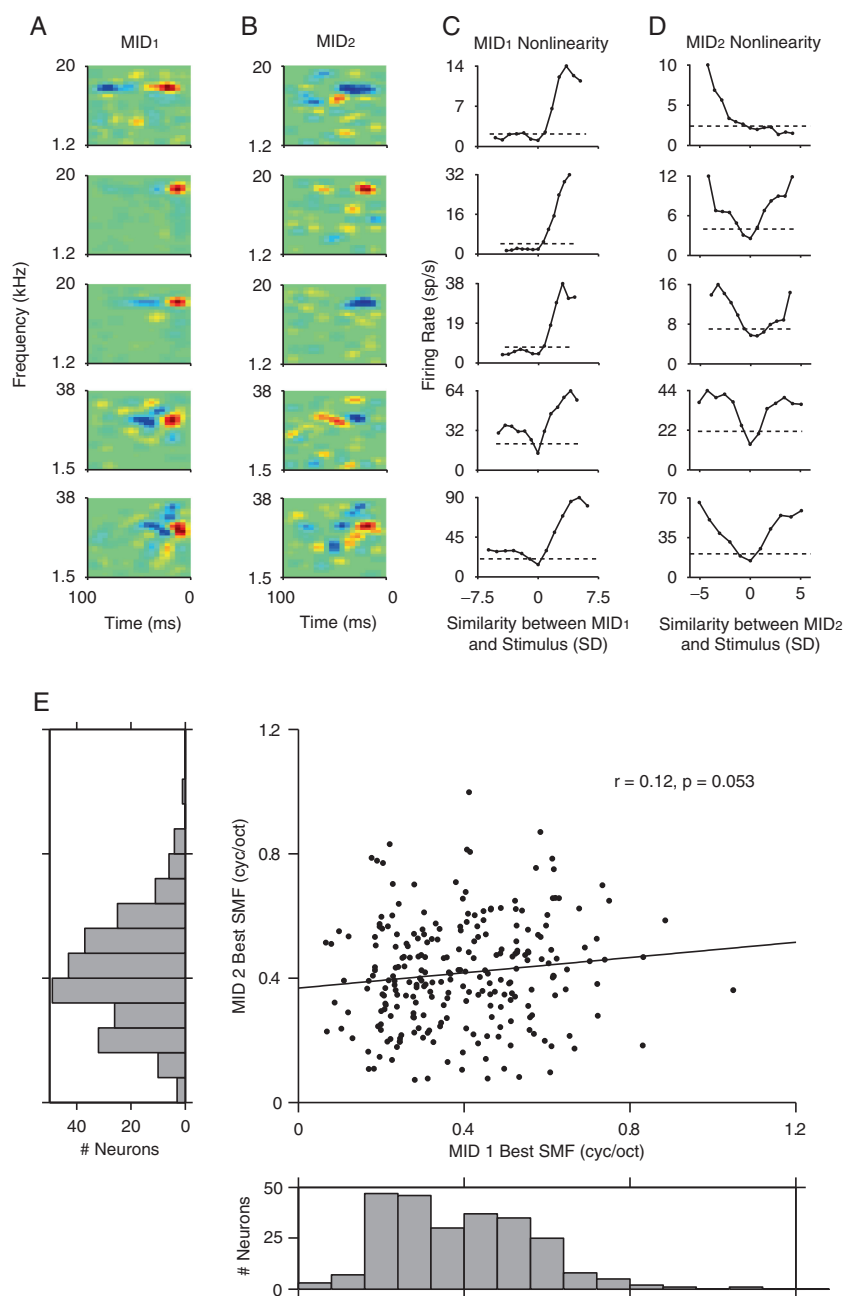
auditory cortex, similar – but not identical – to processing principles emerging in visual cortex, such as simple and complex cells (Hubel and Wiesel 1962; Movshon et al. 1978). This finding suggests that there may be general principles in cortical processing and hierarchical computation across different sensory modalities. As of yet, it is unknown whether higher cortical areas also have multiple STRF/MID filters.

Laminar Organization: For STRFs and MIDs in cat AI, a sequential evolution within the interlaminar columnar microcircuit is evident (Atencio and Schreiner 2010a, b; Atencio et al. 2009). Processing in all AI layers is more completely captured with a two-filter MID characterization. In granular layers, the MID1 is most dominant, with a high degree of feature selectivity and separability (Fig. 13.8). A MID2 is found in all layers although its contribution is smaller in granular layers (Fig. 13.8). The two MIDs, and their nonlinearities, differ in shape, and show different properties with cortical depth. In supra- and infragranular layers, the MID1 contribution is reduced, and the synergy or positive interactions between the filters increases (Atencio et al. 2010a) (Fig. 13.8).

