Characterization of thalamocortical responses of regular-spiking and fast-spiking neurons of the mouse auditory cortex in vitro and in silico

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Schiff ML, Reyes AD. Characterization of thalamocortical responses of regular-spiking and fast-spiking neurons of the mouse auditory cortex in vitro and in silico. J Neurophysiol 107: 1476–1488, 2012. First published November 16, 2011; doi:10.1152/jn.00208.2011.—We use a combination of in vitro whole cell recordings and computer simulations to characterize the cellular and synaptic properties that contribute to processing of auditory stimuli. Using a mouse thalamocortical slice preparation, we record the intrinsic membrane properties and synaptic properties of layer 3/4 regular-spiking (RS) pyramidal neurons and fast-spiking (FS) interneurons in primary auditory cortex (AI). We find that postsynaptic potentials (PSPs) evoked in FS cells are significantly larger and depress more than those evoked in RS cells after thalamic stimulation. We use these data to construct a simple computational model of the auditory thalamocortical circuit and find that the differences between FS and RS cells observed in vitro generate model behavior similar to that observed in vivo. We examine how feedforward inhibition and synaptic depression affect cortical responses to time-varying inputs that mimic sinusoidal amplitude-modulated tones. In the model, the balance of cortical inhibition and thalamic excitation evolves in a manner that depends on modulation frequency (MF) of the stimulus and determines cortical response tuning.

primary auditory cortex; synaptic depression; modulation transfer function

Although the frequency (MF) of the stimulus and determines cortical response tuning. This interplay between inhibition and excitation determines tuning of responses to stimuli at varying MFs. Furthermore, computational models of the auditory TC circuit have not investigated how these dynamic cellular properties shape cortical responses to time-varying stimuli such as drifting sine gratings in visual cortex, repetitive whisker stimulation in barrel cortex, and sinusoidally modulated acoustic stimuli in auditory cortex.

In the primary auditory cortex (AI), in vivo intracortical recordings have shown that both depression and FFI are prominent features of the synaptic responses to auditory stimuli (Wehr and Zador 2003, 2005; Zhang et al. 2003). However, the underlying synaptic and intrinsic membrane properties of excitatory and inhibitory thalamorecipient cells remain incompletely characterized. Furthermore, computational models of the auditory TC circuit have not investigated how these dynamic cellular properties shape cortical responses to time-varying auditory stimuli such as sinusoidal amplitude-modulated (sAM) tones.

Here we characterize the intrinsic properties of layer 3/4 regular-spiking (RS) pyramidal neurons and FS interneurons in AI and their synaptic inputs from thalamus. We performed simultaneous whole cell recordings from RS and FS cells in a mouse slice preparation that contains AI, the medial geniculate nucleus (MGv), and interconnecting fibers (Cruikshank et al. 2002). We use these data to construct a simple model of the auditory TC circuit and subsequently examine the model’s responses to time-varying inputs that mimic sAM tones. In the model, the dynamics governing FFI and STD cause the balance of cortical inhibition and thalamic excitation to evolve in a manner that depends on modulation frequency (MF) of the stimulus. This interplay between inhibition and excitation determines tuning of responses to stimuli at varying MFs. Furthermore, we show that STD can act to disinhibit cortical...
responses acting as an activity-dependent gate on powerful FFI. We find that the differences in intrinsic membrane properties and TC inputs between FS and RS cells observed in vitro are crucial for generating model behavior similar to that observed in vivo.

**METHODS**

**Auditory thalamocortical slice preparation.** All animal handling and surgical procedures were reviewed and approved by the New York University Animal Welfare Committee. Auditory TC brain slices were prepared as in Cruikshank et al. (2002). Briefly, Swiss-Webster mice at P14–P20 were decapitated under halothane anesthesia, and the brain was rapidly excised and immersed in ice-cold, oxygenated artificial cerebral spinal fluid (ACSF, in mM: 125 NaCl, 25 KCl, 25 NaHCO3, 1.25 NaH2PO4, 2 CaCl2, and 1 MgCl2). Five hundred-micrometer-thick brain slices were cut at an ∼15° angle to the horizontal with a vibratome (Campden Instruments). Slices were incubated at 37°C for ∼30 min and then maintained in oxygenated ACSF at room temperature for >30 min until being transferred to the recording chamber. The primary slice was identified by anatomical landmarks and confirmed with local field potential recordings (Cruikshank et al. 2002).

**Whole cell patch-clamp recordings.** Whole cell recordings were obtained at ∼34°C (32–37°C) in a submersion recording chamber continuously perfused with oxygenated ACSF. Slices were visualized on an upright microscope (Olympus BX50WI) with infrared differential interference contrast (IR-DIC) microscopy.

