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Review

Sensitivity and Selectivity of Neurons in Auditory Cortex to the Pitch, Timbre, and Location of Sounds

Jennifer K. Bizley[1] and Kerry M. M. Walker[1]

Abstract

We are able to rapidly recognize and localize the many sounds in our environment. We can describe any of these sounds in terms of various independent "features" such as their loudness, pitch, or position in space. However, we still know surprisingly little about how neurons in the auditory brain, specifically the auditory cortex, might form representations of these perceptual characteristics from the information that the ear provides about sound acoustics. In this article, the authors examine evidence that the auditory cortex is necessary for processing the pitch, timbre, and location of sounds, and document how neurons across multiple auditory cortical fields might represent these as trains of action potentials. They conclude by asking whether neurons in different regions of the auditory cortex might not be simply sensitive to each of these three sound features but whether they might be selective for one of them. The few studies that have examined neural sensitivity to multiple sound attributes provide only limited support for neural selectivity within auditory cortex. Providing an explanation of the neural basis of feature invariance is thus one of the major challenges to sensory neuroscience obtaining the ultimate goal of understanding how neural firing patterns in the brain give rise to perception.

The organ of Corti, located within the cochlea, is the sensory organ responsible for hearing. It encodes sounds in our environment by decomposing them into their constituent frequencies. However, if asked to describe a sound, a listener is unlikely to reflect explicitly upon its frequency content. Rather, he or she might talk about a sound having a high or low pitch, or being loud or quiet. The listener might also be able to identify what or who made the sound or where the sound originated from in space. These features usually do not relate simply to a sound's frequency content but must instead be computed by the brain by integrating information across the frequency spectrum (Hawkins and others 1996). In fact, such perceptual features, such as pitch, can be uninfluenced by large changes in the acoustical signal, as when a violin and piano both play the same musical note. In this article, we discuss how neurons in the auditory cortex encode three basic perceptual features of sound: pitch, timbre, and location. We ask whether cortical areas differ in their sensitivity to these sound features. Furthermore, we consider whether single neurons are capable of representing space, pitch, or timbre in a way that is selective for one of these features but uninfluenced by the other

two—in other words, whether *invariant* representations of each of these features exist in the auditory cortex.

What properties might we expect a "space-selective" neuron to have? First, we might expect that some aspect of the neurons' response to sound to be informative about where a sound is located. That might mean that the neuron fires more spikes when sounds are present at particular locations or that the temporal pattern or latency of spikes in the response changes in a way that provides information about sound source location. Second, we may reason that the neural code of the space-selective neuron should be robust to changes in a wide range of "nuisance" variables, such as intensity, pitch, or timbre changes. We have no difficulty localizing many different sounds in our environment regardless of their identity (and vice versa), and

Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, United Kingdom

Corresponding Author:
Dr J. K. Bizley, Department of Physiology, Anatomy and Genetics, Sherrington Building, University of Oxford, Oxford, OX1 3PT, United Kingdom
Email: jennifer.bizley@dpag.ox.ac.uk

invariant coding within single neurons may give rise to this perceptual independence. Thus, an ideal space-selective neuron should be capable of providing spatial information when presented with a range of different sounds in just the same way a human listener can. Providing evidence that a neuron's response is informative about a particular sound feature is a necessary first step in assigning it a potential role in perception, but to demonstrate that the neuron is specialized for processing a particular feature of sound, it must be shown to respond invariantly to changes in other stimulus dimensions.

Once we have demonstrated that a neuron carries information about a particular stimulus feature, we can start to address the big question of sensory neuroscience—does this neuron give rise to our perceptual experience of sound? Correlating neural response properties with psychophysically obtained thresholds allows us to assess the likelihood that such a neuron might contribute to perceptual judgments. However, any conclusion about causality requires that we manipulate the code itself, such as by inactivating a region of cortex or by microstimulating the candidate neuron, and test the resulting effects on animals' perceptual judgments.

The Auditory Pathway

Sounds are transduced into neural signals by the cochlea, which transmits this information to the brain via the auditory nerve. Auditory nerve fibers are narrowly tuned to a "characteristic" frequency of sound (Pickles 1988), and this frequency specificity is a key feature of neurons throughout the ascending auditory system. Just as neurons within the visual system can respond to a restricted region of visual space and form an anatomical representation of the retina (i.e., a "retinotopic" map), auditory areas also contain a topographic representation of the sensory receptor surface such that sound frequency is mapped "tonotopically." This means that neurons close to each other tend to respond preferentially to similar frequencies of sound, producing a map of frequency space with an orderly progression from neurons that are tuned to high sound frequencies to those that prefer low sounds frequencies.

Figure 1 illustrates the mammalian auditory pathway from the cochlea, via the midbrain and auditory thalamus, to the auditory cortex. Considerable neural processing of the incoming sound signal occurs before this information reaches the auditory cortex. Auditory information is relayed via the cochlear nuclei through a brainstem structure called the superior olive, which is responsible for extracting differences in the timing and intensity of the sound at each ear (Pickles 1988). These parallel processing pathways converge at the inferior colliculus (IC). Spectral processing in both the IC and earlier nuclei may sharpen the representation of spectral peaks in complex
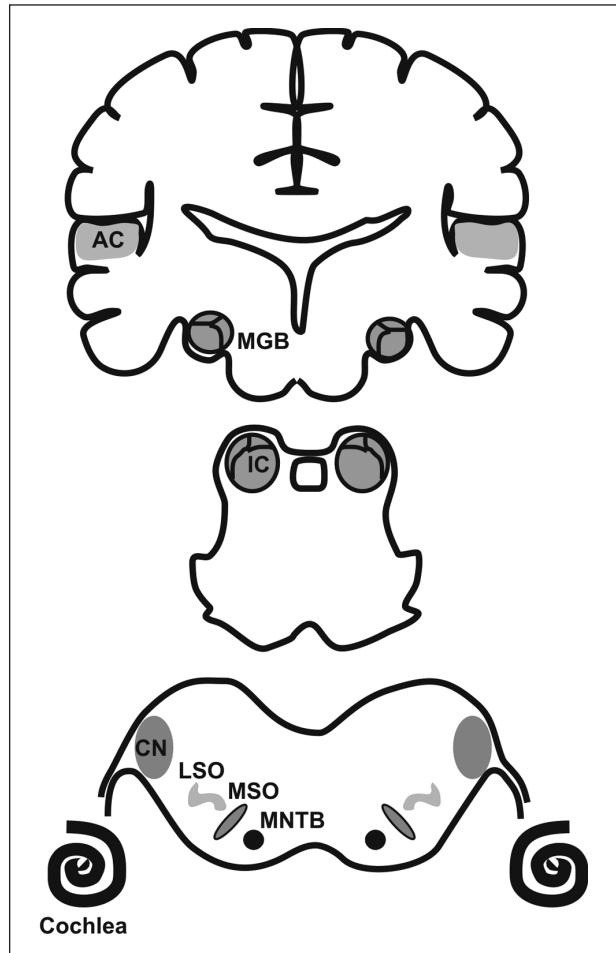

