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Synaptic mechanisms underlying auditory processing

Anne-Marie M Oswald, Max L Schiff and Alex D Reyes

In vivo voltage clamp recordings have provided new insights into the synaptic mechanisms that underlie processing in the primary auditory cortex. Of particular importance are the discoveries that excitatory and inhibitory inputs have similar frequency and intensity tuning, that excitation is followed by inhibition with a short delay, and that the duration of inhibition is briefer than expected. These findings challenge existing models of auditory processing in which broadly tuned lateral inhibition is used to limit excitatory receptive fields and suggest new mechanisms by which inhibition and short term plasticity shape neural responses.

Addresses
Center for Neural Science, New York University, 4 Washington Place, Room 809, New York, NY 10003, USA

Corresponding author: Oswald, Anne-Marie M. (oswald@cns.nyu.edu)

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Introduction

A central issue in auditory neuroscience is how the external acoustic environment is represented by neural activity in the primary auditory cortex (AI). AI plays a role in the perceptual processing of complex acoustic stimuli, contributing to a wide variety of processes including recognition of species-specific vocalizations, sound source localization, identification of auditory objects, stimulus-specific adaptation, and learning and memory [1–4]. Although auditory signals undergo significant subcortical processing, *in vivo* recordings indicate that further refinement takes place in AI [5–7]. AI, in comparison to subcortical regions, has a higher incidence of neurons that exhibit non-monotonic rate-level functions, greater sensitivity to source location, and a decreased ability to phase-lock to high temporal modulation rates. The relationship between acoustic stimuli and cortical spiking patterns has traditionally been characterized using extracellular recordings. Because spikes result from the integration of numerous subthreshold events, the underlying cellular and network mechanisms can be more directly studied with intracellular recording techniques. Unfortunately, *in vivo* intracellular recording in AI is technically challenging and, to date, only a few successful experiments have been performed [8–10]. In this review, we highlight recent *in vivo* whole-cell recordings in AI and focus on two important factors that influence neuronal firing — the interaction of excitatory and inhibitory synaptic inputs and the dynamic properties of synaptic potentials. We discuss how these factors contribute to time-varying firing during tonal stimulation, receptive field properties, and other well-documented response characteristics of AI neurons. These new data narrow the gap between cellular and systems physiology and suggest how current models of auditory processing could be refined.

General synaptic features of primary auditory cortex

The basic organization of AI is generally similar to that of other primary sensory cortices (see [11] for review and notable exceptions). Neurons in AI are tonotopically organized according to the characteristic frequency (CF; see glossary) that evokes a response at the lowest stimulus intensity. The tuning properties of the neurons are inherited from the ventral division of the medial geniculate nucleus of the thalamus but are further refined in AI [5–7]. Thalamic afferents terminate on excitatory and inhibitory neurons primarily in layers 3 and 4 [12,13•,14] that constitute a subset of an extensive (and mostly uncharacterized) network of neurons. Consequently, the firing properties of neurons in A1 are determined by synaptic inputs from both the thalamus and the local network of excitatory and inhibitory neurons.

Short-term plasticity (STP) of postsynaptic potentials (PSPs), occurring on timescales of hundreds of milliseconds, also contributes substantially to neuronal firing [15]. In general, when a presynaptic neuron fires repetitively, the amplitudes of successively evoked PSPs either decrease (depress) or increase (facilitate). Whole-cell recordings *in vitro* indicate that thalamocortical and intracortical inputs in AI exhibit both forms of short-term plasticity [13•,16]. There are three important features of STP. First, the initial amplitudes of PSPs of depressing synapses tend to be larger than those of facilitating synapses, owing to a higher probability of transmitter release. Consequently, depressing synapses are more likely to evoke spikes at the stimulus onset, whereas facilitating synapses are likely to evoke spikes after some delay. Second, complete recovery from STP requires hundreds of milliseconds to seconds, which is much longer than the duration of a single PSP, so that events occurring closely in time interact non-linearly. Third, and finally, STP can be target-cell specific: a single presynaptic cell can produce depressing PSPs in one target neuron and

Glossary
Characteristic frequency: The tone frequency that elicits a neural response at the lowest stimulus intensity.
Click stimuli: Brief (5 ms) white noise stimuli [23••].
Frequency sweep: Stimulus protocol in which progressively increasing or decreasing frequencies tones are presented sequentially and continuously.
Tuning curve: Plot of neural response versus tone frequency. Typically, there is an optimal stimulus frequency that evokes the maximal response.
Two-tone stimulation: Two brief tones, the probe and the test, are presented sequentially at short intervals. The probe can decrease (two-tone suppression) or increase (two-tone enhancement) the neural response to the test.

facilitating PSPs in another [17]. Functionally, these characteristics of STP can provide a means of filtering and segregating specific temporal components of the presynaptic signal [18]. In the next two sections we discuss the contributions of local inhibitory networks and STP to the response properties of neurons in AI.

