Published in final edited form as:

Neurosci Biobehav Rev. 2011 November ; 35(10): 2094–2104. doi:10.1016/j.neubiorev.2011.05.004.

From elementary synaptic circuits to information processing in primary auditory cortex

Guangying K. Wu^{a,b}, Huizhong W. Tao^a, and Li I. Zhang^{a,*}

^a Zilkha Neurogenetic Institute, Keck School of Medicine, University of Southern California, 1501 San Pablo Street, Los Angeles, CA 90033

^b Broad Fellows Program in Brain Circuitry, Division of Biology, California Institute of Technology, 1200 E California Blvd, Pasadena, CA 91125

Abstract

A key for understanding how information is processed in the cortex is to unravel the dauntingly complex cortical neural circuitry. Recent technical innovations, in particular the *in vivo* whole-cell voltage-clamp recording techniques, make it possible to directly dissect the excitatory and inhibitory inputs underlying an individual cortical neuron's processing function. This method provides an essential complement to conventional approaches, with which the transfer functions of the neural system are derived by correlating neuronal spike outputs to sensory inputs. Here, we intend to introduce a potentially systematic strategy for resolving the structure of functional synaptic circuits. As complex circuits can be built upon elementary modules, the primary focus of this strategy is to identify elementary synaptic circuits and determine how these circuit units contribute to specific processing functions. This review will summarize recent studies on functional synaptic circuits in the primary auditory cortex, comment on existing experimental techniques for *in vivo* circuitry studies, and provide a perspective on immediate future directions.

Keywords

Primary auditory cortex; Microcircuit; Cortical processing; Voltage-clamp recording; Balanced excitation and inhibition; Functional synaptic circuit; Frequency tuning; Intensity tuning; Direction selectivity

1. Introduction

Sound is a time-varying signal, specified by frequency and intensity distribution in a time domain. How cortical neurons represent these physical features of sound has been intensively investigated (e.g. Aitkin, 1990; Merzenich and Schriner, 1992; Woolsey, 1960; Goldstein and Knight, 1980; Brugge and Reale, 1985; Clarey et al., 1992; Winer, 1992; de Ribaupierre, 1997; Rouiller, 1997). Neuronal functional properties in auditory cortex such as frequency tuning, intensity tuning and tonotopic organization are highly preserved among different species (mouse: Stiebler et al., 1997; Linden et al., 2003; Bandyopadhyay, et al., 2010; Rothschild, et al., 2010; rat: Horikawa et al., 1988; Polley et al., 2007; cat: Merzenich

© 2011 Elsevier Ltd. All rights reserved.

*Correspondence should be addressed to: L.I.Z. (liizhang@usc.edu).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

et al., 1975; Reale and Imig, 1980; monkey: Imig et al., 1977; Merzenich and Brugge, 1973; Kaas and Hackett, 2000; human: Formisano et al., 2003; Humphries et al., 2010), suggesting that the underlying neural circuits in different species are organized under common principles. In this review, we will focus on the primary auditory cortex (A1) of rats to discuss the recent progress on the synaptic circuitry basis for auditory cortical processing.

2. A reductive approach to unraveling neural circuitry

2.1. Realistic neuronal circuits

Cortical neurons are well organized into ensembles or circuits to process auditory information (Schreiner et al., 2000; Douglas and Martin, 2004; Read et al., 2002; Winer and Lee, 2007). Since neurons communicate with each other through synaptic connections, the ensemble of synaptic strengths can define the connectivity within a neural circuit (Fig. 1A). However, the neural circuitry in the brain is dauntingly complex. The human brain is estimated to contain about 10^{11} neurons (Azevedo et al., 2009). Each neuron makes thousands to tens of thousands of synaptic connections with other neurons, which brings the total number of synaptic connections to a level of 10^{15} . In addition, the intricately intermingled axonal and dendritic processes of neurons make it extremely difficult to trace individual connections. The diagnostic method used in dissecting electronic circuits by removing specific components cannot be easily applied to neural circuits. Finally, the heterogeneity of neuronal populations further adds to the complexity of neural circuits. To overcome these obstacles, a well-defined systematic approach has to be developed to reduce the complexity of neural circuits, which will facilitate our understanding of their function.

2.2. Cortical columnar and laminar organization

A prominent feature of the neocortex is its columnar and laminar organization, which provides a platform for parallel and serial processing, respectively (Schreiner et al., 2000; Winer et al., 2005). Within a cortical column neurons are thought to exhibit similar functional properties, e.g. they are tuned to similar tonal frequencies. As other sensory cortices, the auditory cortex is stratified into six layers (Fig. 1B). Among them, Layer 4 is the major recipient of inputs from the auditory thalamus, while Layer 6 is weakly innervated by the thalamus (Cruikshank et al., 2002; Kimura et al., 2003; Romanski and LeDoux, 1993; Winer and Lee, 2007; Barbour and Callaway, 2008). The non-pyramidal neurons in Layer 1, an integration layer, have also been reported to receive direct thalamic input (Mitani and Shimokouchi, 1985; Huang and Winer, 2000; Zhu and Zhu, 2004; Theyel et al., 2010), although the functional significance of this direct input remains to be determined. Layer 2/3 neurons are largely innervated by Layer 4 projections and they send outputs to other cortical regions for intercortical processing, while Layer 5 neurons receive relayed information from Layer 2/3 and project to various subcortical nuclei to modulate subcortical responses (Winer and Prieto, 2001; Winer, 2005; Barbour and Callaway, 2008). Layer 6 sends cortical feedback specifically to the thalamus (Ojima, 1994; Prieto and Winer, 1999; Winer, 2005). In addition to the direct feedforward input, principal neurons receive prominent intracortical excitatory input. The highest density intracortical excitatory input comes from neurons within a 500 μ m radius (Douglas et al., 1995; Roerig and Chen, 2002; Marino et al., 2005). Besides the excitatory input, inhibition from cortical inhibitory interneurons plays an important role in shaping response properties of principal neurons (Sillito, 1977, 1979; Kyriazi et al., 1996; Wang et al., 2002). Based on the columnar and laminar organization of the cortex, and the belief that even the most complex circuits are built upon repeated circuit modules, we propose that cortical circuits can be reduced by identifying columnar circuit modules at each cortical layer. It is worth noting that within the module, the circuit may involve both intralaminar and interlaminar interactions. The layer-specific circuit modules

can then be integrated and repeated across columns to construct a more complete cortical circuit.

2.3. Simplified elementary circuit module

For each cortical layer, we assume an elementary circuit module lie at the heart of the processing capability. Within the module, the excitatory neurons can be regarded as the core component. No matter how complex the modular circuit is, the spiking response properties of individual excitatory neurons are determined by all the sound-driven synaptic inputs received by the neuron, including both excitatory and inhibitory inputs, as well as the cell's intrinsic membrane properties. In auditory cortex, the ascending synaptic inputs are topographically organized to form a gradient of frequency representation (Schreiner, et al., 2000; Winer et al., 2005). Due to the correspondence between spatial and spectral locations, stimulation with single tones of different frequencies can reveal the information on the spatial distribution of synaptic inputs. In simplification, each tone-evoked input can be viewed as an individual input, although it may not result from a single synaptic connection. Thus, the spectral distribution of synaptic inputs, both excitatory and inhibitory, provides fundamental information on the structure of a functional synaptic input circuit. From the spectrotemporal integration of functional synaptic inputs evoked by simple tones, it would be possible to predict the neuron's other response properties (e.g. direction selectivity) based on this simplified model. A starting place for examining functional synaptic input circuits is the thalamo-recipient layers, since cortical processing starts here. For neurons in these input layers, in principle they receive synaptic input from three major sources: thalamocortical, intracortical excitatory and intracortical inhibitory inputs (Schreiner, et al., 2000; Winer, et al., 2005). The network in Fig. 1A can then be simplified into a more concise form with a single excitatory neuron receiving three sources of input (Fig. 1C). We will discuss recent progresses on dissecting the contribution of these three types of input to auditory processing in the rat A1. It is worth noting that the functional architecture of the rat auditory cortex and the general response properties of rat auditory cortical neurons are similar to those in cats and mice (e.g. Schreiner, et al., 2000; Wu, et al., 2006)

3. Experimental approaches to dissecting neural circuits

The representation and processing of individual neurons is a fundamental basis for cortical function. Many previous studies using the reverse correlation technique have focused on the spike responses of individual neurons as to understand their transfer function under sound stimuli (e.g. Kim and Young, 1994; Klein et al., 2000; Miller et al., 2002). Such “black-box” method only deals with the properties of sensory input and neuronal spike output, without knowing what occurs in the box. Because of the nonlinearity of neurons and a finite number of stimuli that can be applied, it is difficult to obtain a complete understanding of the operations performed by neural circuits. Alternatively, an investigation into the synaptic mechanisms underlying the spike responses can provide insights into the connectivity of neural circuits and the way the connectivity determines the processing function of the neuron.

To access the cell interior, traditional sharp electrodes with high impedances are used to impale the neuron and record sound-driven depolarization or hyperpolarization of the cell's membrane potential (Coombs et al., 1955; Fatt et al., 1951; de Ribaupierre et al., 1972; Volkov and Galazjuk, 1991; Ojima and Murakami, 2002). Although these changes in membrane potential suggest the presence of excitatory or inhibitory inputs, the absolute strength of the inputs cannot be determined since the membrane potential response is an integrated result of the interaction between both excitatory and inhibitory inputs as well as voltage-dependent conductances. Whole-cell current-clamp recordings have been more widely used to measure subthreshold and suprathreshold membrane potential responses

evoked by sensory stimuli (Anderson et al., 2000; Moore and Nelson, 1998; Margrie et al., 2002). Due to a better electronic access to the cell interior, different levels of currents can be injected into the cell while membrane voltages are monitored. Excitatory and inhibitory conductances are derived based on a linear neuron model, which assumes that the recorded neuron is isopotential and that there is a linear relationship between membrane potential and synaptic current (Anderson et al., 2000; Monier et al., 2003; Marino et al., 2005). However, because the membrane potential is not controlled in current-clamp recording, any voltage-gated conductances that have not been blocked by appropriate ion-channel blockers can vary instantaneously in a voltage-dependent manner and contaminate synaptic conductances, sabotaging linearity of the neuron. Not until recently has voltage-clamp recording technique been applied in functional studies of sensory cortices in live animals (Borg-Graham et al., 1998; Zhang et al., 2003; Wehr and Zador, 2003; Tan et al., 2004). By clamping the cell's membrane potential, fluctuation of unblocked voltage-dependent conductances is minimized. With this technique, our knowledge on neural circuits underlying sound processing has been increased. We review here the current progresses, potential limitations, and future directions along this promising research line.

