Notably, H3S10 phosphorylation is also known to affect transcription directly; for example, it facilitates the transition of poised to actively transcribing RNA Pol II in *Drosophila* [17] and transcription initiation at some budding-yeast promoters [18]. In the case of fission-yeast heterochromatin, an indirect effect mediated by displacement of Swi6 is the most parsimonious explanation at this point and is supported by the fact that H3S10ph levels peak before centromeric transcription.

The discovery that RNAi-induced heterochromatin formation is coupled to the cell cycle provides a new tool to investigate the order of events involved in the process. Genetic and biochemical studies have revealed the participation of many factors. It is now possible to examine the order in which these factors associate with centromeres as heterochromatin is being re-established, and the study from Shiv Grewal's laboratory represents an important first step [2]. A technical difficulty in this approach stems from the fact that RNAi is temperature sensitive [1], precluding the use of temperature-sensitive mutants to synchronize cells for these analyses.

Mathematical modeling has suggested that highly localized effects transmitted solely by the state of adjacent nucleosomes are inadequate for the maintenance of heterochromatin [19]. Notably, the requirement for long-range inter-nucleosomal interactions is more pronounced in S phase. Transcription and RNAi could provide a means to satisfy this requirement, because these processes involve an RNA polymerase that moves across many nucleosomes.

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DOI: 10.1016/j.cub.2008.03.044

Auditory Neuroscience: Neuronal Sensitivity in Humans

Microelectrode recordings from the human auditory cortex suggest that the tuning of individual neurons can account for sound frequency discrimination thresholds and that this tuning varies in a context-dependent fashion with the type of sound used to measure it.

Jan W.H. Schnupp and Andrew J. King

Our ears can easily distinguish thousands of objects and events: human voices, musical instruments, approaching vehicles, shattering glass, and so on. What all auditory objects have in common is that they contain vibrating parts — for example, strings, membranes, vocal folds, engine valves, buzzing insect wings — which differ greatly in their mechanical properties, so that each emits its own 'fingerprint' of sound frequencies. The capacity of the auditory system to resolve the constituent frequencies of each 'fingerprint' is therefore a critical step in the identification of auditory objects. A recent paper by Bitterman *et al.* [1] provides new insights into how this may be done, by illustrating the remarkable selectivity and adaptability of the neural filters in the human central auditory system.

Non-invasive techniques for measuring neural activity — or, in the case of functional imaging, the

associated hemodynamic changes — have revolutionized our ability to study the human brain in action. But these are relatively blunt tools that sample the activity of large assemblies of neurons within whole brain regions, rather than at the level of single neurons. Most of our knowledge about information processing by individual neurons has come from electrophysiological recording experiments carried out in animals. Consequently, we are still a long way from identifying the neurophysiological underpinnings of human cognition.

A rare opportunity to carry out comparable electrophysiological studies in humans is, however, provided by epileptic patients in whom intracranial microwire electrodes are implanted to determine where their seizures start. Recordings made from such patients have provided valuable insights into the functional organization of the human auditory cortex [1–4], which is located within the temporal lobe, as well as the relationship between the spiking activity of cortical neurons and functional magnetic resonance imaging measurements made at the same time [5]. In the most recent of these studies, Bitterman *et al.* [1] used this approach to explore the frequency tuning of single neurons in the human auditory cortex.

Frequency Selectivity in the Auditory System

The most characteristic and well documented feature of auditory neurons in the brain is their frequency selectivity. At every level of the auditory system, from the cochlea of the inner ear to the primary auditory cortex, neurons typically respond to tones over a restricted range of frequencies at the lowest sound intensities to which they are responsive, but to a progressively greater range of frequencies as the sound intensity increases. This frequency tuning is derived from a systematic variation in the biomechanical properties of the basilar membrane, which subdivides the cochlea longitudinally. Consequently, different tone frequencies excite different points along the length of the cochlea, setting up the 'tonotopic' maps that are preserved at subsequent levels of the auditory pathway as a result of the spatial order in the neural connections that exist between them.

