

Perspectives on: Information and coding in mammalian sensory physiology

Inhibitory synaptic mechanisms underlying functional diversity in auditory cortex

Li I. Zhang,^{1,2} Yi Zhou,¹ and Huizhong W. Tao^{1,3}¹Zilkha Neurogenetic Institute, ²Department of Physiology and Biophysics, and ³Department of Cell and Neurobiology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033

In the auditory system, acoustic information conveyed by hair cells and auditory nerves is broken up into different components in central neural circuits, which can then be processed and encoded separately. This process relies on the generation of a variety of response features different from auditory nerve activity. Inhibition in the central circuits proves crucial for the creation and refinement of these functional response properties. Previous understanding of inhibitory mechanisms for auditory information processing has been limited by the methodology of deriving inhibition indirectly from spike and membrane potential responses. Recent application of *in vivo* whole cell voltage-clamp recordings (iVCRs) to auditory cortical neurons directly reveals the spectral and temporal properties of synaptic inhibition evoked by auditory stimuli. These findings provide new insights into how cortical inhibition shapes spike responses of excitatory neurons through its specific interaction with their excitatory synaptic input. This review highlights our current understanding of cortical inhibitory mechanisms underlying several fundamental functional properties of auditory cortical neurons. In particular, we propose that the variation in spectrotemporal pattern of cortical inhibition in relation to excitation contributes to the functional diversity of auditory cortex.

In the central auditory system, a variety of response features that do not resemble auditory nerve activity are found. For example, although the auditory nerve fire spikes continuously during sound duration, some central auditory neurons only respond transiently to the onset or the offset of sound stimuli (Fig. 1). The firing rate of the auditory nerve increases monotonically as sound intensity increases, whereas that of some central auditory neurons reaches a peak and then declines with further intensity increments. These diverse functional properties may set a foundation for parallel processing of different components of acoustic information. It is

believed that the generation of many of these novel response properties depends on inhibitory circuits. However, the detailed underlying mechanisms remain largely unclear, as it has been difficult to directly reveal synaptic inhibition in previous studies. Recently, *in vivo* whole cell recording techniques, especially, those of iVCR, have been successfully applied to auditory cortical neurons. These studies provided new insights into the inhibitory synaptic circuitry basis for the generation and refinement of these functional response properties, even though many of them are originated in subcortical nuclei.

Cortical responses are known to be strongly influenced by synaptic inhibition, which plays important roles in defining frequency–intensity receptive fields (RFs) and shaping sound-evoked responses of individual cortical neurons (e.g., Feng and Ratnam, 2000; Wang et al., 2000, 2002; Ojima and Murakami, 2002; Oswald et al., 2006). The inhibitory control is mediated by cortical GABAergic interneurons through their feedforward or feedback projections. To understand the inhibitory contribution to cortical information processing, two major questions need to be addressed: (1) How do GABAergic interneurons respond during cortical processing? (2) What kind of interplay between coactivated excitatory and inhibitory synaptic inputs to the cortical neuron determines the inhibitory shaping of its responses?

Response properties of inhibitory neurons

Because of the relative sparseness of GABAergic interneurons, which account for only 15–25% of total cortical neurons (Peters and Kara, 1985; Hendry et al., 1987; Prieto et al., 1994), our knowledge on *in vivo* functional properties of these cells has lagged far behind that of pyramidal cells. The inhibitory neuron population contains more than a dozen morphologically and neurochemically distinct subgroups (Kawaguchi and Kondo, 2002; Markram et al., 2004). The high heterogeneity of inhibitory neurons, as well as the technical challenge of

Correspondence to Li I. Zhang: liizhang@usc.edu

Abbreviations used in this paper: CF, characteristic frequency; FM, frequency modulated; iVCR, *in vivo* whole cell voltage-clamp recording; RF, receptive field.

© 2011 Zhang et al. This article is distributed under the terms of an Attribution–Noncommercial–Share Alike–No Mirror Sites license for the first six months after the publication date (see <http://www.rupress.org/terms>). After six months it is available under a Creative Commons License (Attribution–Noncommercial–Share Alike 3.0 Unported license, as described at <http://creativecommons.org/licenses/by-nc-sa/3.0/>).

identifying inhibitory neurons with either extracellular or intracellular recordings, greatly increases the difficulty in studying this population of cortical cells. Current understandings of response properties of cortical inhibitory neurons are mostly on fast-spike neurons, which exhibit distinctive narrow spike waveforms and can be identified with extracellular recordings (Mountcastle et al., 1969; Swadlow, 2003; Atencio and Schreiner, 2008; Wu et al., 2008). These cells have also been categorized as basket or chandelier cells based on morphology, and parvalbumin-positive neurons based on molecular markers (Kawaguchi and Kondo, 2002; Markram et al., 2004). Extracellular recording studies demonstrate that fast-spike inhibitory neurons exhibit different functional properties from excitatory neurons (Atencio and Schreiner, 2008; Wu et al., 2008). They display broader spectral tuning, shorter response latency, lower intensity threshold, and higher response reliability, whereas their preferred frequency is essentially the same as that of excitatory neurons in the same column. Intracellular recordings further indicate that the spectral range of excitatory inputs received by fast-spike neurons is not different from that of nearby excitatory neurons (Wu et al., 2008), suggesting that the two classes of cells receive common thalamocortical inputs. However, fast-spike neurons are more efficient in converting synaptic input to spike output, resulting in more broadly tuned spike responses than excitatory neurons. This observed broader tuning of fast-spike neurons is also consistent with results in other sensory cortices (Bruno and Simons, 2002; Swadlow, 2003; Niell and Stryker, 2008; Liu et al., 2009; Kerlin et al., 2010; Ma et al., 2010). These unique response properties of fast-spike

neurons place them in a strong position to supply fast, reliable, and temporally precise feedforward inhibition to other cells (Gabernet et al., 2005). Functional properties of other inhibitory neuron subtypes and their involvement in auditory cortical processing remain to be addressed.

Approaches to unraveling cortical inhibitory mechanisms

To understand the role of inhibition in shaping auditory cortical function, two approaches have been applied. First, functional properties of neurons have been compared before and after removing cortical inhibition pharmacologically. Local iontophoretic application of an antagonist of GABA_A receptors results in the broadening of frequency tuning of cortical neurons (Wang et al., 2000, 2002). These results provide evidence for an inhibitory sharpening of frequency tuning. However, they could not generate deeper insights into detailed underlying mechanisms. Second, RF properties of cortical inhibition have been indirectly derived by examining spike responses. In a two-tone forward-masking paradigm, inhibition is revealed by the suppression of responses to a characteristic frequency (CF) tone caused by a leading tone (Calford and Semple, 1995; Chen and Jen, 2000; Sutter and Loftus, 2003; Zhang et al., 2003). In these studies, it is found that inhibitory RFs flank the excitatory RFs, leading to the proposal of a lateral inhibition model. Inhibition has also been estimated based on the suppression of spontaneous spiking activity (e.g., Qin and Sato, 2004; Sadagopan and Wang, 2010; Zhou et al., 2010). Furthermore, intracellular sharp-electrode recording has revealed inhibition as a hyperpolarizing membrane potential response (Ojima and Murakami, 2002).