Whole cell patch electrodes (4–15 MΩ) were pulled from borosilicate glass capillaries (World Precision Instruments) and filled with (in mM) 130 potassium gluconate, 5 KCl, 2 MgCl2, 4 MgATP, 0.3 GTP, 10 phosphocreatine, and 10 HEPES (pH 7.3 with KOH). In some experiments, 0.5% biocytin (Sigma) was added to label cells for histological identification. Current-clamp recordings were performed with Cornerstone amplifiers (Dagan), filtered at 3–10 kHz, and digitized at 10 kHz. A Power Macintosh G4 (Apple) was used in conjunction with an ITC-18 DA/A and A/D board and IGOR software (Wavemetrics) for stimulus delivery, data acquisition, and data storage for off-line analysis.

Simultaneous whole cell recordings were performed in one FS cell and one to three RS cells separated by less than ∼200 μm and located in lower layer 3 and in layer 4. Cells that lacked prominent apical dendrites and had large, non-pyramidal-shaped somata under IR-DIC were targeted for recordings as presumptive FS cells. Only cells with stable initial resting membrane potentials (< −50 mV), low access resistance (<50 MΩ), and nonsynchronous firing were used. Voltages were not corrected for the junction potential.

Intrinsic membrane and firing properties of cells were characterized by injecting 1-s current steps at varying amplitudes. Action potential (AP) voltage threshold was defined as the membrane potential at the time of the peak of the second derivative of the voltage for a given AP. Current threshold is the smallest current step that evoked an AP. AP amplitude is the difference between the peak AP voltage and the voltage threshold, and AP half-width is the time between half-amplitude voltage crossings. Time to first AP, voltage threshold, and AP half-width are given for the first AP generated by current threshold steps. Adaptation ratio was defined as the ratio of the first interspike interval (ISI) to the average of the last three ISIs for a current injection of 0.5 nA (or the largest current injection delivered < 0.5 nA). The portion of the firing rate vs. current curve between just subthreshold current and the maximum observed firing rate prior to saturation was fit with a line to obtain its slope. A few cells were encountered that exhibited electrophysiological properties consistent with those of non-FS interneurons (low-threshold spiking or burst-spiking nonpyramidal cells); these cells were found infrequently and were excluded from the comparison of RS and FS cells.

**Thalamic stimulation protocols.** Extracellular electrical stimuli (monophasic, 0.1–0.2 ms) of varying intensities were delivered to MGv via a bipolar stimulating electrode (FHC) and a constant-current stimulus isolation unit (A 360, Axon Instruments). MGv was stimulated with five pulses at 10, 20, and 40 Hz with a recovery pulse 500 ms after the last pulse in each train, generally repeated 10–15 times for each frequency and with a delay of 5 s between each train. Extracellular stimulation intensity was initially at or below the intensity needed to evoke a postsynaptic potential (PSP) in a FS cell and then increased in varying increments (2.5–100 μA) up to 250 μA. Throughout the text, the term “threshold stimulus intensity” or “threshold stimulus” is used to denote the lowest extracellular stimulus intensity delivered to thalami that reliably evoked a PSP (<50% failures) that had a fixed latency (<1 ms SD) and whose amplitude, latency, and general shape varied only mildly with small increases in stimulus intensity. The PSP elicited in a given cell at the threshold stimulus intensity is referred to as the threshold response or the threshold PSP. Near-threshold stimulus intensities were sampled more finely (at 2.5–10 μA) than higher-intensity stimuli. We do not use the term “minimal stimulation” or “minimal stimulus intensity” because the term as defined in similar previous studies (for example, Cruikshank et al. 2007; Gabernet et al. 2005) has a strict definition of ∼50% failures with finer sampling (≤1 μA) of near-minimal stimulus intensities. The threshold responses in this study are likely similar to those that would be produced with minimal or near-minimal stimulation, but we avoid using the term “minimal” to avoid any potential confusion.

**Postsynaptic potential analysis.** PSPs were analyzed with a semi-automated procedure that characterized several PSP properties including successes/fails, amplitude, and latency. Failures were defined as a failure of the membrane potential to rise above a hard threshold (usually 200 μV) from a baseline reference point located between the stimulus artifact and the PSP onset within a given period of time from stimulus onset (−10 ms). PSP amplitude was taken as the difference between the baseline voltage and the peak membrane potential within a given time window from stimulus onset (usually 25 ms). PSP latency was defined as the intersection point of a line fit through the baseline voltage and a third-order polynomial fit to the PSP rising phase.

Only cells and responses that had identifiable, individual PSPs for each pulse in a train were selected for the analysis of STD. The lowest stimulus intensity that generated PSP responses with the above criteria was used for each cell. A simple parametric model for fitting STD was used following Abbott et al. (1997) and Tsodyks and Markram (1997):

$$R_{n+1} = 1 - \left[\left(1 - R_n \times Df \right) \times \left(1 - \frac{\Delta}{t_{th}}\right)\right]$$

where $R_n$ and $R_{n+1}$ are PSP amplitudes of the $n$th and $(n + 1)$th stimulus pulse normalized by the PSP amplitude of the first pulse in a train, $Df$ is a multiplicative depressing factor, $t_{th}$ is the time constant of recovery from depression, and $\Delta$ is the interval between $n$th and $(n + 1)$th pulses. In this model, when a presynaptic afferent fires, the synaptic efficacy $R$ immediately decreases by the factor $Df$ and then recovers to 1 as exponential with time constant of $t_{th}$.