Contribution of local inhibitory networks

During acoustic stimulation, some AI neurons fire only at the onset or offset of a stimulus (phasic), whereas others fire continuously throughout the stimulus (tonic, phasic–tonic) [8,9,19]. Intracellular recordings indicate that these responses are partly due to the interaction of excitatory (EPSPs) and inhibitory (IPSPs) postsynaptic potentials [8–10]. Neurons that fire phasically receive a barrage of EPSPs followed after a short delay by IPSPs. Tonically firing neurons also receive a similar EPSP–IPSP sequence, except that the EPSPs dominate throughout the stimulus. Thus, the neural response is determined by the relative strength and the temporal relationship of excitation and inhibition.

Recently, the underlying excitatory and inhibitory inputs were examined more systematically *in vivo* using voltage clamp techniques [20,21•,22,23••]. Synaptic currents evoked during acoustic stimulation were recorded at several holding potentials and the associated excitatory and inhibitory conductances were separated using current balance equations. Two important results came out of these studies. First, inhibitory conductances follow excitatory conductances with a short delay (1–6 ms) [21•,22] that does not vary with stimulus frequency and intensity. This delay is a combination of the synaptic delay and the integration time needed to bring the inhibitory neuron to firing threshold. Second, the excitation and inhibition are co-tuned [20,21•,22]. The conductances peak at CF and co-vary such that their ratio remains constant across frequency and intensity (Figure 1a). These results suggest that the excitatory and inhibitory neurons receive common inputs from the thalamus (or other cortical neurons) (Figure 1a). The stereotyped EPSP–IPSP sequence suggests that thalamocortical inputs onto inhibitory neurons are powerful and highly reliable, as supported by a recent *in vitro* study [13•]. The short delay between the co-tuned excitation and the inhibition narrows the window for spike generation, producing phasic responses and enhancing the temporal precision of action potentials [22].

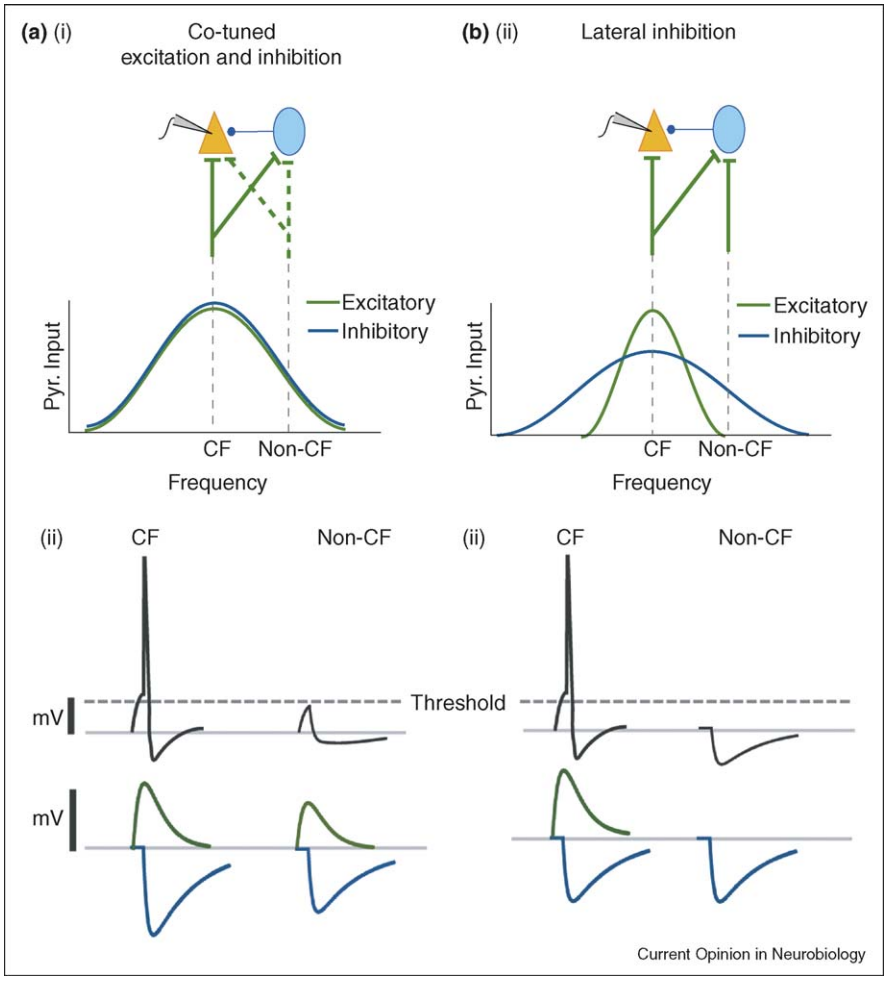
Activation of the local inhibitory circuitry is postulated to sharpen the tuning curves (see glossary) of the neurons and give rise to two-tone suppression [21•,24–26]. Pure tone stimuli are used to construct excitatory receptive fields (ERFs). These tuning curves are broadened by local iontophoresis of $GABA_A$ receptor antagonists and narrowed by the application of agonists [26,27]. In addition, the response of a neuron to a CF tone is often reduced when a non-CF tone is presented simultaneously or with a short lead. Two-tone stimulation (see glossary) has been used to show that inhibitory receptive fields (IRFs) flank the ERFs [20,28]. Finally, spontaneous spiking activity can be suppressed by stimuli with frequencies near those that produce robust responses [29]. Results such as these have led to the idea that inhibitory interneurons provide lateral inhibition to the excitatory cells (Figure 1b). The main feature of this model is that inhibition is more broadly tuned than excitation, such that the input to a cell is predominantly inhibitory during non-CF tonal stimulation (Figure 1bii). This prediction, however, is not supported by the finding that the excitation and inhibition are co-tuned.