Frequency selectivity can also be estimated behaviorally by measuring the threshold for detecting a tone of a particular frequency in the presence of masking noise containing energy over different frequency ranges. This shows that the auditory system contains a series of 'bandpass filters' or 'critical bands', within which different sounds are not easily distinguished and interact in ways that influence how they are perceived [6]. These psychophysical filters have their origin in the frequency analysis performed by the cochlea, but also seem to be influenced by processing that takes place within the brain [7,8].

But the auditory filters appear to be too coarse to account for our perceptual ability to detect a change in the frequency of a sound. Trained human listeners can discriminate tones that differ in frequency by less than 1%, whereas the bandwidth of the filters has been estimated to be much broader at about one fifth of an octave, closer to 15% of the center frequency. Consequently, it is thought that our ability to resolve different tones might be based — at least for the low frequencies where discrimination thresholds are best — more on the neural coding of temporal cues to sound frequency that are present in the stimulus waveform, than a change in the excitation pattern within the cochlea [6,9].

But the frequency selectivity of neurons higher up in the auditory pathway is not just a reflection of the mechanical tuning of the cochlear filters. Microelectrode recordings from neurons in the auditory cortex of different species have revealed a range of tuning curve shapes and bandwidths. In some neurons, frequency selectivity can be preserved over the full range of sound intensities to which the neuron is responsive, most likely as a result of inhibitory processing at higher levels of the auditory pathway [10]. Such sharp frequency tuning contributes, for example, to the ability of certain echolocating bats to judge relative target velocity through a comparison of the constant-frequency components of the animals' ultrasonic pulses and their Doppler-shifted echoes [11]. The functional significance of the diverse frequency selectivity exhibited by cortical neurons in other, less specialized species is, however, unclear.

Recording from the Human Auditory Cortex

The patients studied by Bitterman *et al.* [1] were asked to listen to two different classes of acoustic stimuli, either an artificial stimulus known as a random chord sequence or to a movie sound track consisting of spoken dialogue and background music. The electrical activity of individual neurons in the auditory cortex was recorded through the microelectrodes, and a method known as 'reverse correlation' was then used to assess the frequency selectivity of the neurons. Reverse correlation assumes, plausibly, that the discharges of the recorded sensory neurons are likely to be triggered by the stimulus episodes that immediately preceded them. By observing a large number of discharges, it is then possible to infer the optimal stimulus for the neuron by asking, using 'spike triggered averaging', what all the stimulus episodes that precede these responses have in common [12].

When using this technique, care must be exercised to take the 'autocorrelation structure' of the stimuli into account. Imagine that a neuron is sensitive only to frequency A, but if, in the stimulus set used to characterize the neuron, frequency A regularly occurs together with frequency B, then frequency B may feature prominently in the spike-triggered average, even though the neuron is not directly sensitive to that frequency. Bitterman *et al.* [1] were therefore careful to correct their measurements for stimulus auto-correlation, using methods pioneered by Frederic Theunissen [13].

Representative examples of the sort of neural frequency responses — commonly referred to as 'spectro-temporal receptive fields' or STRFs — which Bitterman *et al.* [1] obtained are shown in Figure 1, next to spectrograms of the stimuli used to measure them. Several aspects of the STRFs shown in Figure 1 are worth noting. For instance, the STRF obtained with the random chord stimulus reveals surprisingly sharp frequency tuning (Figure 1B). The excitatory frequency regions, shown in red, are no more than a tenth of an octave wide, considerably sharper than the frequency tuning afforded by the inner ear.