**Statistical tests.** Results are reported as means ± SD to emphasize population variability. Paired-sample Student’s $t$-tests or Wilcoxon signed-rank tests were used for comparison of FS-RS cell pairs. Two-sample $t$-tests and Kolmogorov-Smirnov tests were used to compare the FS and RS cell populations. Statistical tests were performed with functions from the statistics toolbox in MATLAB (The MathWorks).

**Firing rate neuronal model.** We constructed a simplified network model consisting of one thalamic and one cortical layer (see Fig. 4). Simulated stimuli were delivered to the thalamic layer composed of 50 cells evenly distributed along a one-dimensional tonotopic axis (de la Rocha et al. 2008). Input to the thalamic layer had a Gaussian
profile, with the center cell receiving the largest input and inputs to the other thalamic cells smoothly decreasing farther from the center:

\[ g_{\text{TH}}(\Delta f) = e^{-\left(\frac{\Delta f}{\sigma_{\text{TH}}}\right)^2} \quad (2) \]

where \( g_{\text{TH}}(\Delta f) \) is a Gaussian weighting function on the stimulus, \( \Delta f \) indicates the difference between the stimulus tonotopic frequency and a thalamic cell characteristic frequency (cf), and \( \sigma_{\text{TH}} \) determines the spread of thalamic activity along the tonotopic axis. Default parameters for the thalamic layer were 50 cells spread over 1 octave and \( \sigma_{\text{TH}} = 0.15 \) octaves. The thalamic cells had only a transfer function (Eq. 4) and no temporal dynamics; therefore the output of this layer \( r_{\text{TH}}(f, t) \) represented an instantaneous transformed response to a given stimulus. The cortical layer consisted of only two populations of Default parameters for cortical populations were \( G_{\text{E}} = 67.15 \pm 6.51 \) Hz/nA, \( G_{\text{I}} = 200 \) Hz/nA, \( r_{\text{THmax}} = 75 \) Hz, and \( r_{\text{max}} = 200 \) Hz.

Total input current \( h_i \) was obtained as a linear sum of the individual input currents \( h_{iX}(t) \):

\[ h_i(t) = \sum_{X \in \{E, I\}} h_{iX}(t) \]

Table 1. Comparison intrinsic membrane properties for FS and RS cells

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FS (n = 16)</th>
<th>RS (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Input resistance, ( M_{\Omega}^* )</td>
<td>163.92 ± 48.10</td>
<td>285.10 ± 80.61</td>
</tr>
<tr>
<td>Membrane time constant, ms*</td>
<td>11.83 ± 4.94</td>
<td>29.38 ± 10.32</td>
</tr>
<tr>
<td>( V_{\text{rest}} ), mV</td>
<td>-67.68 ± 6.51</td>
<td>-67.15 ± 7.75</td>
</tr>
<tr>
<td>AP threshold, mV*</td>
<td>-30.57 ± 6.24</td>
<td>-37.27 ± 7.54</td>
</tr>
<tr>
<td>Threshold f, nA*</td>
<td>0.16 ± 0.08</td>
<td>0.05 ± 0.03</td>
</tr>
<tr>
<td>Number of APs at threshold*</td>
<td>10.25 ± 10.72</td>
<td>3.65 ± 2.50</td>
</tr>
<tr>
<td>1st AP time, ms</td>
<td>266.13 ± 304.10</td>
<td>223.09 ± 237.20</td>
</tr>
<tr>
<td>AP half-width, ms*</td>
<td>0.46 ± 0.13</td>
<td>0.89 ± 0.20</td>
</tr>
<tr>
<td>Adaptation ratio*</td>
<td>0.78 ± 0.17</td>
<td>0.31 ± 0.09</td>
</tr>
<tr>
<td>Max firing rate, Hz*</td>
<td>199.00 ± 64.31</td>
<td>75.71 ± 15.53</td>
</tr>
<tr>
<td>( V_{\text{FR}} ) vs. I slope, Hz/nA*</td>
<td>273.28 ± 81.56</td>
<td>109.90 ± 24.69</td>
</tr>
</tbody>
</table>

Values are means ± SD. FS, fast spiking; RS, regular spiking; \( V_{\text{rest}} \), resting membrane potential; AP, action potential; I, current; FR, firing rate.

* \( P < 0.01 \) by Student’s t-test.
Let $h_a(t) = \sum h_{a\beta}(t) = j_{a\beta} \times \sum g_a(f - \Delta f) \times r_\beta(f, t) \tag{5}$

where $j_{a\beta}$ is the synaptic weight of the input onto cell type $\alpha$ from cell type $\beta$ in units of picoamperes per hertz, e.g., $j_{ITH}$ is the synaptic weight of the thalamic cell input onto the I population. $r_\beta(f, t)$ represents the firing rate of all cells of a given type across the tonotopic axis over the stimulus. Because there is only one cortical population of each type, $r_\beta(f, t)$ is simply $r_\beta(t)$, so that $h_{a\alpha} = j_{a\alpha} \times r_\alpha(t)$. Thus $j_{a\alpha}$ converts the rate of the presynaptic cortical population, $r_\alpha(t)$, into current. For $j_{ITH}$, the total current from thalamus, current is summed over all thalamic cell inputs, $r_{TH}(f, t)$, with weights on each thalamic cell determined by $g_\alpha(\Delta f)$ as in Eq. 2.

