

Research paper

Toward the mechanisms of auditory attention

Tomáš Hromádka, Anthony M. Zador *

Cold Spring Harbor Laboratory, 1 Bungtown Road, Cold Spring Harbor, NY 11724, United States

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Abstract

Since the earliest studies of auditory cortex, it has been clear that an animal's behavioral or attentional state can play a crucial role in shaping the response characteristics of single neurons. Much of what has been learned about attention has been made using human and animal models, but little is known about the cellular and synaptic mechanisms by which attentional modulation of neuronal responses occurs. The use of rodent experimental models allows us to exploit the full armamentarium of modern cellular and molecular neuroscience techniques. Here we present our program for studying auditory attention, specifically for development of rodent models of attention and finding the neural correlates of attention.

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1. Introduction

Imagine you hear a shout: “fire!” If you are part of a firing squad, you might pull a trigger; and if you are on the receiving end of the firing squad, you might merely brace yourself for the inevitable. If you are in your hotel room watching TV, you might decide to put on your slippers and see what the commotion is about; if you are, however, reading the latest issue of *Hearing Research*, it will be very hard to distract your attention by any outcry. It is clear that how you respond to the exclamation will depend on the behavioral or cognitive context.

How would the neural activity elicited under these conditions differ? Although we do not know all the steps in the neural pathways involved, we do have a pretty good idea about the endpoints. On the sensory side, small variations in sound pressure are transformed at the cochlea into spikes that traverse the auditory nerve, pass several subcortical auditory stations, and eventually reach the auditory cortex. From here the signal must pass through some inter-

mediate cortical areas (e.g. language and sensorimotor integration areas). On the motor side, spikes from the motor cortex pass down the spinal cord and eventually trigger contractions in a set of muscles appropriate for the particular motor reaction.

It might appear, then, that neural processing on the sensory side ought to be simple enough to study. One might begin by studying the transformation of sound into spikes at the auditory nerve, and then follow the neural representation of the sound through the various subcortical stations. Eventually one would have to grapple with the more complex representations necessary for the computationally challenging pattern recognition needed to recognize words; presumably these are computations that begin at the level of the auditory cortex and continue at the level of higher cortical areas specialized for language. But the basic research program seems straightforward: study how sound is represented at each stage of the processing hierarchy, *without regard to the behavioral or cognitive context*.

An analogous research paradigm dominated the study of *visual* cortex for several decades since Hubel and Wiesel's seminal work on V1, and remains important even today. Hubel and Wiesel showed that many of the neurons in area V1 could be driven to fire at high rates in response

* Corresponding author. Tel.: +1 516 367 6950; fax: +1 516 367 8866.
E-mail address: zador@cshl.edu (A.M. Zador).

to oriented bars appropriately positioned in the visual field. This eventually led to an appealing general model of sensory processing in which visual (and analogously auditory) recognition is achieved by constructing an appropriate series of representations of the visual (or auditory) world from the simpler representations at the previous stage, a view supported by evidence for an anatomical hierarchy of connections in visual cortex (Felleman and Van Essen, 1991). It is an appealing framework because it posits a series of feedforward, possibly non-linear, filters organized into feedforward networks, which are much easier to understand than recurrent networks.

Unfortunately for us scientists, the mammalian brain is not a simple feedforward network. One cannot simply model the flow of information as undergoing a unidirectional transformation from sensory input to motor output. Particularly in the cortex, it is clear that the *representation of sensory information depends also on the animal's behavioral and/or cognitive state*, and on how that information is to be used, and not only on the activity at the sensory epithelium (the eyes, the ears, etc).

An important corollary is that even precise knowledge of the representation of a sensory signal at the sensory periphery, or at a previous stage of processing, is not sufficient to understand the representation at a “higher” cortical level. (“Higher” is placed in quotes here to emphasize that viewing neural processing in a strictly hierarchical way can be misleading). Assuming that neural activity in the “higher” processing stages is more strongly influenced by cognitive (non-sensory) factors than activity in the lower stages, knowledge of the detailed response characteristics of auditory nerve fibers, or of neurons in the inferior colliculus, though useful, might merely help to guide experiments aimed at later stages. The representations at these later stages, starting at least with primary auditory cortex, must then be studied on their own.