The majority of the neurons recorded in this study exhibited similarly sharp

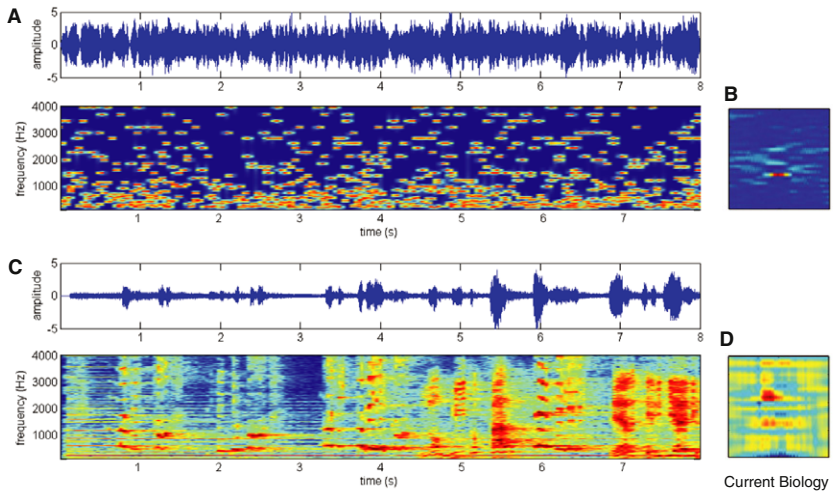

Figure 1. Probing the frequency selectivity of neurons in the auditory cortex.

(A) Example of a 'random chord' sound stimulus. Random chords consist of numerous brief tone pips presented at random time intervals. The sound spectrogram is shown beneath the stimulus waveform. 'Warm' (yellow and red) colors in the spectrogram indicate high sound intensities at the times and frequencies shown on the x- and y-axes, respectively. (B) The spectro-temporal receptive field (STRF) of a single neuron in the human auditory cortex, estimated by reverse correlation with the random chord stimuli. In the STRF, warm colors show which frequencies excite the neuron and over what time course. (C) Example of a 'sound track' stimulus, consisting of a human speech dialogue against faint background music. (D) STRF of the same neuron shown in B, but this time recorded with the sound-track stimulus. Note that the neuron's frequency tuning adapts to the stimulus and becomes broader (based on data in Bitterman *et al.* [1]).

frequency tuning. Bitterman *et al.* [1] used these data to estimate neuronal discrimination thresholds and found that these were comparable to those measured psychophysically in naïve listeners. Their findings therefore suggest that auditory cortical neurons in humans are consistently more selective for sound frequency than in most other mammalian species, although given that frequency-discrimination thresholds measured in animals are generally higher than those in humans [14], this is perhaps not surprising.

Context-Dependent Frequency Selectivity?

Although the cortical neurons tended to be most sensitive to the same frequencies when stimulated with random chord sequences and natural sounds, the STRFs obtained with the 'sound track' acoustic stimulus were more broadly tuned. This can be seen by comparing the STRFs in Figure 1B and D, which are from the same neuron but recorded with different stimuli. Just inspecting the spectrograms of the stimuli and their corresponding STRFs, one gets the distinct impression that the STRFs are adapted to match the type of stimulus that the neuron is listening to.

In order to understand what someone is saying, the auditory system must extract both the rapid fluctuations in the sound envelope (note how the amplitude of the sound track stimulus shown in Figure 1C alternates between silent periods and sudden bursts of sound) and the 'speech formants' — the broad resonant peaks in the spectrum of the sound waves. Very fine frequency discrimination is not essential for speech comprehension. Broad frequency selectivity coupled with a good sensitivity to amplitude modulations is sufficient, and so the broadly-tuned STRF shown in Figure 1D appears to be well adapted to the processing of speech stimuli. In contrast, the random chord stimulus shown in Figure 1A contains neither informative envelope modulations nor interesting formants, and the neuron appears to re-tune its STRF to extract the only interesting feature of this particular stimulus, namely the countless tone pips occurring randomly across independent, closely spaced frequency bands.

These results suggest that the neural filters used by our auditory system to analyze the sounds around us can adapt rapidly to changing task demands and can become surprisingly sharp if necessary. Task-dependent plasticity has also been observed by measuring STRFs from neurons in the auditory cortex of ferrets, so that the same tone stimulus can evoke quite different responses according to the context in which it is presented [15]. These findings highlight the importance of higher-level processing — even for spectral tasks that were once thought to have their basis in the auditory periphery — and of considering both the types of sound stimuli that are used, and the situation in which they are presented, when exploring the nature of this processing.

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DOI: 10.1016/j.cub.2008.03.017

Optimal Foraging: A Bird in the Hand Released

Optimal foraging theory aims to elucidate strategies that maximize resource intake. Although traditionally used to understand animal foraging behavior, recent evolutionary experiments with viruses offer a new twist on an old idea.