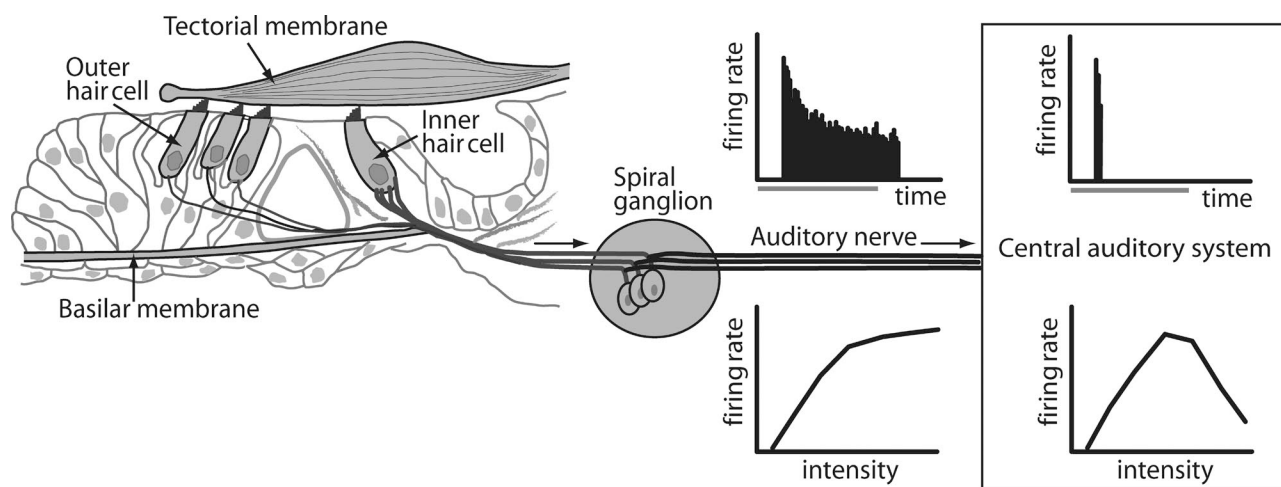


Figure 1. New functional response features are generated in the central auditory system. Two examples are shown. First, the discharge pattern of the auditory nerve in response to tones (marked by the gray line) exhibits a sustained response, with strong firing at stimulus onset. Many central auditory neurons, however, only exhibit transient responses to the onset or offset (not depicted) of stimulus. Second, the firing rate of the auditory nerve increases monotonically with the increase of sound intensity and may reach a plateau at high intensities. Central auditory neurons, however, can be intensity selective, as demonstrated by their nonmonotonic response-intensity functions.

The above studies, although providing persuasive evidence for inhibition, cannot give a quantitative measurement of inhibition. For example, in the two-tone suppression experiments, the leading tone may result in both excitation and inhibition, and the apparent suppression of the CF-tone response cannot be simply viewed as a pure inhibitory effect. In addition, short-term plasticity of excitatory and inhibitory inputs should also be considered because the temporally close two tones may not activate completely independent pathways.

In previous intracellular or whole cell recording experiments, many attempts to derive synaptic conductances may have been compromised by the high impedance of recording microelectrodes. Recently, the successful application of high-quality iVCR technique opens the door to probing into synaptic circuits underlying cortical processing. Only with low access-resistance whole cell recording and sufficient voltage clamp of neuronal membranes has it become possible to isolate excitatory and inhibitory synaptic conductances reliably (Wehr and Zador, 2003; Tan et al., 2004; Wu et al., 2006; Liu et al., 2007). It is worth noting that an evaluation of clamping quality cannot be based simply on the linearity of current-voltage relationship, but should also be based on the proximity of measured reversal potentials of synaptic currents to theoretical values. The iVCR technique is particularly important and useful for investigating inhibition because indirect derivations of inhibition could be problematic, as discussed above. Recent studies in the primary auditory cortex (A1) using the iVCR technique have revealed inhibitory patterns underlying several fundamental functional properties of cortical neurons, such as selectivity for auditory features and specific temporal response profiles (Wehr and Zador, 2003, 2005; Zhang et al., 2003; Tan et al., 2004, 2007; Wu et al., 2006, 2008; Liu et al., 2007; Sun et al., 2010; Zhou et al., 2010). The results provide us with a more thorough picture on the inhibitory mechanisms underlying auditory cortical processing.

Temporal shaping of auditory responses by cortical inhibition

Sound-evoked responses of individual cortical neurons are primarily determined by the temporal integration of coactivated excitatory and inhibitory synaptic inputs to the cell. Recent iVCR studies have allowed a detailed comparison of onset latency between excitation and inhibition evoked by the same stimulus. The results revealed that the temporal relationship between excitation and inhibition is not fixed, but varies in different cortical locations as to fulfill different processing functions. Three salient excitatory-inhibitory temporal relationships have been observed.

Canonical inhibitory delay. A stereotyped excitatory-inhibitory temporal relationship is found for layer 4

neurons in the auditory cortex, with the onset of inhibition delayed by 2–3 ms compared with that of excitation (Wehr and Zador, 2003; Tan et al., 2004; Wu et al., 2008; Zhou et al., 2010). This relative onset of inhibition appears constant across different tone frequencies (Wehr and Zador, 2003). A similar excitation-inhibition response sequence is also widely observed in other sensory cortices (Douglas and Martin, 1991, 2004; Higley and Contreras, 2006; Liu et al., 2010). As shown in Fig. 2 A, the briefly delayed inhibition has three effects on the membrane potential response: (1) suppressing the depolarization response level; (2) narrowing the time window for depolarizing response; and (3) creating a relatively long period of hyperpolarization after the initial depolarization. Such excitatory-inhibitory interplay selectively allows spikes to occur within the narrow depolarization window while it prevents spiking during the delayed long period of hyperpolarization (Fig. 2 A). This leads to transient onset spike responses in cortical neurons with relatively precise spike timing, and also allows the neuron to behave as a coincidence detector for synchronous inputs (Pouille and Scanziani, 2001; Wehr and Zador, 2003; Tan et al., 2004; Higley and Contreras, 2006). This canonical excitatory-inhibitory temporal relationship can be attributed to a feedforward inhibitory circuit, with disynaptic inhibitory inputs provided most likely by fast-spike inhibitory neurons (Tan et al., 2004; Gabernet et al., 2005; Wu et al., 2008; Ma et al., 2010).