3.1. Voltage-clamp recording to dissect synaptic inputs

A key for dissecting excitatory and inhibitory inputs is to achieve low access-resistance whole-cell recording, which requires using patch pipettes with relatively large tip openings (1–2 μm). In a typical blind recording experiment, the electrode resistance is continuously monitored as the pipette advances in small steps. When the tip contacts cell membrane, the pipette resistance increases. The positive pressure within the pipette is then released. In a lucky case, a tight seal between the pipette and cell membrane (a few giga-ohms in seal resistance) is formed, which is essential for high-quality experiments. Pulses of negative pressure are then applied to break in the cell's membrane and bring the recording to whole-cell mode. With sufficient compensations of whole-cell capacitance and series resistance, the cell's membrane potential is clamped at -70mV (the reversal potential for GABA_A receptor-mediated Cl^- currents) to record excitatory currents, or 0mV (the reversal potential for glutamate receptor-mediated excitatory currents) to record inhibitory currents (Fig. 2). From the recorded synaptic currents under different levels of membrane potentials, excitatory and inhibitory conductances can be derived, assuming that the neuron is isopotential and linear. The large pipette opening and the low effective series resistance after compensation ($\sim 10\text{--}20$ mega-ohms) allows a better control of the cell's membrane voltage. However, the space-clamp issue (Hille, 1992) cannot be omitted when estimating synaptic inputs, which will be discussed below.

3.2. Reconstruction of the output response by integrating synaptic inputs

The functional properties of the neuron are usually defined by its spike responses. By comparing the evoked synaptic inputs and spike outputs of the same cell, we would gain an understanding of how the synaptic input circuit contributes to the function. However, for high-quality voltage-clamp recording, various blockers of voltage-gated conductances, including those blocking Na^+ spikes, are infused into the cell through the patch pipette. Under this circumstance, the *bona fide* spike responses cannot be obtained. Nonetheless, the membrane potential response resulting from the integration of excitatory and inhibitory inputs can be estimated by feeding the experimentally determined synaptic conductances into an integrate-and-fire neuron model (Wehr and Zador, 2003; Wu et al., 2008; Sun et al., 2010; Zhou et al., 2010). Without knowing the detailed dendritic distribution of individual inputs, the model is a single-compartment neuron with inputs all arriving near the soma. Thus this model is better applied to inputs that are known to be close to the soma, e.g. thalamocortical inputs in layer 4 (Richardson et al., 2005). Spike rate can be calculated from the derived membrane potential based on either a “threshold-linear” or a power-law model

(Carandini and Ferster, 2000; Priebe et al., 2004). One advantage of the computational simulation of membrane potential responses is that the inhibitory component can be easily removed to examine its contribution to the spike response, while the experimental feasibility of removing intracellular inhibition specifically is still unclear.

To estimate the accuracy of the computational simulation of output responses, the simulated membrane potential responses can be compared to those recorded under current-clamp mode. It should be noted that as spikes are blocked, the recorded membrane potentials can be considered as bona fide because they have not been disturbed by spike generation. Alternatively, a technically more challenging experiment can be performed: cell-attached recording followed by whole-cell recording (Sun et al., 2010). In the cell-attached recording, the cell membrane seals the pipette tip, allowing a superb isolation of a single unit, i.e. spikes only from the patched cell can be recorded (DeWeese et al., 2003; Hromadka et al., 2008; Wu et al., 2008). The subsequent tight-seal whole-cell voltage-clamp recording determines the evoked excitatory and inhibitory conductances. It is worth noting that under cell-attached mode the cell's intracellular milieu is intact, while voltage-dependent channels may be blocked after forming the whole-cell. If the functional property (e.g. frequency tuning) as exhibited in simulated spike responses is close to that in recorded spike responses, it may be concluded that the experimentally measured excitatory and inhibitory conductances contribute largely to the observed functional property of the neuron.

3.3. Quality control for in vivo whole-cell recording

When deriving excitatory and inhibitory synaptic conductances, it is assumed that the neuron is isopotential (like a small spherical cell) and linear (Zhang et al., 2003; Wehr and Zador, 2003; Tan et al., 2004). However, the real neuron extends dendritic processes and is far from spherical. Although the soma may be well clamped at the set holding potential, local membrane potentials in distal dendrites are not controlled as well due to an imperfect space clamp. As synaptic inputs arrive at the distal dendrites, there may be a large deviation of the local potential from the set holding potential. Under this circumstance, when the holding potential (e.g. 0mV) differs from the resting membrane potential substantially, there can be large errors in the measured synaptic conductances (Spruston et al., 1993). Such space-clamp error will be less an issue if all inputs are close to the soma, and can be alleviated by using cesium and tetraethylammonium (TEA, a blocker of potassium channels) in the intracellular solution, which reduces membrane permeability and cable attenuation (Spruston et al., 1993). To estimate how well the evoked synaptic current as measured from the soma is clamped, the current-voltage (I-V) relationship can be examined for the synaptic current at different time points. The linear I-V relationship supports linearity of the neuron, which may have been improved by the blockade of various voltage-dependent conductances including NMDA-receptor conductances. In addition, the instantaneous reversal potential of synaptic current can be derived from the I-V curve. Since inhibitory input usually follows the excitatory input by a temporal delay (Zhang et al., 2003; Wehr and Zador, 2003), within a small time window right after the response onset, the current is almost exclusively contributed by excitatory conductance. Space-clamp error can be detected when the reversal potential within this small time window deviates largely from the actual reversal potential for excitatory currents (0mV). In our high-quality recordings from layer 4 neurons, we consistently observed a close proximity of the reversal potential for early currents to 0mV (Wu et al., 2006, 2008; Liu et al., 2007; Sun et al., 2010). This indicates that the synaptic inputs under examination are mostly in close proximity to the cell body.

3.4. Criteria for studies under anesthesia

Because of the level of mechanical stability required for high-quality voltage-clamp recordings, up to now the recording technique has only been applied in anesthetized animals.

A few studies have explored the feasibility of whole-cell recordings in awake animals (Margrie et al., 2002; Lee et al., 2006; Gentet et al., 2010; Okun et al., 2010), but none of them have attempted to dissect synaptic inputs or conductances. Notably, anesthetized animals can only be considered as a reduced model, as anesthesia reduces activity level and may affect the temporal pattern of sound evoked responses even in the primary sensory processing pathway (e.g. Young and Brownell, 1976; Evans and Nelson, 1973; Kuwada et al., 1987; Gaese and Ostwald, 2001; Wang et al., 2005). Among commonly used anesthetics, pentobarbital prolongs the opening time of GABA-activated chloride channels (MacDonald et al., 1989; Nicoll et al., 1975), and ketamine blocks NMDA receptors and reduces the general activity level (Thomson et al., 1985; Rennaker et al., 2007). One important criterion for using anesthetized animal models is that the studied response property can be observed in both anesthetized and awake animals. Various fundamental processing properties mostly involving ascending sensory pathways (e.g. tonal receptive field and frequency tuning) are likely preserved in anesthetized animals. The temporal relationship between sensory evoked excitatory and inhibitory inputs, especially at the early phase of response, is also likely preserved. Thus, the results on the spectrotemporal distribution of excitatory and inhibitory responses to simple tones obtained from anesthetized animals would still be valuable in addressing functional synaptic circuitry in awake models. Nonetheless, the limitation of anesthetized models should be recognized and experimental data should be interpreted with appropriate caution. It is recommended that results be further verified by using a different anesthesia method.

4. Functional Neural Circuitry underlying feature selectivity in the primary auditory cortex

4.1. Recurrent and feedforward circuits in the recipient layer 4

4.1.1. Approximately balanced excitation and inhibition underlying tonal receptive field—Neurons in the auditory system are tuned to specific frequencies (and intensities). The distribution pattern of synaptic inputs within the frequency-intensity tonal receptive field (TRF) reflects the basic synaptic input circuitry, and is a basis for processing properties such as frequency/intensity selectivity and direction selectivity in response to frequency modulated (FM) sound sweeps. Neurons in the recipient layer 4 (L4) of primary sensory cortices receive synaptic input from three major sources: thalamocortical inputs which are excitatory, and intracortical excitatory and inhibitory inputs (Liu et al., 2007; Zhou et al., 2010; Happel et al., 2010). With the application of whole-cell voltage-clamp recordings, tone evoked excitatory and inhibitory synaptic inputs underlying the TRF have been analyzed. As observed in several studies, receptive field composed of inhibitory inputs matches that of excitatory inputs (Zhang et al., 2003; Wehr and Zador, 2003; Tan et al., 2004; Wu et al., 2006, 2008). Inhibition is tuned to the same frequency as excitation, with essentially the same (or sometimes slightly narrower) total frequency responding range. The amplitudes of inhibitory and excitatory conductances evoked by the same tone exhibit a strong linear correlation (Zhang et al., 2003; Wehr and Zador, 2003; Tan et al., 2004; Tan and Wehr, 2009; Dorn et al., 2010). In addition, inhibition always follows excitation with a short temporal delay (about 2–4ms), which is essentially constant across different frequencies (Wehr and Zador, 2003). These observations led to the conclusion that excitation and inhibition are balanced (Wehr and Zador, 2003). The balanced inhibition is easily achieved by a feedforward circuit with the cortical inhibitory neurons driven by the same set of thalamocortical projections as the recorded L4 neuron (Fig. 3A; a potential inhibitory relay from layer 1 remains to be investigated -see Mitani and Shimokouchi 1985; Huang and Winer, 2000). Under balanced excitation and inhibition, inhibition sharpens frequency tuning of spike responses through an “ice-berg” effect, suppressing membrane potential responses to off-optimal frequencies below the spike threshold. In addition, the

shortly delayed inhibition enhances the temporal precision of the evoked spike (Wehr and Zador, 2003). A more detailed analysis, however, reveals that the inhibitory tuning is in fact broader than the excitatory tuning (in terms of tuning shape) within a frequency range flanking the best frequency (Wu et al., 2008). Comparing the normalized tuning curves, the frequency range of inhibitory input is about 27% broader than that of excitatory input at a level of 60% maximum. Through an analogous lateral-inhibition effect, the broader inhibition within the putative suprathreshold response range further sharpens the frequency tuning of membrane potential response (Wu et al., 2008). Thus, excitation and inhibition can only be viewed as approximately balanced. The disparity between inhibitory and excitatory tunings can be explained by the tuning properties of inhibitory neurons and intracortical excitatory inputs (see below).

