Cortical representations of pitch in monkeys and humans

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Pitch perception is crucial for vocal communication, music perception, and auditory object processing in a complex acoustic environment. How pitch is represented in the cerebral cortex has for a long time remained an unanswered question in auditory neuroscience. Several lines of evidence now point to a distinct non-primary region of auditory cortex in primates that contains a cortical representation of pitch.

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Introduction

Our ability to distinguish pitch enables us to determine if an acoustic signal sounds ‘higher’ or ‘lower’ than another acoustic signal. We can track pitch changes over time to hear a musical melody or to recognize intonations in tonal languages, such as Chinese, and to do so robustly across different musical instruments or speakers. Different musical instruments, such as an oboe and a flute, have dissimilar sounds because of how they spectrally shape the acoustic energy they produce (i.e., which frequencies are amplified or attenuated). Yet they can still play the same musical note, and thus the same pitch, if the fundamental frequencies (see glossary) of the acoustic waveforms match. For a string instrument such as a violin, the fundamental frequency is equal to the vibration frequency of the plucked or bowed string. In a more general sense, this fundamental frequency is related to the temporal periodicity of the acoustic waveform of the sound [1].

How does the auditory system extract the fundamental frequency from the complex spectrum of a sound in order to generate a percept of pitch? Several recent findings indicate that there is a specialized region in the auditory cortex of primates that is involved in the representation of pitch [2,3,4••,5,6••,7••,8–10]. Here, we review several key studies in the identification of a pitch processing center in primate auditory cortex, and discuss issues concerning the neural substrate of pitch perception.

What is pitch?

Pitch is defined as ‘‘that attribute of auditory sensation in terms of which sounds may be ordered on a musical scale’’ (American National Standards Institute: www.ansi.org). The key distinction between frequency and pitch is that frequency is a physical description of a sound, whereas pitch is a perceptual attribute of a sound. Although frequency and pitch are typically similar for sounds composed of a single spectral component (pure tones), this relationship becomes more complicated when sounds are composed of multiple spectral components (e.g., harmonic complex sounds). For such sounds, the pitch is related to their fundamental frequency. Spectrally, the fundamental frequency can be thought of as the highest frequency for which the spectral components of the sound are integer multiples. Thus, a harmonic complex sound consisting of 100, 200 and 300 Hz tones has a pitch of 100 Hz (Figure 1a). Temporally, pitch is typically related to the repetition rate of periodic envelope (see glossary) changes in a complex acoustic signal. For example, a sequence of brief bursts of broadband noise (see glossary) repeated periodically at 100 times per second has a pitch of 100 Hz (Figure 1b).

Both speech and many animal vocalizations are spectrally complex, harmonically structured sounds. Pitch functions to group these harmonics together into a single percept that is related to the periodicity of the source generating a sound (the vibration of the vocal apparatus). Pitch perception, a necessary feature of our auditory system, enables us to hear two speech sounds as distinct from each other when both have similar spectrums and source locations but differ in their fundamental frequencies, for example, distinguishing between the sound of the same word spoken by a male and a female speaker standing next to each other. One of the remarkable features of pitch perception is that a spectral component does not need to be present at the fundamental frequency in order for a pitch equal to the fundamental frequency to be perceived [1]. In other words, although individual components of a harmonic complex sound consisting of 200, 300, and 400 Hz tones do not generate a pitch of 100 Hz when they are played one at a time, a listener would hear a pitch of 100 Hz when these components are played together, even though there is no spectral energy at 100 Hz (Figure 1c). This is a well-known phenomenon called ‘missing fundamental pitch’ and is a hallmark of pitch perception [1]. Our ability to perceive pitch from

Glossary

Broadband noise: Noise containing a wide range of spectral frequencies.

Characteristic frequency: The frequency of a single tone stimulus that evokes responses in an auditory neuron at the lowest sound level.

Combination tone: A distortion product created by the non-linear properties of the cochlea when stimulated by a complex sound. Combination tone effectively activates a region of the basilar membrane where the complex sound has no corresponding spectral energy.

Envelope: Variation over time in the overall amplitude of an acoustic signal.

Fourier transform: A mathematical technique used to convert an amplitude–time representation of a signal into a frequency-based representation.

Fundamental frequency: The repetition rate of the periodic structure of an acoustic signal.