The sequential information processing across the different AI layers is progressive and becomes more complex, and synergistic, as the auditory signal moves from
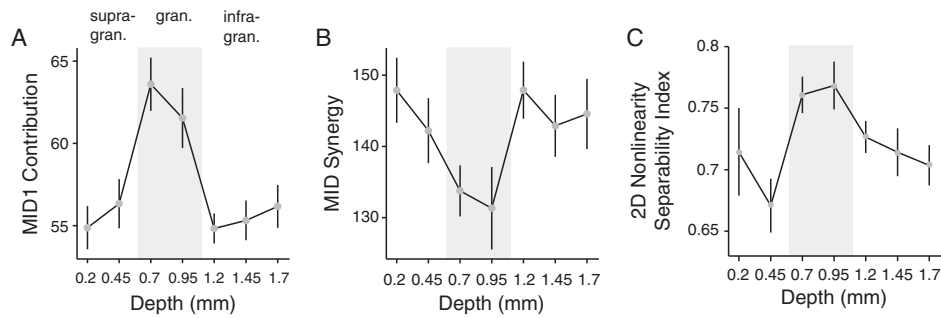
Fig. 13.8 Laminar differences exist for basic multi-MID characteristics. **a** MID1 contribution across the cortical laminae. The MID1 contribution (in %) quantifies the MID1 mutual information relative to the information from the joint MID1 and MID2 processing. *Gray area* corresponds to the granular layers IIIb and IV. Supra- and infragranular layer regions are indicated. MID1 provides the strongest contribution to granular layers. In the supra- and infragranular layers, the contribution of MID2 is, on average, nearly as strong as that of MID1. **b** MID synergy (in %) expresses the cooperativity between the two MIDs. Joint application of the two filters often results in higher mutual information values than the sum of the two MIDs applied in isolation. Highest cooperativity is typically found outside the granular layers. **c** Separability of the joint 2D nonlinearities of the two MIDFs. High values correspond to reduced interactions between the two nonlinearities. Supragranular layers show the least separability suggestive of nonlinear interactions between the two MIDs and their individual nonlinearities. Adapted from Atencio et al. (2009)

thalamic input to cortical output layers. Spectral and temporal processing becomes more complex in structure, less linear in interaction and response generation, and potentially more abstract and stimulus-variation tolerant. All AI neurons exhibit some degree of inseparability of their two-dimensional nonlinearity, i.e., the two filters cooperate to various degrees. The most separable joint nonlinearities are in granular layers, with significantly lower separability and, thus, increased cooperativity, in supragranular and infragranular layers (Fig. 13.8). This indicates that the rule that governs the joint, two-filter processing is not a simple product of two one-dimensional nonlinearities, and implies that information processing becomes more nonlinear and complex as the synaptic distance from granular layers increases. The relationship of the emergence of multiple spectro-temporal filters in auditory cortex with specific computations and task-specific processing remains elusive. Formation of enhanced stimulus invariance may indicate improvements in foreground/background separation and noise tolerance as well as in perceptual and conceptual category formation.

5.4 Receptive Fields: Constancy Versus Malleability

5.4.1 Short-Term Changes of Receptive Fields

Receptive field properties are measured at certain points in time, after presentation of a specific stimulus set. Thus, the empirically determined receptive fields of cortical neurons are thought to be approximations of their "true," intrinsic functional characteristics. However, many aspects can affect the outcome of receptive field estimations. Neuronal parameter sensitivity and selectivity may depend, among other conditions, on stimulus statistics, response adaptation, task conditions, context, and attention, consistent with complex, nonlinear and recurrent processing in neural assemblies (Christianson et al. 2008; Fritz et al. 2007c; Pienkowski and Eggermont 2009).

Spontaneous variations of STRF parameters in repeated estimations have been shown to usually be quite small, suggesting that neuronal properties can be stable over hours and days (Blake and Merzenich 2002; Elhilali et al. 2007).

However, state-dependencies, such as arousal, alertness, attention, stimulus statistics dependencies – including variance, mean, and skewness of the distributions – and behavioral context and task-dependencies can induce temporary RF perturbations that, under certain circumstance, may become long-lasting changes, usually referred to as reorganizational plasticity.

A main utility of STRFs is their versatility in capturing and classifying the large range of cortical processing properties. However, a significant problem is that responses are nonlinear, adaptive, and sensitive to biased stimuli. With nonlinear processing, STRFs inevitably become stimulus and context dependent, e.g., altering polarity, shape and extent of STRFs (Christianson et al. 2008). Especially when applying non-Gaussian, natural stimulus statistics, STA methods may produce biased STRFs leading to features that are shifted away from the most relevant dimensions (David et al. 2009; Machens et al. 2004; Nagel and Doupe 2006; Rotman et al. 2001). STRFs computed for natural stimuli in a nonlinear MID model have been shown to be significantly different from those computed with a linear STA model, and usually show a better description of the neuronal responses (Sharpee 2007). A number of potential causes for nonlinear responses

have been proposed, including short-term depression (David et al. 2009), divisive surround inhibition (Carandini et al. 1998), or thresholding of spiking output (Qiu et al. 2003), although definitive links between cellular and synaptic mechanisms and the model nonlinearities remain to be fully established.

STRF perturbations have been described for a number of stimulus parameters, such as the density and bandwidth of random cord and ripple stimuli (Blake and Merzenich 2002; Gourevitch et al. 2009; Norena et al. 2008), and for stimuli with more natural parameter statistics, such as speech and vocalizations (David et al. 2009; Theunissen and Shaevitz 2006). For random chord stimuli with different sound densities, STRFs often develop larger inhibitory fields and narrower spectral tuning (Valentine and Eggermont 2004; Blake and Merzenich 2002). Comparing STRFs obtained for dynamic ripple stimuli (composed of a single pair of spectral/temporal properties at any given time) and ripple noise stimuli (composed of multiple spectral and temporal features at any given time) also revealed some differences. Cells with low firing rates often respond better to the dynamic ripple than to the ripple noise, a highly nonlinear behavior (Escabí and Schreiner 2002). More natural stimulus statistics, as compared to Gaussian distributions, also have large effects on the estimated filters and nonlinearities, and seem to increase precision of temporal coding and emphasize the most informative features of natural sounds (Theunissen and Shaevitz 2006; Woolley et al. 2006).