Intensity-dependent inhibitory delay. Intensity-tuned auditory neurons are characterized by their nonmonotonic responses to sound intensities (Phillips et al., 1995; Heil and Irvine, 1998; Sutter and Loftus, 2003) and have been proposed to play important roles in encoding sound loudness and envelop transients (Heil and Irvine, 1998; Polley et al., 2004). Because auditory nerve responses all exhibit monotonic rate-level functions, intensity tuning must be created in the central auditory pathway, likely through specific spectral and temporal interactions between excitation and inhibition (Suga and Manabe, 1982; Faingold et al., 1991; Pollak and Park, 1993; Calford and Semple, 1995; Ojima and Murakami, 2002; Wang et al., 2002; Sutter and Loftus, 2003; Sivaramakrishnan et al., 2004). Recent iVCR recordings from intensity-tuned cortical neurons indicate that although excitatory input already exhibits intensity tuning, cortical intensity tuning is greatly strengthened by inhibitory input recruited in an imbalanced manner (Wu et al., 2006; Tan et al., 2007). As intensity increases, the amplitude of inhibition increases monotonically, and the temporal delay of inhibition relative to excitation is shortened. As a result, the suppression of excitation by the inhibitory input is enhanced at intensities above the preferred intensity, and intensity selectivity of spike responses is sharpened. More interestingly,

neuron modeling work indicates that even if excitatory input is not intensity tuned, intensity tuning can still be generated by shortening the relative onset of inhibition with intensity increments (Wu et al., 2006) (Fig. 2 B). This result suggests that controlling the relative timing between excitation and inhibition can be a good strategy used by synaptic circuits to achieve a *de novo* construction of intensity selectivity.

Inhibitory advance in layer 6 (L6). L6 of the A1 has been implicated in a major corticothalamic feedback loop. It receives direct thalamocortical input and conversely sends feedback projections predominantly to the first-order thalamic nucleus (Ojima, 1994; Prieto and Winer, 1999; Rouiller and Welker, 2000; Winer et al., 2001, 2005; Kaur et al., 2005; Winer, 2005; Takayanagi and Ojima, 2006; Lakatos et al., 2007; Llano and Sherman, 2008; Wallace and Palmer, 2008). This corticothalamic feedback has been thought to mediate thalamic responses (Villa et al., 1991; Zhang and Suga, 1997; Yan and Ehret, 2002). However, sensory stimuli do not drive

spike responses in a large proportion of L6 excitatory neurons (Tsumoto and Suda, 1980; Sirota et al., 2005; Zhou et al., 2010), but suppress their spontaneous firing within the expected tonal RF (Zhou et al., 2010). The suppression of evoked spike responses results from a strong inhibitory input preceding the coactivated excitatory input (Zhou et al., 2010) (Fig. 2 C). Such a reversed excitatory–inhibitory temporal relationship can be attributed to a parallel feedforward circuit in L6, with excitatory and inhibitory inputs both disynaptically relayed from the thalamus. Because of earlier spiking of the first-order L6 inhibitory neurons than the first-order excitatory neurons (Zhou et al., 2010), the second-order excitatory neuron would receive inhibition before the arrival of the disynaptic excitatory inputs. It is proposed that the preceding inhibition may be relieved under specific conditions, such as during the arrival of attention-related inputs. Then, the corticothalamic feedback is allowed to be activated to mediate the induction of sound-specific plasticity in the auditory thalamus (Zhang and Suga, 2000; Suga and Ma, 2003; Zhang and Yan, 2008).

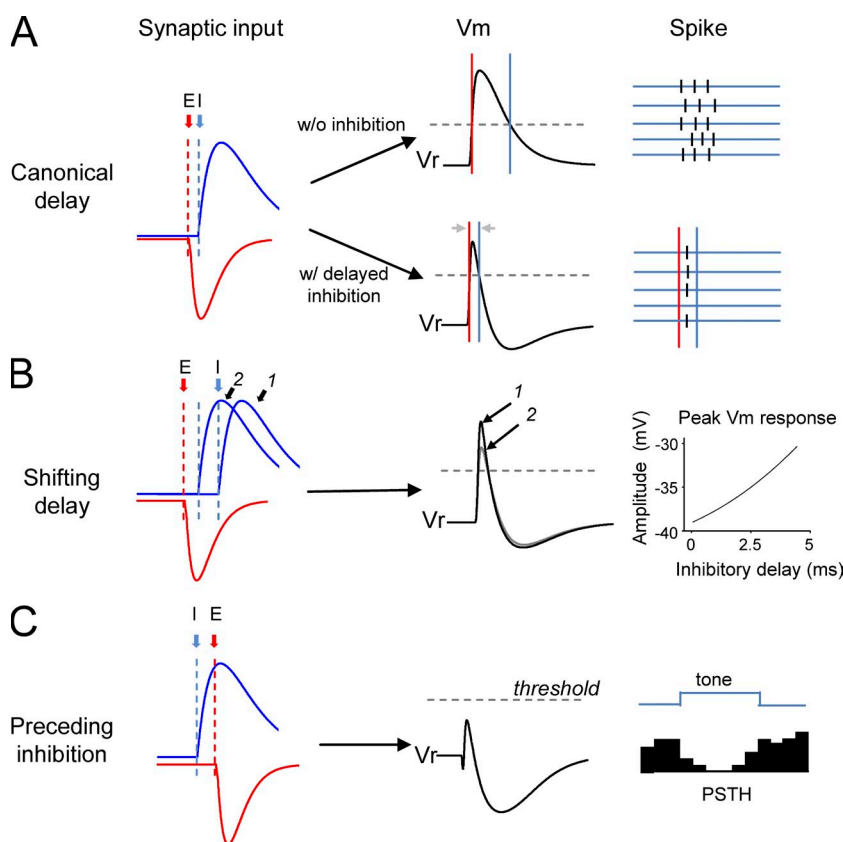


Figure 2. Temporal shaping of auditory responses by cortical inhibition. (A) A brief delay of inhibition narrows the time window for membrane depolarization, resulting in spikes with high temporal precision. (Left) Relative timing of model tone-evoked excitatory (red) and inhibitory (blue) inputs. Dashed line indicates the onset. (Middle) Derived membrane potential response resulting from excitation alone (top) or from the interplay of excitation and inhibition (bottom) using a simple neuron model. Dashed line indicates the spike threshold. Vertical lines mark the time window for spike generation. Vm, membrane potential response; Vr, resting membrane potential. (Right) Derived spike responses to tones in different trials. (B) Varying the onset of inhibition modulates the response of the cortical neuron, a mechanism underlying intensity selectivity. (Left) Blue curve 1 represents the inhibitory response to tone of optimal intensity, whereas 2 represents that to tone at higher intensity. (Middle) The derived membrane potential response to tone at higher intensity is weaker than that at optimal intensity. (Right) A simulation result showing the relationship between the peak amplitude of membrane potential response and the relative delay of inhibition. (C) Preceding inhibition silences spike output of the cortical neuron. (Left) Similar excitatory and inhibitory synaptic inputs as in A and B, except that the onset of inhibition is 2 ms earlier than that of excitation. (Middle) The derived membrane potential response is lower than the spike threshold. (Right) The expected post-stimulus spike-time histogram (PSTH) in response to a tone. The spontaneous firing is suppressed during tone stimulation.

Spectral shaping of auditory feature selectivity by cortical inhibition

In the auditory system, frequency or spectral information is mainly coded spatially in a tonotopic map. Therefore, the spatial distribution of presynaptic neurons largely determines the spectral range of synaptic inputs to the postsynaptic cell. Through specific spectral interactions between excitation and inhibition, feature selectivity represented by auditory cortical neurons can be enhanced or even created.