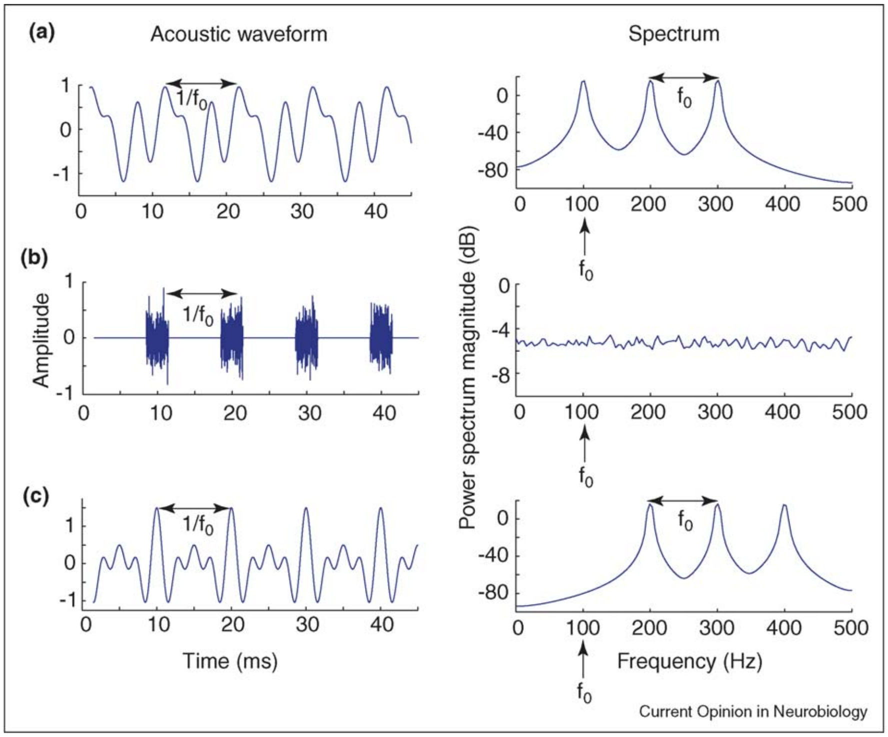
MEG: Magnetoencephalography, a technique in which neural activity is recorded by detecting small changes in the magnetic fields produced by neuronal circuits in the brain.

missing fundamental harmonic complex sounds explains why we are able to hear the pitch of someone's voice over the telephone system that effectively cuts out lower frequencies at which fundamental frequencies of human voices are normally present. In this sense, the perception of missing fundamental pitch in audition is analogous to the detection of illusory contours in the visual system.

Potential neural representation schemes of pitch in the brain

Acoustic signals can be mathematically analyzed by the Fourier transform (see glossary), which decomposes a sound into its spectral components. The auditory system performs a similar transformation in the cochlea where low frequency sounds or components excite the apical end of the basilar membrane, whereas the basal end responds best to high frequency sounds or components [11]. This tonotopic representation is preserved at each level of the auditory system, up to and including auditory cortex, such that neurons typically respond to a restricted range of frequencies and are physically ordered within a brain area by the frequency to which each neuron is most sensitive (the 'tonotopicity' or 'tonotopic map'). Although tonotopicity provides an explicit representation of frequency, it does not provide an explicit representation of pitch for complex sounds. Previous magnetoencephalography (MEG; see glossary) experiments in humans have suggested that a pitch map coexists with the tonotopic map in primary auditory cortex (AI) [12,13]. Pitch map topographies both parallel [12] and orthogonal [13] to the tonotopic map of AI have been proposed, but these topographies have not been confirmed using imaging techniques that directly measure spatial locations of neural activity with sufficient resolution. Another possibility is

Figure 1



Example of the spectrum and acoustic waveform for three different acoustic signals that have the same pitch (100 Hz). **(a)** Harmonic complex tone: composed of the 1st (fundamental), 2nd, and 3rd harmonic, each with randomized phase. **(b)** Repeated broadband noise burst (100 Hz repetition rate). **(c)** Missing fundamental harmonic complex tone: composed of the 2nd, 3rd, and 4th harmonic, all in cosine phase.

that pitch is processed in parallel with frequency but in separate brain regions, such that frequency is represented topographically in AI and pitch is represented in a non-primary area. In the pursuit of neural mechanisms for pitch perception, human and animal studies have been complementary to each other. In order to bridge pitch-related research between animal and human studies, it is important to establish similarities in how pitch is perceived, in addition to the anatomical and physiological properties of the brain areas studied. In this regard, non-human primate models play an essential role to help reveal the neural mechanisms of pitch perception.