Accommodation of the neural response to an ongoing stimulus is called adaptation. Input–output functions for intensity, temporal preferences, or spectral receptive fields are shifted or altered (Gourevitch and Eggermont 2008; Ohl and Scheich 1996; Pienkowski and Eggermont 2009; Ulanovsky et al. 2004). Consequences of adaptation are thought to rearrange the neural response sensitivity of neurons to optimize their information transmission. This can be achieved by providing a better match of the statistical distribution in the ongoing stimulus and the response preferences.

Attention is essential for performing auditory tasks (see Chapter 29). Neural correlates of this perceptual ability have been demonstrated in STRFs of AI in behaving ferrets (Fritz et al. 2003; Fritz et al. 2005, 2007c) during the detection of a target tone embedded in noise. Compared with responses in the passive state, the gain of STRFs decreased in most cells and STRF shape changes were specific to the stimuli in the task, and were strongest in cells with best frequencies near the target tone. These adaptations accentuate the spectro-temporal representation of the target tone relative to the noise (Atiani et al. 2009).

The non-static properties of spectral integration can also be seen with changes in behavioral states such as sleep versus wakefulness (Edeline et al. 2001; Edeline 2003; Issa and Wang 2008; Pena et al. 1999). During slow-wave-sleep, as compared to waking animals, the receptive field size – and implicitly the spectral integration behavior – varied as a function of the changes in evoked responses: it was reduced for cells whose responses were decreased, and enlarged for the cells whose responses were increased (Edeline et al. 2001).

5.4.2 Long-Term Plasticity of Spectral Modulation Filters

Cortical representations of signal dimensions have been shown to be alterable over extended periods of time when behavioral significance is attached to parts of those dimensions (Allard et al. 1985; Calford and Tweedle 1988; Gilbert et al. 2009; Recanzone 1998; Recanzone et al. 1992, 1993). Animals that learn to distinguish between certain spectral or temporal properties of sensory stimuli show an expanded and/or more refined cortical representation of relevant stimulus features and concomitant changes in perceptual ability (Jenkins et al. 1990; Recanzone et al. 1993).

Many studies have been undertaken which demonstrate plasticity in the receptive field of auditory cortical neurons during classical conditioning (e.g., Diamond and Weinberger 1986, 1989; Edeline 1998; see Chapter 22). Significant changes in discharge activity in auditory cortical cells follow the associative pairing of an acoustic conditioned stimulus with an unconditioned stimulus. Since the extent of these physiological changes does not occur during the sensitization and extinguishing phases of the training session, it becomes clear that the associative process plays the most salient role in discharge plasticity. Plasticity in auditory cortical neurons and the spatial distribution of receptive field properties have been demonstrated for a number of other learning conditions, e.g., operant detection and discrimination training and exposure to altered sensory inputs (e.g., Diamond and Weinberger 1986; Harrison et al. 1991; Rajan 2001; Robertson and Irvine 1989). For example, the distribution of the CF of AI neurons can be altered by frequency discriminative training (Recanzone et al. 1993). The representation of the frequency domain over which animals were trained expanded, and the excitatory bandwidth of cortical neurons was sharpened with training, reflecting task-dependent demands on sound processing.

Changes in spectral bandwidth properties of auditory cortical receptive fields occur during and after certain forms of perceptual learning. Prolonged exposure to a spectral profile with a fixed spectral periodicity (e.g., 1 ripple/octave) embedded into a perceptual training task influences the distribution of neuronal ripple transfer functions and pure-tone tuning curves (Keeling et al. 2008). The animals had to discriminate between stimuli that contained equally spaced formants but differed in their frequency positions. Following discrimination training, the preferred ripple density shifted toward the spectral spacing in the training stimuli (Fig. 13.9).
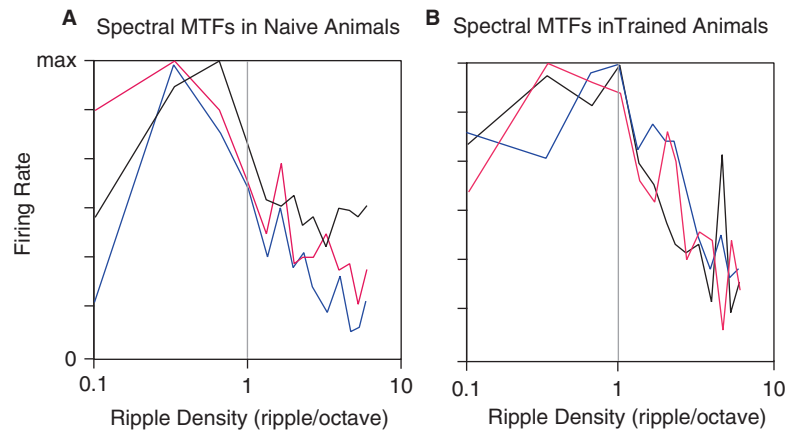
Fig. 13.9 Effects of behavioral training on spectral modulation transfer functions (sMTFs). **a** Population sMTFs for three untrained cats (Keeling et al. 2008). **b** population sMTFs for cats that were trained to perform a spectral envelope discrimination task. The training stimulus was a three-octave wide ripple sound with a sinusoidal spectral envelope of 1 ripple/octave (indicated by the *vertical gray line*). Animals were required to discriminate between stimuli with shifted positions of the spectral peaks (envelope phase) but with constant peak spacing. Note the shift in the preferred ripple frequency toward the trained ripple spacing and the relative increase in firing rate at the trained ripple density. Adapted from Keeling et al. (2008)