Figure 1. The auditory pathway. Information about sound is encoded in the cochlea and travels, via the auditory nerve, to the cochlear nucleus (CN). Several specialized nuclei in the midbrain extract binaural timing cues (medial superior olive [MSO]) and level cues (lateral superior olive [LSO]). Parallel auditory pathways converge at the inferior colliculus (IC) and then pass via the medial geniculate body (MGB) of the thalamus to the auditory cortex. AC = auditory cortex; MNTB = medial nucleus of the trapezoid body.

sounds, via lateral inhibition across tonotopically arranged neurons (McLachlan 2009; Rhode and Greenberg 1994). Many neurons within the IC respond to the periodic modulation of a sound's amplitude within a restricted range. These responses are phase-locked to stimuli with modulations of up to 500 hertz, but modulation rates are encoded with unsynchronized spike rates for faster periodicities (up to 1 kHz; Langner and Schreiner 1988). The neural representations of binaural level and timing difference cues that are extracted in the superior olive also undergo further processing in the IC. Although anatomical subtypes of neurons are predominantly responsible for different localization cues, there is evidence some IC
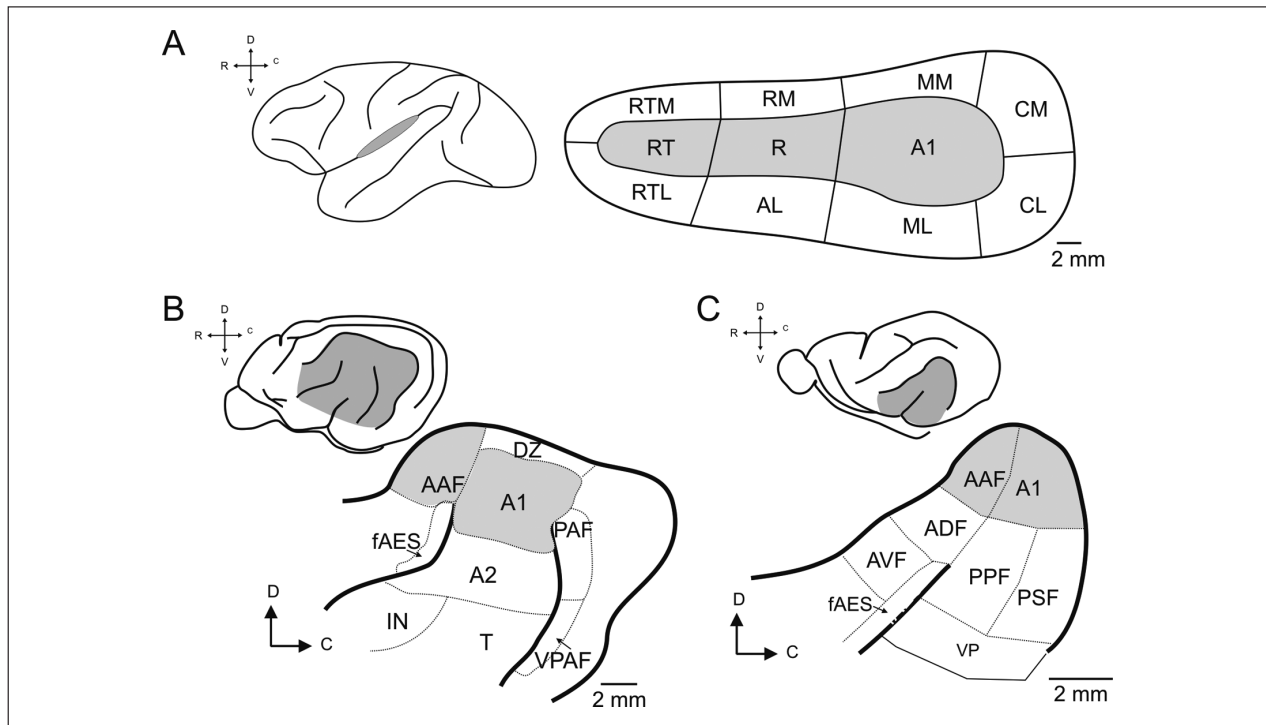
Figure 2. Auditory cortex in the macaque, cat, and ferret. (*A*) Macaque auditory cortex. The inset shows the location of the auditory cortex, and the schematic illustrates the location of identified auditory fields with core areas shaded in gray. (*B*) Cat auditory cortex. (*C*) Ferret auditory cortex. The scale bars each indicate 2 mm. A1 = primary auditory cortex; R = rostral field; RT = rostral temporal field; CM = caudomedial belt; CL = caudolateral belt; ML = mediolateral belt; AL = anterolateral belt; MM = mediomedial belt; RM = rostromedial belt; RTM = rostrotemporal medial belt; AAF = anterior auditory field; PAF = posterior auditory field; VPAF = ventral posterior auditory field; A2 = secondary auditory area; fAES = anterior ectosylvian sulcal field; INS = insular; T = temporal; PPF = posterior pseudosylvian field; PSF = posterior suprasylvian field; ADF = anterior dorsal field; AVF = anterior ventral field; VP = ventral posterior field.

neurons integrate binaural cues to extract representations of positions in space (Chase and Young 2005). Information about sound passes from the IC to the medial geniculate body (MGB) of the thalamus and from there to the auditory cortex (Winer and Schreiner 2005). The MGB has often been assumed to simple relay information from the IC to auditory cortex. However, the multiple subdivisions of the MGB have diverse connections with brain circuits responsible for a number of functions, including conditioned avoidance behavior (reviewed Winer 1992). There is also physiological evidence that MGB may play a role in novelty detection (Anderson and others 2009), so the function of this nucleus is significantly more complicated than the passive transfer of information along the auditory pathway.

The term *auditory cortex* is classically defined as those areas of neocortex that are innervated directly by neurons in the MGB, and this classification includes a number of regions that differ in their physiological, anatomical, and functional characteristics. Auditory cortical fields are frequently defined on the basis of their tonotopic organization, with a reversal in the frequency gradient signifying a transition

or boundary between distinct cortical areas (Winer 1992). These areas may also differ in their anatomical connectivity and cytoarchitectonic features (Kaas and Hackett 2005; Lee and Winer 2008). Areas that are innervated to a greater extent by the ventral division of the MGB as opposed to the dorsal or medial divisions, show a more precise tonotopic organization and greater frequency selectivity (Winer 1992; Kaas and Hackett 2005). The fields of the auditory cortex are often grouped hierarchically into core, belt, and parabelt areas, corresponding to primary, secondary, and tertiary areas, respectively. Neurons in belt and parabelt areas are increasingly less likely to respond to pure tones and instead prefer more naturalistic, spectrally, or temporally rich sounds, and they respond with longer latencies and more diverse temporal firing patterns (Rauschecker and others 1995; Heil and Irvine 1998a, 1998b; Rutkowski and others 2002; Bizley and others 2005; Bendor and Wang 2008; Kusmierek and Rauschecker 2009). The auditory cortices of three animal models that are commonly used in hearing research (namely, macaque monkey, cat, and ferret) are shown in Figure 2. The unique role of the primary

auditory cortex (A1) in hearing remains a topic of debate and much ongoing research, but increasingly, attention is being directed to nonprimary auditory fields for explanations of how complex features of sound are represented.