The perception of pitch is not unique to humans

An advantage of using non-human primates as experimental models for studying pitch-related questions is that the frequency range of their hearing is similar to that of humans [14]. The ability of monkeys to hear the pitch of the missing fundamental was first demonstrated in a behavioral study by Tomlinson and Schwarz [15]. Rhesus monkeys were trained to push a button if the two complex tones presented sequentially had the same fundamental frequency. The monkeys were able to perform the task even when a missing fundamental complex tone was used, demonstrating their ability to hear missing fundamental pitch. The ability to perceive this missing fundamental is not unique to primates, it has also been shown in several other animal species including birds [16] and cats [17]. In addition, monkeys are capable of spectral pitch discrimination [18], melody recognition [19,20] and octave generalization [21], each of which requires the perception of pitch. One important difference between humans and some animal species is the size of their cochlea. For smaller cochleae, excitations on the basilar membrane caused by individual components of a harmonic complex tone are more closely spaced than those in larger cochleae. Different pitch processing mechanisms have been postulated for sounds with harmonics producing segregated regions of excitation on the basilar membrane ('resolved harmonics') and for sounds with harmonics that are close together and, therefore, only produce a single region of excitation ('unresolved harmonics') [1,11]. Thus, animals with smaller cochleae might need to rely more on the pitch processing mechanism that utilizes unresolved harmonics than do humans.

Anatomical and physiological similarity of auditory cortex among primates

The anatomical studies of Brodmann [22] suggested that the structure of the temporal lobe is largely preserved across primate species (New World monkeys, Old World monkeys and humans). Studies in recent years have revealed distinctions among various auditory cortical areas using anatomical [23–29] and physiological criteria [23,24,30–39,40•]. Accumulating evidence indicates that humans and monkeys share similar organization of primary, primary-like and secondary cortical areas [26,27,33,40•], suggesting a generalizable structure and function of auditory cortex among primates.

Primate auditory cortex is divided into a core region of primary and primary-like areas that is surrounded by a belt of multiple secondary areas. In humans and monkeys, the core areas of auditory cortex can be distinguished from belt areas by their cytoarchitecture, namely a more prominent granular layer [23,24,27,29]. The core areas receive thalamic inputs from the principal (ventral) nucleus of the medial geniculate body (MGB) [26]. By contrast, the belt areas receive more dominant thalamic inputs from the non-lemniscal divisions (dorsal and medial) of the MGB [26]. In both monkeys and humans, neurons in core areas respond strongly to narrowband sounds such as tones, whereas neurons in belt areas respond better to more complex sounds (e.g., noise, frequency modulation, low-contrast spectrums and vocalizations) [32,36–39,40•]. Within the core areas, in both monkeys [23,24,40•] and humans [33], two mirror symmetric tonotopic maps sharing a low-frequency border have been identified, corresponding to AI and the rostral field (R). In humans, the core areas are generally confined to Heschl's gyrus [27], with AI located medially to R (Figure 2a). However, this is difficult to determine precisely by anatomical landmarks because of substantial intra-subject variability. Monkeys do not possess an anatomical landmark for the location of AI and, therefore, the location of AI must be determined physiologically or histologically. AI is typically buried within the lateral sulcus in monkeys, except for in a few New World species (e.g. marmosets, owl monkeys), for which the lateral portion of AI is located on the surface of the superior temporal gyrus [7••,23]. In monkeys, there is anatomical [23] and physiological evidence [7••,23,40•] for a third core area (RT) that lies rostral to R (Figure 2b). Kaas and Hackett [26] have postulated that each core area is connected to a medial and lateral neighboring belt area, with additional belt areas located on the rostral and caudal ends of the core region of auditory cortex (AI, R and RT). Three of these lateral belt areas, caudal-lateral (CL), middle-lateral (ML) and antero-lateral (AL), have been mapped electrophysiologically, and possess similar mirror symmetric tonotopic maps to those of their adjacent core areas [38,39]. Using a high resolution fMRI technique in macaque monkeys, Petkov *et al.* recently identified a total of eight tonotopically organized fields in the belt region of auditory cortex [40•]. Additional higher auditory areas, such as parabelt [41,42] and the rostral pole [43], have been defined anatomically, but little is known about their physiological properties.