Importantly, the TH input onto the I population was two times stronger than the input onto the E population, i.e., $j_{ITH} = 2 \times j_{ETH}$, matching the approximately twofold greater TC PSPs seen in FS versus RS cells (Fig. 2, Table 2). Default parameters were $j_{ETH} = 1$ pA/Hz, $j_{ITH} = 2$ pA/Hz, and $j_{EI} = -4$ pA/Hz.

Stimuli. Stimuli consisted of a single spectral frequency aligned to the characteristic frequency of the middle cell of the thalamic layer. The amplitude (dB) of this stimulus was sinusoidally modulated at varying frequencies (MF). The gain (G) of the thalamic cells transfer function was in hertz per decibel; decibel and nanoampere are interconvertible, with 1 nA = 100 dB and transformed as described above. These stimuli therefore represent amplitude-modulated (AM) stimuli with 100% modulation at the MF of a single carrier frequency. Fourier transforms were performed on cortical population responses during stimulus presentation. Simulated stimuli were of 1,000-ms duration for the two-population network or 500 ms for the full network model unless otherwise indicated.

STD. Thalamic STD was modeled with a mean-field version of the model presented in Eq. 1 (Carandini et al. 2002; Chance et al. 1998; Tsodyks et al. 1998):
Table 2. Comparison of FS and RS PSP properties

<table>
<thead>
<tr>
<th></th>
<th>FS</th>
<th>RS</th>
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<tbody>
<tr>
<td>Threshold PSP amplitude, mV</td>
<td>2.57 ± 2.42</td>
<td>1.42 ± 1.44</td>
</tr>
<tr>
<td>Maximum PSP amplitude, mV*</td>
<td>6.33 ± 4.34</td>
<td>3.65 ± 3.65</td>
</tr>
<tr>
<td>Threshold stimulus intensity, μA</td>
<td>56.25 ± 66.63</td>
<td>61.25 ± 69.46</td>
</tr>
<tr>
<td>FS threshold amp/RS threshold amp</td>
<td>3.21 ± 3.96</td>
<td></td>
</tr>
<tr>
<td>FS maximum amp/RS maximum amp</td>
<td>3.51 ± 3.30</td>
<td></td>
</tr>
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</table>

Values are means ± SD. PSP, postsynaptic potential. *P < 0.05 by paired-sample Wilcoxon signed-rank test. Top 3 data rows describe data presented in Fig. 2, C-E.

\[
dR_s(\Delta f, t) = \frac{1 - R_s(\Delta f, t)}{r_{TH}(\Delta f, t)} - \left[ \left( 1 - D_f \right) \times R_s(\Delta f, t) \times r_{TH}(\Delta f, t) \right]
\]

with \( r_{TH}(\Delta f, t) \) representing the rate of a presynaptic thalamic fiber with characteristic frequency \( \Delta f \) and \( R_s(\Delta f, t) \) acting as a weight on that cell such that:

\[
h_{TH}(t) = j_{TH} \times \sum_i \left[ R_s(f, t) \times g_s(f - \Delta f) \times r_{TH}(f, t) \right]
\]

Initially \( R_s(f, 0) = 1 \); therefore if \( D_f = 1 \) (i.e., no depression) then this variable is constant. Default parameters for depression were \( \tau_{rec} = 1 \text{ s}, D_f = 0.8, \) and \( D_f = 0.7 \).

Simulations. Equations 2 and 5 were solved numerically in MATLAB (The MathWorks) with the forward Euler method with a fixed time step of 0.1 ms.

RESULTS

Comparison of intrinsic membrane properties of FS and RS cells. Simultaneous whole cell recordings were made from RS pyramidal cells and FS cells in the lower half of layer 3 and in layer 4. Putative FS and RS cells were identified on the basis of morphology under IR-DIC, by their spiking responses to hoc labeling with biocytin (Connors and Gutnick 1990; McCormick et al. 1985). The defining electrophysiological features of FS cells are high adaptation ratio, narrow AP half-width, high maximum evoked firing rate, short membrane time constant, and deep afterhyperpolarizations with rapid near-linear repolarization (see Fig. 1B, Table 1; Oswald and Reyes 2011). The two populations were generally well separated by AP half-width, adaptation ratio, and maximum firing rate, with some overlap at the extremes for each group (Fig. 1, C and D). Despite having resting membrane potentials similar to RS cells, FS cells needed approximately threefold higher currents to evoke APs because of their low input resistance (Table 1, Fig. 1E). The higher current thresholds and maximum firing rates of FS cells produced a much steeper slope to their firing rate vs. current curve (Fig. 1E, Table 1).