We have seen how the early auditory system encodes some of the basic physical parameters of sounds, and we will now ask how the auditory system, especially the auditory cortex, encodes three higher-level perceptual attributes. First, we will discuss the acoustic cues that determine the pitch, timbre, and location of a sound and how the early auditory system encodes these cues. We will then explore our current understanding of how a sound's pitch, timbre, and location might be represented by auditory cortical neurons. Finally, we will examine the extent to which current evidence supports the idea that some cortical areas might form invariant representations of these three perceptual attributes.

What Acoustical Features Determine a Sound's Pitch, Timbre, and Location?

Pitch

Many naturally occurring sounds, particularly vocalization sounds, have waveforms that are periodic—that is, they repeat at a regular interval. When we listen to such sounds, our brain interprets their periodicity as the perceptual quality of pitch. Pitch has been defined as "that attribute of sound according to which sounds can be ordered on a scale from low to high" (American National Standards Institute [ANSI] 1994). In addition to forming the basis for music, pitch cues can be used to identify a speaker (Gelfer and Mikos 2005; Smith and others 2005) or determine the speakers' emotional state (Fuller and others 1992; Reissland and others 2003). In tonal languages, or when a speaker uses strong intonation, the pitch can even change the meaning of a spoken word. Behavioral studies have shown that monkeys (Koda and Masataka 2002), apes (Kojima and others 2003), frogs (Capranica 1966), and songbirds (Nelson 1989) also use periodicity cues to interpret their species-specific vocalizations, so pitch perception seems to be a fundamental feature of hearing for a wide variety of vocalizing animals.

Pitch perception is limited to periodicities within the range of approximately 30 to 5000 Hz, within which sounds with faster repetition rates evoke a higher pitch (Krumbholz and others 2000). Sounds with only approximate repetition of their waveforms can still evoke a pitch percept, but the salience of pitch is determined by a sound's temporal regularity. Although conceptualizing pitch as a consequence of the temporal properties of a sound wave is instructive, pitch can alternatively be understood as a perceptual correlate of spectral properties. Periodic sounds are made up of harmonics (i.e., frequencies that

are integer multiples of a fundamental frequency). The pitch of a sound is roughly equivalent to the fundamental frequency, which is the highest common devisor of the sound's harmonics. In most naturally occurring sounds, the fundamental frequency corresponds to the lowest harmonic present in the sound. But when energy at the fundamental frequency is removed to produce a missing *fundamental* sound, the percept of pitch persists at the fundamental value as long as the relation between the remaining harmonics is unchanged (Schouten 1938). Monkeys (Tomlinson and Schwarz 1988), songbirds (Cynx and Shapiro 1986), and cats (Heffner and Whitfield 1976) have been trained to respond to the pitch of missing fundamental sounds, demonstrating that this phenomenon is not unique to human listeners.

The temporal and spectral explanations of the acoustics of pitch have led to two theories of how the auditory system might encode pitch cues as neural spiking responses. Predicting the pitch that will be evoked by a pure tone is rather straightforward—the pitch will be equal to the frequency of the tone. In this special case, the pitch can be derived as the place of maximal activation along the tonotopic map. However, for more complex sounds, the relation between pitch and frequency composition is not one to one, and so the neural computations necessary to extract pitch are more demanding. Temporal theories of pitch encoding propose that pitch cues are extracted based on the timing of action potentials, probably by calculating the all-order autocorrelation of spikes across neurons that are phase-locked to the acoustic waveform (Cariani 1999). Temporal models of pitch encoding are consistent with the upper limit of pitch perception because auditory nerve fibers only respond in phase to frequencies up to about 5 kHz in the cat (Johnson 1980). In spectral theories of pitch encoding, the auditory system determines the pitch of a sound by matching its harmonic structure to a spectral template (Cohen and others 1995). But note that this strategy requires that the harmonics of the sound are spaced widely enough that they evoke resolved areas of activation along the tonotopic map. Although pitch perception is more salient for sounds with more resolved harmonics, listeners can also identify the pitch of sounds in which the harmonics are entirely unresolved (Houstma and Smurzynski 1990). These findings suggest that the auditory system makes use of both spectral and temporal representations to extract the pitch of a sound (reviewed by de Cheveigne 2005).

Timbre

Timbre is formally defined as the difference in quality of two sounds that have the same pitch, intensity, duration, and location (ANSI 1994). It is a multidimensional property

that is determined by both the spectral and temporal features of a sound (Plomp 1970). It is the term timbre that we use to describe the difference in sound quality that distinguishes two musical instruments playing the same note or two vowel sounds spoken at the same pitch. The precise temporal envelope of a sound's onset (i.e., whether the sound starts very suddenly or more gradually) is sometimes called the "nature of attack" and is an important determinant of timbre (Iverson and Krumhansl 1993). This is especially the case for musical instruments such as the harp or piano, whose notes originate from a plucked string and contain little or no steady state sound at all (Campbell and Greated 1994). In this case, the shape of the amplitude envelope at the beginning of the sound will largely determine the perceived quality. However, the onset dynamics of a sound is not the only factor that influences timbre. The source of steady state sounds can be identified by differences in their spectral shape, even when their pitch, is the same (Plomp 1970). In this case, it is the distribution of energy throughout the sound spectrum and, for harmonic sounds, the relative amplitudes of each of the harmonics that is responsible for the differences in sound quality that sounds with the same pitch, intensity, and location might have. For example, notes played by the trombone only have energy at the first and second harmonics, where as those played by a violin contain energy distributed across many harmonics (Campbell and Greated 1994). In human speech, the vibrating vocal chords produce a periodic train, and timbral differences are then imposed upon this train by the filtering of the throat, mouth, and tongue. This filtering results in peaks, or formants, in the distribution of energy among the harmonics of the sound, and it is the relative locations of these energy peaks, especially the first and second formants, that determine vowel identity (Peterson and Barney 1952).

Thus, the extraction of sound timbre requires analysis of both the temporal and spectral envelope of a sound source (Lyon and Shamma 1996). The auditory system processes the frequency content of sound at multiple resolutions. This allows the pitch, which is present in the fine spectral detail of sounds, to be extracted independently from the larger scale frequency structure that determines the sound's timbre (Shamma 2001).