The rest of this review focuses on *auditory attention* (in its various forms) as a particular example of a cognitive state which readily influences neuronal activity. We briefly review several important milestones of research of auditory attention from our electrophysiological point of view. In the end we summarize our research program concentrated on circuit mechanisms underlying various forms of auditory attention.

2. A brief and idiosyncratic review of auditory attentional modulation

Since the earliest studies of auditory cortex, it has been clear that an animal's behavioral or attentional state can play a crucial role in shaping the response characteristics of single neurons. For example, one of the first reports using single unit tungsten extracellular recording technology by David Hubel, Robert Galambos and colleagues (Hubel et al., 1959) is entitled “Attention units in the auditory cortex.” The authors described “a population of cells (in the auditory cortex of awake cats) that appears to be sensitive

to auditory stimuli only if the cat pays attention to a sound source.” For example, one unit was activated by keys jingled outside the room in which the cat was isolated, but only when the animal's attention was directed toward the door. The authors estimated that about 10% of neurons they encountered fell into this category. The authors concluded that “the neural processes responsible for attention play an important role in determining whether or not a given acoustic stimulus proves adequate,” but cautioned that “unfortunately attention is an elusive variable that no one has yet been able to quantify.” Possibly because of that cautionary note, Hubel appears to have retreated from this single foray into auditory cortex research, and subsequently directed his energy-not without success-exclusively on early visual processing.

Surprisingly, Hubel's initial study did not immediately generate a series of follow-up reports, although it did attract attention of other groups (Evans and Whitfield, 1964). Perhaps the difficulties noted by Hubel in quantifying attention slowed progress; or perhaps delays were due to the gradual shift to the anesthetized preparation, possibly inspired by the apparent success of Hubel and Wiesel's research program for studying area V1 responses in the anesthetized cat. Whatever the cause, it appears that follow-up studies on the cortical correlates of auditory attention in animal models over the next decades were sparse (Miller et al., 1972; Hocherman et al., 1976; Miller et al., 1980), although in recent years a series of exciting results has renewed interest (Fritz et al., 2003; Brosch et al., 2005; Fritz et al., 2005a,b).

To demonstrate that changes in neural activity result from changes in attention, rather than simply from changes in the stimulus itself, modern paradigms compare neural responses to identical stimuli under conditions when only the attentional state is varied; in this way, the effect of the attentional modulation can be isolated. One of the first studies to employ what is now the standard paradigm for studying the neural correlates of attention came again from Robert Galambos's laboratory (Picton et al., 1971). The study was conducted not in an animal model, but in humans, using electroencephalogram (EEG) recording techniques. In this experiment, click-evoked cortical responses were compared under two behavioral conditions. In the first condition, subjects were asked to read a text, thereby drawing their attention away from the clicks; whereas in the second condition they were asked to detect the occasional faint click, requiring them to attend to the clicks. Since sound was delivered through headphones, stimuli could be kept constant under the two conditions, ensuring that changes in neural responses did not result from simple changes in the stimuli.

Picton and colleagues found that the click-evoked response was larger when subjects attended to the auditory stimuli. This finding is consistent with the classical psychologists' view of attention, so clearly articulated by William James over a century ago (James, 1890): “Everyone knows what attention is. It is the taking possession by the mind, in

clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are its essence. *It implies withdrawal from some things in order to deal effectively with others* (emphasis added)." (p. 403, chapter XI). This last sentence foreshadows the modern psychological view of *attention as a limited resource*, where neural activity is expected to increase in brain areas required to process attentional information, and decrease in brain areas irrelevant for the given task.

This view is generally supported by many studies measuring brain activity under different attentional conditions and using different recording techniques in different experimental preparations. Studies in animal preparations, starting with (possibly the earliest) observation that "attention" can increase "electric activity" in cochlear nucleus of awake cats (Hernandez-Peon et al., 1956), and continuing with single unit recording methods in auditory cortex of primates (Miller et al., 1972; Hocherman et al., 1976); and studies in human subjects using both EEG (Picton et al., 1971), or functional magnetic resonance imaging (fMRI) (Johnson and Zatorre, 2005), have generally supported the limited resource model, with the finding that directing attentional resources toward a brain region results in an increase in neural activity.