A pitch-processing center in primate auditory cortex

Where is the pitch of a sound encoded in the brain? The information needed to extract the pitch of a complex

Figure 2

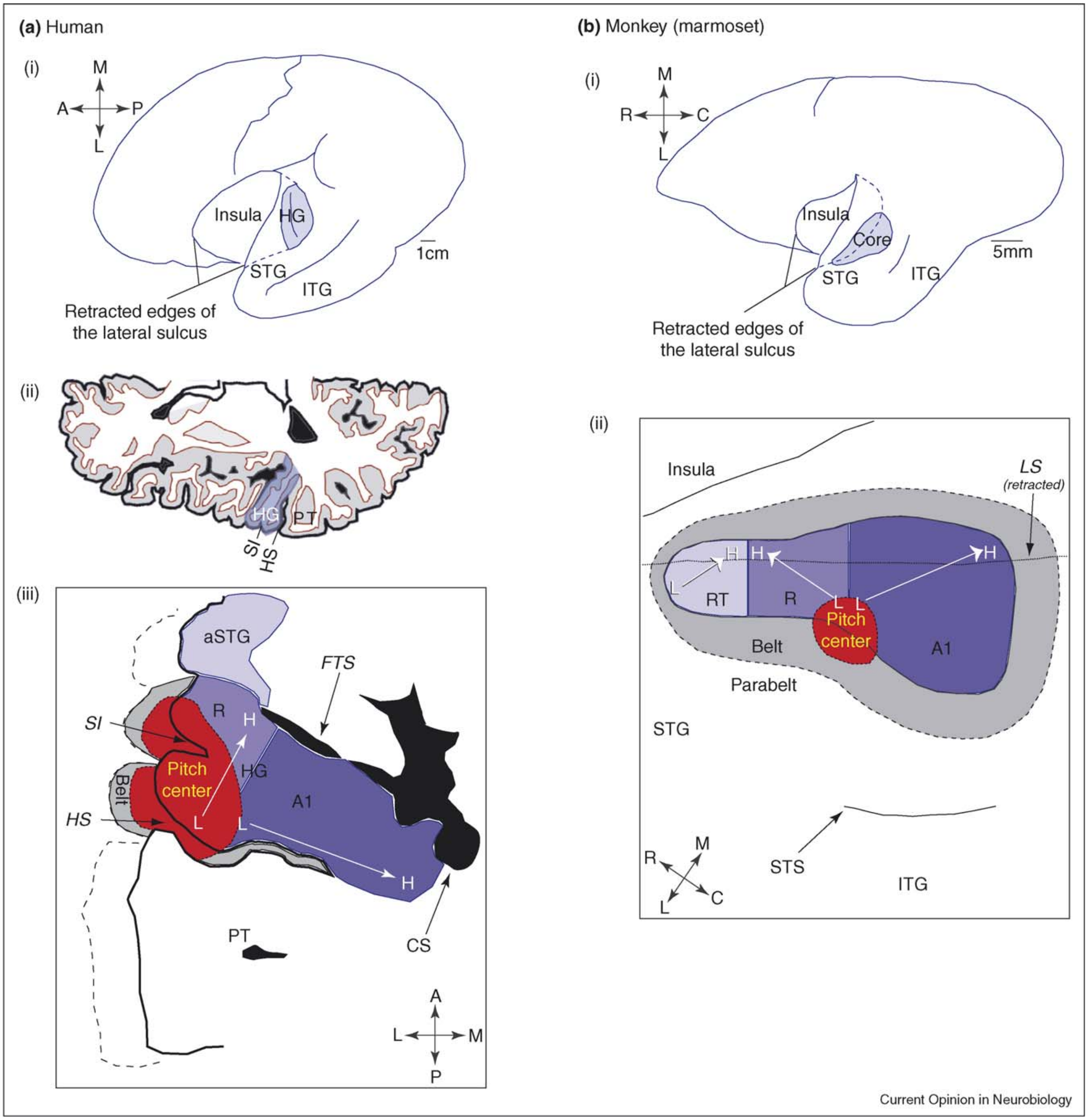


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Diagram of human and marmoset auditory cortex. **(a)** **(i)** Side view of a human brain, **(ii)** horizontal cross section of temporal lobe, and **(iii)** magnified view of Heschl's gyrus. Primary auditory cortex is presumed to occupy the medial portion of Heschl's gyrus (with variability between subjects). The location of neighboring areas (R, pitch center, lateral belt) is an approximation based on Schneider *et al.* [6••], Formisano *et al.* [33], and Patterson *et al.* [3]. **(b)** **(i)** Side view of the brain of a marmoset monkey and **(ii)** a magnified view of the temporal lobe, indicating core, belt, parabelt, and the pitch center. The borders between each auditory area are estimated on the basis of data from Bendor and Wang [7••], and Pistorio *et al.* [64]. Abbreviations: AI, primary auditory cortex; aSTG, anterior superior temporal gyrus; CS, circular sulcus; FTS, first transverse sulcus; H, high frequency; HG, Heschl's gyrus; HS, Heschl's sulcus; ITG, inferior temporal gyrus; L, low frequency; LS, lateral sulcus; PT, planum temporale; R, area R (rostral auditory cortex); RT, area RT (rostrotemporal auditory cortex); SI, intermediate sulcus; STG, superior temporal gyrus; STS, superior temporal sulcus.

sound is contained in both the discharge rates and the temporal firing patterns of the population of auditory nerve fibers [44,45,46•]. There is no clear evidence that subcortical stations of the ascending auditory pathway explicitly encode pitch. In cats, bilateral lesions of the entire auditory cortex impair the discrimination of changes in the pitch of the missing fundamental, but not changes in frequency alone, demonstrating the necessity of auditory cortex in pitch perception [47]. Humans with partial auditory cortex lesions have poorer pitch discrimination than healthy hearing subjects [48], with patients with lesions of the right auditory cortex showing larger deficits [49,50]. Behavioral studies in patients with auditory cortex lesions have further suggested that lesions anterior to primary auditory cortex result in more pronounced deficits in pitch discrimination [50]. These studies point to a possible cortical source of pitch representation. Several recent studies have identified a specific region in primate auditory cortex that appears to be involved in representing the pitch of a sound [2,3,4••,5,6••,7••,8–10]. A schematic showing the location of this pitch-processing center in relation to its neighboring cortical areas for both humans and monkeys is shown in Figure 2.