This is equivalent to an expansion of cortical space for the most task-relevant stimulus feature and increases stimulus sensitivity. In addition, the bandwidth of ripple transfer functions, a direct measure of the selectivity of neurons to specific formant spacings, became significantly narrower (Keeling et al. 2008) in conjunction with a narrowing of the bandwidth of pure-tone tuning curves. This change corresponds to an increase in selectivity.

Exposure to stimuli without overt behavioral consequence or explicit learning task can also have a long-term effect on the properties of cortical receptive fields (Gourevitch et al. 2009).

These observations indicate that the rules of short- and long-term cortical plasticity alike can operate on elemental stimulus features independent or in conjunction with others. The effect is governed by the stimulus statistics and their relationship to associative tasks. The cortex seems to use these features to guide several forms of receptive field reorganization, including reorganization of feature maps, plasticity of spectral and temporal specificity and selectivity, emphasis of relevant parameter ranges and combinations, and altered strength of evoked responses.

6 Synaptic Mechanisms of Spectral Processing

6.1 Synaptic Frequency Tuning

Most studies of cortical receptive fields have relied on extracellular recordings of spike output. However, recent advances in understanding the organization and dynamics of cortical circuits have been obtained using intracellular techniques such as in vivo whole-cell voltage-clamp recording. This is primarily for two reasons: first, spiking receptive fields necessarily are subsets of the underlying synaptic receptive fields; and second, excitatory responses are strongly governed by the inhibitory inputs received by a given neuron. Extracellular and optical approaches cannot at present directly measure these subthreshold inhibitory responses. Thus in vivo whole-cell recording experiments have provided the highest resolution descriptions of cortical tuning curves and receptive field properties, particularly for responses to pure tones and frequency modulation sweeps.

In terms of spectral tuning in adult cat, rat, and mouse AI, a major feature of synaptic receptive fields is that the relative strengths of excitatory and inhibitory inputs are proportional across tone frequency, i.e., synaptic excitation and inhibition are essentially balanced in mature AI (Froemke et al. 2007; Tan and Wehr 2009; Tan et al. 2004; Volkov and Galazjuk 1991; Wehr and Zador 2003; Zhang et al. 2003). Excitatory and inhibitory responses are balanced in the sense that they are usually co-tuned, i.e., sharing best frequencies and having correlated response magnitudes across other frequencies (Fig. 13.10a, c, d). However, although the relative amplitudes of inhibitory responses scale with the size of excitatory responses for a given stimulus, the onset of inhibition is delayed by a few milliseconds (Wehr and Zador 2003). As a consequence, there is a brief window in which excitatory responses can sum together and generate action potentials. This phase lag for inhibition is likely due to the architecture of thalamocortical circuitry in that there are few if any direct inhibitory projections from the MGB to AI (Winer 1992), leading to a short disynaptic delay between the onset of excitation and the onset of inhibition.
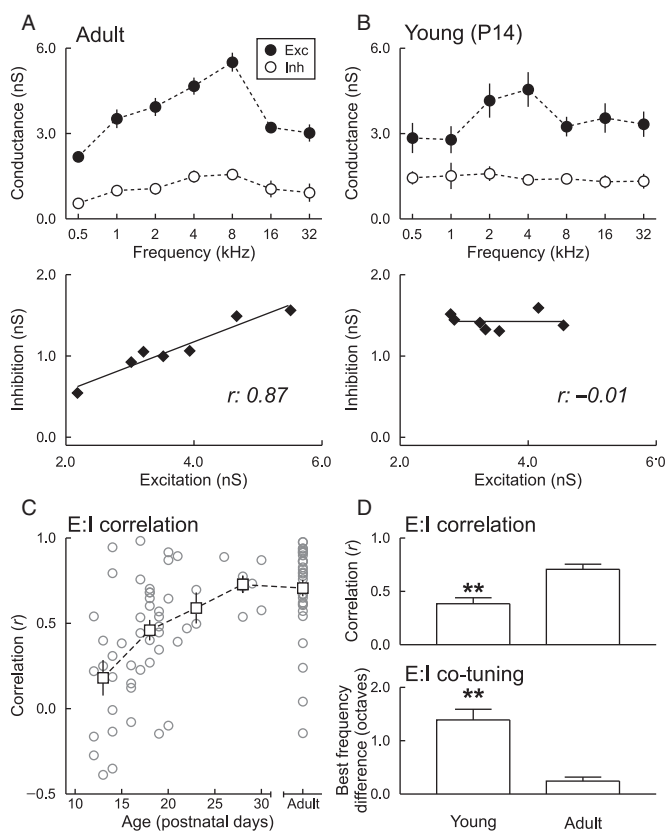
Fig. 13.10 Spectral tuning of synaptic excitation and inhibition in adult and developing rat AI. **a** Balanced tone-evoked excitation and inhibition in adult AI. Whole-cell recording from an adult (3-month old) rat. *Top*, frequency tuning of excitatory (*filled symbols*) and inhibitory (*open symbols*) conductances. *Bottom*, correlation between excitation and inhibition. Error bars represent s.e.m. **b** Imbalanced excitatory and inhibitory frequency tuning early in development. Whole-cell recording from AI of a young (P14) rat. **c** Increase of excitatory–inhibitory balance during the AI critical period. At the end of the second postnatal week, excitation and inhibition were uncorrelated. By the end of the third week, the correlation rapidly improved, and by the end of the first month, the excitation–inhibition correlation was similar to that measured in adult animals. **d** Summary of changes to excitatory–inhibitory balance during development. *Top*, mean correlation between excitation and inhibition in young (P12-21) and adult animals. *Bottom*, mean difference in excitatory and inhibitory best frequencies in young and adult animals