FS cells receive larger-amplitude TC PSPs than RS cells. FS and RS cells are organized to produce FFI. Both cell types receive monosynaptic connections from auditory thalamus, and FS cells innervate RS cells (Fig. 2A; Rose and Metherate 2005). To compare directly the PSPs evoked by thalamic stimulation in RS and FS cell populations and control for slicing artifacts across preparations, we obtained simultaneous whole cell recordings from an FS cell and one to three RS cells located within 200 μm from each other and electrically stimulated the ventral division of the MGv (Fig. 1A). Stimulation intensity was increased in small increments (2.5–5 μA) until a PSP could be reliably evoked in a given cell; this lowest stimulus intensity for evoking a response is referred to as the threshold stimulus intensity (see METHODS). Extracellular stimulus intensity was increased gradually to examine compound PSPs evoked when additional thalamic afferents are recruited. FS cells generally had larger-amplitude PSPs than simultaneously recorded RS cells (Fig. 2), although the threshold stimulus intensity for each cell type did not differ significantly on average (Fig. 2C, Table 2).

Several factors may have contributed to the larger PSPs evoked in FS compared with RS cells (Fig. 2). One possibility is that the intensity of stimulation required for activating afferents to FS cells is lower than that for activating RS cells. This is unlikely because 1) threshold stimulus intensities did not differ between the two cell types (Fig. 2C); 2) PSPs evoked with threshold stimulation were larger in FS than RS cells (Fig. 2B); and 3) PSPs evoked in FS cells were on average significantly larger than those evoked in RS cells at all stimulus intensities (Fig. 2E) and remained greater even at saturating intensities where maximal PSP amplitudes were reached (Fig. 2D). Another possibility is that the FS cells receive more numerous thalamic afferents than RS cells. If so, increasing stimulus intensities should recruit progressively more fibers onto FS cells (Cruikshank et al. 2007; Gabernet et al. 2005). However, a plot of the PSP amplitude versus stimulus shows that the slope of the curve for FS cells was not substantially steeper than that for RS cells (Fig. 2E). Furthermore, the ratio of the average maximum evoked amplitudes for FS and RS cell pairs (6.33 mV/3.65 mV = 1.8) was similar to the ratio of threshold PSP amplitudes (2.57 mV/1.42 mV = 1.73). Taken together, these observations suggest that single-fiber thalamic PSPs evoked in FS cells are larger, but FS and RS cells receive approximately equal numbers of thalamic inputs.

Since thalamic afferents innervate wide regions of auditory cortex and contact both RS and FS cells with synapses with high probability of release (Cetas et al. 1999; Gil et al. 1999; Hersch and White 1981; Hull et al. 2009; Lee and Sherman 2008; McMullen and de Venecia 1993; Rose and Metherate 2005), simultaneously recorded FS and RS cell pairs were expected to receive divergent input from collaterals of shared thalamic fibers. This would be manifested as a perfect concurrence of PSP successes and failures in each cell at the same threshold stimulation intensity (Cruikshank et al. 2007; Gabernet et al. 2005; Inoue and Imoto 2006). We occasionally observed this phenomenon (Fig. 2F); however, most RS-FS cell pairs differed in their threshold stimulation intensities and did not show perfect correspondence of PSP successes and failures (Fig. 2G; only 4/28 cell pairs appeared to receive single-fiber innervation). These data indicate that either 1) these cells receive input from different TC afferents or 2) FS or RS cells are contacted by collaterals of the same TC fiber that differ in the number of synaptic contacts, probabilities of release, or degree of axon failure according to postsynaptic cell type.

Short-term dynamic properties of TC PSPs. Thalamically evoked PSPs generally exhibit STD (Castro-Alamancos and
Differences in synaptic depression of PSPs in RS and FS cells are likely to determine how each population is recruited by thalamic activity (Gabernet et al. 2005). Repetitive stimulation of MGv with pulse trains at varying frequencies revealed that PSPs evoked in FS cells generally depressed more than those evoked in RS cells (Fig. 3). This greater degree of depression is evident when PSP amplitudes are averaged across cells for each pulse in a train or normalized to the first pulse in the train for each cell and then averaged (Fig. 3, B and C, respectively). Synaptic depression was adequately described with a simple phenomenological model (Eq. 1). As expected, the depression factor (Df) that describes the degree of decrease in response amplitude for each presynaptic event was significantly smaller (indicating greater depression) for FS versus RS cell PSPs \( \text{Df} = 0.59 \pm 0.14 \) for FS cells \((n = 14)\), \( \text{Df} = 0.77 \pm 0.07 \) for RS cells \((n = 14)\), means \( \pm SD; P < 0.01\), 2-sample Kolmogorov-Smirnoff test. However, the time constant governing recovery from depression \( (\tau_{\text{REC}})\) was not significantly different between FS and RS cells \( \tau_{\text{REC}} = 2.17 \pm 3.32 \text{s} \) for FS cells \((n = 14)\), \( \tau_{\text{REC}} = 2.45 \pm 2.67 \text{s} \) for RS cells \((n = 14)\), means \( \pm SD; P > 0.05\).