Frequency selectivity. Three models have been proposed to explain the inhibitory sharpening of frequency selectivity. First, in the balanced excitation and inhibition model (Fig. 3 A), excitation and inhibition exhibit the same tuning profiles (Fig. 3 A); that is, they are cotuned (Wehr and Zador, 2003; Zhang et al., 2003; Tan et al., 2004; Oswald et al., 2006). In this model, inhibition

scales down the level of membrane depolarization responses and thus narrows the frequency range for spike responses through an “iceberg” or thresholding effect (Wehr and Zador, 2003; Tan et al., 2004). The cotuned inhibition can be explained by a feedforward circuit in which inhibitory neurons providing the inhibition receive the same set of thalamic inputs as the excitatory neuron under examination. Second, in the lateral inhibition model (Fig. 3 B), the spectral range of inhibitory inputs is much broader than that of excitatory inputs, resulting in suppressive sidebands flanking the excitatory RF and the narrowing of frequency tuning of spike responses (Suga and Manabe, 1982; Shamma, 1985; Shamma and Symmes, 1985; Calford and Semple, 1995; Sutter and Loftus, 2003; Oswald et al., 2006). This second model is primarily based on extracellular recording results of two-tone suppression experiments (Suga and Manabe, 1982; Calford and Semple, 1995; Sutter and Loftus, 2003),

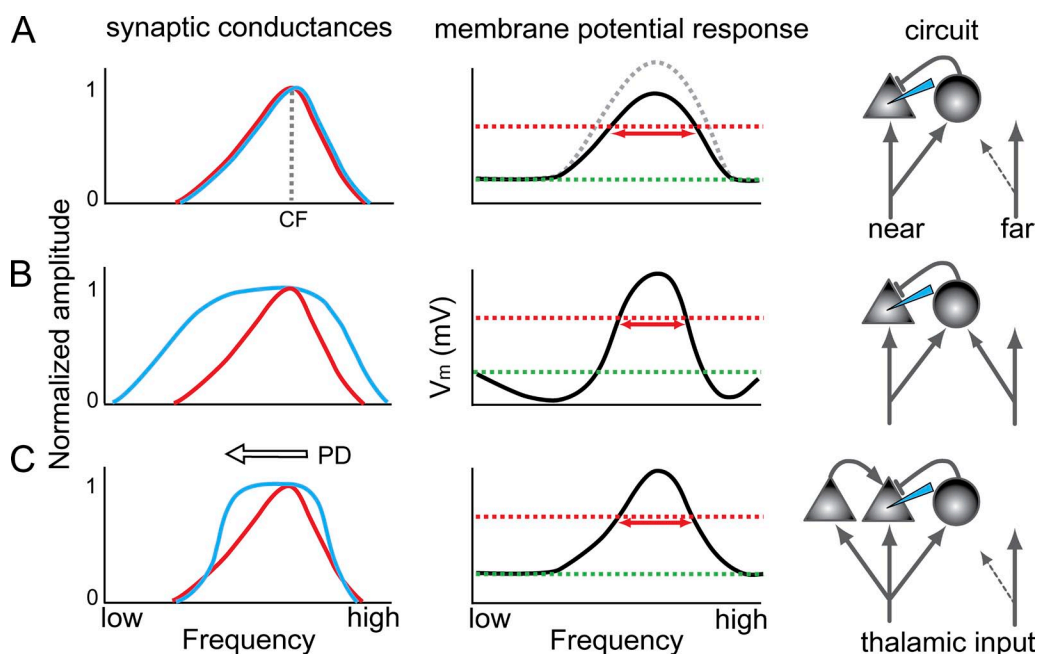


Figure 3. Three models for the spectral shaping of auditory feature selectivity by cortical inhibition. (A) Balanced excitation and inhibition model. (Left) Cotuned frequency tuning curves for excitation (red) and inhibition (blue). CF, characteristic frequency. (Middle) Tuning curves for membrane potential responses resulting from excitation alone (dashed gray curve) and from integrating excitation and inhibition (solid black curve). Note that the tuning curve is scaled down without changes in shape. Red dashed line indicates the level of spike threshold. Green dash line indicates the level of resting membrane potential. Red arrows mark the frequency range for spike response. (Right) Proposed underlying circuit. The recorded cortical excitatory neuron (triangle cell) receives thalamic inputs (excitatory) and inhibition from local inhibition neurons (round cell), which are innervated by the same set of thalamic inputs. Thus, inhibition is disynaptically relayed. “Far” means thalamic input with represented frequency far away from the CF of the recorded neuron. (B) Lateral inhibition model. Note that hyperpolarizing responses (V_m below the resting membrane potential) result in apparent suppressive sidebands. In this case, the inhibitory neurons receive thalamic input with represented frequency far away from the CF of the recorded neuron. (C) Approximately balanced excitation and inhibition model. Note that the inhibitory tuning curve has a more flattened peak than the excitatory tuning curve. The cell is a high-CF cell, so that the excitatory tuning curve is skewed toward the high-frequency side. The relative inhibition is stronger on the left side than the right side of the excitatory tuning curve. The arrow indicates the preferred direction, that is, from high frequency to low frequency (downward FM sweeps). Upward sweeps would activate an earlier strong inhibition, which would suppress later activated strong excitation. Compared with the model in A, the membrane potential tuning is further sharpened. In the circuit, the cortical excitatory neurons connecting to the recorded cell have narrower frequency tuning of spike response compared with the inhibitory neurons connecting to the same cell. As a result, inhibitory inputs are broader than summed excitatory inputs.

and can only be explained by a circuit in which inhibitory neurons receive a broader range of thalamic inputs than excitatory neurons. Third, detailed analysis of frequency tunings of synaptic inputs at high resolutions reveals that the spectral range of inhibition is in fact slightly narrower than that of excitation, and the shapes of excitatory and inhibitory tuning curves are different (Wu et al., 2008; Sun et al., 2010). The inhibitory tuning curve appears broader, especially within a putative spiking frequency range around the CF (Fig. 3 C). This current model unites the two previous models by demonstrating that on a global scale, excitation and inhibition are approximately balanced, but on a finer scale, excitation and inhibition can be significantly imbalanced. It also fits better with the properties of inhibitory neurons. Recordings from layer 4 fast-spike inhibitory neurons show that their spectral range of synaptic inputs (which is primarily determined by thalamocortical inputs) is not different from nearby excitatory neurons, but spike responses of fast-spike inhibitory neurons are more broadly tuned than those of excitatory neurons (Atencio and Schreiner, 2008; Wu et al., 2008). Because layer 4 excitatory neurons receive a significant amount of excitatory input from other cortical excitatory neurons (Liu et al., 2007; Happel et al., 2010; Zhou et al., 2010), this differential tuning between fast-spike inhibitory neurons and excitatory neurons introduces a break of excitatory–inhibitory balance; that is, inhibitory inputs are more broadly tuned than summed excitatory inputs (Fig. 3 C). Compared with the cotuned inhibition, the more broadly tuned inhibition around the preferred frequency has an advantage in that it can exert an equivalent lateral inhibition effect and further narrow the frequency range of spike responses (Wu et al., 2008).