While on average, synaptic frequency tuning of AI neurons is balanced, sensory-evoked excitatory and inhibitory responses are not always so closely matched. For some cells in adult AI, excitation and inhibition are uncorrelated or even anti-correlated (Fig. 13.10c). There is additional evidence for untuned or cross-tuned inhibitory inputs from intracellular recording studies in visual cortex (Douglas et al. 1991; Ferster 1986; Monier et al. 2003; Pei et al. 1991; Schummers et al. 2002). Recordings from interneurons in both auditory and visual cortex indicate that inhibitory cells are frequently less tuned than excitatory neurons (Atencio and Schreiner 2008; Liu et al. 2009; Niell and Stryker 2008; Sohya et al.

2007; Wu et al. 2008). Also, depending on the position of a neuron within the AI frequency map, there may be asymmetrical sidebands of inhibitory inputs within an octave or so, helping to selectively shape the responses to up or down frequency sweeps (Zhang et al. 2003). Likewise, other receptive field properties, such as intensity tuning, may be regulated by focally imbalanced inhibition (Tan et al. 2007; Wu et al. 2006). In general, diversity in the synaptic organization of cortical receptive fields might be important for detection and discrimination of different classes of auditory stimuli, and theoretical models suggest that both balanced inhibition and relatively broad lateral inhibition schemes are required to explain the range of spiking responses observed in extracellular recordings in vivo (de la Rocha et al. 2008). One challenge for future studies will be to determine how the various types of interneurons, such as basket cells and Martinotti cells (Petilla International Nomenclature Group 2008), might be activated by specific patterns of auditory stimulation and differentially affect synaptic receptive fields.

While the exact sources of intracortical inhibition remain unknown, it is also still unclear to what degree thalamic or intracortical excitatory inputs contribute to the net excitation evoked by tones or other stimuli. Kaur and colleagues (2004) reported that intracortical injections of muscimol, a GABA$_A$ receptor agonist, reduced the bandwidth of frequency-intensity receptive fields, but left characteristic frequency responses relatively intact. These results suggest that intracortical inputs help define the width of excitatory receptive fields, broadening frequency tuning curves beyond the extent determined by more sharply tuned thalamic input. However, a study by a different group attempted to isolate thalamic inputs using muscimol in combination with SCH50911 (a GABA$_B$ receptor antagonist), to prevent reduction of presynaptic transmitter release at thalamocortical afferents while simultaneously reducing intracortical excitation. They found that tuning curve width was unaffected by this pharmacological treatment (Liu et al. 2007), suggesting that the range of thalamic input alone may set the width of subthreshold frequency tuning. Regardless of the anatomical basis of synaptic receptive fields, the relative connection strengths of thalamic and intracortical inputs can be changed by various forms of experience, with intracortical synapses seemingly expressing a higher degree of plasticity than thalamic inputs (Diamond et al. 1994; Froemke et al. 2007).

6.2 Development of Synaptic Frequency Tuning

Although cortical synapses can be modified all throughout life, receptive fields are especially plastic during

developmental critical periods, epochs during which cortical circuits are particularly susceptible to changes in sensory input (Buonomano and Merzenich 1998; Hensch 2005; Katz and Shatz 1996). Auditory cortical critical periods usually last for a few days or weeks, beginning just after the start of hearing, and possibly are overlapping or staggered for different components of the auditory system or different receptive field properties.

In rodent AI, representations of sound frequency and intensity can be profoundly altered if young animals are exposed to pulsed pure tones for a brief period immediately after hearing onset, between postnatal day (P) 11 and 13. This form of patterned exposure was found to both rapidly alter tonotopic map structure and close the cortical critical period for frequency tuning (de Villers-Sidani et al. 2007; Dorrn et al. 2010). Conversely, exposure to pulsed white noise stimuli early in life was found to degrade the tonotopic organization of rodent AI (Zhou and Merzenich 2007). Therefore, exposure to either pulsed pure tones or white noise bursts has opposing effects on AI feature selectivity. In both cases, however, receptive fields are remodeled to match the statistics of the sensory environment.

Exposure to continual white noise, rather than periodic bursts of noise, has also been found to degrade cortical receptive fields. However, continual noise exposure prolongs the extent of the critical period into adulthood (Chang and Merzenich 2003). Thus while the spectral structure of acoustic stimuli controls the formation of AI frequency tuning profiles, the temporal pattern of sensory input regulates the overall duration of the AI critical period. Continual stimuli keep the critical period open, perhaps because of the strong neuronal adaptation driven by tonic input, while pulsed or phasic input precociously close the critical period, probably because of the increase in correlated or coincident neuronal activity that should drive long-term synaptic modifications throughout the cortical network (Dorrn et al. 2010).