4.1.2. Contribution of intracortical excitation to frequency tuning—Whether the functional properties of L4 neurons are determined by the convergence of thalamocortical inputs or are attributed mainly to intracortical inputs has been an issue of intense debate (Reid and Alonso, 1995; Ferster et al., 1996; Douglas et al., 1995; Somers et al., 1995). It is a great challenge to determine the respective functional roles of thalamocortical and intracortical inputs. Previously three methods have been used to isolate thalamocortical inputs by preventing spiking of cortical neurons: a) pharmacologically silencing the cortex with muscimol (Fox et al., 2003; Kaur et al., 2004; Zhang and Suga, 1997); b) cooling the cortex (e.g. Ferster et al., 1996; Volgushev et al., 2000; Villa et al., 1991); c) local electrical stimulation of the cortex (Ferster et al., 1996). In these methods, the thalamocortical transmission can potentially be affected significantly, confounding the interpretation of results. For example, a widely used method is to apply muscimol through microinjection, iontophoresis or surface perfusion, assuming that muscimol specifically activates GABA_A receptors. However, it was found recently that muscimol can activate GABA_B receptors at relatively low concentrations and can thus reduce transmission through presynaptic GABA_B receptors (Yamauchi et al., 2000). To prevent muscimol's effect on release from thalamic axons (Porter and Nieves, 2004), we recently developed a new pharmacological method for cortical silencing: co-applying muscimol and a specific antagonist of GABA_B receptors which prevents activation of GABA_B receptors by muscimol (Liu et al., 2007; Khibnik, et al., 2010). Using this method, the frequency tunings of excitatory input before and after cortical silencing have been compared (Liu et al., 2007). The total frequency range is not reduced after cortical silencing, indicating that thalamocortical input determines the area of synaptic receptive field. However, the tuning of thalamocortical input exhibits a broad and flat tuning peak, and is significantly weaker compared to that of total excitatory input. In contrast, the tuning of derived intracortical input is much sharper, and closely resembles that of total excitatory input within the putative frequency range of suprathreshold response. Thus, it is the intracortical excitatory input that largely defines the frequency tuning of the neuron by selectively amplifying responses at the optimal and near-optimal frequencies. Using a similar silencing method, a current source density (CSD) study in gerbil A1 (Happel et al., 2010) confirms that short-range recurrent input amplifies the thalamocortical afferent signal. Different from our conclusion, the study suggests that the subthreshold responses to off-optimal tones are attributed to long-range horizontal inputs between cortical sites in layer 2/3, while the sensitivity of CSD for detecting small responses (Mitzdorf, 1985) and the specificity of perfusion of drug in cortical surface need to be further examined. It is worth noting that a recent study in the mouse barrel cortex indicates that the range of horizontal connections within layer 2/3 is within 300 μ m (Adesnik and Scanziani, 2010).

4.1.3. Broader inhibitory tuning—As described above, high-resolution mapping of excitatory and inhibitory inputs has revealed a broader tuning of inhibition than excitation within the putative frequency range of suprathreshold response (Wu et al., 2008). This

observation is consistent with extracellular studies (e.g. Sadagopan and Wang, 2010), and can be sufficiently explained by the known circuit in layer 4. Inhibitory input is likely attributed to a feedforward circuit, with the local inhibitory neurons providing the input directly driven by thalamic axons (Fig. 3A). Therefore, the receptive field property of L4 inhibitory neurons is key to understanding the tuning of inhibitory input. Because fast-spiking inhibitory neurons are the major source of cortical inhibition in layer 4 (Agmon and Connors, 1992; Gil and Amitai, 1996; Gibson et al., 1999; Inoue and Imoto, 2006; Sun et al., 2006; Atencio and Schreiner, 2008), we developed a method of cell-attached recording combined with subsequent juxtacellular labeling or intracellular recording to selectively target fast-spiking inhibitory neurons (Wu et al., 2008). Compared to nearby excitatory neurons, fast-spiking inhibitory neurons exhibit a lower threshold and a broader bandwidth of spike TRFs, despite that the two types of neurons receive similar ranges of excitatory input and are organized by the same tonotopic map. The broader spike TRF of inhibitory neurons is thus due to their higher efficiency in converting synaptic input to spike output, which may be attributed to a stronger thalamocortical input to L4 inhibitory neurons than L4 excitatory neurons (Gibson et al., 1999; Beierlein et al., 2003). Also as discussed above, the tuning of thalamocortical input is broad while that of intracortical excitatory input is sharp, which indicates that intracortical excitatory input derives from cortical neurons with similar frequency tuning properties. The summation of thalamocortical and intracortical excitatory inputs is analogous to adding a pyramid on top of a flat base. Since L4 inhibitory neurons have a broader spiking response tuning than excitatory neurons, inhibition would exhibit a broader tuning than excitation near the apex of the pyramid. Such intracortical inhibition with higher sensitivity and lower selectivity than intracortical excitation can laterally sharpen the frequency tuning of neurons, ensuring their highly selective representation (Fig. 3A).

4.2. A “silent” circuit in layer 6

It has been widely observed that sensory stimulation or stimulation of the thalamus results in a stereotypic temporal relationship between evoked excitation and inhibition, with inhibition occurring shortly after excitation (Douglas and Martin, 1991; Zhang, et al., 2003; Wehr and Zador, 2003; Tan, et al., 2004). The later arriving inhibition can curtail the evoked spiking responses, preventing runaway excitation within the cortical circuit. Besides layer 4, layer 6 of the A1 also receives direct thalamocortical input (Winer et al., 2001; Winer et al., 2005; Llano and Sherman, 2008; Kaur et al., 2005; Lakatos et al., 2007; Wallace and Palmer, 2008). Conversely, layer 6 sends feedback projections predominantly to the first-order thalamic nucleus (i.e. ventral nucleus of the medial geniculate body, MGBv) (Ojima, 1994; Prieto and Winer, 1999; Winer, 2005; Takayanagi and Ojima, 2006; Rouiller and Welker, 2000; Llano and Sherman 2008). It has been proposed that the corticothalamic feedback from layer 6 modulates thalamic responses (Villa et al. 1991; Zhang and Suga, 1997; Yan and Ehret, 2002), and plays a role in mediating the induction of sound-specific plasticity in the auditory thalamus (Zhang and Suga, 2000; Suga and Ma, 2003; Zhang and Yan, 2008). Surprisingly, sensory stimuli do not drive spike responses in a large proportion of L6 excitatory neurons (Zhou et al., 2010; Tsumoto and Suda, 1980; Sirota et al., 2005), but suppress their spontaneous firings within the expected tonal receptive field (Zhou et al., 2010). Whole-cell recordings reveal that the suppression of evoked spike responses results from a novel synaptic integration pattern with a strong inhibitory input preceding the co-activated excitatory input. The reversed temporal relationship between excitatory and inhibitory inputs in many L6 neurons can be attributed to a parallel feedforward circuit with both the excitatory and inhibitory inputs disynaptically relayed (Fig. 3B). Since the first-order L6 inhibitory neurons spike earlier than the first-order excitatory neurons (Zhou et al., 2010), the second-order excitatory neuron would receive inhibition preceding the disynaptic excitatory input. Interestingly, anatomical evidence suggests that the silenced L6 neurons

may project back to the thalamus, leading to a hypothesis that the corticothalamic feedback is only activated under specific circumstances such as conditioning during which the suppression by preceding inhibition can be relieved (Zhou et al., 2010). While this hypothesis awaits future investigations, the specific “silent” circuit in layer 6 highlights an essential role of inhibition in creating a diversity of response properties, through its specific spectral and temporal patterns inherited from the local circuitry.

4.3. From elementary circuits to more complex auditory processing

As discussed above, the spatial distributions and temporal patterns of excitatory and inhibitory synaptic inputs underlying the TRF can reveal the basic cyto-architecture of neuronal connectivity. Receptive field structures have been shown to be major determinants of cortical responses to complex sound stimuli (Kowalski, et al., 1996; deCharms, et al., 1998; Schnupp, et al., 2001; Sen, et al., 2001; Linden, et al., 2003; Zhang, et al., 2003), although dynamic properties of synaptic inputs may also be important in generating responses to complex sound. The elementary circuits derived from synaptic TRFs will allow us to better understand how cortical neurons process complex acoustic signals.

4.3.1. FM direction selectivity—Frequency-modulated (FM) sweeps are important cues in animal vocalization and human communication (Winter et al., 1966; Kanwal et al., 1994; Wang, 2000; Lindblom and Studdert-Kennedy, 1967; Gold and Morgan, 2000; Zeng et al., 2005). Neurons selective for direction of FM sweeps are found in the A1 (Suga, 1965; Mendelson and Cynader, 1985; Zhang et al., 2003), the auditory thalamus (O’Neill and Brimijoin, 2002) as well as other subcortical nuclei such as the inferior colliculus (Nelson et al., 1966; Gordon and O’Neill, 1998; Fuzessery et al., 2006). Mapping studies suggest that in the auditory cortex, direction selectivity is topographically ordered in parallel with characteristic frequency (CF): low CF neurons prefer upward sweeps, whereas high CF neurons prefer downward sweeps (Heil, et al., 1992; Zhang, et al., 2003; Godey, et al., 2005). Both the topographic organization of direction selectivity and the selectivity per se can be well explained by the spectral distributions of excitation and inhibitory inputs and their temporal interaction. Firstly, the spectral distribution of input strength is asymmetric or skewed in direction-selective neurons. The skewness co-varied with CF, as well as of the measured direction selectivity, suggesting a synaptic circuitry basis for the topographic ordering of the cortical representation of direction selectivity (Zhang et al., 2003). Secondly, the slightly delayed inhibitory input further strengthens the directional selectivity inherited from excitatory input by suppressing synaptic excitation more effectively when stimulus is in the non-preferred direction than in the preferred direction (Zhang et al., 2003). Thirdly, there appears to be a spectral offset between excitation and inhibition in direction-selective neurons (Suga, 1965; Shamma et al., 1993; Nelken and Versnel, 2000; Zhang et al., 2003; Razak and Fuzessery, 2006; Ye et al., 2010). For example, “inhibitory sidebands”, the suppressive regions flanking the TRF of spiking response exhibit asymmetry, and the asymmetry co-varied with CF (Zhang, et al., 2003). In addition, relatively stronger inhibition on one side of excitatory spectral tuning curve has been observed for direction selective A1 neurons (Ye et al., 2010). In fact, the inhibitory sidebands revealed by extracellular recording experiments with two-tone suppression, and the spectral offset between excitation and inhibition can be attributed, at least partially, to a broader tuning of inhibition than excitation (Wu et al., 2008). A schematic diagram of synaptic inputs to a direction selective neuron is shown in Fig. 3C.