Firing rate model of thalamocortical circuit. The combined effect of the observed intrinsic and synaptic properties of RS and FS cells on TC transformations is difficult to predict: Some of these properties appear to bias the circuit toward recruiting inhibition, while others bias toward excitation. For example, the larger-amplitude PSPs evoked in FS cells coupled with their steeper \( f/I \) slope would favor robust recruitment of inhibition, while the lower current thresholds and less depression of thalamic PSPs onto RS cells would favor net excitation. The dynamic balance of inhibition and excitation is particularly difficult to predict for time-varying input.

To gain insights into how network dynamics are affected by cellular and synaptic properties, we constructed a simple two-population cortical network consisting of one excitatory (E, analogous to RS cells) and one inhibitory (I, analogous to FS cells) population (de la Rocha et al. 2008; Pinto et al. 1996, 2003; Wilson and Cowan 1972; see METHODS and Fig. 4). The two populations were configured as a feedforward circuit in which both E and I populations received thalamic input and the I population inhibited the E population (Fig. 4). This highly simplified feedforward network produced results similar to those obtained with larger networks with recurrent cortical connections and a pseudo-tonotopic organization (data not shown; de la Rocha et al. 2008).

The activities of E and I populations were generated with simple rate models (de la Rocha et al. 2008; Pinto et al. 1996, 2003; Wilson and Cowan 1972). The model parameters were adjusted to preserve differences in RS and FS cells observed experimentally such as their \( f/I \) curves, strength of thalamic input, and degree of thalamic STD (Table 1; see METHODS for details). The auditory stimuli delivered to the thalamic layer were sinusoids of different MFs and are analogous to AM tones (see METHODS). The effects of FFI and thalamic STD on E
respectively; Preuss and Muller-Preuss 1990). The F0 component (Fig. 6A) without FFI (i.e., j_EI = 0) is flat across frequencies, while the F1 component (Fig. 6B) is low pass with the cutoff frequency determined by the E population time constant, τ_E (data not shown). Increasing the inhibitory synaptic strength not only decreased the magnitude of F0 and F1 as expected but also altered their tuning properties (Fig. 6): The F0 tuning became increasingly high pass, while the F1 tuning became band pass with increasing j_EI (Fig. 6). Thus both the F0 and F1 components showed greater suppression at lower MF.

The changes that occur in the E population responses with MF are due to the interplay between excitatory inputs from thalamus [h_ETH(t)] and inhibitory inputs [h_EI(t)] (Fig. 7). Figure 7A shows these currents for the first cycle of the stimulus, each normalized to its respective peak. With increasing MF, the excitatory thalamic input does not change appreciably (Fig. 7A), while inhibitory input increases proportionately with the I cell population firing rate [r_I(t), data not shown]. The I population time constant (τ_I, Eq. 3) produces low-pass filtering of the stimulus (Fig. 7A). At low MFs, the I population response tracks the thalamic input (e.g., MF = 4 Hz). Consequently, there is considerable temporal overlap between the excitatory [h_ETH(t)] and inhibitory [h_EI(t)] currents onto the E population, producing net cancellation (Fig. 7A). With increasing MF, the temporal overlap decreases as the slower inhibition can no longer track the excitatory input from thalamus (e.g., MF = 64 Hz; Fig. 7A). These effects can be seen by calculating the difference between the normalized thalamic and inhibitory currents at each MF (Fig. 7B). The maximum difference between these currents increases monotonically with MF, indicating that FFI, for the first cycle, acts as a high-pass filter (Fig. 7B). The suppression of E population responses to low-MF stimuli with increasing inhibition (Fig. 6) is primarily due to this high-pass filtering of thalamic inputs by FFI.

The temporal interactions of excitation and inhibition differ later in the stimulus (Fig. 7, C and D). With sufficient time, the firing rates of E and I cell populations reach a steady state at which responses to each subsequent stimulus cycle are identical. The absolute time and number of cycles it takes to reach steady state vary across MF. At low MFs, responses decay to zero during each stimulus cycle and there is no change in synaptic currents or responses over time (e.g., MF = 4 Hz; Fig. 7, A and C). At high MFs, slowly changing inhibitory currents do not decay to zero between stimulus cycles and summate such that the peak-to-trough amplitude decreases (compare normalized currents for MF = 64 and 256 Hz in Fig. 7, A and C). The inhibitory current eventually reaches a relatively constant level, and there is no longer a time window in which thalamic excitation is unopposed by inhibition (Fig. 7, A and C). Consequently, the peak normalized synaptic current for high MF at steady state (Fig. 7D) is smaller than that for the first cycle (Fig. 7B), resulting in the changes in maximum r_E(t) over the course of the stimulus. Unlike the first cycle, the peak normalized current at steady state increases to a maximum (MF = 32 Hz in Fig. 7D) and then decreases, indicating band-pass filtering (Fig. 7D).