Location

Being able to accurately localize the source of a sound is vital for any organism's survival. Unlike vision and somatosensation, where the sensory receptor surfaces from a map of the external world, the location of a sound is not represented explicitly by the cochlea, and so the brain must compute the location of sounds in space indirectly (Hawkins and others 1996; Moore 2004). Three cues allow the brain to achieve this task (reviewed in Schnupp and Carr 2009). Having two ears allows a listener to compare the sound signal as it arrives at each side of his or her head. Differences in the relative timing and intensity of these two signals are highly informative about the location of the sound source. Sounds to the listener's left will arrive earlier at the left ear than the right, and due to the acoustic shadow provided by the head, sounds will be slightly louder in the left ear than the right (Thompson 1877; Rayleigh 1907). A third location cue results comes from the direction-dependent filtering of sounds by the outer ear, which is especially important for determining the elevation of sounds and differentiating between sources to the front of and behind the listener (Humanski and Butler 1988).

How Does the Auditory Cortex Represent Sound Pitch, Timbre, and Location?

Neural Representations of Pitch

Neural representations of pitch are likely to arise at the cortical level. Although neurons in subcortical nuclei of the auditory pathway have been shown to encode sound periodicity based on either spectral tuning or interspike interval firing patterns, these neurons do not exhibit firing properties that respond to periodicity invariantly, regardless of the level and timbre of sound. Furthermore, cortical lesion studies have suggested that the auditory cortex is essential to animals' judgments about shifts in the pitch of missing fundamental sounds (Whitfield 1980) but not the discrimination of shifts in the frequency of pure tones. Similarly, neurological patients with bilateral damage to Heschl's gyrus (HG), the region of the human temporal lobe where the primary and secondary auditory cortices are located, are impaired on tasks that require them to discriminate the frequency of pure tones (Kazui and others 1990; Tramo and others 2002) or the pitch of harmonic tone complexes (Zatorre 1988; Tramo and others 2002; Warrier and Zatorre 2004). Patients with damage to the right auditory cortex seem particularly prone to show impairments on pitch discrimination tasks (Sidtis and Volpe 1988; Robin and others 1990), and some studies have suggested that right HG may be critical to labeling the direction of pitch changes (Johnsrude and others 2000) and discriminating the pitch of missing fundamental sounds (Zatorre 1988).

Studies that image the functional activation associated with pitch perception have suggested that a restricted region of auditory cortex, the lateral HG, may play a special role in

pitch processing. Patterson and coauthors (2002) used fMRI to show that lateral HG, but not the primary auditory cortex, is more strongly activated by periodic sounds than white noise. The periodic sounds used were iterated rippled noises (IRN), which are created by repeatedly shifting a noise in time by a given duration and then adding it to the original waveform. By varying the resolution of harmonics within tone complexes, Penagos and colleagues (2004) demonstrated that activation in lateral HG is correlated with the pitch salience of sounds. The role of lateral HG in pitch perception has been further supported by experiments that measure, at the surface of the skull, the magnetic fields produced by currents of neural activity. The activity of a current source located in the lateral HG is dependent on the temporal regularity of click trains presented to human listeners but is insensitive to changes in sound level (Gutschalk and others 2002). Conversely, activation in planum temporale, a cortical region further along the cortical hierarchy, was shown to be sensitive to level but not pitch changes. Finally, a "pitch onset response" is evoked in HG when there is a change in the pitch of a continuous IRN. The latency and amplitude of this response depend on both the pitch height (i.e., how "high" or "low" a sound is) and salience (Krumbholz and others 2003; Ritter and others 2005), the source of the pitch onset response appears to be located in the lateral HG for transitions between IRNs that differ in pitch (Ritter and others 2005) and in medial HG for transitions from noise to a periodic sound (Krumbholz and others 2003).

The above investigations provide compelling evidence that lateral HG plays a key role pitch perception, but this does not mean that other cortical regions do not contribute to pitch perfection. Further studies suggest that neural representations of pitch may be distributed across multiple regions of the auditory cortex, with different areas contributing to different types of pitch judgments. For example, the cortical activation associated with pitch height is located posterior to A1, but a region that is modulated by pitch chroma is found anterior to A1 (Warren and others 2003). The analysis of pitch patterns across a sequence of periodic sounds is a yet higher level of pitch processing and is associated with activity in frontoparietal regions that are more widely distributed, further along the cortical hierarchy, and more widely lateralized than earlier pitch centers (Zatorre and others 1994; Schiavetto and others 1999; Patterson and others 2002). The impairments resulting from auditory cortical lesions in humans also argue for a distributed, yet locally specialized pitch processing network (Stewart and colleagues 2006).

The cortical areas giving rise to pitch perception may also vary with the type of stimulus presented and thus the type of computations required by neurons to calculate the sound's periodicity. Stimuli that produce "Huggins pitch" are nonperiodic at each ear, but a periodicity is produced from correlations in the sound signal across the two ears. Although magnoencephalographic investigations have concluded that the pitch onset response associated with the onset of Huggins pitch is produced in HG (Hertrich and others 2005; Chait and others 2006), fMRI studies have found neural correlates of Huggins pitch in planum temporale but not lateral HG (Hall and Plack 2007). The latter authors further showed that a number of pitch-evoking stimuli (including pure tones, resolved and unresolved tone complexes, Huggins stimuli, and IRN) produce distinctive distributions of cortical activation. Only IRN stimuli were associated with increased lateral HG activation (Hall and Plack 2009). Taking a similar approach, Nelken and colleagues (2004) imaged intrinsic optical signals in primary and secondary regions of ferret auditory cortex during the presentation of sounds that differed in spectral content but produce a similar pitch. The different types of periodic sounds resulted in different patterns of activation across the auditory cortex, providing no clear indication of a region that might be specialized for pitch processing in general. Thus, in contrast to our expectation to find a universal pitch center within the auditory cortex where neurons respond invariantly to the perceived pitch of all sounds, there is evidence to suggest that, instead, a network of pitch-sensitive regions in the auditory cortex exists to support a variety of periodicity judgments.