These forms of receptive field plasticity can also be observed at the synaptic level. In rodent AI, synaptic maturation occurs between P12-21 (Dorrn et al. 2010; Oswald and Reyes 2008). Excitatory inputs seem to mature first, and are tuned for sound frequency by approximately P14 (de Villers-Sidani et al. 2007; Dorrn et al. 2010; Sun et al. 2010). However, inhibitory inputs are potentially equally as strong in young versus adult AI, but exhibit little to no frequency tuning after the second postnatal week, resulting in imbalanced excitation and inhibition and erratic receptive field organization (Fig. 13.10b). After three postnatal weeks of relatively normal acoustic experience, though, cortical inhibition progressively becomes tuned to sound frequency, matching and balancing excitatory inputs (Fig. 13.10c, d). This experience-dependent process of inhibitory maturation can be affected in a similar manner to tonotopic maps: continual white noise exposure delays maturation, while

repetitive tonal exposure accelerates balancing of excitation and inhibition (Dorrn et al. 2010). Furthermore, studies in AI brain slices have revealed that postnatal hearing loss, even to a partial degree, leads to persistent changes in the efficacy of cortical synapses (Kotak et al. 2008). Thus early in life, the patterns of acoustic experience – or lack thereof – lead to rapid modifications of excitatory and inhibitory synaptic strength, which in turn govern the organization of receptive fields, the output of cortical circuitry, and the perception of auditory stimuli.

6.3 Plasticity of Frequency Tuning in the Adult Cortex

After the critical period has ended, patterned auditory stimulation by itself is no longer sufficient to drive long-term synaptic modifications or enduring changes to cortical receptive field properties. Rather, adult receptive field plasticity also depends on stimulus history and internal state variables such as arousal level and motivation. This behavioral context is often conveyed by activation of subcortical neuromodulatory systems that directly project to AI, e.g., the cholinergic nucleus basalis (Weinberger 2007; see Chapter 22).

Acetylcholine release is essential for learning and memory, and is believed to be involved in arousal and attentional modulation of cortical responses (Froemke et al. 2007; Parikh et al. 2007). Classic studies using extracellular recordings have shown that pairing pure tones of a specific frequency with electrical stimulation of nucleus basalis induces large, long-lasting enhancements of spontaneous and tone-evoked spiking (Bakin and Weinberger 1996; Kilgard and Merzenich 1998; Rasmusson and Dykes 1988). Although electrical stimulation of nucleus basalis should activate a heterogeneous population of projection neurons, including those that release acetylcholine, glutamate, GABA, and various peptides (Henny and Jones 2008; Lin and Nicolelis 2008), pharmacological evidence indicates that cortical muscarinic acetylcholine receptors are specifically required for the long-term effects on AI receptive fields of this pairing procedure. Acetylcholine has a wide range of effects on cortical neurons, but a consistent observation is increased excitability (Woody and Gruen 1987) and suppression of intracortical synaptic transmission (Metherate et al. 2005; Sarter and Parikh 2005; Xiang et al. 1998).