4.3.2. Intensity selectivity—Intensity tuned auditory neurons are characterized by their nonmonotonic responses to sound intensities (Greenwood and Maruyama, 1965). Such neurons (also named nonmonotonic neurons) have been observed along the central auditory pathway, including the cochlear nucleus (Greenwood and Maruyama, 1965; Young and

Brownell, 1976), inferior colliculus (Aitkin, 1991; Kuwabara and Suga, 1993), medial geniculate body (Aitkin and Webster, 1972; Rouiller et al., 1983), and auditory cortex (Davies et al., 1956; Evans and Whitfield, 1964; Brugge et al., 1969; Schreiner et al., 1992; Phillips et al., 1995). In the rat auditory cortex, the response properties of intensity-tuned neurons (Phillips et al., 1995; Heil and Irvine, 1998) and their susceptibility to specific changes after training animals with a sound magnitude discrimination task (Polley et al., 2004, 2006) suggest that these neurons may play important roles in encoding sound loudness and envelop transients. Studies using extracellular recordings with two-tone masking paradigms (Suga and Manabe, 1982; Calford and Semple, 1995; Sutter and Loftus, 2003) and GABA receptor blockade (Faingold et al., 1991; Pollak and Park, 1993; Wang et al., 2002; Sivaramakrishnan et al., 2004), as well as those using intracellular recordings (Ojima and Murakami, 2002) suggest that intensity tuning may be created by spectral and temporal interactions between excitation and inhibition. Recently, voltage-clamp recordings from intensity-tuned and non-intensity-tuned neurons indicate that cortical intensity tuning is determined by the interplay between imbalanced excitatory and inhibitory synaptic inputs (Wu et al., 2006; Tan et al., 2007). In intensity-tuned neurons, excitatory input already exhibits intensity tuning. On the other hand, the strength of inhibitory input increases monotonically with intensity increments and quickly saturates. Interestingly, the temporal delay of inhibitory input relative to excitatory input is reduced as intensity increases, resulting in an enhanced suppression of excitation at high intensities and a significant sharpening of intensity selectivity. These findings imply a unit circuit controlling the relative timing of excitation and inhibition, which may also be capable of creating intensity selectivity at the first step (Fig. 3D).

5. Conclusions and future directions

5.1. Imbalanced excitation and inhibition underlying functional diversity

The initial whole-cell recording studies in the rat A1 have led to the conclusion that balanced excitation and inhibition underlie the frequency-intensity tonal receptive field (Zhang et al., 2003; Wehr and Zador, 2003; Tan et al., 2004). The balance is defined as matched excitatory and inhibitory tunings together with a constant temporal interval between excitation and inhibition. However, a series of more recent studies with high-resolution mapping and more detailed analysis indicate that balanced excitation and inhibition cannot be taken as a universal rule (Wu et al., 2006, 2008; Tan et al., 2007; Zhou et al., 2010; Ye et al., 2010). First, the tunings of excitation and inhibition do not match perfectly. For frequency tuning, inhibition is broader than excitation within the frequency range that generates spike responses. For intensity tuning, in a subset of neurons excitation exhibits nonmonotonic amplitude-intensity function, whereas inhibition displays monotonic intensity tuning. Second, the temporal interaction can vary with stimulus parameter. For intensity-tuned neurons, the relative delay of inhibition reduces with the intensity increment. In a subset of L6 neurons, the temporal sequence of excitation-inhibition is completely reversed. Through various spectral and temporal interactions between excitation and inhibition, a wide diversity of feature-selective response properties is created. Thus, deviations from perfectly balanced excitation and inhibition endow the cortex with much increased computational capacity.

5.2. Elementary circuit modules

The canonical microcircuit (Douglas and Martin, 1991) was initially proposed to account for the response profile of cortical neurons to thalamic stimulation, which shows a stereotypic temporal sequence of activation of inhibition shortly after that of excitation. The core of the canonical microcircuit is a tripartite feedforward circuit involving disynaptic inhibitory inputs from cortical inhibitory neurons driven by the same set of afferents as the excitatory

neuron of interest (Fig. 3A). Such circuit module is prevalent in layer 4 of the A1, and is also observed for a subpopulation of L6 neurons (Zhou et al., 2010). Other circuit modules cannot be described as canonical. In layer 4 of the “nonmonotonic” zone, i.e. an area posterior-ventrally adjacent to the A1 where neurons mostly exhibit nonmonotonic intensity tunings (Wu et al., 2006), the disynaptic inhibitory input is from inhibitory neurons driven by a different set of thalamic axons (Fig. 3D). In a second subpopulation of L6 neurons in the A1, both excitatory and inhibitory inputs are disynaptic (Fig. 3B). While it remains to be tested whether these elementary circuits also exist in subcortical nuclei, it is already remarkable that cortical circuits, by exploiting such simple connectivity strategies, can create a wide variety of functional properties. It is likely that we will be more amazed by the cortex during further explorations of other layers as well as other functional auditory cortical areas.

5.3. Inhibitory neurons in cortical circuits

Most of the *in vivo* recordings so far are obtained from excitatory neurons, a dominant cell type in the cortex. Although cortical neurons receive prominent inhibitory inputs through feedforward or feedback circuits, these inputs only come from a small population (15–20%) of cortical neurons (Peters and Kara, 1985; Hendry et al., 1987; Priet et al., 1994). To obtain a complete understanding of the structure of functional circuits, it is essential to know the functional properties of inhibitory neurons themselves. The difficulty in studying inhibitory neurons lies not only in the small number of these neurons, but also in their morphological and neurochemical diversity (Kawaguchi and Kubota, 1997; Gonchar and Burkhalter, 1997; Gupta et al., 2000) (Fig. 4), which suggests that inhibitory neurons are also functionally diverse. Although in a few cases, *in vivo* whole-cell recordings combined with *post hoc* histology have identified inhibitory neurons in the sensory cortex (Azouz et al., 1997; Hirsch et al., 2003), in general it is extremely difficult to encounter inhibitory neurons in blind recordings, especially those minor types of inhibitory neurons. Recent development in two-photon imaging of Ca^{2+} responses (Sohya et al., 2007; Kerlin et al., 2010; Runyan et al., 2010) and two-photon imaging guided targeted recording (Margrie et al., 2003; Liu et al., 2009; Gentet et al., 2010; Ma et al., 2010) allows efficient examinations of functional properties of inhibitory neurons in transgenic mice in which a specific type of inhibitory neurons is genetically labeled. It is expected that our knowledge on inhibitory neurons in auditory cortex will grow rapidly as better imaging and genetic tools are being developed.

Finally, for a realistic model of cortical circuitry, further understanding of the distribution pattern of excitatory and inhibitory neurons projecting to a single neuron will be needed. The recent development of trans-synaptic labeling (Marshall et al., 2010) will allow neurons presynaptic to a transfected neuron to be labeled. Ca^{2+} imaging or targeted recording can then be performed on these neurons to understand their functional relationship. Taken together, the renovations of electrophysiology, imaging and genetic techniques will greatly facilitate a quantitative analysis of elementary neuronal circuits with a bottom-up approach. The results will enhance our understanding of circuitry mechanisms underlying both normal and abnormal brain functions.

Acknowledgments

This work was supported by National Institute of Health (DC008983, DC008588, EY019049), the Searle Scholar Program, the Esther A. and Joseph Klingenstein Fund, and the David and Lucile Packard Foundation. G.K.W. is a Broad Fellow.