Once pitch-sensitive regions of the auditory cortex have been identified in imaging studies, we next aim to discover how single neurons within these fields use patterns of spike trains to compute and represent pitch. To answer this question, the action potential responses of single neurons in the auditory cortex have been be recorded during the presentation of periodic sounds. Neurons with spike rates that correlate with the periodicity of particular types of sounds have been found throughout the primary auditory cortex. For instance, the repetition rate of click trains is represented as phase-locked discharges of some A1 neurons when the repetition rate is relatively slow, and a separate group of A1 neurons uses a monotonic spike rate response to represent faster repetitions (Steinschneider and others 1998; Lu and others 2001). Monotonic spike rate representations of these stimuli are preferred over synchronized responses for click rates beyond about 40 Hz (Lu and others 2001), which corresponds to the lower limit of pitch perception (Krumbholz and others 2000). A subset of A1 neurons has also been shown to be sensitive to the harmonic relations of tone complexes. Not only do these cells respond to harmonics of their characteristic frequency, but their response to tones at the characteristic frequency

A1	Primary auditory cortex
CF	Characteristic frequency
ERM	Event-related magnetic field
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
HG	Heschl's gyrus
IC	Inferior colliculus
IRN	Iterated rippled noise
LSO	Lateral superior olive
MGB	Medial geniculate body
MNTB	Medial nucleus of the trapezoid body
MSO	Medial superior olive
STRF	Spectrotemporal receptive field

itself is often enhanced by the presence of harmonics (Sutter and Schreiner 1991; Kadia and Wang 2003). However, the characteristic frequencies of such neurons are outside of the pitch range (>5 kHz), and these cells do not respond to the pitch of the missing fundamental of a tone complex, but rather to the spectral components in the sound. Therefore, although these neurons compute acoustic cues that might be useful for building representations of pitch, they alone are not sufficient to explain pitch perception.

A number of studies have searched for missing fundamental responses in the primary auditory cortex. Studies that have presented harmonic tone complexes to awake monkeys have failed to find neurons that respond to the pitch of the missing fundamental (Fishman and others 1998), even when the monkeys have been trained to discriminate the pitch of these sounds (Schwarz and Tomlinson 1990). When the amplitude of a tone is sinusoidally modulated over time, a periodicity is produced at the modulation frequency. Schulze and colleagues presented these types of sounds to gerbils and found A1 neurons that respond to the sound periodicity, even though the fundamental was not physically present in the stimulus (Schulze and Langner 1997; Schulze and others 2002). Although this result does suggest that missing fundamental pitch may be represented in A1. Some have suggested that these responses may be accounted for by mechanical artefacts associated with SAM tones (McAlpine 2004).

A1 neurons are sensitive to periodicity changes and thus carry information about the pitch of stimuli, but the above studies do not conclusively demonstrate that these cells are selective (i.e., invariant) for pitch. A neuron that is pitch selective should be shown to respond to the periodicity of the sound beyond what can be explained by simple frequency tuning. Because pitch can

remain constant despite changes to a sound's spectral content and level, a neural representation of pitch should ultimately show similar invariance to these features. Furthermore, we might expect the response of a pitch-selective neuron to covary with pitch salience, which can be tested using randomized ("jittered") click trains or unresolved harmonics. Along these lines, Bendor and Wang (2006) presented multiple stimulus types (including pure tones, tone complexes, and jittered click trains) to awake, passively listening marmosets to search for auditory cortical neurons that were selectively responsive to the pitch of sounds. They found a subpopulation of such neurons in the lateral, low-frequency border of area A1 and R. These neurons responded to the missing fundamental of tone complexes and were sensitive to the periodicity of jittered click trains. This region is homologous to lateral HG in humans, providing convergent evidence that this area of cortex plays a key role in pitch processing (Bendor and Wang 2006). Although this study has provided the most compelling evidence to date of a single-neuron basis for pitch perception, it should be noted that even these "pitch neurons" did not encode periodicity in a manner that was independent of the level and spectral content of the sounds (discussed by Tramo and others 2005).

Many questions remain concerning how auditory cortical neurons encode the percept of pitch. For instance, how are the harmonic template and autocorrelation representations of periodicity observed at the subcortical level transformed into a single spike code for pitch by auditory cortical neurons? Is pitch, in fact, represented by single cortical neurons, or can level- and spectral-invariant representations of pitch only exist across populations of neurons? Finally, are neurons in different cortical regions specialized to extract different aspects of pitch, such as pitch chroma and height?

Neural Representations of Timbre

Far fewer physiological investigations into the neural basis of timbre perception exist than for either pitch or location processing, probably in part due to the multidimensional nature of timbre perception. The auditory cortex is functionally implicated in timbre perception by the demonstration that rats with cortical lesions show deficits in performing vowel identification judgments (Kudoh and others 2006) and from studies of human patients with temporal lobe lesions (Samson 2003). Many neurological studies have focused on the differences between right and left auditory cortical function in timbre processing, following the early observation that patients with right- but not left-sided temporal lesions are impaired on a timbre discrimination task (Samson and Zatorre

1988). This lateralization effect is present in tasks that require timbre discriminations based on temporal cues. Harmonic tone complexes that had the same fundamental frequency but that differed in the number of harmonics or the duration of their rise and fall times (i.e., the rate at which the sound onset/offset occurs) were used to investigate timbre processing deficits in neurological patients. Patients with right temporal lobe lesions were impaired on both the spectral timbre (i.e., differentiating tone complexes with different harmonics) and temporal timbre (i.e., onset dynamics) tasks. In contrast, patients with left temporal lobe lesions performed as well as control subjects on these tasks (Samson and Zatorre 1994). More recently, however, both auditory cortices have been implicated in timbre processing. Patients with left temporal lobe lesions were shown to be unimpaired in discriminating single tones based on their onset properties, but when the tones were presented in the context of a melody, these same patients were unable to make dissimilarity judgments. Patients with right hemisphere lesions were impaired on both single harmonic complexes and melodic comparisons (Samson and others 2002). Although these studies demonstrate a requirement for the intact auditory cortex to support timbre judgments, they do not help us to localize a precise neural substrate for timbre perception.

To distinguish brain activation patterns that might correlate with timbre extraction from those concerned with fine-scale spectral processing, Warren and coauthors (2005) used a set of artificially generated sounds, in which the fine frequency spectrum and envelope structure could be independently varied. By including a condition in which the detailed spectrotemporal structure was constantly changing, the authors were able to demonstrate that overlapping areas of the human auditory cortex were involved in pitch extraction and spectral envelope processing, but an additional area, located in the midportion of the right superior temporal sulcus, was engaged in the more abstract level of spectral analysis required when the stimuli's fine structure was constantly changing. Thus, the spectral analysis performed at a larger scale frequency resolution, which enables sound envelope extraction and thus timbre differentiation, may be lateralized to the right auditory cortex in humans. Further evidence that spectral processing occurs in a hierarchical fashion is provided by the finding that spectral envelope processing selectively enhances a connection running from HG to the planum temporale (Kumar and others 2007).