Evidence from human studies

In an fMRI study, Patterson *et al.* [3] identified a specific region of human auditory cortex (lateral Heschl's gyrus) that was preferentially activated by temporally regular sounds with a pitch. The acoustic stimulus used in this study is iterated rippled noise (IRN), which is generated by iteratively adding delayed broadband noise [1,51]. By adjusting the delay and the number of iterations, the fundamental frequency and pitch salience of the resulting sound can be changed, respectively. For IRN sounds with low frequency pitches, auditory filters in the high frequency range cannot distinguish between noise and IRN stimuli, because of the spectral resolvability limitation, even though these two sounds have physically different spectrums. Yet, subjects hear a pitch from IRN sounds but not from noise because of the temporally regular acoustic structure of the IRN sound (extracted presumably by temporal pitch mechanisms). By subtracting the blood oxygenation level dependent (BOLD) signal originating from the IRN sound from that evoked by noise, Patterson *et al.* determined that only lateral Heschl's gyrus, a non-primary auditory region anterolateral to primary auditory cortex, responded to the temporal regularity or pitch of the acoustic stimuli (this occurred bilaterally) [3].

In another imaging study by Penagos, Melcher and Oxenham [4••], the BOLD signal was compared among four harmonic complex sounds that had either a low or a high pitch and occupied either a low or a high spectral range. Of these four sounds, only the harmonic complex sound with the low pitch and high spectral components had unresolved harmonics. Sounds with unresolved harmonics have a weaker pitch salience than sounds with resolved harmonics, for which spectral cues are available [1]. Thus, Penagos *et al.* [4••] were able to compare BOLD signals of sounds that evoked a strong or a weak pitch salience, but that were matched in their fundamental frequency or spectral range. Bilaterally, a restricted region of non-primary auditory cortex, anterolateral to AI, was found more weakly responsive to the sound with low pitch salience than to the other three sounds with high pitch salience [4••]. This study, therefore, confirms the location of the pitch-processing center identified by Patterson *et al.* [3] using a different type of acoustic stimuli, and extends the earlier finding to demonstrate the sensitivity for pitch salience within this pitch-processing center.