Frequency-modulated (FM) direction selectivity. Neurons selective for direction of FM sweeps are found in the A1 (Suga, 1965; Mendelson and Cynader, 1985; Zhang et al., 2003). Mapping studies suggest that direction selectivity is topographically ordered in parallel with frequency representation. 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). It is found that the spectral distribution of excitatory synaptic input is asymmetric or skewed in direction-selective neurons, and the skewness is strongly correlated with direction selectivity (Zhang et al., 2003). However, the skewed excitatory inputs by themselves do not account for the generation of direction selectivity, as the integration of single-tone evoked excitatory inputs sequentially to simulate FM sweep stimulation results in an optimal direction for excitation opposite to the cell's preferred direction (Zhang et al., 2003). The correct directional preference on the other hand can be achieved by spectral and temporal interplays between excitatory and inhibitory inputs. 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), and relatively stronger inhibition appears on one side of the excitatory frequency tuning curve in a manner consistent with the cell's preferred direction (Zhang et al., 2003; Ye et al., 2010). It has been thought that this spectral offset is important for the generation of direction selectivity. In fact, the apparent offset can be attributed to the broader tuning of inhibition than excitation and its less asymmetric tuning shape (Fig. 3 C). When FM sweeps are applied in the preferred direction, both strong excitation and inhibition are activated earlier, but the delayed nature of inhibition allows spiking response to be generated. In contrast, in the opposite direction, relatively strong inhibition is activated earlier, which effectively suppresses the later arriving strong excitation and prevents spiking response (Zhang et al., 2003). Thus, the detailed excitatory–inhibitory imbalance can contribute significantly to direction selectivity in response to FM sweeps.

Variety of excitatory–inhibitory interplay and functional diversity

Having been supported by several earlier iVCR studies (Wehr and Zador, 2003; Zhang et al., 2003; Tan et al., 2004; Oswald et al., 2006; Tan and Wehr, 2009), the concept of balanced excitation and inhibition has received broad attention. The balance is characterized by a relatively constant ratio between amplitudes of excitation and inhibition across different stimuli. In addition, a stereotyped sequence of excitation followed by inhibition is evoked by sensory input, with the time interval between them relatively constant across stimuli. Under balanced excitation and inhibition, functional selectivity is primarily determined by the property of excitatory synaptic inputs, and inhibition only helps to sharpen the selectivity. Considering that central auditory neurons exhibit a wide variety of functional properties very different from auditory nerves (Schreiner et al., 2000; de la Rocha et al., 2008), neural circuits with only balanced excitation and inhibition seem too limited for explaining the functional diversity. Indeed, in the cortex, even the balanced excitation and inhibition can only be viewed as being approximate. Neural circuits with different organization principles together with neuronal populations with different response properties can result in various patterns of excitatory–inhibitory interplay deviating from the perfect balance, which would be essential for creating diverse functional properties.

Future directions

The inhibitory mechanisms discussed so far are largely consistent with the functional properties of fast-spike inhibitory neurons and their involved circuits. Functional properties of other types of inhibitory neurons in

the auditory cortex are yet unknown. Although in a few cases, in vivo whole cell recordings combined with post hoc histology have helped to identify inhibitory neurons in the visual 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. The fast growing transgenic mouse lines wherein genetic labeling of specific subtypes of inhibitory neurons has been achieved greatly facilitate a targeted examination of a desired inhibitory cell type. With technical innovations on in vivo Ca^{2+} imaging of neuronal responses (Sohya et al., 2007; Bandyopadhyay et al., 2010; Kerlin et al., 2010; Runyan et al., 2010; Zariwala et al., 2011) as well as two-photon imaging-guided patch-clamp recording (Margrie et al., 2003; Liu et al., 2009; Gentet et al., 2010; Ma et al., 2010), some major breakthroughs will likely be made in the next few years to greatly enhance our understanding of the differential functional roles of inhibitory neuron subtypes (Ma et al., 2010) and their associated synaptic circuitry.

An important functional aspect of inhibition, its dynamic property, has not been extensively studied previously. The dynamic property concerns the temporal profile (duration and decay time) and short-term plasticity of inhibitory synaptic responses, as well as the firing pattern of inhibitory neurons (transient or sustained). Such information is important for understanding the inhibitory shaping of responses under temporally complex sounds, which are predominant in a natural acoustic environment. The current data on the duration of inhibition remain somewhat controversial (with short duration: Wehr and Zador, 2003, 2005; with relatively long duration: Tan et al., 2004; Wu et al., 2008). For example, the short duration of inhibition observed in excitatory cells in a couple of studies (Wehr and Zador, 2003, 2005) seems inconsistent with the more sustained spike responses elicited in inhibitory neurons by similar tone stimulation (Wu et al., 2008). Further studies will be needed for our understanding on the contribution of the temporal profile of inhibition to the outstanding phenomenon of two-tone feedforward masking (Tan et al., 2004; Wehr and Zador, 2005).

In addition to comparing patterns of sound-evoked excitation and inhibition, a straightforward strategy for elucidating the inhibitory shaping of single cortical neuron's functional properties is to compare its responses before and after eliminating inhibition in that cell. With iVCR, it remains extremely difficult to change the intrapipette solution to directly record the responses of the same cell with and without intracellular blockers for GABA receptors. However, essential understandings of inhibitory mechanisms can be gained first by modeling membrane potential responses with neuronal models. By including or removing the inhibitory conductance, these computational models can qualitatively reveal the

effects of inhibition (Wu et al., 2008; Liu et al., 2010). Second, the dynamic-clamp technique (Sharp et al., 1993) can be combined with in vivo whole cell recording to inject experimentally determined synaptic conductances into the cell and monitor its membrane potential response. Finally, the newly developed optogenetic technique (Lima et al., 2009; Zhang et al., 2010) will allow light-controlled reversible inactivation of local inhibitory neurons, while leaving the network activity largely intact. Responses of single cells can be examined before and after activation or inactivation. Collectively, these experiments will be able to provide invaluable insights into the inhibitory synaptic mechanisms underlying auditory cortical functions.

This Perspectives series includes articles by Farley and Sampath, Schwartz and Rieke, Bautista and Lumpkin, and Reisert and Zhao.

This work was supported by National Institutes of Health (grants DC008983 and DC008588 to L.L. Zhang and grant EY019049 to H.W. Tao), the Searle Scholar Program, the Esther A. and Joseph Klingenstein Fund, and the David and Lucile Packard Foundation.

Robert S. Farley served as guest editor.