Electrophysiological investigations suggest that neurons in the primary auditory cortex do indeed analyze the sound spectrum at multiple spectral and temporal resolutions (Shamma and others 1993). Spectral encoding at the level of the auditory cortex is therefore complex and influenced by many factors. The auditory cortex of the cat is probably the most thoroughly characterized of all animal models, and a systematic change in spectral sensitivity to pure tones has been observed along the isofrequency laminae of this species (e.g., Schreiner and others 1992). Across the length of each isofrequency band, neurons differ in their excitatory frequency tuning, with cells in ventral and, most notably, central A1 having much narrower frequency tuning (Schreiner and others 1992). Neurons throughout cat A1 also differ systematically in the way in which their responses are influenced by sounds that are harmonically related to their characteristic frequency (Kadia and Wang 2003) and demonstrate orderly differences in the way in which inhibition shapes their receptive fields (Sutter and others 1999). Neurons in central and ventral regions are more likely to have a surround inhibitory structure, in which frequencies immediately above and below the neuron's characteristic frequency inhibit spiking activity. Cells in dorsal A1, on the other hand, more commonly exhibit much broader ranges of inhibition, which may be continuous or may consist of several different frequency regions (Sutter and others 1999). Similar structure has been observed across the isofrequency bands of ferret A1 (Shamma and others 1993). Finally, A1 neurons in the cat (Heil and others 1992; Mendelson and others 1993) and ferret (Shamma and others 1993) exhibit a systematic variation in their sensitivity to the direction and rate at which sounds change in frequency. In the temporal domain, differential sensitivity of neurons to the amplitude envelope, or repetition rate, has been described (Lu and others 2001; Sakai and others 2009), and auditory cortical neurons systematically represent tone intensity (Heil and others 1994). A1 neurons are also exquisitely sensitive to the precise onset dynamics of sounds (Heil 1997a, 1997b). In this organization, in which arrays of neurons are tuned to the same characteristic frequency but are differentially modulated by the broader spectral attributes or dynamics of sound, any sound source will be processed in parallel by many neurons. This provides a neural basis for the multiple scales of temporal and frequency analysis necessary to extract the acoustic features associated with timbre.

The differences in spectral and temporal sensitivity outlined above are likely to underlie the clustering of neural response sensitivity to features such as localization cues and vocalization sensitivity that is observed in the primary auditory cortex (Wallace and Palmer 2009). Predictions based on measurements of spectrotemporal receptive fields (STRFs) are able to predict responses to steady-state vowel sounds in over 70% of A1 neurons measured and are significantly better than predictions based on characteristic frequency tuning alone (Versnel and Shamma 1998). However, traditional estimates of the STRF include only linear components of the receptive

field (Machens and others 2004) and can often provide poor predictions of a neuron's response to natural sounds. Beyond the primary fields, a decreasing proportion of auditory cortical neurons have responses from which an STRF can even be derived. Although advances have been made in deriving STRFs that can model some of the nonlinear characteristics inherent to auditory cortical neurons (Ahrens and others 2008), accurately depicting the relationship between a natural sound and the consequent neural response in areas outside of the auditory core remains a challenge.

Neural Representations of Auditory Space

Although various centers in the midbrain are responsible for extracting interaural timing and intensity differences (see Fay and Popper 2005 for a review), the auditory cortex has been demonstrated to also play an essential role localizing sounds, presumably involving the integration of multiple location cues into the percept of a single sound in space. Studies of sound localization behavior following damage to or inactivation of the auditory cortex have found that cortical activity is important both for localizing sounds in the horizontal plane (Heffner 1997; Smith and others 2004; Malhotra and Lomber 2007; Nodal and others 2008) and in elevation (Bizley and others 2007). This, in turn, suggests that the auditory cortex is required for the utilization of both interaural difference cues and monaural spectral cues. Previous studies have demonstrated that a unilateral lesion to the auditory cortex creates an exclusively contralateral deficit (Kavanagh and Kelly 1987; Malhotra and Lomber 2007). The extent of localization deficits scales with the size of the auditory cortical lesion (Heffner 1997; Bizley and others 2007), which was initially suggestive of a distributed representation of space in the auditory cortex. However, in an elegant series of studies using reversible cortical deactivation, Lomber and colleagues have demonstrated that a specific subset of auditory cortical areas is required for cats to perform a localization task, whereas others are not (Malhotra and Lomber 2007).

Human lesion studies provide some evidence for distinct localization pathways within the auditory cortex (Clarke and others 1996; Clarke and others 2000), although others demonstrate that the relationship between lesion sites and behavioral deficits is not straightforward (Adriani and others 2003). Functional MRI studies in humans reveal that the planum temporale is activated when listeners are engaged in a task requiring spatial processing (e.g., Bushara and others 1999; Zatorre and Penhune 2001) and also in studies where listeners were not deliberately attending to the sound (Griffiths and Green 1999; Deouell and others 2007). Studies contrasting the activation associated with sounds that vary in location as opposed to their identification support the role of distinct cortical networks for these features (Maeder and others 2001), with the posterior planum temporale playing a key role in spatial processing (but see Barrett and Hall 2006). However, interpretations of these studies are not necessarily straightforward, and other results are equally compatible with the idea of distributed spatial sensitivity in the auditory cortex (Zatorre and others 2002).

Studies of spatial tuning in single auditory cortical neurons demonstrate that they are typically responsive to sounds presented throughout the contralateral hemifield (Middlebrooks and others 1994; Brugge and others 2001; Schnupp and others 2001), fitting with the contralateral deficits observed following unilateral lesions of the auditory cortex. A small proportion of cells here are tuned to ipsilateral or frontal space. Although the receptive field of an auditory cortical neuron is usually large, modulations in the spike rates and latencies are typically informative throughout the receptive field (Middlebrooks and others 1998; Brugge and others 2001; Mrsic-Flogel and others 2005). The most comprehensive investigations of spatial tuning across multiple auditory cortical fields come from studies in the cat, which demonstrate only subtle quantitative differences in the manner in which single neurons in different areas represent space (Middlebrooks and others 1994; Stecker and others 2003; Stecker and others 2005; Harrington and others 2008; Las and others 2008). For example, neurons in fields DZ and PAF (see Fig. 2B) tend to have richer temporal firing patterns, tighter spatial tuning, and a higher proportion of cells tuned to ipsilateral space, as compared to neurons in A1. Fitting with these results, both DZ and PAF are implicated by Malhotra and Lomber's (2007) cortical deactivation studies of localization. Neurons in the anterior ectosylvian sulcus (AES), which is also required for sound localization (Malhotra and Lomber 2007), seem specialized to represent frontal space (Las and others 2008). Although these three areas appear to have a higher spatial sensitivity than other cortical fields, the responses of neurons in fields that have not been implicated in sound localization behavior by deactivation studies are also spatially informative. In fact, neurons in these fields can be used to train an artificial neural network to localize sounds as accurately as animals (Middlebrooks and others 1998; Harrington and others 2008).

The sensitivity of single neurons to spatial location also varies throughout the primate auditory cortex, with neurons in field caudomedial belt (CM) and caudolateral belt (CL) (Fig. 2A) having a greater spatial sensitivity than those in the more rostral fields (Tian and others 2001; Woods and others 2006). The responses of populations of neurons in field CL can be used to predict the location of sounds as accurately as human listeners (Miller and

Recanzone 2009). However, as seen in studies of the cat auditory cortex, if the decoding algorithm used is sophisticated enough, the responses of neural populations in any of the auditory cortical fields examined can support localization behavior. Thus, again, although some fields seem particularly sensitive to localization cues, the information necessary to support listeners' localization judgments can be found in the responses of neurons in any of the auditory cortical fields.