\[ r_E(t) = \frac{1}{\tau_E} \int_0^t \left( j_E(t) - j_I(t) \right) dt \]

**Effect of thalamic synaptic depression.** PSPs evoked with thalamic stimulation depressed more in FS cells than in RS cells (Fig. 3). To determine how this differential depression

![Figure 4](http://jn.physiology.org/)

**Fig. 4.** Model design. A: transfer functions, Ï€_E and Ï€_I, for E (gray) and I (black) populations. Ï€_E and Ï€_I are threshold-linear functions. Note the narrow range of current intensities for which the E population firing rate lies above the I population. B: schematic depiction of 2-population feedforward network. Examples are shown next to specific processing stages for a given stimulus. A modeled stimulus (bottom) is delivered to the thalamic populations. This input is transformed by Ï€_ETH into thalamic firing rate r_E(Δt). Thalamic activity is summed and then converted by synaptic strength (j_ETH, j _ITH in pA/Hz) and scaled by synaptic depression into thalamic currents h_ETH(t) and h_IH(t) (in pA). The I population response, r_I(t), is converted by j_EI (arrow) into the inhibitory current onto the E population, h_EI (not shown). h_ETH(t) and h_IH(t) summed linearly to h_E(t) to generate the E population rate response r_E(t) (top left).

Population responses \([r_E(t)]\) to dynamic stimuli were evaluated in isolation as well as concurrently.

**Effect of inhibition on model E population responses.** To examine the effect of FFI on E cell rate, sinusoidal stimuli of varying MFs were delivered to the thalamic layer without synaptic depression while varying the strength of the I-to-E connection, \(j_{EI}\) (Fig. 5). With strong inhibition \((j_{EI} = −4\) pA/Hz), the response of the E cells \([r_E(t)]\) decreased in both amplitude and duration and was phase shifted relative to the stimulus (Fig. 5). These effects were greater for low than for high MFs (Fig. 5, B and C). In addition, the effect of FFI varied between initial and steady-state responses for higher MFs (see below).

To quantify the E population activity at varying MFs, the Fourier transform of \(r_E(t)\) was calculated. The amplitudes of the frequency-modulated component of \(r_E(t)\) corresponding to MF (F1) and the unmodulated component (F0) were calculated and compared across the different conditions (Fig. 6, A and B, respectively; Preuss and Muller-Preuss 1990). The F0 component is the mean firing rate during a stimulus for a given MF. The F1 component measures how faithfully \(r_E(t)\) tracks MF. As expected for a passive leaky integrator (Eq. 3), the F0 component (Fig. 6A) without FFI (i.e., j_EI = 0) is flat across frequencies, while the F1 component (Fig. 6B) is low pass with the cutoff frequency determined by the E population time constant, τ_E (data not shown). Increasing the inhibitory synaptic strength not only decreased the magnitude of F0 and F1 as expected but also altered their tuning properties (Fig. 6): The F0 tuning became increasingly high pass, while the F1 tuning became band pass with increasing j_EI (Fig. 6). Thus both the F0 and F1 components showed greater suppression at lower MF.

The changes that occur in the E population responses with MF are due to the interplay between excitatory inputs from thalamus [h_ETH(t)] and inhibitory inputs [h_EI(t)] (Fig. 7). Figure 7A shows these currents for the first cycle of the stimulus, each normalized to its respective peak. With increasing MF, the excitatory thalamic input does not change appreciably (Fig. 7A), while inhibitory input increases proportionately with the I cell population firing rate [r_I(t), data not shown]. The I population time constant (τ_I, Eq. 3) produces low-pass filtering of the stimulus (Fig. 7A). At low MFs, the I population response tracks the thalamic input (e.g., MF = 4 Hz). Consequently, there is considerable temporal overlap between the excitatory [h_ETH(t)] and inhibitory [h_EI(t)] currents onto the E population, producing net cancellation (Fig. 7A). With increasing MF, the temporal overlap decreases as the slower inhibition can no longer track the excitatory input from thalamus (e.g., MF = 64 Hz; Fig. 7A). These effects can be seen by calculating the difference between the normalized thalamic and inhibitory currents at each MF (Fig. 7B). The maximum difference between these currents increases monotonically with MF, indicating that FFI, for the first cycle, acts as a high-pass filter (Fig. 7B). The suppression of E population responses to low-MF stimuli with increasing inhibition (Fig. 6) is primarily due to this high-pass filtering of thalamic inputs by FFI.