REFERENCES

- Atencio, C.A., and C.E. Schreiner. 2008. Spectrotemporal processing differences between auditory cortical fast-spiking and regular-spiking neurons. *J. Neurosci.* 28:3897–3910. doi:10.1523/JNEUROSCI.5366-07.2008
- Azouz, R., C.M. Gray, L.G. Nowak, and D.A. McCormick. 1997. Physiological properties of inhibitory interneurons in cat striate cortex. *Cereb. Cortex.* 7:534–545. doi:10.1093/cercor/7.6.534
- Bandyopadhyay, S., S.A. Shamma, and P.O. Kanold. 2010. Dichotomy of functional organization in the mouse auditory cortex. *Nat. Neurosci.* 13:361–368. doi:10.1038/nn.2490
- Bruno, R.M., and D.J. Simons. 2002. Feedforward mechanisms of excitatory and inhibitory cortical receptive fields. *J. Neurosci.* 22:10966–10975.
- Calford, M.B., and M.N. Semple. 1995. Monaural inhibition in cat auditory cortex. *J. Neurophysiol.* 73:1876–1891.
- Chen, Q.-C., and P.H. Jen. 2000. Bicuculline application affects discharge patterns, rate-intensity functions, and frequency tuning characteristics of bat auditory cortical neurons. *Hear. Res.* 150:161–174. doi:10.1016/S0378-5955(00)00197-0
- de la Rocha, J., C. Marchetti, M. Schiff, and A.D. Reyes. 2008. Linking the response properties of cells in auditory cortex with network architecture: cotuning versus lateral inhibition. *J. Neurosci.* 28:9151–9163. doi:10.1523/JNEUROSCI.1789-08.2008
- Douglas, R.J., and K.A. Martin. 1991. A functional microcircuit for cat visual cortex. *J. Physiol.* 440:735–769.
- Douglas, R.J., and K.A. Martin. 2004. Neuronal circuits of the neocortex. *Annu. Rev. Neurosci.* 27:419–451. doi:10.1146/annurev.neuro.27.070203.144152
- Faingold, C.L., C.A. Boersma Anderson, and D.M. Caspary. 1991. Involvement of GABA in acoustically-evoked inhibition in inferior colliculus neurons. *Hear. Res.* 52:201–216. doi:10.1016/0378-5955(91)90200-S
- Feng, A.S., and R. Ratnam. 2000. Neural basis of hearing in real-world situations. *Annu. Rev. Psychol.* 51:699–725. doi:10.1146/annurev.psych.51.1.699

- Gabernet, L., S.P. Jadhav, D.E. Feldman, M. Carandini, and M. Scanziani. 2005. Somatosensory integration controlled by dynamic thalamocortical feed-forward inhibition. *Neuron*. 48:315–327. doi:10.1016/j.neuron.2005.09.022
- Gentet, L.J., M. Avermann, F. Matyas, J.F. Staiger, and C.C. Petersen. 2010. Membrane potential dynamics of GABAergic neurons in the barrel cortex of behaving mice. *Neuron*. 65:422–435. doi:10.1016/j.neuron.2010.01.006
- Godey, B., C.A. Atencio, B.H. Bonham, C.E. Schreiner, and S.W. Cheung. 2005. Functional organization of squirrel monkey primary auditory cortex: responses to frequency-modulation sweeps. *J. Neurophysiol.* 94:1299–1311. doi:10.1152/jn.00950.2004
- Happel, M.F., M. Jeschke, and F.W. Ohl. 2010. Spectral integration in primary auditory cortex attributable to temporally precise convergence of thalamocortical and intracortical input. *J. Neurosci.* 30:11114–11127. doi:10.1523/JNEUROSCI.0689-10.2010
- Heil, P., and D.R. Irvine. 1998. The posterior field P of cat auditory cortex: coding of envelope transients. *Cereb. Cortex*. 8:125–141. doi:10.1093/cercor/8.2.125
- Heil, P., G. Langner, and H. Scheich. 1992. 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*. 171:583–600.
- Hendry, S.H., H.D. Schwark, E.G. Jones, and J. Yan. 1987. Numbers and proportions of GABA-immunoreactive neurons in different areas of monkey cerebral cortex. *J. Neurosci.* 7:1503–1519.
- Higley, M.J., and D. Contreras. 2006. Balanced excitation and inhibition determine spike timing during frequency adaptation. *J. Neurosci.* 26:448–457. doi:10.1523/JNEUROSCI.3506-05.2006
- Hirsch, J.A., L.M. Martinez, C. Pillai, J.M. Alonso, Q. Wang, and F.T. Sommer. 2003. Functionally distinct inhibitory neurons at the first stage of visual cortical processing. *Nat. Neurosci.* 6:1300–1308. doi:10.1038/nn1152
- Kaur, S., H.J. Rose, R. Lazar, K. Liang, and R. Metherate. 2005. Spectral integration in primary auditory cortex: laminar processing of afferent input, in vivo and in vitro. *Neuroscience*. 134:1033–1045. doi:10.1016/j.neuroscience.2005.04.052
- Kawaguchi, Y., and S. Kondo. 2002. Parvalbumin, somatostatin and cholecystikinin as chemical markers for specific GABAergic interneuron types in the rat frontal cortex. *J. Neurocytol.* 31:277–287. doi:10.1023/A:1024126110356
- Kerlin, A.M., M.L. Andermann, V.K. Berezovskii, and R.C. Reid. 2010. Broadly tuned response properties of diverse inhibitory neuron subtypes in mouse visual cortex. *Neuron*. 67:858–871. doi:10.1016/j.neuron.2010.08.002
- Lakatos, P., C.M. Chen, M.N. O’Connell, A. Mills, and C.E. Schroeder. 2007. Neuronal oscillations and multisensory interaction in primary auditory cortex. *Neuron*. 53:279–292. doi:10.1016/j.neuron.2006.12.011
- Lima, S.Q., T. Hromádka, P. Znamenskiy, and A.M. Zador. 2009. PINP: a new method of tagging neuronal populations for identification during in vivo electrophysiological recording. *PLoS ONE*. 4:e6099. doi:10.1371/journal.pone.0006099
- Liu, B.H., G.K. Wu, R. Arbuckle, H.W. Tao, and L.I. Zhang. 2007. Defining cortical frequency tuning with recurrent excitatory circuitry. *Nat. Neurosci.* 10:1594–1600. doi:10.1038/nn2012
- Liu, B.H., P. Li, Y.T. Li, Y.J. Sun, Y. Yanagawa, K. Obata, L.I. Zhang, and H.W. Tao. 2009. Visual receptive field structure of cortical inhibitory neurons revealed by two-photon imaging guided recording. *J. Neurosci.* 29:10520–10532. doi:10.1523/JNEUROSCI.1915-09.2009
- Liu, B.H., P. Li, Y.J. Sun, Y.T. Li, L.I. Zhang, and H.W. Tao. 2010. Intervening inhibition underlies simple-cell receptive field structure in visual cortex. *Nat. Neurosci.* 13:89–96. doi:10.1038/nn.2443
- Llano, D.A., and S.M. Sherman. 2008. Evidence for nonreciprocal organization of the mouse auditory thalamocortical-corticothalamic projection systems. *J. Comp. Neurol.* 507:1209–1227. doi:10.1002/cne.21602
- Ma, W.P., B.H. Liu, Y.T. Li, Z.J. Huang, L.I. Zhang, and H.W. Tao. 2010. Visual representations by cortical somatostatin inhibitory neurons—selective but with weak and delayed responses. *J. Neurosci.* 30:14371–14379. doi:10.1523/JNEUROSCI.3248-10.2010
- Margrie, T.W., A.H. Meyer, A. Caputi, H. Monyer, M.T. Hasan, A.T. Schaefer, W. Denk, and M. Brecht. 2003. Targeted whole-cell recordings in the mammalian brain in vivo. *Neuron*. 39:911–918. doi:10.1016/j.neuron.2003.08.012
- Markram, H., M. Toledo-Rodriguez, Y. Wang, A. Gupta, G. Silberberg, and C. Wu. 2004. Interneurons of the neocortical inhibitory system. *Nat. Rev. Neurosci.* 5:793–807. doi:10.1038/nrn1519
- Mendelson, J.R., and M.S. Cynader. 1985. Sensitivity of cat primary auditory cortex (AI) neurons to the direction and rate of frequency modulation. *Brain Res.* 327:331–335. doi:10.1016/0006-8993(85)91530-6
- Mountcastle, V.B., W.H. Talbot, H. Sakata, and J. Hyvärinen. 1969. Cortical neuronal mechanisms in flutter-vibration studied in unanesthetized monkeys. Neuronal periodicity and frequency discrimination. *J. Neurophysiol.* 32:452–484.
- Nelken, I., and H. Versnel. 2000. Responses to linear and logarithmic frequency-modulated sweeps in ferret primary auditory cortex. *Eur. J. Neurosci.* 12:549–562. doi:10.1046/j.1460-9568.2000.00935.x
- Niell, C.M., and M.P. Stryker. 2008. Highly selective receptive fields in mouse visual cortex. *J. Neurosci.* 28:7520–7536. doi:10.1523/JNEUROSCI.0623-08.2008
- Ojima, H. 1994. Terminal morphology and distribution of corticothalamic fibers originating from layers 5 and 6 of cat primary auditory cortex. *Cereb. Cortex*. 4:646–663. doi:10.1093/cercor/4.6.646
- Ojima, H., and K. Murakami. 2002. Intracellular characterization of suppressive responses in supragranular pyramidal neurons of cat primary auditory cortex in vivo. *Cereb. Cortex*. 12:1079–1091. doi:10.1093/cercor/12.10.1079
- Oswald, A.M., M.L. Schiff, and A.D. Reyes. 2006. Synaptic mechanisms underlying auditory processing. *Curr. Opin. Neurobiol.* 16:371–376. doi:10.1016/j.conb.2006.06.015
- Peters, A., and D.A. Kara. 1985. The neuronal composition of area 17 of rat visual cortex. II. The nonpyramidal cells. *J. Comp. Neurol.* 234:242–263. doi:10.1002/cne.902340209
- Phillips, D.P., M.N. Semple, and L.M. Kitzes. 1995. Factors shaping the tone level sensitivity of single neurons in posterior field of cat auditory cortex. *J. Neurophysiol.* 73:674–686.
- Pollak, G.D., and T.J. Park. 1993. The effects of GABAergic inhibition on monaural response properties of neurons in the mustache bat’s inferior colliculus. *Hear. Res.* 65:99–117. doi:10.1016/0378-5955(93)90205-F
- Polley, D.B., M.A. Heiser, D.T. Blake, C.E. Schreiner, and M.M. Merzenich. 2004. Associative learning shapes the neural code for stimulus magnitude in primary auditory cortex. *Proc. Natl. Acad. Sci. USA*. 101:16351–16356. doi:10.1073/pnas.0407586101
- Pouille, F., and M. Scanziani. 2001. Enforcement of temporal fidelity in pyramidal cells by somatic feed-forward inhibition. *Science*. 293:1159–1163. doi:10.1126/science.1060342
- Prieto, J.J., and J.A. Winer. 1999. Layer VI in cat primary auditory cortex: Golgi study and sublamina origins of projection neurons. *J. Comp. Neurol.* 404:332–358. doi:10.1002/(SICI)1096-9861(19990215)404:3<332::AID-CNE5>3.0.CO;2-R
- Prieto, J.J., B.A. Peterson, and J.A. Winer. 1994. Morphology and spatial distribution of GABAergic neurons in cat primary auditory cortex (AI). *J. Comp. Neurol.* 344:349–382. doi:10.1002/cne.903440304