However, it is interesting to note that, at the single neuron level, auditory attention has sometimes been reported to increase, but also sometimes to decrease, neural responsiveness (Hocherman et al., 1976; Miller et al., 1980). In this way auditory attention seems to behave differently from visual attention, where only increases are typically reported at the single neuron level (Desimone and Duncan, 1995). Whether this is due to a difference in experimental methodology (e.g. neurons are usually probed with near optimal stimuli in visual studies, but typically with much simpler stimuli in auditory studies), or reflects instead a more fundamental difference between the two areas, is an open question. To study mechanisms of auditory attentional modulation, and resolve the differences (if any) between attentional modulation in different modalities, one must approach the question directly and study activity of neuronal circuits underlying (and perhaps responsible for) these attentional modulations.

3. Toward the mechanisms of attentional modulation

The goal of our laboratory is to understand the mechanisms underlying attentional modulation of neuronal activity, using rodents as a model system. As discussed above, it is clear that attention can modulate neuronal activity, and there has been substantial progress in understanding the behavioral and stimulus conditions under which this modulation occurs, particularly in the visual system (Desimone and Duncan, 1995). Our specific goal is to understand, *at the level of the neuronal circuit*, how this modulation occurs in the auditory cortex. For example, when a neuron's firing rate is enhanced by attention, does this enhancement arise

from an increase in excitatory input, a decrease in inhibitory input, a change in firing properties (perhaps arising from a change in the neuromodulatory bath), or some other mechanism? Our goal, in other words, is to continue opening the "black box" of cortical processing, of converting a psychological question (What is attention?) into a neurophysiological one (How do changes in neuronal spiking output with attention arise from the cortical circuits?).

Although much of what we know about the mechanisms of attentional modulation was gleaned in studies using human and non-human primates (but also ferrets and cats; see (Oatman, 1971; Oatman, 1976; Anderson and Oatman, 1980; Fritz et al., 2003, 2005a,b)), rodents offer several advantages as a model system. First, rodents are relatively inexpensive to maintain, and can be trained in parallel. Furthermore, training protocols can be optimized and tasks streamlined, so that even relatively complex tasks require weeks rather than months to train. As a consequence, it is realistic to assay neural activity in dozens of subjects in the course of a single set of experiments. It is therefore, feasible to vary task constraints systematically and parametrically in a reasonably large subject population, or to make use of low-yield physiological approaches.

Second, the choice of rodents allows us to exploit modern electrophysiological, molecular and imaging approaches that are currently difficult or impossible to apply in primates. For example, our laboratory routinely records activity using *in vivo* whole cell patch-clamp methods in both anesthetized and awake rats (Wehr and Zador, 2003; Hromádka et al., 2004). Knowledge of intracellular mechanisms governing neuronal responses under different attentional conditions can be crucial in understanding what (i.e. which mechanisms) determines probable differences in neuronal responses. For example, changes in temporal relationship between synaptic excitation and inhibition can lead to changes in neuronal firing rate, or even changes in neuronal response threshold (as determined by its spiking output). In addition, differential changes in tuning of excitatory and inhibitory inputs can lead to changes in, for example, spectral selectivity (frequency tuning).

Our laboratory has also used viruses to deliver genes of interest to spatially restricted neuronal populations, such as the auditory cortex and amygdala (Rumpel et al., 2005). We are particularly interested in molecules that allow *monitoring* neural activity (Miesenbock, 2004). Monitoring activity of large populations of neurons simultaneously (as already established in, for example visual cortex: (Ohki et al., 2005)) can bring important insights about organization and also computations performed in auditory cortex. Most importantly, however, we are exploring the use of molecules that allow for *perturbing* neuronal activity *in vivo* optically, such as Channelrhodopsin2 (Boyden et al., 2005). The ability to perturb activity of a specified subset of neuronal population while the animal is performing a behavioral task is very important for our understanding of the chain of events leading to attentional modulation of neuronal activity. One can even imagine perturbing activity of either specific

subset of neurons in one cortical area (for example layers 2/3 in A1), or neurons that either project to or receive projections from a specific area.