Intracellular recordings in vivo revealed the mechanisms by which stimulation of the nucleus basalis neuromodulatory system activates cortical networks (Metherate and Ashe 1993; Metherate et al. 1992) and enables receptive field plasticity (Froemke et al. 2007). In these latter experiments, whole-cell voltage-clamp recordings from individual neurons were obtained in anesthetized adult rat
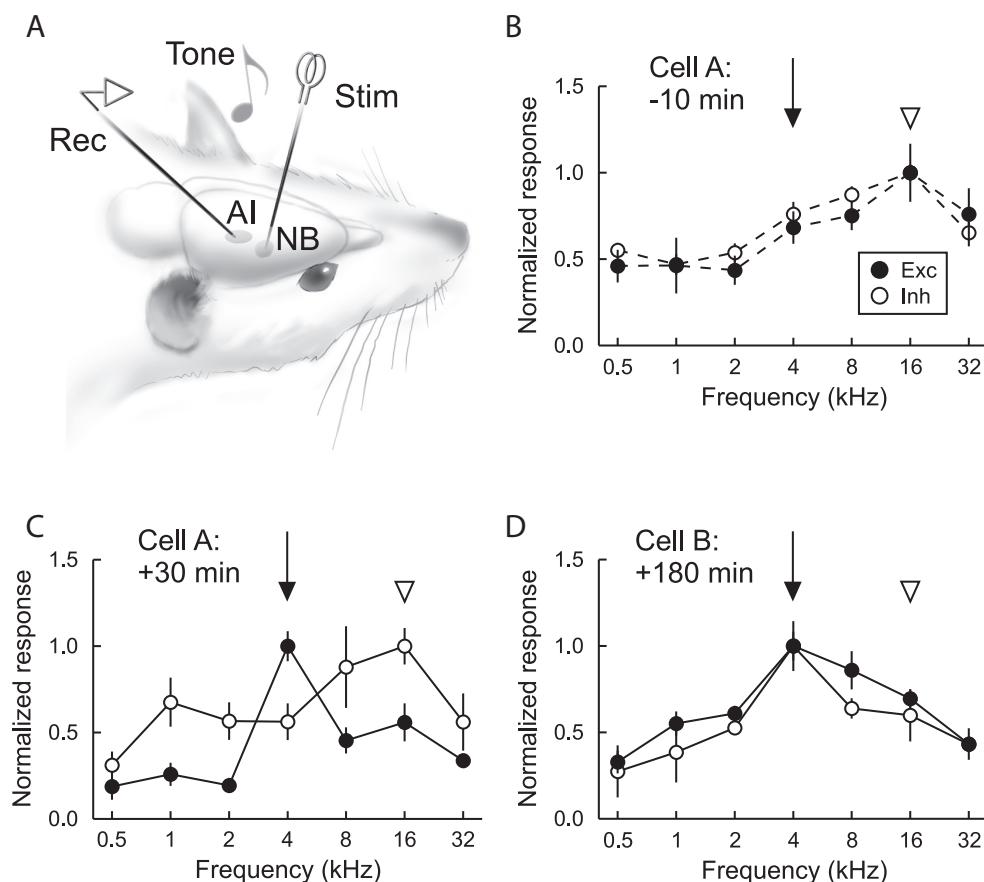
Fig. 13.11 Temporal dynamics of progressive synaptic receptive field plasticity induced by nucleus basalis pairing. **a** Experimental configuration. The stimulation electrode was acutely implanted in the right nucleus basalis, and whole-cell recordings were obtained from neurons in right AI. Pure tones of various frequencies were played to the contralateral ear, and synaptic responses were recorded in voltage-clamp. **b** Frequency tuning of synaptic excitation (*filled*) and inhibition (*open*) for the first cell 10 min prior to nucleus basalis pairing. Note the initial balance of excitation and inhibition across frequencies (linear correlation coefficient *r*: 0.9). *Arrow* indicates the paired frequency (4 kHz). *Arrowhead* indicates the original best frequency (16 kHz) for this region of AI. Error bars represent s.e.m. **c** Frequency tuning of the same cell in (**b**), recorded 30 min after nucleus basalis pairing. The paired frequency had become the best frequency for excitatory tuning but not inhibitory tuning because of the enhancement of excitation and suppression of inhibition, leading to a decrease in excitatory–inhibitory balance (*r*: 0.3). **d** Another cell from same region of AI, recorded 180 min after nucleus basalis pairing. The paired frequency was now the best frequency for both excitation and inhibition, and excitatory–inhibitory balance across all frequencies was restored (*r*: 0.9). Adapted from Froemke et al. (2007)

AI (Fig. 13.11a), and excitatory and inhibitory synaptic frequency tuning was initially determined (Fig.13.11b). Afterwards, tones of a specific non-preferred frequency were paired with electrical stimulation of nucleus basalis. Several seconds after the start of pairing, there was a large suppression of inhibitory events evoked by the paired tone, followed by a more gradual enhancement of tone-evoked excitation. These changes were long-lasting, persisting at least 20 min or more after the end of the pairing procedure. While nucleus basalis stimulation has immediate effects on both thalamo-cortical and intracortical transmission, longer-term synaptic modifications appear to be specific to intracortical connections and not to the primary thalamic input to AI (Metherate and Ashe 1993; Froemke et al. 2007).

Due to the cooperative effects of suppression of inhibition and enhancement of excitation, nucleus basalis pairing disrupted excitatory–inhibitory balance in adult AI (Fig. 13.11c). However, over a longer time period (several hours), synaptic modifications continually evolved, with inhibition progressively increasing to a higher level than before, eventually re-balancing the persistent increase of excitation at the paired frequency (Fig. 13.11d). These results indicate that the dynamics of inhibitory transmission could serve as a synaptic memory trace of the brief pairing event (Froemke et al. 2007). The duration of input-selective disinhibition may permit self-reorganization of AI receptive fields to emphasize the new preference for paired stimuli, in a manner independent of further evoked neuromodulator release. Under natural conditions, this memory trace could represent episodes or events that have acquired new behavioral meaning, or might be similar to the sorts of cortical changes that occur during perceptual learning, especially for those tasks

requiring focal attention and sensory discrimination. In this way, neuromodulatory systems allow cortical networks to selectively respond to important or novel stimuli.

Transient, focal suppression of inhibition may be a general mechanism for induction of receptive field modification in the adult cortex. During developmental critical periods, the high level of plasticity may be due to a less-refined inhibitory tone (Chang et al. 2005; Dorrn et al. 2010), permissive for alterations of cortical networks by passive stimuli. In adult cortex, however, receptive field plasticity also requires activation of neuromodulator systems, reflecting the importance of behavioral context in associative learning and memory provided by subcortical systems (Weinberger 2007). This is further demonstrated by a series of studies from Fritz and colleagues (Fritz et al. 2003, 2005), using single-unit recordings in AI of head-restrained behaving ferrets. Receptive fields of AI neurons were powerfully modified after behavioral conditioning. Excitatory and suppressive subregions of spectro-temporal receptive fields evoked by certain stimuli were altered when those stimuli were followed by tail-shock. The predominant changes to spectro-temporal receptive fields were increases of excitatory regions and reductions of suppressive regions around the conditioned tone (Fritz et al. 2003), strikingly similar to the synaptic effects of nucleus basalis pairing (Froemke et al. 2007). These changes in receptive field structure could endure for minutes to hours after conditioning, possibly serving as a memory in sensory cortex for the contingencies of behavioral training and reinforcement.