References

- Adesnik H, Scanziani M. Lateral competition for cortical space by layer-specific horizontal circuits. *Nature*. 2010; 464:1155–1160. [PubMed: 20414303]
- Agmon A, Connors BW. Correlation between intrinsic firing patterns and thalamocortical synaptic responses of neurons in mouse barrel cortex. *J Neurosci*. 1992; 12:319–329. [PubMed: 1729440]
- Aitkin L. Rate-level functions of neurons in the inferior colliculus of cats measured with the use of freefield sound stimuli. *J Neurophysiol*. 1991; 65:383–392. [PubMed: 2016647]
- Aitkin, L. The auditory cortex. Chapman and Hall; London: 1990.
- Aitkin LM, Webster WR. Medial geniculate body of the cat: organization and responses to tonal stimuli of neurons in ventral division. *J Neurophysiol*. 1972; 35:365–380. [PubMed: 5029955]
- Anderson JS, Carandini M, Ferster D. Orientation tuning of input conductance, excitation, and inhibition in cat primary visual cortex. *J Neurophysiol*. 2000; 84:909–926. [PubMed: 10938316]
- Atencio CA, Schreiner CE. Spectrotemporal processing differences between auditory cortical fast-spiking and regular-spiking neurons. *J Neurosci*. 2008; 28:3897–38910. [PubMed: 18400888]
- Azevedo FA, et al. Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. *J Comp Neurol*. 2009; 513:532–541. [PubMed: 19226510]
- Azouz R, Gray CM, Nowak LG, McCormick DA. Physiological properties of inhibitory interneurons in cat striate cortex. *Cereb Cortex*. 1997; 7:534–545. [PubMed: 9276178]
- Bandyopadhyay S, Shamma SA, Kanold PO. Dichotomy of functional organization in the mouse auditory cortex. *Nat Neurosci*. 2010; 13:361–368. [PubMed: 20118924]
- Barbour DL, Callaway EM. Excitatory local connections of superficial neurons in rat auditory cortex. *J Neurosci*. 2008; 28:11174–11185. [PubMed: 18971460]
- Beierlein M, Gibson JR, Connors BW. Two dynamically distinct inhibitory networks in layer 4 of the neocortex. *J Neurophysiol*. 2003; 90:2987–3000. [PubMed: 12815025]
- Borg-Graham LJ, Monier C, Fregnac Y. Visual input evokes transient and strong shunting inhibition in visual cortical neurons. *Nature*. 1998; 393:369–373. [PubMed: 9620800]
- Brugge JF, Dubrovsky NA, Aitkin LM, Anderson DJ. Sensitivity of single neurons in auditory cortex of cat to binaural tonal stimulation; effects of varying interaural time and intensity. *J Neurophysiol*. 1969; 32:1005–1024. [PubMed: 5347704]
- Brugge, JF.; Reale, RA. Auditory cortex. In: Peters, A.; Jones, EG., editors. *Cerebral cortex*, vol 4. Association and auditory cortices. Plenum Press; New York: 1985. p. 229–27.
- Calford MB, Semple MN. Monaural inhibition in cat auditory cortex. *J Neurophysiol*. 1995; 73:1876–1891. [PubMed: 7623087]
- Carandini M, Ferster D. Membrane potential and firing rate in cat primary visual cortex. *J Neurosci*. 2000; 20:470–484. [PubMed: 10627623]
- Chung S, Ferster D. Strength and orientation tuning of the thalamic input to simple cells revealed by electrically evoked cortical suppression. *Neuron*. 1998; 20:1177–1189. [PubMed: 9655505]
- Clarey, JC.; Barone, P.; Imig, TJ. Physiology of thalamus and cortex. In: Popper, AN.; Fay, RR., editors. *The mammalian auditory pathway: neurophysiology*. Springer; Berlin Heidelberg New York: 1992. p. 232–334.
- Coombs JS, Eccles JC, Fatt P. Excitatory synaptic action in motoneurons. *J Physiol (Lond)*. 1955; 130:374–395. [PubMed: 13278906]
- Cruikshank SJ, Rose HJ, Metherate R. Auditory thalamocortical synaptic transmission in vitro. *J Neurophysiol*. 2002; 87:361–384. [PubMed: 11784756]
- Davies PW, Erulkar SD, Rose JE. Single unit activity in the auditory cortex of the cat. *Bull Johns Hopkins Hosp*. 1956; 99:55–86. [PubMed: 13356091]
- deCharms RC, Blake DT, Merzenich MM. Optimizing sound features for cortical neurons. *Science*. 1998; 280:1439–1443. [PubMed: 9603734]
- DeWeese MR, Wehr M, Zador AM. Binary spiking in auditory cortex. *J Neurosci*. 2003; 23:7940–7949. [PubMed: 12944525]
- Dorrn AL, Yuan K, Barker AJ, Schreiner CE, Froemke RC. Developmental sensory experience balances cortical excitation and inhibition. *Nature*. 2010; 465:932–936. [PubMed: 20559387]

- Douglas RJ, Martin KA. A functional microcircuit for cat visual cortex. *J Physiol.* 1991; 440:735–769. [PubMed: 1666655]
- Douglas RJ, Martin KA. Neuronal circuits of the neocortex. *Annu Rev Neurosci.* 2004; 27:419–51. [PubMed: 15217339]
- Douglas RJ, Koch C, Mahowald M, Martin KA, Suarez HH. Recurrent excitation in neocortical circuits. *Science.* 1995; 269:981–985. [PubMed: 7638624]
- Evans EF, Nelson PG. The responses of single neurones in the cochlear nucleus of the cat as a function of their location and the anaesthetic state. *Exp Brain Res.* 1973; 17:402–427. [PubMed: 4725899]
- Evans EF, Whitfield IC. Classification of unit responses in the auditory cortex of the unanesthetized and unrestrained cat. *J Physiol (Lond).* 1964; 171:476–493. [PubMed: 14193935]
- Faingold CL, Boersma Anderson CA, Caspary DM. Involvement of GABA in acoustically-evoked inhibition in inferior colliculus neurons. *Hear Res.* 1991; 52:201–216. [PubMed: 2061208]
- Fatt P, Katz B. An analysis of the end-plate potential recorded with an intra-cellular electrode. *J Physiol (Lond).* 1951; 115:320–370. [PubMed: 14898516]
- Ferster D, Chung S, Wheat H. Orientation selectivity of thalamic input to simple cells of cat visual cortex. *Nature.* 1996; 380:249–252. [PubMed: 8637573]
- Formisano E, Kim DS, Di Salle F, van de Moortele PF, Ugurbil K, Goebel R. Mirror-symmetric tonotopic maps in human primary auditory cortex. *Neuron.* 2003; 40:859–69. [PubMed: 14622588]
- Fox K, Wright N, Wallace H, Glazewski S. The origin of cortical surround receptive fields studied in the barrel cortex. *J Neurosci.* 2003; 23:8380–8391. [PubMed: 12968000]
- Fuzessery ZM, Richardson MD, Coburn MS. Neural mechanisms underlying selectivity for the rate and direction of frequency-modulated sweeps in the inferior colliculus of the pallid bat. *J Neurophysiol.* 2006; 96:1320–1336. [PubMed: 16790604]
- Gaese BH, Ostwald J. Anesthesia changes frequency tuning of neurons in the rat primary auditory cortex. *J Neurophysiol.* 2001; 86:1062–1066. [PubMed: 11495976]
- Gentet LJ, Avermann M, Matyas F, Staiger JF, Petersen CC. Membrane potential dynamics of GABAergic neurons in the barrel cortex of behaving mice. *Neuron.* 2010; 65:422–435. [PubMed: 20159454]
- Gibson JR, Beierlein M, Connors BW. Two networks of electrically coupled inhibitory neurons in neocortex. *Nature.* 1999; 402:75–79. [PubMed: 10573419]
- Gil Z, Amitai Y. Properties of convergent thalamocortical and intracortical synaptic potentials in single neurons of neocortex. *J Neurosci.* 1996; 16:6567–6578. [PubMed: 8815933]
- Godey B, Atencio CA, Bonham BH, Schreiner CE, Cheung SW. Functional organization of squirrel monkey primary auditory cortex: responses to frequency-modulation sweeps. *J Neurophysiol.* 2005; 94:1299–1311. [PubMed: 16061492]
- Gold, B.; Morgan, N. *Speech and audio signal processing: processing and perception of speech and music.* New York: Wiley; 2000.
- Goldstein, MH.; Knight, PL. Comparative organization of mammalian auditory cortex. In: Popper, AN.; Fay, RR., editors. *Comparative studies of hearing in vertebrates.* Springer; Berlin Heidelberg New York: 1980. p. 375–398.
- Gonchar Y, Burkhalter A. Three distinct families of GABAergic neurons in rat visual cortex. *Cereb Cortex.* 1997; 7:347–358. [PubMed: 9177765]
- Gordon M, O'Neill WE. Temporal processing across frequency channels by FM selective auditory neurons can account for FM rate selectivity. *Hear Res.* 1998; 122:97–108. [PubMed: 9714578]
- Greenwood DD, Maruyama N. Excitatory and inhibitory response areas of auditory neurons in the cochlear nucleus. *J Neurophysiol.* 1965; 28:863–892. [PubMed: 5867883]
- Gupta A, Wang Y, Markram H. Organizing principles for a diversity of GABAergic interneurons and synapses in the neocortex. *Science.* 2000; 287:273–278. [PubMed: 10634775]
- Happel MF, Jeschke M, Ohl FW. Spectral integration in primary auditory cortex attributable to temporally precise convergence of thalamocortical and intracortical input. *J Neurosci.* 2010; 30:11114–11127. [PubMed: 20720119]