- Qin, L., and Y. Sato. 2004. Suppression of auditory cortical activities in awake cats by pure tone stimuli. *Neurosci. Lett.* 365:190–194. doi:10.1016/j.neulet.2004.04.092
- Razak, K.A., and Z.M. Fuzessery. 2006. Neural mechanisms underlying selectivity for the rate and direction of frequency-modulated sweeps in the auditory cortex of the pallid bat. *J. Neurophysiol.* 96:1303–1319. doi:10.1152/jn.00020.2006
- Rouiller, E.M., and E. Welker. 2000. A comparative analysis of the morphology of corticothalamic projections in mammals. *Brain Res. Bull.* 53:727–741. doi:10.1016/S0361-9230(00)00364-6
- Runyan, C.A., J. Schummers, A. Van Wart, S.J. Kuhlman, N.R. Wilson, Z.J. Huang, and M. Sur. 2010. Response features of parvalbumin-expressing interneurons suggest precise roles for subtypes of inhibition in visual cortex. *Neuron.* 67:847–857. doi:10.1016/j.neuron.2010.08.006
- Sadagopan, S., and X. Wang. 2010. Contribution of inhibition to stimulus selectivity in primary auditory cortex of awake primates. *J. Neurosci.* 30:7314–7325. doi:10.1523/JNEUROSCI.5072-09.2010
- Schreiner, C.E., H.L. Read, and M.L. Sutter. 2000. Modular organization of frequency integration in primary auditory cortex. *Annu. Rev. Neurosci.* 23:501–529.
- Shamma, S.A. 1985. Speech processing in the auditory system. II: lateral inhibition and the central processing of speech evoked activity in the auditory nerve. *J. Acoust. Soc. Am.* 78:1622–1632. doi:10.1121/1.392800
- Shamma, S.A., and D. Symmes. 1985. Patterns of inhibition in auditory cortical cells in awake squirrel monkeys. *Hear. Res.* 19:1–13. doi:10.1016/0378-5955(85)90094-2
- Shamma, S.A., J.W. Fleshman, P.R. Wiser, and H. Versnel. 1993. Organization of response areas in ferret primary auditory cortex. *J. Neurophysiol.* 69:367–383.
- Sharp, A.A., M.B. O'Neil, L.F. Abbott, and E. Marder. 1993. The dynamic clamp: artificial conductances in biological neurons. *Trends Neurosci.* 16:389–394. doi:10.1016/0166-2236(93)90004-6
- Sirota, M.G., H.A. Swadlow, and I.N. Beloozerova. 2005. Three channels of corticothalamic communication during locomotion. *J. Neurosci.* 25:5915–5925. doi:10.1523/JNEUROSCI.0489-05.2005
- Sivaramakrishnan, S., S.J. Sterbing-D'Angelo, B. Filipovic, W.R. D'Angelo, D.L. Oliver, and S. Kuwada. 2004. GABA(A) synapses shape neuronal responses to sound intensity in the inferior colliculus. *J. Neurosci.* 24:5031–5043. doi:10.1523/JNEUROSCI.0357-04.2004
- Sohya, K., K. Kameyama, Y. Yanagawa, K. Obata, and T. Tsumoto. 2007. 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.* 27:2145–2149. doi:10.1523/JNEUROSCI.4641-06.2007
- Suga, N. 1965. Functional properties of auditory neurones in the cortex of echo-locating bats. *J. Physiol.* 181:671–700.
- Suga, N., and X. Ma. 2003. Multiparametric corticofugal modulation and plasticity in the auditory system. *Nat. Rev. Neurosci.* 4:783–794. doi:10.1038/nrn1222
- Suga, N., and T. Manabe. 1982. Neural basis of amplitude-spectrum representation in auditory cortex of the mustached bat. *J. Neurophysiol.* 47:225–255.
- Sun, Y.J., G.K. Wu, B.H. Liu, P. Li, M. Zhou, Z. Xiao, H.W. Tao, and L.I. Zhang. 2010. Fine-tuning of pre-balanced excitation and inhibition during auditory cortical development. *Nature.* 465:927–931. doi:10.1038/nature09079
- Sutter, M.L., and W.C. Loftus. 2003. Excitatory and inhibitory intensity tuning in auditory cortex: evidence for multiple inhibitory mechanisms. *J. Neurophysiol.* 90:2629–2647. doi:10.1152/jn.00722.2002
- Swadlow, H.A. 2003. Fast-spike interneurons and feedforward inhibition in awake sensory neocortex. *Cereb. Cortex.* 13:25–32. doi:10.1093/cercor/13.1.25
- Takayanagi, M., and H. Ojima. 2006. Microtopography of the dual corticothalamic projections originating from domains along the frequency axis of the cat primary auditory cortex. *Neuroscience.* 142:769–780. doi:10.1016/j.neuroscience.2006.06.048
- Tan, A.Y., and M. Wehr. 2009. Balanced tone-evoked synaptic excitation and inhibition in mouse auditory cortex. *Neuroscience.* 163:1302–1315.
- Tan, A.Y., L.I. Zhang, M.M. Merzenich, and C.E. Schreiner. 2004. Tone-evoked excitatory and inhibitory synaptic conductances of primary auditory cortex neurons. *J. Neurophysiol.* 92:630–643. doi:10.1152/jn.01020.2003
- Tan, A.Y., C.A. Atencio, D.B. Polley, M.M. Merzenich, and C.E. Schreiner. 2007. Unbalanced synaptic inhibition can create intensity-tuned auditory cortex neurons. *Neuroscience.* 146:449–462. doi:10.1016/j.neuroscience.2007.01.019
- Tsumoto, T., and K. Suda. 1980. Three groups of cortico-geniculate neurons and their distribution in binocular and monocular segments of cat striate cortex. *J. Comp. Neurol.* 193:223–236. doi:10.1002/cne.901930115
- Villa, A.E., E.M. Rouiller, G.M. Simm, P. Zurita, Y. de Ribaupierre, and F. de Ribaupierre. 1991. Corticofugal modulation of the information processing in the auditory thalamus of the cat. *Exp. Brain Res.* 86:506–517. doi:10.1007/BF00230524
- Wallace, M.N., and A.R. Palmer. 2008. Laminar differences in the response properties of cells in the primary auditory cortex. *Exp. Brain Res.* 184:179–191. doi:10.1007/s00221-007-1092-z
- Wang, J., D. Caspary, and R.J. Salvi. 2000. GABA-A antagonist causes dramatic expansion of tuning in primary auditory cortex. *Neuroreport.* 11:1137–1140. doi:10.1097/00001756-200004070-00045
- Wang, J., S.L. McFadden, D. Caspary, and R. Salvi. 2002. Gamma-aminobutyric acid circuits shape response properties of auditory cortex neurons. *Brain Res.* 944:219–231. doi:10.1016/S0006-8993(02)02926-8
- Wehr, M., and A.M. Zador. 2003. Balanced inhibition underlies tuning and sharpens spike timing in auditory cortex. *Nature.* 426:442–446. doi:10.1038/nature02116
- Wehr, M., and A.M. Zador. 2005. Synaptic mechanisms of forward suppression in rat auditory cortex. *Neuron.* 47:437–445. doi:10.1016/j.neuron.2005.06.009
- Winer, J.A. 2005. Decoding the auditory corticofugal systems. *Hear. Res.* 207:1–9. doi:10.1016/j.heares.2005.06.007
- Winer, J.A., J.J. Diehl, and D.T. Larue. 2001. Projections of auditory cortex to the medial geniculate body of the cat. *J. Comp. Neurol.* 430:27–55. doi:10.1002/1096-9861(20010129)430:1<27::AID-CNE1013>3.0.CO;2-8
- Winer, J.A., L.M. Miller, C.C. Lee, and C.E. Schreiner. 2005. Auditory thalamocortical transformation: structure and function. *Trends Neurosci.* 28:255–263. doi:10.1016/j.tins.2005.03.009
- Wu, G.K., P. Li, H.W. Tao, and L.I. Zhang. 2006. Nonmonotonic synaptic excitation and imbalanced inhibition underlying cortical intensity tuning. *Neuron.* 52:705–715. doi:10.1016/j.neuron.2006.10.009
- Wu, G.K., R. Arbuckle, B.H. Liu, H.W. Tao, and L.I. Zhang. 2008. Lateral sharpening of cortical frequency tuning by approximately balanced inhibition. *Neuron.* 58:132–143. doi:10.1016/j.neuron.2008.01.035
- Yan, J., and G. Ehret. 2002. Corticofugal modulation of midbrain sound processing in the house mouse. *Eur. J. Neurosci.* 16:119–128. doi:10.1046/j.1460-9568.2002.02046.x
- Ye, C.Q., M.M. Poo, Y. Dan, and X.H. Zhang. 2010. Synaptic mechanisms of direction selectivity in primary auditory cortex. *J. Neurosci.* 30:1861–1868. doi:10.1523/JNEUROSCI.3088-09.2010