Intracellular recordings have been essential for describing cortical organization and dynamics at the synaptic level. During development, perturbations in the sensory environment drive changes in synaptic strength, functioning to model cortical receptive fields around the statistics of sensory inputs. In the adult brain, receptive field plasticity is controlled by behavioral context and motivational state, acting through neuromodulators to gate long-term changes in excitatory and inhibitory synaptic receptive fields. It remains an open question how distinct elements of cortical networks and subcortical neuromodulatory systems are recruited by various forms of sensation, experience, and internal drive for the control of synaptic modifications, circuit dynamics, perception, and cognition.

7 Conclusions and Future Directions

Elucidating stimulus-centered complex coding principles and placing them into a functional and behavioral context remains a primary goal of future studies of the auditory cortex. Without that information, hypotheses about local and global tasks and mechanisms as well as the properties of

potential processing streams in higher cortical areas and parallels among modalities remain speculative or untestable.

Linking functional organization and structural substrates that govern complex sound processing in auditory cortex is an essential step in understanding how the brain represents the auditory world and performs specific auditory tasks. Similar approaches in visual and somatic sensory cortices of cats and primates revealed fundamentally different information processing mechanisms from subcortical processing strategies. In early visual cortex, locally created stimulus-based representations include substrates for binocularity, orientation selectivity, and motion selectivity (Bishop et al. 1973; Henry et al. 1974; Hubel and Livingstone 1990; Hubel and Wiesel 1970; Movshon 1975). In somatic sensory cortex, the segregation of slowly and rapidly adapting peripheral mechanoreceptors (Mountcastle 1957), single-to-multiple whisker integration (Mirabella et al. 2001), and integration mechanisms for vibrotactile frequency information (Luna et al. 2005) each offer essential clues as to how the brain interprets sensory experience. Comparable and emergent stimulus processing attributes have not yet been clearly identified for early auditory cortical stations. Instead, it is often assumed (King and Nelken 2009) that cortical processing is largely an extension of subcortical processes with little conceptual changes in content ("what") and manner ("how") of processing. One major impediment to progress is that uniquely auditory cortical processing principles have not been unambiguously identified. The observation of emergent, multi-dimensional spectro-temporal feature processing in AI (Atencio et al. 2008) may hold the key to an advancement in stimulus-centered cortical processing attributes.

The observation of an ordinal laminar progression of *how* information is processed – as opposed to *what* stimulus content is processed – represents a departure from traditional models of auditory cortical stimulus feature extraction and representation (Atencio et al. 2009). The additional informative dimensions express further relevant spectro-temporal aspects. Their interactions with the traditional, feature-selective filter (Atencio et al. 2008) are reminiscent of the notion of combination-sensitivity epitomized in the processing of biosonar signal (Portfors and Felix 2005; Suga 1984; Yan and Suga 1996). However, differences in the filter nonlinearity and the synergistic cooperation of the filters introduce new processing dimensions beyond the combination of highly defined stimulus features that is already present in subcortical stations (Gans et al. 2009; Olsen and Suga 1991; Peterson et al. 2008; Portfors and Felix 2005). Further investigations along these lines, especially in non-primary/belt areas may provide a key step in our understanding of laminar RF transitions and the evolution toward increasingly more complex, nonlinear, robust, stimulus invariant, categorical and/or abstract processing principles.

Cortical microcircuits should be understood according to their different tasks, requirements of the auditory system, and how cortical connection patterns subserve these operations. Simple stereotypical columnar maps repeated across the spatial extent of auditory cortex can be excluded as a dominant computational principle. However, it is conceivable that the main functions of auditory cortex circuits may remain hidden when applying simple, stimulus-based parameter analyses. For the processing rules to emerge fully, a more task-dependent analysis, including determining more complete and higher-order receptive field properties, may have to be performed (Ahissar et al. 2009; Fritz et al. 2003; King and Nelken 2009). The manner in which stimulus information is processed may be a more relevant organizing principle for auditory cortex than the encoding of acoustic content itself. In this framework, increased nonlinear dynamics may emerge as information moves from input to output layers (Ahmed et al. 2006) analogous to the different nonlinearities inherent in simple and complex cell processing in the cat primary visual cortex (Hubel and Wiesel 1962; Linden and Schreiner 2003; Martinez and Alonso 2003).

While much is known about how the brain processes and encodes basic sensory features such as color, orientation, or motion direction in vision and frequency, intensity, and sound source location in audition, much less is known about how the brain acquires and represents the behavioral relevance of stimuli. The neuronal encoding of meaning, as expressed in the creation of sound categories, must involve something beyond the neuronal encoding observed for basic stimulus features. The gradual emergence of these coding aspects, or at least initial steps toward such goals, and their redistribution via extensive feedback connections (Winer 2006) likely renders most stations that have been traditionally considered purely sensory as substrates for combined sensory and cognitive processes.

An array of new methods, including optical methods to record from hundreds of neurons simultaneously, optogenetic methods to manipulate activity in specific cell classes, and computational approaches to dissect and model neuronal ensemble activity across multiple stations during behaviors, are being increasingly exploited to address fundamental issues of spectral and spectral–temporal coding in auditory cortex. It is clear that the focus of research has to shift from single neurons to neuron assemblies, from early cortical regions to later cortical regions, from stimulus-based to cognition-based aspects, and from animal-based to human-based studies in order to fully appreciate and understand the complexity of auditory cortical processing.

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