- Heil P, Irvine DR. The posterior field P of cat auditory cortex: coding of envelope transients. *Cereb Cortex*. 1998; 8:125–141. [PubMed: 9542892]
- Heil P, Langner G, Scheich H. Processing of frequency-modulated stimuli in the chick auditory cortex analogue: evidence for topographic representations and possible mechanisms of rate and directional sensitivity. *J Comp Physiol A*. 1992; 171:583–600. [PubMed: 1494138]
- Hendry SH, Schwark HD, Janes EG, Yan J. Numbers and proportions of GABA-immunoreactive neurons in different areas of monkey cerebral cortex. *J Neurosci*. 1987; 7:1503–1519. [PubMed: 3033170]
- Hille, B. Ionic channels of excitable membranes. 2. Sinauer Associates; 1992.
- Hirsch JA, Martinez LM, Pillai C, Alonso JM, Wang Q, Sommer FT. Functionally distinct inhibitory neurons at the first stage of visual cortical processing. *Nat Neurosci*. 2003; 6:1300–1308. [PubMed: 14625553]
- Horikawa J, Ito S, Hosokawa Y, Homma T, Murata K. Tonotopic representation in the rat auditory cortex. *Proc Jpn Acad Ser B*. 1988; 64:260–263.
- Hromádka T, DeWeese M, Zador AM. Sparse Representation of Sounds in the Unanesthetized Auditory Cortex. *PLoS Biol*. 2008; 6:e16. [PubMed: 18232737]
- Huang CL, Winer JA. Auditory thalamocortical projections in the cat: laminar and areal patterns of input. *J Comp Neurol*. 2000; 427:302–331. [PubMed: 11054695]
- Humphries C, Liebenthal E, Binder JR. Tonotopic organization of human auditory cortex. *Neuroimage*. 2010; 50:1202–1211. [PubMed: 20096790]
- Imig TJ, Ruggero MA, Kitzes LM, Javel E, Brugge JF. Organization of auditory cortex in the owl monkey (*Aotus trivirgatus*). *J Comp Neurol*. 1977; 171:111–128. [PubMed: 401509]
- Inoue T, Imoto K. Feedforward inhibitory connections from multiple thalamic cells to multiple regularspiking cells in layer 4 of the somatosensory cortex. *J Neurophysiol*. 2006; 96:1746–1754. [PubMed: 16855112]
- Kaas JH, Hackett TA. Subdivisions of auditory cortex and processing streams in primates. *Proc Natl Acad Sci U S A*. 2000; 97:11793–11799. [PubMed: 11050211]
- Kanwal JS, Matsumura S, Ohlemiller K, Suga N. Analysis of acoustic elements and syntax in communication sounds emitted by mustached bats. *J Acoust Soc Am*. 1994; 96:1229–1254. [PubMed: 7962992]
- Kaur S, Rose HJ, Lazar R, Liang K, Metherate R. Spectral integration in primary auditory cortex: laminar processing of afferent input, in vivo and in vitro. *Neuroscience*. 2005; 134:1033–1045. [PubMed: 15979241]
- Kaur S, Lazar R, Metherate R. Intracortical pathways determine breadth of subthreshold frequency receptive fields in primary auditory cortex. *J Neurophysiol*. 2004; 91:2551–2567. [PubMed: 14749307]
- Kawaguchi Y, Kubota Y. GABAergic cell subtypes and their synaptic connections in rat frontal cortex. *Cereb Cortex*. 1997; 7:476–486. [PubMed: 9276173]
- Kerlin AM, Andermann ML, Berezovskii VK, Reid RC. Broadly tuned response properties of diverse inhibitory neuron subtypes in mouse visual cortex. *Neuron*. 2010; 67:858–871. [PubMed: 20826316]
- Khibnik LA, Cho KK, Bear MF. Relative contribution of feedforward excitatory connections to expression of ocular dominance plasticity in layer 4 of visual cortex. *Neuron*. 2010; 66:493–500. [PubMed: 20510854]
- Kim PJ, Young ED. Comparative analysis of spectro-temporal receptive fields, reverse correlation functions, and frequency tuning curves of auditory-nerve fibers. *J Acoust Soc Am*. 1994; 95:410–422. [PubMed: 8120252]
- Kimura A, Donishi T, Sakoda T, Hazama M, Tamai Y. Auditory thalamic nuclei projections to the temporal cortex in the rat. *Neuroscience*. 2003; 117:1003–1016. [PubMed: 12654352]
- Klein DJ, Depireux DA, Simon JZ, Shamma SA. Robust spectrotemporal reverse correlation for the auditory system: optimizing stimulus design. *J Comput Neurosci*. 2000; 9:85–111. [PubMed: 10946994]

- Kowalski N, Depireux DA, Shamma SA. Analysis of dynamic spectra in ferret primary auditory cortex. II Prediction of unit responses to arbitrary dynamic spectra. *J Neurophysiol.* 1996; 76:3524–3534. [PubMed: 8930290]
- Kuwabara N, Suga N. Delay lines and amplitude selectivity are created in subthalamic auditory nuclei: the brachium of the inferior colliculus of the mustached bat. *J Neurophysiol.* 1993; 69:1713–1724. [PubMed: 8389837]
- Kuwada S, Stanford TR, Batra R. Interaural phase-sensitive units in the inferior colliculus of the unanesthetized rabbit: effects of changing frequency. *J Neurophysiol.* 1987; 57:1338–1360. [PubMed: 3585471]
- Kyriazi HT, Carvell GE, Brumberg JC, Simons DJ. Quantitative effects of GABA and bicuculline methiodide on receptive field properties of neurons in real and simulated whisker barrels. *J Neurophysiol.* 1996; 75:547–60. [PubMed: 8714634]
- Lakatos P, Chen CM, O'Connell MN, Mills A, Schroeder CE. Neuronal oscillations and multisensory interaction in primary auditory cortex. *Neuron.* 2007; 53:279–292. [PubMed: 17224408]
- Lee AK, Manns ID, Sakmann B, Brecht M. Whole-cell recordings in freely moving rats. *Neuron.* 2006; 51:399–407. [PubMed: 16908406]
- Lindblom BE, Studdert-Kennedy M. On the role of formant transitions in vowel recognition. *J Acoust Soc Am.* 1967; 42:830–843. [PubMed: 6075568]
- Linden JF, Liu RC, Sahani M, Schreiner CE, Merzenich MM. Spectrotemporal structure of receptive fields in areas AI and AAF of mouse auditory cortex. *J Neurophysiol.* 2003; 90:2660–2675. [PubMed: 12815016]
- Liu BH, Li P, Li YT, Sun YJ, Yanagawa Y, Obata K, Zhang LI, Tao HW. Visual receptive field structure of cortical inhibitory neurons revealed by two-photon imaging guided recording. *J Neurosci.* 2009; 29:10520–10532. [PubMed: 19710305]
- Liu BH, Wu GK, Arbuckle R, Tao HW, Zhang LI. Defining cortical frequency tuning with recurrent excitatory circuitry. *Nat Neurosci.* 2007; 10:1594–1600. [PubMed: 17994013]
- Liu BH, Li P, Li YT, Sun YJ, Zhang LI, Tao HW. Intervening inhibition underlies simple-cell receptive field structure in visual cortex. *Nat Neurosci.* 2010; 13:89–96. [PubMed: 19946318]
- Llano DA, Sherman SM. Evidence for nonreciprocal organization of the mouse auditory thalamocortical-corticothalamic projection systems. *J Comp Neurol.* 2008; 506:1209–1227. [PubMed: 18181153]
- Ma WP, Liu BH, Li YT, Huang ZJ, Zhang LI, Tao HW. Visual representations by cortical somatostatin inhibitory neurons—selective but with weak and delayed responses. *J Neurosci.* 2010; 30:14371–14379. [PubMed: 20980594]
- MacDonald RL, Rogers CJ, Twyman RE. Barbiturate regulation of kinetic properties of the GABAA receptor channel of mouse spinal neurones in culture. *J Physiol.* 1989; 417:483–500. [PubMed: 2482885]
- Margrie TW, Brecht M, Sakmann B. In vivo, low-resistance, whole-cell recordings from neurons in the anaesthetized and awake mammalian brain. *Pflugers Arch.* 2002; 444:491–498. [PubMed: 12136268]
- Mariño J, Schummers J, Lyon DC, Schwabe L, Beck O, Wiesing P, Obermayer K, Sur M. Invariant computations in local cortical networks with balanced excitation and inhibition. *Nat Neurosci.* 2005; 8:194–201. [PubMed: 15665876]
- Marshall JH, Mori T, Nielsen KJ, Callaway EM. Targeting single neuronal networks for gene expression and cell labeling in vivo. *Neuron.* 2010; 67:562–574. [PubMed: 20797534]
- Mitani A, et al. Morphology and laminar organization of electrophysiologically identified neurons in the primary auditory cortex in the cat. *J Comp Neurol.* 1985; 235:430–447. [PubMed: 3998218]
- Mitani A, Shimokouchi M. Neuronal connections in the primary auditory cortex: an electrophysiological study in the cat. *J Comp Neurol.* 1985; 235:417–429. [PubMed: 2987316]
- Mitzdorf U. Current source-density method and application in cat cerebral cortex: investigation of evoked potentials and EEG phenomena. *Physiol Rev.* 1985; 65:37–100. [PubMed: 3880898]
- Mendelson JR, Cynader MS. Sensitivity of cat primary auditory cortex (AI) neurons to the direction and rate of frequency modulation. *Brain Res.* 1985; 327:331–335. [PubMed: 3986511]

- Merzenich MM, Brugge JF. Representation of the cochlear partition on the superior temporal plane of the macaque monkey. *Brain Res.* 1973; 50:275–296. [PubMed: 4196192]
- Merzenich MM, Knight PL, Roth GL. Representation of cochlea within primary auditory cortex in the cat. *J Neurophysiol.* 1975; 38:231–249. [PubMed: 1092814]
- Merzenich, MM.; Schreiner, CE. Mammalian auditory cortex some comparative observations. In: Webster, DB.; Fay, RR.; Popper, AN., editors. *The evolutionary biology of hearing*. Springer; Berlin Heidelberg New York: 1992. p. 673–689.
- Miller LM, Escabi MA, Read HL, Schreiner CE. Spectrotemporal receptive fields in the lemniscal auditory thalamus and cortex. *J Neurophysiol.* 2002; 87:516–527. [PubMed: 11784767]
- Monier C, Chavane F, Baudot P, Graham LJ, Frégnac Y. Orientation and direction selectivity of synaptic inputs in visual cortical neurons: a diversity of combinations produces spike tuning. *Neuron.* 2003; 37:663–80. [PubMed: 12597863]
- Moore CI, Nelson SB. Spatio-temporal subthreshold receptive fields in the vibrissa representation of rat primary somatosensory cortex. *J Neurophysiol.* 1998; 80:2882–2892. [PubMed: 9862892]
- Nelken I, Versnel H. Responses to linear and logarithmic frequency-modulated sweeps in ferret primary auditory cortex. *Eur J Neurosci.* 2000; 12:549–562. [PubMed: 10712634]
- Nelson PG, Erulkar SD, Bryan JS. Responses of units of the inferior colliculus to time-varying acoustic stimuli. *J Neurophysiol.* 1966; 29:834–860. [PubMed: 5970670]
- Nicoll RA, Eccles JC, Oshima T, Rubia F. Prolongation of hippocampal inhibitory postsynaptic potentials by barbiturates. *Nature.* 1975; 258:625–627. [PubMed: 1207741]
- O'Neill WE, Brimijoin WO. Directional selectivity for FM sweeps in the supragenulate nucleus of the mustached bat medial geniculate body. *J Neurophysiol.* 2002; 88:172–187. [PubMed: 12091543]
- Ojima H, Murakami K. Intracellular characterization of suppressive responses in supragranular pyramidal neurons of cat primary auditory cortex in vivo. *Cereb Cortex.* 2002; 12:1079–1091. [PubMed: 12217972]
- Ojima H. Terminal morphology and distribution of corticothalamic fibers originating from layers 5 and 6 of cat primary auditory cortex. *Cereb Cortex.* 1994; 4:646–663. [PubMed: 7703690]
- Okun M, Naim A, Lampl I. The subthreshold relation between cortical local field potential and neuronal firing unveiled by intracellular recordings in awake rats. *J Neurosci.* 2010; 30:4440–4448. [PubMed: 20335480]
- Peters A, Kara DA. The neuronal composition of area 17 of rat visual cortex. II The nonpyramidal cells. *J Comp Neurol.* 1985; 234:242–263. [PubMed: 3988984]
- Phillips DP, Semple MN, Kitzes LM. Factors shaping the tone level sensitivity of single neurons in posterior field of cat auditory cortex. *J Neurophysiol.* 1995; 73:674–686. [PubMed: 7760126]
- Pollak GD, Park TJ. The effects of GABAergic inhibition on monaural response properties of neurons in the mustache bat's inferior colliculus. *Hear Res.* 1993; 65:99–117. [PubMed: 8384613]
- Polley DB, Heiser MA, Blake DT, Schreiner CE, Merzenich MM. Associative learning shapes the neural code for stimulus magnitude in primary auditory cortex. *Proc Natl Acad Sci USA.* 2004; 101:16351–16356. [PubMed: 15534214]
- Polley DB, Read HL, Storace DA, Merzenich MM. Multiparametric auditory receptive field organization across five cortical fields in the albino rat. *J Neurophysiol.* 2007; 97:3621–38. [PubMed: 17376842]
- Polley DB, Steinberg EE, Merzenich MM. Perceptual learning directs auditory cortical map reorganization through top-down influences. *J Neurosci.* 2006; 26:4970–4982. [PubMed: 16672673]
- Porter JT, Nieves D. Presynaptic GABAB receptors modulate thalamic excitation of inhibitory and excitatory neurons in the mouse barrel cortex. *J Neurophysiol.* 2004; 92:2762–2770. [PubMed: 15254073]
- Priebe NJ, Mechler F, Carandini M, Ferster D. The contribution of spike threshold to the dichotomy of cortical simple and complex cells. *Nat Neurosci.* 2004; 7:1113–1122. [PubMed: 15338009]
- Priet JJ, Peterson BA, Winer JA. Morphology and spatial distribution of GABAergic neurons in cat primary auditory cortex (A1). *J Comp Neurol.* 1994; 334:349–382.