Are Auditory Cortical Neurons Selective (or Just Sensitive) to the Pitch, Timbre, and Location of Sounds?

So far, we have examined how neurons in the auditory cortex are *sensitive* to a change in any one of these fundamental sound attributes, but natural sounds will frequently vary across all three parameters simultaneously. Therefore, there must be a neural code for pitch, for example, that reliably indicates the pitch of sounds despite changes in timbre and azimuth. The benefit of such invariant feature coding has been demonstrated in the songbird analog of the primary auditory cortex, where neurons that are more invariant to the intensity of vocalizations support better discrimination of the identity of these vocalizations (Billimoria and others 2008). An invariant code might take the form of neural *selectivity* for pitch, in which the response of a single neuron is invariant to changes in a sound's timbre and location. Alternatively, a neuron might reliably represent multiple stimulus features by modulating different aspects of its response (say, the onset and sustained response) independently. Examining sensitivity to more than one sound attribute simultaneously makes it possible to discriminate neural sensitivity from neural selectivity.

One of the first studies to attempt to address such questions at the level of single auditory neurons in multiple cortical fields examined the responses to monkey vocalizations that varied in their identity and location in space (Tian and others 2001). The authors demonstrate that neurons in caudal belt areas tended to be more spatially selective, whereas those in rostral belt areas were more selective to the type of vocalization presented. However, this study identified very few neurons whose responses were completely uninfluenced by either the location or identity of a monkey call. The natural vocalizations used in this experiment varied in both their spectral and temporal structures, not only making it difficult to disambiguate "call selectivity" from tuning to more basic acoustic features but also potentially masking an invariance to lower level perceptual features. More recent studies of vocalization selectivity in the primate

auditory cortex have suggested that information about call identity is distributed throughout multiple fields of the auditory core and belt (Recanzone 2008), but call-selective responses can be found in higher cortical areas, including the insular cortex (Remedios and others 2009), higher auditory areas (Petkov and others 2008), and prefrontal cortex (Romanski and others 2005).

In a recent study (Bizley and others 2009b), we investigated whether auditory cortical neurons encode the pitch, timbre, and location of sounds independently or interdependently. By using artificial vowels as stimuli (Fig. 3A), we were able to independently and parametrically vary sounds across each of these three perceptual dimensions. The stimulus set comprised all possible combinations of four vowels (/a/, /i/, /e/, /u/), four pitches (200-, 336-, 565-, and 951-Hz fundamental frequencies), and four spatial locations (–45°, –15°, +15°, +45°, where negative values indicate locations contralateral to the recording site). The stimuli along each of these dimensions are easily discriminated by ferrets (Parsons and others 1999; Bizley and others 2009a; Walker and others 2009). A variance decomposition technique was used to quantify the degree to which each neuron's spike patterns in response to the vowels could be attributed to the sound's pitch, timbre, and azimuth (i.e., location in the horizontal plane). In all five cortical fields studied (Fig. 3B), we identified neurons that were sensitive to changes in stimulus pitch, timbre, and location, and crucially, neurons were commonly influenced by two or more of these features. Figure 3C illustrates how sensitivity to each of these parameters was distributed across auditory cortex. The implication of these findings is that if invariant responses to each of these features exist within these cortical fields, they are extremely rare. Although the proportions of neurons that were sensitive to each feature statistically differed across fields, these subtle differences suggest that regional specializations do not imply neural response selectivity.

Studies investigating human neurological patients also suggest that information about multiple sound features is distributed across the auditory cortex. One such study examined the ability of 30 patients, who had circumscribed lesions in either their left or right auditory cortex, to perform sound recognition, sound localization, and sound motion detection tasks (Adriani and others 2003). The results failed to show the predicted correlation between the site of the lesion and the deficit observed. For example, there was a frequent occurrence of auditory spatial deficits after lesions of the frontal-parietal convexity, which is thought to form the neural basis for sound identification processing.

Although very few single-neuron investigations have addressed the question of invariant coding in the auditory
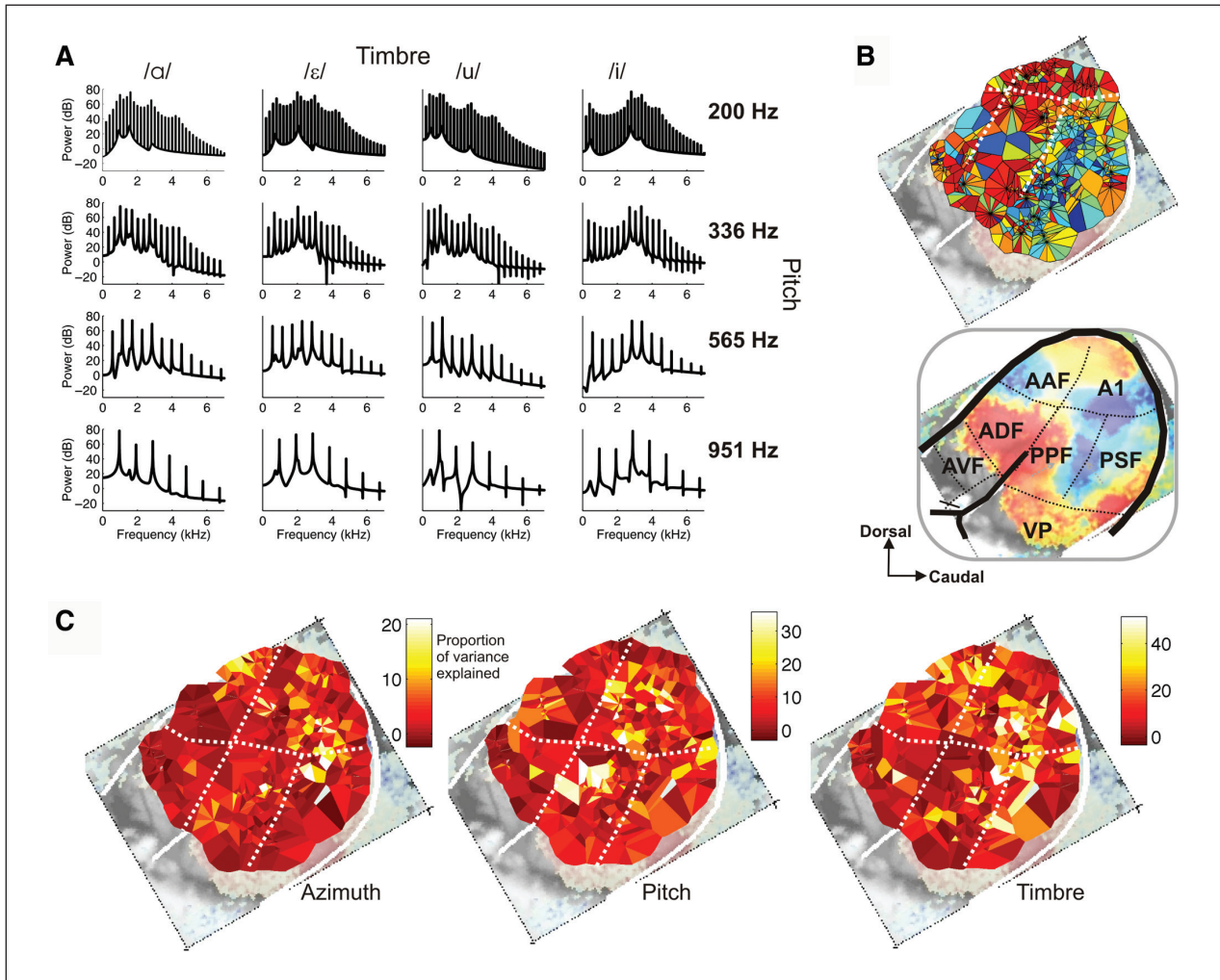
Figure 3. Interdependent encoding of pitch, timbre, and location cues in the ferret auditory cortex. (*A*) Amplitude spectra of the vowel stimuli used by Bizley and others (2009b). The vowels in each row have the same pitch, and those in each column have the same timbre (vowel identity). (*B*) Location and frequency organization of the ferret auditory cortex, as visualized with optical imaging of intrinsic signals. Red colors indicate areas where neurons prefer high sound frequencies, whereas blue areas show those preferring low sound frequencies. Adapted from Nelken and others (2004). (*C*) Distribution of sensitivity to the pitch, timbre, and azimuth of vowel sounds, where higher sensitivity is indicated by more white/yellow coloring. Each tessellation represents a recording from a single neuron or multineuron cluster. Adapted from Bizley and others (2009b).