Co-tuning can account for some of the receptive field properties of AI neurons previously attributed to lateral inhibition. Co-tuned inhibition could sharpen the tuning curves by ensuring that only the relatively large excitatory inputs near CF stimulation trigger action potentials; non-CF excitation is offset by inhibition so that inputs that would otherwise be suprathreshold remain subthreshold (Figure 1aii). Co-tuned inhibition can also produce IRFs and frequency sweep (see glossary) direction selectivity. During IRF mapping, the IPSP elicited by the leading tone overlaps with the EPSP from the CF tone to suppress action potentials [20] (Figure 2bi). Frequency sweeps are similar to two-tone stimulation, except that a continuous sequence of tones is presented at increasing or decreasing frequencies. Neurons have preferred sweep directions: those with high CFs prefer downward sweeps, whereas those with low CFs prefer upward sweeps [20]. In the preferred direction, excitatory conductances peak 10–30 ms prior to inhibitory conductances, and can thus evoke spikes before substantial inhibition has had time to develop. In the non-preferred direction, inhibition significantly overlaps with excitation, preventing spikes. The circuitry that accounts for the asymmetry in the timing between excitation and inhibition and strengths of synaptic inputs remains to be determined.

Contribution of short-term plasticity

Short-term plasticity also contributes to the time-varying firing patterns and receptive field properties of AI