- Prieto JJ, Winer JA. Layer VI in cat primary auditory cortex: Golgi study and sublaminal origins of projection neurons. *J Comp Neurol.* 1999; 404:332–358. [PubMed: 9952352]
- Razak KA, Fuzessery ZM. Neural mechanisms underlying selectivity for the rate and direction of frequency-modulated sweeps in the auditory cortex of the pallid bat. *J Neurophysiol.* 2006; 96:1303–1319. [PubMed: 16775213]
- Read HL, Winer JA, Schreiner CE. Functional architecture of auditory cortex. *Curr Opin Neurobiol.* 2002; 12:433–440. [PubMed: 12139992]
- Reale RA, Imig TJ. Tonotopic organization in auditory cortex of the cat. *J Comp Neurol.* 1980; 192:265–291. [PubMed: 7400399]
- Reid RC, Alonso JM. Specificity of monosynaptic connections from thalamus to visual cortex. *Nature.* 1995; 378:281–284. [PubMed: 7477347]
- Rennaker RL, Carey HL, Anderson SE, Sloan AM, Kilgard MP. Anesthesia suppresses nonsynchronous responses to repetitive broadband stimuli. *Neuroscience.* 2007; 145:357–369. [PubMed: 17207583]
- de Ribaupierre, F. Acoustic information processing in the auditory thalamus and cerebral cortex. In: Ehret, G.; Romand, R., editors. *The central auditory system.* Oxford University Press; New York: 1997. p. 317–397.
- de Ribaupierre F, Goldstein MH Jr, Yeni-Komshian G. Intracellular study of the cat's primary auditory cortex. *Brain Res.* 1972; 48:185–204. [PubMed: 4345594]
- Richardson RJ, Blundon JA, Bayazitov IT, Zakharenko SS. Connectivity patterns revealed by mapping of active inputs on dendrites of thalamorecipient neurons in the auditory cortex. *J Neurosci.* 2009; 29:6406–6417. [PubMed: 19458212]
- Roerig B, Chen B. Relationships of local inhibitory and excitatory circuits to orientation-preference maps in ferret visual cortex. *Cereb Cortex.* 2002; 12:187–198. [PubMed: 11739266]
- Romanski LM, LeDoux JE. Organization of rodent auditory cortex: anterograde transport of PHA-L from MGv to temporal neocortex. *Cereb Cortex.* 1993; 3:499–514. [PubMed: 7511011]
- Rothschild G, Nelken I, Mizrahi A. Functional organization and population dynamics in the mouse primary auditory cortex. *Nat Neurosci.* 2010; 13:353–360. [PubMed: 20118927]
- Rouiller E, de Ribaupierre Y, Morel A, de Ribaupierre F. Intensity functions of single unit responses to tone in the medial geniculate body of cat. *Hear Res.* 1983; 11:235–247. [PubMed: 6619007]
- Rouiller, EM. Functional organization of the auditory pathways. In: Ehret, G.; Romand, R., editors. *The central auditory system.* Oxford University Press; New York: 1997. p. 3–96.
- Rouiller EM, Welker E. A comparative analysis of the morphology of corticothalamic projections in mammals. *Brain Res Bull.* 2000; 53:727–741. [PubMed: 11179837]
- Runyan CA, Schummers J, Van Wart A, Kuhlman SJ, Wilson NR, Huang ZJ, Sur M. Response features of parvalbumin-expressing interneurons suggest precise roles for subtypes of inhibition in visual cortex. *Neuron.* 2010; 67:847–857. [PubMed: 20826315]
- Sadagopan S, Wang X. Contribution of inhibition to stimulus selectivity in primary auditory cortex of awake primates. *J Neurosci.* 2010; 30:7314–7325. [PubMed: 20505098]
- Schnupp JW, Msrac-Flogel TD, King AJ. Linear processing of spatial cues in primary auditory cortex. *Nature.* 2001; 414:200–204. [PubMed: 11700557]
- Schreiner CE, Mendelson JR, Sutter ML. Functional topography of cat primary auditory cortex: representation of tone intensity. *Exp Brain Res.* 1992; 92:105–122. [PubMed: 1486946]
- Schreiner CE, Read HL, Sutter ML. Modular organization of frequency integration in primary auditory cortex. *Annu Rev Neurosci.* 2000; 23:501–529. [PubMed: 10845073]
- Sen K, Theunissen FE, Doupe AJ. Feature analysis of natural sounds in the songbird auditory forebrain. *J Neurophysiol.* 2001; 86:1445–1458. [PubMed: 11535690]
- Shamma SA, Fleshman JW, Wiser PR, Versnel H. Organization of response areas in ferret primary auditory cortex. *J Neurophysiol.* 1993; 69:367–383. [PubMed: 8459273]
- Sillito AM. Inhibitory mechanisms influencing complex cell orientation selectivity and their modification at high resting discharge levels. *J Physiol.* 1979; 289:33–53. [PubMed: 458666]
- Sillito AM. Inhibitory processes underlying the directional specificity of simple, complex and hypercomplex cells in the cat's visual cortex. *J Physiol.* 1977; 271:699–720. [PubMed: 926020]

- Sirota MG, Swadlow HA, Beloozerova IN. Three channels of corticothalamic communication during locomotion. *J Neurosci*. 2005; 25:5915–5925. [PubMed: 15976080]
- Sivaramakrishnan S, Sterbing-D'Angelo SJ, Filipovic B, D'Angelo WR, Oliver DL, Kuwada S. GABA (A) synapses shape neuronal responses to sound intensity in the inferior colliculus. *J Neurosci*. 2004; 24:5031–5043. [PubMed: 15163696]
- Sohya K, Kameyama K, Yanagawa Y, Obata K, Tsumoto T. GABAergic neurons are less selective to stimulus orientation than excitatory neurons in layer II/III of visual cortex, as revealed by in vivo functional Ca²⁺ imaging in transgenic mice. *J Neurosci*. 2007; 27:2145–2149. [PubMed: 17314309]
- Somers DC, Nelson SB, Sur M. An emergent model of orientation selectivity in cat visual cortical simple cells. *J Neurosci*. 1995; 15:5448–5465. [PubMed: 7643194]
- Spruston N, Jaffe DB, Williams SH, Johnston D. Voltage- and space-clamp errors associated with the measurement of electrotonically remote synaptic events. *J Neurophysiol*. 1993; 70:781–802. [PubMed: 8410172]
- Stiebler I, Neulist R, Fichtel I, Ehret G. The auditory cortex of the house mouse: left-right differences, tonotopic organization and quantitative analysis of frequency representation. *J Comp Physiol A*. 1997; 181:559–571. [PubMed: 9449817]
- Suga N. Functional properties of auditory neurones in the cortex of echo-locating bats. *J Physiol*. 1965; 181:671–700. [PubMed: 5881249]
- Suga N, Ma X. Multiparametric corticofugal modulation and plasticity in the auditory system. *Nat Rev Neurosci*. 2003; 4:783–794. [PubMed: 14523378]
- Suga N, Manabe T. Neural basis of amplitude-spectrum representation in auditory cortex of the mustached bat. *J Neurophysiol*. 1982; 47:225–255. [PubMed: 7062098]
- Sun QQ, Huguenard JR, Prince DA. Barrel cortex microcircuits: thalamocortical feedforward inhibition in spiny stellate cells is mediated by a small number of fastspiking interneurons. *J Neurosci*. 2006; 26:1219–1230. [PubMed: 16436609]
- Sun YJ, Wu GK, Liu BH, Li P, Zhou M, Xiao Z, Tao HW, Zhang LI. Fine-Tuning of Pre-Balanced Excitation and Inhibition During Auditory Cortical Development. *Nature*. 2010; 465:927–931. [PubMed: 20559386]
- Sutter ML, Loftus WC. Excitatory and inhibitory intensity tuning in auditory cortex: evidence for multiple inhibitory mechanisms. *J Neurophysiol*. 2003; 90:2629–2647. [PubMed: 12801894]
- Takayanagi M, Ojima H. Microtopography of the dual corticothalamic projections originating from domains along the frequency axis of the cat primary auditory cortex. *Neuroscience*. 2006; 142:769–780. [PubMed: 16890371]
- Tan AY, Atencio CA, Polley DB, Merzenich MM, Schreiner CE. Unbalanced synaptic inhibition can create intensity-tuned auditory cortex neurons. *Neuroscience*. 2007; 146:449–462. [PubMed: 17320296]
- Tan AY, Wehr M. Balanced tone-evoked synaptic excitation and inhibition in mouse auditory cortex. *Neuroscience*. 2009; 163:1302–1315. [PubMed: 19628023]
- Tan AY, Zhang LI, Merzenich MM, Schreiner CE. Tone-evoked excitatory and inhibitory synaptic conductances of primary auditory cortex neurons. *J Neurophysiol*. 2004; 92:630–643. [PubMed: 14999047]
- Theyel BB, Lee CC, Sherman SM. Specific and nonspecific thalamocortical connectivity in the auditory and somatosensory thalamocortical slices. *Neuroreport*. 2010; 21:861–864. [PubMed: 20647961]
- Thomson AM, West DC, Lodge D. An N-methylaspartate receptor-mediated synapse in rat cerebral cortex: a site of action of ketamine? *Nature*. 1985; 313:479–481. [PubMed: 2982106]
- Tsumoto T, Suda K. Three groups of cortico-geniculate neurons and their distribution in binocular and monocular segments of cat striate cortex. *J Comp Neurol*. 1980; 193:223–236. [PubMed: 7430428]
- Villa AE, Rouiller EM, Simm GM, Zurita P, de Ribaupierre Y, de Ribaupierre F. Corticofugal modulation of the information processing in the auditory thalamus of the cat. *Exp Brain Res*. 1991; 86:506–517. [PubMed: 1761088]