The significance of lateral Heschl's gyrus in pitch representation was further investigated by Schneider *et al.* [6••] using a combination of psychophysics, anatomical magnetic resonance imaging (MRI) scans and MEG measurements. For missing fundamental harmonic complex tones with a few components, a listener might hear the pitch increasing or decreasing when the frequencies of harmonics are decreased while the fundamental frequency is increased [1]. Different subjects showed a bias towards using the fundamental frequency or the spectrum frequency when discriminating pitch changes. These biases correlated highly with hemispheric asymmetry in relative size between the right and the left lateral Heschl's gyrus (and not with other regions of auditory cortex) [6••]. Subjects that relied more on fundamental frequency to discriminate pitch had a larger left lateral Heschl's gyrus, whereas subjects using spectrum frequency had a larger right lateral Heschl's gyrus. In addition, MEG responses recorded from a source estimated as lateral Heschl's gyrus showed a similar asymmetry between hemispheres. Stronger responses were obtained from the left hemisphere for subjects with a bias towards using fundamental frequency in pitch discrimination. By contrast, subjects with a bias towards using spectrum frequency had larger MEG responses recorded from the right hemisphere.

Evidence from non-human primate studies

Given the evidence for a pitch-processing center in human auditory cortex and the anatomical and physiological similarities of auditory cortex between humans and monkeys, it is reasonable to expect that monkeys also possess a pitch-processing center in their auditory cortex. Schwarz and Tomlinson [52] searched for single-unit responses to the fundamental frequency of missing fundamental harmonic complex sounds in AI of three awake macaque monkeys previously trained on a pitch discrimination task, but failed to find any neurons responsive to the fundamental frequency centered at the characteristic frequency (CF; see glossary) of a neuron. Schwarz and Tomlinson concluded that pitch is either represented implicitly across a population of neurons in AI or an explicit representation exists outside of AI. However, using multi-unit recordings in awake macaque monkeys, Fishman *et al.* [53] were unable to find an implicit representation for the missing fundamental in AI based on population neuronal responses.

In a recent study in awake marmoset monkeys (a New World primate species), Bendor and Wang [7••] searched for single-unit responses to the missing fundamental in AI and in surrounding non-primary areas and identified a restricted region anterolateral to AI containing pitch-selective neurons. Neurons were identified as pitch-selective if they responded to missing fundamental sounds (with harmonics outside the excitatory frequency response area of the neuron) and pure tones with a similar pitch. A typical pitch-selective neuron responded to an array of spectrally dissimilar sounds (harmonic complex tones, click trains, iterated ripple noise) when the pitch was near the preferred fundamental frequency of the neuron, which, as determined by pure tones, was found to be similar to the CF of the neuron. Relative to the position of AI, this newly identified region containing pitch-selective neurons in marmoset monkeys is in a similar location to the pitch-processing center found in humans [2,3,4••,5,6••,8–10] (Figure 2). In addition, Bendor and Wang [7••] found that pitch-selective neurons preferred temporally regular sounds and were sensitive to pitch salience changes caused by harmonic frequency and order, in agreement with the imaging studies by Patterson *et al.* [3] and Penagos *et al.* [4••]. The microelectrode recording study by Bendor and Wang [7••] also showed that the pitch-processing region found in marmosets contained non-pitch-selective neurons (spanning a similar range of CFs) that responded to the spectral frequency of the sound, rather than the fundamental frequency. Potentially, these two classes of neurons, non-pitch and pitch-selective, that are co-localized within the pitch-processing center could encode spectral and missing fundamental pitch percepts, respectively. For ambiguous pitch changes, in which the fundamental frequency and spectrum shift in opposite directions, as in the study by Schneider *et al.* [6••], these two types of neurons would provide conflicting information. Unequal weighting of the numbers or responses of one of these neuron types within the pitch-processing center (and/or between hemispheres) could be the cause of a subject's perceptual bias of hearing pitch changes on the basis of the fundamental or spectral frequency. No topography has yet been identified within the primate's pitch-processing center in above cited studies [2,3,4••,5,6••,7••,8–10], possibly due to spatial resolution constraints arising from the small size of this area.