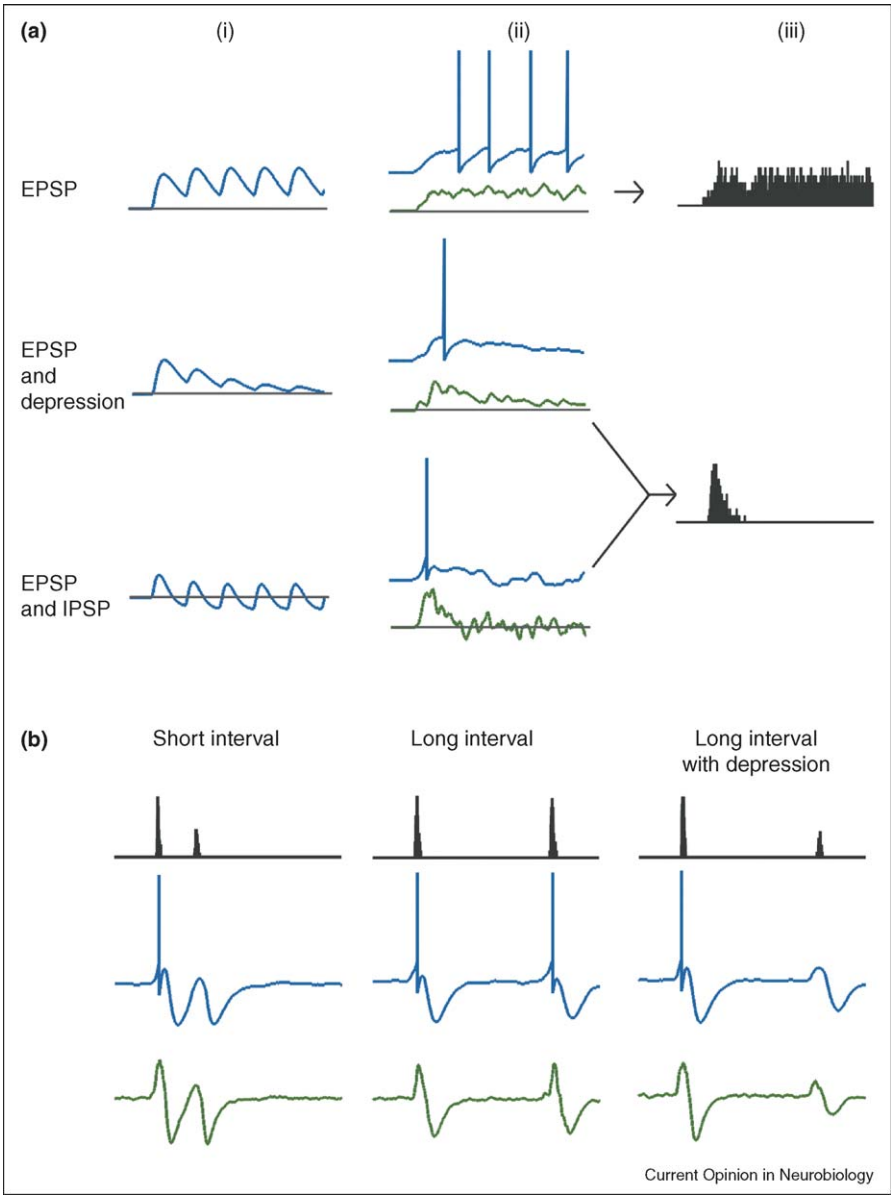
Figure 1



Co-tuning and lateral inhibition. **(ai)** Schematic of co-tuned excitation and inhibition. The pyramidal cell (triangle) and the interneuron (oval) receive common excitatory inputs (green lines); in addition, the pyramidal cell is innervated by the inhibitory cell (dark blue line). The frequency tuning curves for excitatory (green) and inhibitory (blue) inputs that would be recorded in the pyramidal cell (indicated by grey microelectrode) are shown below. For both cells, CF inputs are strong (thick green lines) and non-CF inputs are weak (dashed green lines). **(ii)** Hypothetical membrane potential responses of the pyramidal cell to CF (left) and non CF stimuli (right). CF stimulation elicits a strong EPSP (green) followed after a short delay by a strong IPSP (blue). This produces an EPSP–IPSP sequence that is suprathreshold (dashed line) and elicits an action potential (black, left). Non-CF stimulation produces a similar but weaker EPSP–IPSP sequence (black, right) that fails to evoke an action potential. The scale bars indicate equivalent but arbitrary values of membrane potential in (mV). **(bi)** Schematic of lateral inhibition. The interneuron receives strong input during both CF and non-CF stimulation, whereas the pyramidal cell receives strong input only during CF stimulation. Inhibitory input (blue) to pyramidal cell is more broadly tuned than excitatory input (green). **(ii)** Membrane potential responses to CF and non-CF stimulation. CF stimulation elicits a strong, suprathreshold EPSP that produces a spike followed after a short delay by a strong IPSP. Unlike co-tuning, non-CF stimulation can elicit a purely inhibitory response. Although the subthreshold responses are different from those of the co-tuned model, the firing response profiles are similar. Abbreviation: CF, characteristic frequency; pyr, pyramidal cell.

neurons. Phasic responses evoked with tonal stimulation can be attributed to synaptic depression: the EPSPs are initially suprathreshold but then taper off to become subthreshold (Figure 2ai). By contrast, tonic responses could be mediated by non-depressing or facilitating synapses (Figure 2aii). Auditory thalamocortical synapses on average depress, although there is substantial heterogeneity ranging from strong depression to mild facilitation [13•]. For connections between pyramidal cells in layer 2/3, there is a bimodal distribution of synapses: one population consists of large amplitude, depressing EPSPs with low failure rates and the other has small amplitude, facilitating EPSPs with high failure rates [16]. Such heterogeneity in both thalamocortical and intracortical synaptic dynamics could give rise to diverse responses evoked by auditory stimuli, with specific firing patterns depending on the combination of depressing and facilitating inputs.