Joshua Nahum and Benjamin Kerr

Resources ‘at hand’ have intrinsic value over uncertain future resources. Given that resources differ in quality, however, sometimes it may be advantageous to relinquish an inferior item in pursuit of something better. This is the forager’s choice between taking the “bird in the hand” and pursuing “birds in the bush”. The forager’s optimal decision is likely based on quality and distribution of different resources. Optimal foraging theory addresses how this decision depends on the characteristics of resources [1–4].

To appreciate some of the predictions of the theory, imagine a treesnake feeding on bird eggs. Our snake must make (at least) two decisions: whether to forage within a given tree (patch acceptance); and how long to remain in a tree foraging (patch residence time). As our snake forages within a tree, imagine that cumulative egg acquisition increases with diminishing returns (for example, reaching an asymptote). Further, imagine there are two types of tree: a ‘good’ tree species with many nests, and a ‘poor’ tree species with few nests. Optimal foraging theory predicts that, as the abundance of good trees increases, or as the disparity in nest-number between the tree species increases, the snake should be more likely to avoid foraging in a poor tree [2–4]. Suppose our snake specializes on one tree species. As the travel time between individual trees decreases, the snake is predicted to spend less time foraging per tree [1,4]. Thus, our snake faces a (half-literal) “bird in the hand” dilemma — specifically, whether to reject available trees or remaining eggs within a tree.

In the same way that the treesnake must decide whether and how long to forage in different trees, a virus must ‘decide’ what host cell to enter and how long to co-opt the resources of that cell. Lytic phage — viruses that infect bacteria — are particularly conducive to testing predictions from optimal foraging theory [5–8] (see Figure 1 for the life cycle). A phage particle may adsorb (attach) to its bacterial host upon encounter (the transition from stage 2 to stage 3 in Figure 1). But a phage particle may also fail to adsorb to a host after encounter, bringing it back to a dispersal stage (from stage 2 to stage 1). This phage particle may then encounter a new host (from stage 1 to stage 2) and potentially adsorb. Adsorbed phage injects its genome into its host, produces progeny inside and, at a very specific time, lyses the host releasing the progeny. The length of infection is termed the latent period (from stage 3 to stage 5). For some phage species, experimentally delaying lysis past its normal time increases the number of progeny released [7,9]. In such cases, the phage has not exhausted the resources of its host at the time of lysis. Like our treesnake, the phage faces the “bird in the hand” dilemma: whether to reject encountered hosts and whether to destroy a host that can be used to make more phage.

Indeed, the phage particle can be likened to a forager moving between resource patches (bacterial cells). In this analogy, the dispersal period is the inter-patch travel time, adsorption is a choice to enter a patch, latent period is the residence time within a patch, and the rate of progeny accumulation gives patch quality. While some of these elements are outside phage control (for example, host density will influence dispersal time and host physiology will influence progeny accumulation [5,7,8]), other elements are influenced by the phage directly. For instance, phage tail proteins affect patch choice (adsorption) and phage holins affect residence time (latent period) [6,7,9–11]. These components are thought to be modular [7], suggesting that the evolution of one phage property may be unconstrained by pleiotropic effects. Further, given the short generation time and large population size of phage, real-time experimental evolution can be executed in which predictions from optimal foraging theory can be put to the test [10–12].

Two ingenious recent studies [10,11] used phage T7 for just such a test. In the first of these, Heineman *et al.* [11] allowed T7 to evolve in the presence of two host strains differing in their phage-attachment surface moieties. In a preliminary experiment, one host was permissive (allowing progeny production), but another was genetically engineered to abort phage progeny during infection. While the ancestral phage adsorbed to both hosts, the authors discovered that the virus evolved to adsorb preferentially to the permissive host, a change mediated by a single mutation in a tail fiber gene. Thus, the viral forager evolved to become a ‘picky eater.’

The authors then tested some predictions of optimal foraging theory by competing the evolved ‘choosy’ T7 against its non-choosy ancestor under a set of different conditions. For these competitions, the formerly non-permissive host now supported phage production (red cell in Figure 1), but progeny accumulation