Many marmoset AI neurons located outside the pitch-processing region are tuned to the modulation frequency (repetition rate) of an amplitude- or frequency- modulated sound. However, in sharp contrast to pitch-selective neurons, these responses require that the spectral components of an acoustic signal be within the frequency response area of the neuron [54]. In awake marmoset AI, neural responses to stimulus repetition rates below ~40 Hz (near the lower limit of pitch [55,56]) are represented temporally by stimulus-synchronized discharges, whereas a monotonically tuned rate code is used by another population of neurons to represent higher repetition rates [57]. Neurons that have more than one excitatory frequency response area in their receptive fields with multiple harmonically related characteristic frequencies (integer multiples of a common fundamental frequency) have previously been observed in marmoset AI [58]. However, these multi-peaked neurons differ from pitch-selective neurons in two major aspects. First, multi-peaked neurons respond to frequencies that are generally outside the range of human pitch perception. Second, unlike pitch-selective neurons, multi-peaked neurons respond to harmonic frequencies as well as the fundamental frequency, and thus represent spectral information rather than pitch. Taken together, the findings from marmoset auditory cortex suggest that pitch-processing is a specialized function performed by a subpopulation of neurons in a restricted region of non-primary auditory cortex, whereas processing of temporally modulated or harmonically rich signals is a general function performed by other auditory neurons located across the tonotopic axis.

Differences between observations from studies in primate and observations in non-primate species

Several previous studies have investigated how missing fundamental sounds are represented in the auditory cortex of non-primate species. Microelectrode recordings in gerbils suggested that AI neurons could respond to the periodicity of amplitude-modulated tones that had spectral components located outside neuron's excitatory frequency response area [59], in contrast to the pitch center found in primates, which was located in a non-primary region of auditory cortex [2,3,4••,5,6••,7••,8–10]. Schulze *et el.* [60] have also found a semi-circularly shaped map of best fundamental frequency in gerbil auditory cortex using optical imaging techniques. Differences in the results from these studies in primate and non-primate species could be due to an evolutionary divergence of pitch-processing strategies within auditory cortex, or could result from methodological differences. Combination tones (see glossary) at the fundamental frequency are produced within the cochlea by missing fundamental sounds, creating potential ambiguity regarding whether a missing fundamental or combination tone is the source of the evoked response of the neuron [1]. The use of appropriate sound levels (to ensure that combination tones are below the pure tone response threshold of a neuron) [7••], in addition to the use of noise maskers [4,7] or a cancellation tone [61], are among the necessary control conditions to confirm that a true missing fundamental response is observed.

Conclusions and further questions

The discovery of a pitch-processing center in human (Figure 2a) and monkey (Figure 2b) auditory cortex is only the first step in understanding the physiological mechanisms of pitch perception. Several important questions remain unanswered. First, what is the source of inputs to pitch-selective neurons (corticocortical and/or thalamocortical)? The location of the pitch center appears to be overlapping low-frequency portions of both field R (primary-like) and lateral belt areas AL and ML. This suggests that the pitch-selective neurons can receive inputs from both ventral and dorsal divisions of the medial geniculate body (MGB) that respond to narrowband and broadband sounds, respectively [26,62]. This is a possible source of the response to pure tones and missing fundamental sounds. Alternatively, given the extensive connectivity among AI, R and neighboring belt areas surrounding the pitch-processing center, the pitch-selective neurons could extract the fundamental frequency using inputs from neighboring cortical areas (including AI). Second, do pitch-selective neurons use a spectral and/or temporal mechanism to extract the fundamental frequency of complex sounds? This is an issue that has been at the center of debate among auditory researchers for over half a century. Computational models and auditory nerve data support the possibility of both a purely temporal mechanism and a hybrid mechanism using both spectral and temporal information [1,44,45,46•]. In monkeys, AI neurons with temporal and spectral response properties potentially useful for these pitch models have been observed [54,57,58,63], but whether they provide input to pitch-selective neurons is unknown.

We conclude by proposing three potential mechanisms that pitch-selective neurons could use to extract the missing fundamental pitch. First, that pattern-matching neural circuitry integrates harmonically related thalamocortical inputs or corticocortical inputs from across the tonotopic axis of AI and/or R. This strategy could be the auditory equivalent to how illusionary contours are recognized in the visual system. Second, that an intrinsic cellular mechanism of pitch-selective neurons is tuned to the periodicity of the thalamic inputs synchronizing to the envelope of a harmonic complex sound. And third, that specialized thalamic inputs convey missing fundamental pitch information already extracted at a subcortical locus.

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