In order to exploit advantages offered by rodent model system, we must (1) develop suitable behavioral models of auditory attention in rodents; and (2) identify robust neural correlates of attention. The focus of the remainder of this review is to describe our progress toward achieving these goals.

Auditory behavioral paradigms in rodents. Over the past few years, our laboratory has developed a variety of behavioral tasks for studying auditory processing and attention in the rat. These tasks are based on two main behavioral paradigms. The first one is the two alternative choice (2AC) paradigm, suitable for studying behavior in freely moving subjects (Uchida and Mainen, 2003). In the most basic auditory variant of this task (Fig. 1), animals are required to perform a sensory discrimination, and are rewarded when they make the correct of two choices. Subjects are trained to initiate trials by poking their nose into a central port, and learn to associate one stimulus (e.g. 15 kHz tone) with the right water port, and the other (e.g. 2 kHz tone) with the left water port. (We have also used other variants, e.g. with spatial stimuli, so that sound from the right speaker predicts availability of reward from the right water port, and sound from the left speaker predicts availability of reward from the left water port). Well-trained subjects perform many (>500) trials in a single session, and can achieve high asymptotic performance (>95% correct), after 1–4 weeks of training (training times depend on task difficulty). Training has been highly automated; facilities are in place to train as many as sixteen subjects in parallel, and it is currently feasible for a single technician to train eight subjects simultaneously. This basic paradigm can be modified to yield a variety of attentional tasks (see below).

A second behavioral paradigm we have used is a go/no-go design in the head-fixed rat (Hromádka and Zador, unpublished). In our head-fixed paradigm rats are respond-

ing by licking at water port and rewarded for correctly identifying a target stimulus. Incorrect responses, i.e. licking in response to non-target (distractor) stimuli, and licking during intertrial intervals are penalized by air-puffs. During training, rats move freely in a narrow plastic tube. After the rats can perform the required task with low false-positive and false-negative rates, they are implanted with headposts and retrained in a head-fixed position. During the first 1–2 sessions, the head-fixed rats usually reach their previous behavioral performance and are ready for recordings. Training times and basic performance are comparable to the 2AC design shown in Fig. 1. The main advantage of the head-fixed preparation is that certain experimental techniques, such as intrinsic imaging, two-photon imaging, and intracellular recording are more convenient in the head-fixed configuration.

Neural correlates of attention in the rat. We use different variants of the aforementioned behavioral paradigms to study different aspects of attentional modulation. In one set of experiments we examined *task-dependent modulation* of neuronal responses by auditory attention. We used tetrodes to compare neural responses in the auditory cortex under two behavioral conditions: attending/active and idle (Otazu and Zador, unpublished). In the active condition, the subject performed a spatial version of the 2AC task shown in Fig. 1, whereas in the second condition the rat merely remained idle (but not asleep) in the behavior box, while the same stimuli as in the first condition were presented. However, unlike the simple version of the task shown in Fig. 1, in this version we preceded a *relevant* stimulus (i.e. the chord emanating from the left or right speaker, indicating whether the rat should go left or right) with an *irrelevant* stimulus (a series of short white noise bursts). Sounds were presented through head-mounted earphones to ensure that the stimuli were identical under the two conditions. What we found was a consistent and robust suppression of the response to the irrelevant stimulus during the performance of the task, but little change in the response to the