Figure 2



Synaptic mechanisms underlying neuronal firing patterns. **(ai)** Hypothetical trains of unitary EPSPs with no STP (top), with depression (middle), or with delayed IPSPs (bottom). **(ii)** Voltage responses (blue) to synaptic current input (green) from a population of presynaptic cells. EPSPs with no STP (top) evoke tonic firing, whereas EPSPs with depression (middle) or EPSPs followed by IPSPs (bottom) evoke phasic firing. **(iii)** Poststimulus time histograms illustrating tonic (top) and phasic (bottom) responses. **(b)** Possible synaptic mechanisms for forward suppression. Two stimuli are separated by either short or long intervals. Each stimulus evokes the EPSP–IPSP sequence as in (ai) bottom. **(i)** At short intervals, IPSPs from the first stimulus suppress the response to the second stimulus. **(ii)** At longer intervals, inhibition decays and does not affect the responses to the second stimulus. **(iii)** Synaptic depression has a long recovery time constant and can suppress the responses at longer intervals. Abbreviations: STP, short-term plasticity.

Synaptic depression and facilitation, rather than inhibitory synaptic conductances, can also explain the prolonged effects of a stimulus on the response to the subsequent stimuli [23••,30–32]. Forward suppression, in which a test stimulus reduces the response to the probe stimulus presented at a short delay, can last hundreds of milliseconds. A simple explanation is that a long duration IPSP evoked by the first stimulus decreases the probability that the second stimulus will elicit a spike [21•] (Figure 2bi). However, *in vivo* whole-cell recordings in AI show that the duration of the inhibitory conductance is too short to account for

suppression beyond ~100 ms [23••] (Figure 2bii). Synaptic depression, which has a long recovery time, could account for suppression at longer durations (Figure 2biii).

In many cells, the probe enhances, rather than suppresses, the response to the test stimuli [23••,30–33]. Enhancement could be mediated by facilitation of excitatory inputs during the test stimuli [31,32]. Alternatively, enhancement could be due to disinhibition of responses. The loss of inhibitory drive could be attributed to depression of IPSPs or the EPSPs onto inhibitory cells. This is supported by *in vivo* recordings [23••] that show that approximately 20% of the cells examined showed a greater decrease in inhibitory conductances as compared with excitatory conductances in response to sequential click stimuli (see glossary).

Because STP imparts context-dependence to synaptic responses, it can potentially explain complex dynamic properties such as adaptation to frequently occurring stimuli [34,35], adaptive shifts in tuning curves [36], and low-pass temporal modulation transfer functions in cortical neurons [37]. To establish the extent to which STP contributes to specific auditory processes, it will be necessary to document systematically the degree and type of STP between specific cell types and the time scales for STP for the relevant synapses.

Caveats

Some important caveats about *in vivo* intracellular recordings are worth noting. First, the studies have been performed entirely in anesthetized animals in order to maintain recording stability. However, cortical activity depends significantly on the type of anesthesia and the level of arousal [23••,38,39,40••]. Second, for practical reasons, only brief and relatively simple stimuli were used to probe synaptic responses. There is strong evidence that neural responses, and by inference network activities, vary non-linearly with longer and more complex stimuli [41,42]. Third, the identities and locations of the recorded neurons were not systematically catalogued. Laminar [9,10] and regional [11] heterogeneity in stimulus preference and evoked responses suggest significant differences in local network architecture. All of the above could affect the timing and tuning of EPSPs and IPSPs in addition to synaptic depression or facilitation. Further studies are needed to confirm the generality of the results obtained thus far. Finally, co-tuning implies that inhibition is confined to a small region of the tonotopic axis.

This could be problematic given that many interneurons in AI as in other cortical areas have extensive axonal arbors [43,44] and a high probability of connection with pyramidal cells [45] (AM Oswald, AD Reyes, unpublished observations). Such anatomical features are more consistent with lateral inhibition.

Conclusions

Decades of research in auditory physiology have yielded valuable insights into the mechanisms by which auditory stimuli are encoded and processed in the central nervous system. Recent *in vivo* intracellular studies have enhanced our understanding of cortical auditory processing by elucidating underlying synaptic mechanisms. These studies have challenged previous explanations of how inhibitory receptive fields and forward suppression arise. First, co-tuned excitation and inhibition does not support models of lateral inhibition that predict broader tuning of inhibitory inputs. Second, the slow recovery from synaptic depression better matches the time scale of forward suppression, which far outlasts inhibitory PSPs. Although network interactions and STP can independently account for specific auditory processes, the neural responses are probably a combination of these and other mechanisms such as the intrinsic membrane properties of cells [46]. In addition to further *in vivo* intracellular and extracellular studies, parallel *in vitro* studies are needed to elucidate the details of cellular properties, synaptic mechanisms and interactions among the specific cell types that comprise cortical circuits.

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