- Volgushev M, Vidyasagar TR, Chistiakova M, Yousef T, Eysel UT. Membrane properties and spike generation in rat visual cortical cells during reversible cooling. *J Physiol (Lond)*. 2000; 522:59–76. [PubMed: 10618152]
- Volkov IO, Galazjuk AV. Formation of spike response to sound tones in cat auditory cortex neurons: interaction of excitatory and inhibitory effects. *Neuroscience*. 1991; 43:307–21. [PubMed: 1922775]
- Wallace MN, Palmer AR. Laminar differences in the response properties of cells in the primary auditory cortex. *Exp Brain Res*. 2008; 184:179–191. [PubMed: 17828392]
- Wang J, McFadden SL, Caspary D, Salvi R. Gamma-aminobutyric acid circuits shape response properties of auditory cortex neurons. *Brain Res*. 2002; 944:219–231. [PubMed: 12106684]
- Wang X. On cortical coding of vocal communication sounds in primates. *Proc Natl Acad Sci USA*. 2000; 97:11843–11849. [PubMed: 11050218]
- Wang X, Lu T, Snider RK, Liang L. Sustained firing in auditory cortex evoked by preferred stimuli. *Nature*. 2005; 435:341–346. [PubMed: 15902257]
- Wehr M, Zador AM. Balanced inhibition underlies tuning and sharpens spike timing in auditory cortex. *Nature*. 2003; 426:442–446. [PubMed: 14647382]
- Winer, JA. The functional architecture of the medial geniculate body and the primary auditory cortex. In: Webster, DB.; Popper, AN.; Fay, RR., editors. *The mammalian auditory pathways: neuroanatomy*. Springer; Berlin Heidelberg New York: 1992. p. 222-409.
- Winer JA, Diehl JJ, Larue DT. Projections of auditory cortex to the medial geniculate body of the cat. *J Comp Neurol*. 2001; 430:27–55. [PubMed: 11135244]
- Winer JA, Lee CC. The distributed auditory cortex. *Hear Res*. 2007; 229:3–13. [PubMed: 17329049]
- Winer JA, Miller LM, Lee CC, Schreiner CE. Auditory thalamocortical transformation: structure and function. *Trends Neurosci*. 2005; 28:255–263. [PubMed: 15866200]
- Winer JA, Prieto JJ. Layer V in cat primary auditory cortex (AI): cellular architecture and identification of projection neurons. *J Comp Neurol*. 2001; 434:379–412. [PubMed: 11343289]
- Winer JA. Decoding the auditory corticofugal systems. *Hear Res*. 2005; 207:1–9. [PubMed: 16091301]
- Winter P, Ploog D, Latta J. Vocal repertoire of the squirrel monkey (*Saimiri sciureus*), its analysis and significance. *Exp Brain Res*. 1966; 1:359–384. [PubMed: 4958770]
- Woolsey, CN. Organization of cortical auditory system: a review and a synthesis. In: Rasmussen, GL.; Windle, WF., editors. *Neural mechanisms of the auditory and vestibular systems*. Thomas; Springfield: 1960. p. 165-180.
- Wu GK, Arbuckle R, Liu BH, Tao HW, Zhang LI. Lateral sharpening of cortical frequency tuning by approximately balanced inhibition. *Neuron*. 2008; 58:132–143. [PubMed: 18400169]
- Wu GK, Li P, Tao HW, Zhang LI. Nonmonotonic synaptic excitation and imbalanced inhibition underlying cortical intensity tuning. *Neuron*. 2006; 52:705–715. [PubMed: 17114053]
- Yamauchi T, Hori T, Takahashi T. Presynaptic inhibition by muscimol through GABAB receptors. *Eur J Neurosci*. 2000; 12:3433–3436. [PubMed: 10998126]
- Yan J, Ehret G. Corticofugal modulation of midbrain sound processing in the house mouse. *Eur J Neurosci*. 2002; 16:119–128. [PubMed: 12153536]
- Ye CQ, Poo MM, Dan Y, Zhang XH. Synaptic mechanisms of direction selectivity in primary auditory cortex. *J Neurosci*. 2010; 30:1861–1868. [PubMed: 20130195]
- Young ED, Brownnell WE. Response to tones and noise of single cells in dorsal cochlear nucleus of unanesthetized cats. *J Neurophysiol*. 1976; 39:282–300. [PubMed: 1255224]
- Zeng FG, Nie K, Stickney GS, Kong YY, Vongphoe M, Bhargava A, Wei C, Cao K. Speech recognition with amplitude and frequency modulations. *Proc Natl Acad Sci USA*. 2005; 102:2293–2298. [PubMed: 15677723]
- Zhang LI, Tan AY, Schreiner CE, Merzenich MM. Topography and synaptic shaping of direction selectivity in primary auditory cortex. *Nature*. 2003; 424:201–205. [PubMed: 12853959]
- Zhang Y, Suga N. Corticofugal amplification of subcortical responses to single tone stimuli in the mustached bat. *J Neurophysiol*. 1997; 78:3489–3492. [PubMed: 9405567]

- Zhang Y, Suga N. Modulation of responses and frequency tuning of thalamic and collicular neurons by cortical activation in mustached bats. *J Neurophysiol.* 2000; 84:325–333. [PubMed: 10899207]
- Zhang Y, Yan J. Corticothalamic feedback for sound-specific plasticity of auditory thalamic neurons elicited by tones paired with basal forebrain stimulation. *Cereb Cortex.* 2008; 18:1521–1528. [PubMed: 18203697]
- Zhou Y, Liu BH, Wu GK, Kim YJ, Xiao Z, Tao HW, Zhang LI. Preceding inhibition silences layer 6 neurons in auditory cortex. *Neuron.* 2010; 65:706–717. [PubMed: 20223205]
- Zhu Y, Zhu JJ. Rapid arrival and integration of ascending sensory information in layer 1 nonpyramidal neurons and tuft dendrites of layer 5 pyramidal neurons of the neocortex. *J Neurosci.* 2004; 24:1272–1279. [PubMed: 14960597]

Highlights

- A systematic reductive approach is developed to resolve the cortical circuitry.
- In vivo whole-cell voltage-clamp recordings represent a key to probe circuitry.
- Excitatory-inhibitory interplay largely determines functional response properties.
- Elementary circuits can be derived from spatiotemporal patterns of synaptic inputs.

Fig. 1. Schematic diagrams of cortical circuits

A. Upper: a general neural network. Blue and triangle, principal cell; red and circle, inhibitory cell. Thin line, axon; thick line, dendrite; dot, synapse. Lower: the connectivity of this network can be described by a matrix with synaptic strength of synapses between each pair of neurons as individual elements.

B. Columnar and laminar processing in auditory cortex. Layer 4 (L4) and Layer 6 (L6) are recipient layers of thalamic inputs. Layer 2/3 (L2/3) and Layer 5 (L5) send outputs to other cortical regions and subcortical nuclei respectively. L6 sends corticothalamic feedback.

C. A simplified input circuit for a L4 neuron.

Fig. 2.

In vivo voltage-clamp recording to dissect different components of input. Excitatory and inhibitory components are separated by clamping the membrane potential of the recorded neuron at two different voltages. Thalamocortical inputs are further isolated by silencing the cortex. Cell morphology is recovered by post hoc histological staining.

Fig. 3. Diverse cortical functional circuits

A. A schematic diagram of a canonical circuit in Layer 4 of the primary auditory cortex (A1). Triangle, excitatory neuron; circle, inhibitory neuron. The frequency tuning of each connection is also presented along the projections. Gray curve depicts the frequency tuning curve. The thalamic and feedforward inhibitory inputs have a broad tuning, while the recurrent excitatory input has a sharp tuning. Together, the summed input exhibits a sharp frequency representation.

B. A “silent” circuit in Layer 6 of A1. The recorded neuron is not directly innervated by thalamic neurons. Instead, it receives disynaptic excitatory input.

C. A circuitry mechanism for cortical FM direction selectivity. The recorded neuron has a low CF and prefers upward FM sweeps. The spectral distribution of its excitatory inputs is skewed to low frequency side, and that of inhibition inputs is relatively broader and less skewed.

D. A hypothesized circuit for intensity-tuned neurons in Layer 4 of non-monotonic zone (NM), which is adjacent to A1. The recorded neuron receives intensity-tuned thalamic input (green), and non-intensity-tuned inhibitory input from interneurons which are innervated by non-intensity-tuned thalamic neurons. The amplitude-intensity tuning curves for each type of input and the summed input are shown. T_e and T_i represent the latencies of thalamic and inhibitory inputs. Their difference reduces as intensity increases (left), which further contributes to the sharpening of intensity selectivity of the recorded neuron.

Fig. 4.
A cortical excitatory neuron receives inhibitory input from a diversity of interneurons, which have differential subcellular targeting preferences.