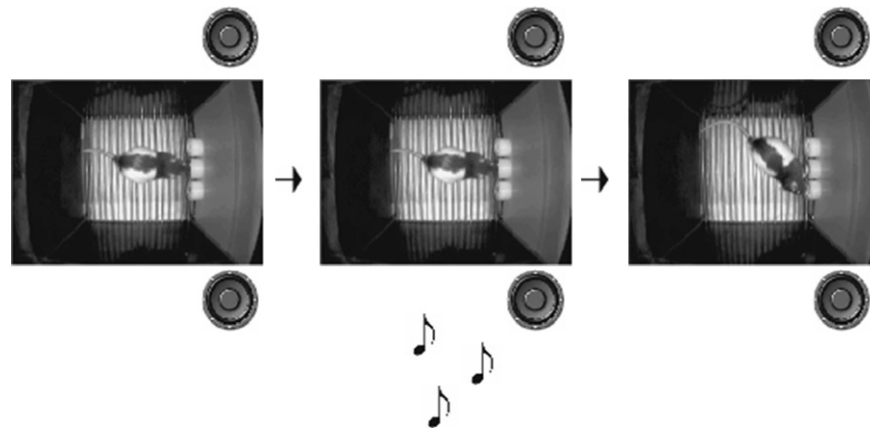


Fig. 1. Structure of basic two-alternative choice (2-AC) task. Rats are trained to poke into the center port (*left*). This elicits the presentation of an acoustic stimulus (*middle*), which in this case is a tone played from the right speaker. (In other variants of the task, the stimulus is either a high- or low-frequency tone or chord, presented from a single central speaker). If the subject responds with a poke into the correct port, he is rewarded with a water reward. Well-trained subjects perform many (>500) trials in a single session, and can achieve high asymptotic performance (>95% correct).

relevant stimulus. The consistency of this effect, and the simplicity of the training paradigm (subjects can be trained in less than one week), make it an ideal candidate for studying the mechanisms of task-dependent modulation.

In a second set of experiments, we used tetrodes to compare neural responses in the auditory cortex in a *cross-modal attentional paradigm* (Tai and Zador, unpublished). Subjects were simultaneously presented with auditory and olfactory stimuli while performing a 2AC task. In one condition (“auditory attention block”), the subject was required to base his/her behavioral responses on the auditory stimulus (a low- or a high-frequency tone), and to ignore the olfactory stimulus; whereas in the second condition (“olfactory attention block”), the subject was required to base his/her response on the olfactory stimulus (one of two odors), and ignore the auditory stimulus. The key in this experiment is that the auditory stimuli were precisely the same in the two conditions, allowing us to compare responses to the exact same auditory stimulus but two different behavioral conditions (auditory or olfactory attention). We found that about 15% of neurons showed attentional modulation. Interestingly, almost as many neurons showed suppression during the auditory block as enhancement, a somewhat surprising result in the context of the “limited resource model” of attention, but consistent with similar results in a primate model (Hocherman et al., 1976).

In the head-fixed paradigm we have been using sound discrimination go/no-go task to study effects of *vigilance/alertness* on neuronal responses. During the task, rats listening to a continuous stream of 500 ms sounds separated by few seconds of silence were rewarded when licking in response to target sounds (for example warbles, i.e. frequency modulated tones), and were penalized when licking otherwise. Using patch-clamp cell-attached recordings in rats performing the task we could compare neuronal responses in correct and error trials for the same stimuli. We have also been developing a more complex task, in which we study *covert spatial auditory attention*. In this task rats are presented with two (different) auditory streams coming from opposite speakers. One of the streams is cued and usually contains a target sound which logically belongs to the cued stream, but has additional properties which allow for its (easier or harder) identification. Correct responses (licks) to target sounds are rewarded with water, and incorrect responses (licks outside target window) are penalized by air-puffs. Thus in this task we are studying modulation of neuronal activity by spatial attention in a rat performing spatial auditory stream segregation.

4. Conclusions

The auditory cortex is far more than a non-linear filter converting subcortical signals for further processing in higher cortical stages. Responses in the auditory cortex depend not only on the acoustic stimuli presented, but also on the behavioral context. We study activity in neuronal circuits in rodent experimental preparation(s) developed in

our laboratory using a wide variety of electrophysiological and molecular tools.

Our long term goal is to understand how non-sensory factors such as attention, motivation, and various other task contingencies modulate activity of cortical circuits and give rise to different neuronal responses under different behavioral conditions. This will ultimately help us understand how the cortex is able to solve challenging context-dependent computational problems, such as the cocktail party problem (Asari et al., 2006).

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