cortex, many fMRI studies look for regional specialization by comparing patterns of activity associated with different perceptual features. By contrasting activation patterns across two different conditions, the investigator aims to look for activity that is specific to only one of them. A recent functional imaging study took a different approach and used machine-learning algorithms to identify patterns of blood oxygen-level dependent (BOLD) activation that were predictive of the stimulus that had elicited them (Staeren and others 2009). The stimulus set comprised four sound categories (pure tones, singers, cats, and guitars), and each of these sounds was presented at four

fundamental frequencies. All stimuli were matched in terms of their spectrotemporal characteristics (e.g., fundamental frequency, duration, and intensity), such that the only remaining difference among categories was the timbre of the sounds. The maps of discriminative activity produced showed that information about sound category was widely distributed across the auditory cortex, whereas information relating to fundamental frequency was restricted to an area lateral to the primary auditory cortex. Importantly, the discriminative maps for category and fundamental frequency were overlapping, suggesting that the regions responsible for encoding these sound features were not

mutually exclusive. This study demonstrates that there is widespread sensitivity to multiple stimulus dimensions, but small areas may be specialized for a particular sound feature. Within these specialized areas, we may find invariant responses to a feature at the single neuron level.

Further evidence of functional specialization beyond core and belt auditory cortex comes from a study that examined differences in cortical activity elicited when subjects listened to a set of sounds and attended to either pitch or location. In an attempt to reconcile conflicting reports as to whether pitch and location elicited different event-related potential (ERP) distributions (e.g., Alho and others 1994; Woods and others 2001), Degerman and colleagues (2008) combined ERP recordings with their magnetic equivalent (ERFs). They found no difference in the ERF source distribution between the attend pitch and attend location conditions. However, they did see that the location-dependent ERP was more posterior than the one observed while subjects attended to pitch. They speculate that the scalp distribution differences observed might be caused by activations of brain areas outside of the superior temporal cortex.

Perhaps the key to reconciling the apparent contradiction between the promiscuity of feature sensitivity within single neurons and the feature selectivity implied by behavioral inactivation studies lies in studies of higher cortical fields. Undoubtedly, specialized pathways in the frontal and parietal cortices are responsible for our perception of space (Burgess 2008), as well as our ability to identify objects and people in our environment. The projection pathways (Kaas and Hackett 2005; Romanski and others 1999) from the auditory cortex to these frontopartial areas may define the function of any given auditory cortical field in the absence of any clear difference in the way in which the neurons within that field respond to sounds.

Summary and Conclusions

It remains unclear whether or, if so, how auditory cortical neurons encode features in a strictly invariant fashion. The limited available evidence does not provide strong support for discrete cortical areas containing single neurons that selectively encode the pitch, timbre, or location of sounds. However, to conclude that invariant representations do not exist at all would be premature; increasing our understanding of the physiology and function of auditory cortex requires that more studies move beyond simply mapping neural sensitivity to a single acoustical dimension and instead examine the effects of varying multiple stimulus parameters. The sensitivity to multiple sound features that has been documented throughout the auditory core and belt (Romanski and others 1999, Tian and

others 2001, Recanzone 2008; Miller and Recanzone 2009; Bizley and others 2009b) appears in contradiction to reversible inactivation studies that show clear differences in the consequences of inactivating specific areas (Lomber and Malhotra 2008). However, it may be that the key determinant of the functional consequences of inactivating a cortical field is not how neurons in that field are modulated by the acoustics of sound but rather which higher level fields they connect to. That is, one must ask, for what function or purpose is the sound feature being encoded? Anatomical studies document a clear segregation of two hierarchical pathways, which both travel through the core auditory cortex and carry on in parallel to either prefrontal or parietal areas (Romanski and others 1999). Perhaps it is the removal of a specific output pathway from auditory cortical regions to these higher centers that results in a clearly defined behavioral deficit.

It also remains possible that with more investigation, particularly in belt and parabelt areas, invariant representations of stimulus pitch, timbre, and location will be uncovered. In this regard, investigations of brain regions beyond those areas classically defined as the auditory cortex may be particularly important. Finally, a deeper understanding of the effect of the behavioral state of the animal on neural tuning properties may uncover the physiological underpinnings of auditory cortical functions. Current studies have focused on recording single neuron activity in anesthetized or passively listening animals. Although there are undoubtedly physiological differences between these states (Wang and others 2005), responses recorded under nonbarbiturate anesthetics share many characteristics with those recorded in passively listening animals (Mickey and Middlebrooks 2003; Hromadka and Zador 2009). More marked differences have been observed when animals are actively engaged in a listening task (Fritz and others 2003; Otazu and others 2009). Thus, it may be only under conditions where an animal is actively using its auditory cortex that neural invariance emerges within the core and belt fields. Future research should focus an equal emphasis on examining neural selectivity as well as simply documenting sensitivity to sound features, preferably in neurons that are recorded while animals are carrying out psychoacoustic tasks.

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