- Zariwala, H.A., L. Madisen, K.F. Ahrens, A. Bernard, E.S. Lein, A.R. Jones, and H. Zeng. 2011. Visual tuning properties of genetically identified layer 2/3 neuronal types in the primary visual cortex of cre-transgenic mice. *Front Syst Neurosci.* 4:162. doi:10.3389/fnsys.2010.00162
- Zhang, F., V. Gradinaru, A.R. Adamantidis, R. Durand, R.D. Airan, L. de Lecea, and K. Deisseroth. 2010. Optogenetic interrogation of neural circuits: technology for probing mammalian brain structures. *Nat. Protoc.* 5:439–456. doi:10.1038/nprot.2009.226
- Zhang, L.I., A.Y. Tan, C.E. Schreiner, and M.M. Merzenich. 2003. Topography and synaptic shaping of direction selectivity in primary auditory cortex. *Nature.* 424:201–205. doi:10.1038/nature01796
- Zhang, Y., and N. Suga. 1997. Corticofugal amplification of sub-cortical responses to single tone stimuli in the mustached bat. *J. Neurophysiol.* 78:3489–3492.
- Zhang, Y., and N. Suga. 2000. Modulation of responses and frequency tuning of thalamic and collicular neurons by cortical activation in mustached bats. *J. Neurophysiol.* 84:325–333.
- Zhang, Y., and J. Yan. 2008. Corticothalamic feedback for sound-specific plasticity of auditory thalamic neurons elicited by tones paired with basal forebrain stimulation. *Cereb. Cortex.* 18:1521–1528. doi:10.1093/cercor/bhm188
- Zhou, Y., B.H. Liu, G.K. Wu, Y.J. Kim, Z. Xiao, H.W. Tao, and L.I. Zhang. 2010. Preceding inhibition silences layer 6 neurons in auditory cortex. *Neuron.* 65:706–717. doi:10.1016/j.neuron.2010.02.021