The temporal interactions of excitation and inhibition differ later in the stimulus (Fig. 7, C and D). With sufficient time, the firing rates of E and I cell populations reach a steady state at which responses to each subsequent stimulus cycle are identical. The absolute time and number of cycles it takes to reach steady state vary across MF. At low MFs, responses decay to zero during each stimulus cycle and there is no change in synaptic currents or responses over time (e.g., MF = 4 Hz; Fig. 7, A and C). At high MFs, slowly changing inhibitory currents do not decay to zero between stimulus cycles and summate such that the peak-to-trough amplitude decreases (compare normalized currents for MF = 64 and 256 Hz in Fig. 7, A and C). The inhibitory current eventually reaches a relatively constant level, and there is no longer a time window in which thalamic excitation is unopposed by inhibition (Fig. 7, A and C). Consequently, the peak normalized synaptic current for high MF at steady state (Fig. 7D) is smaller than that for the first cycle (Fig. 7B), resulting in the changes in maximum r_E(t) over the course of the stimulus. Unlike the first cycle, the peak normalized current at steady state increases to a maximum (MF = 32 Hz in Fig. 7D) and then decreases, indicating band-pass filtering (Fig. 7D).

**Effect of thalamic synaptic depression.** PSPs evoked with thalamic stimulation depressed more in FS cells than in RS cells (Fig. 3). To determine how this differential depression

![Figure 5](http://jn.physiology.org/)

**Fig. 5.** Thalamic synaptic depression. The F0 component \(r_E(t)\) of thalamic activity is unopposed by inhibition (Fig. 7, A and C). The inhibitory current eventually reaches a relatively constant level, and there is no longer a time window in which thalamic excitation is unopposed by inhibition (Fig. 7, A and C). Consequently, the peak normalized synaptic current for high MF at steady state (Fig. 7D) is smaller than that for the first cycle (Fig. 7B), resulting in the changes in maximum r_E(t) over the course of the stimulus. Unlike the first cycle, the peak normalized current at steady state increases to a maximum (MF = 32 Hz in Fig. 7D) and then decreases, indicating band-pass filtering (Fig. 7D).
might affect the balance of inhibition and excitation during a time-varying stimulus, short-term synaptic depression was incorporated into the model and FFI was removed. In general, depression of thalamic inputs decreased the excitatory drive and suppressed $r_E(t)$ at all MFs (Fig. 8, A and C). At low MFs, STD does not substantially affect the first cycle of the stimuli because the time constant for depression (Eq. 5) is relatively long compared with a given stimulus period. As a result, depression accumulates gradually over the stimulus (Fig. 8 A). In these ways, synaptic depression acts similarly to inhibition but on a slower time scale.

When FFI is reincorporated into the model, the overall effect of depression is disinhibition of the E cell population (Fig. 8C). Compared with STD alone, the E population rate is preferentially suppressed at low MFs, though the decrease is less than with inhibition only (Fig. 8C; i.e., the solid black traces are intermediate between the dot-dashed and dashed traces at low MFs). Disinhibition occurs because the I cell population has thalamic inputs that depress more than those for the E cell population ($D_{I_E}/H_{11002}-D_{I_E}$, Eq. 5) as well as a higher threshold ($\theta_I$) for firing than the E cell population. Consequently, depression leads to a greater decrease in I cell population firing and the E cell population is disinhibited. If the E and I populations are identical, disinhibition is not observed (data not shown).

Diverse patterns of E cell activity emerge as a consequence of the temporal evolution of disinhibition and depend on MF and the time constants of inhibition and depression (Fig. 8B). Disinhibition changes the peak amplitude of E population activity at successive stimulus cycles (Fig. 8B): Depending on

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**Fig. 5.** Effect of inhibition on $r_E(t)$ for stimuli of varying modulation frequencies (MFs). A: example E population responses to stimuli of different MF in the absence (gray) and presence (black) of inhibition (INH). MFs for each row from bottom to top are 4 Hz, 16 Hz, and 64 Hz. Peak amplitude of stimulus was 50 dB, and $j_{EI} = -4$ pA/Hz for the case with inhibition. Scale bars are 10 Hz, 200 ms for MF = 4 Hz, 10 Hz, 100 ms for MF = 16 and 64 Hz. B: comparison of cycle of $r_E(t)$ at steady state for stimuli of varying MFs with (right) and without (left) inhibition. Each cycle of the $r_E(t)$ is plotted vs. phase angle for each MF. Steady-state responses are taken as the cycle beginning at 500 ms after stimulus onset. The value of $r_E(t)$ at the start of the cycle (phase angle = 0) has been subtracted for each MF. Responses are taken from the example in A. C, left: peak $r_E(t)$ amplitudes plotted vs. MF with and without inhibition. $r_E(t)$ amplitudes are measured from the steady-state cycle beginning 500 ms after stimulus onset. Amplitude is taken as the maximum minus minimum $r_E(t)$ for the cycle. Right: phase of the $r_E(t)$ peak of the steady-state cycle is plotted against MF with and without inhibition.

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**Fig. 6.** Effect of varying levels of inhibition on the E population tuning. A, top: mean $r_E(t)$ (F0) vs. MF for varying inhibitory synaptic strengths, $j_{EI}$. Bottom: F0 tuning curves normalized to peak response for each $j_{EI}$. Increasing inhibition makes the F0 vs. MF tuning more high pass. B, top: magnitude of the Fourier transform of the $r_E(t)$ at the stimulus frequency (F1) vs. MF. Bottom, F1 tuning curves normalized to the peak response for each $j_{EI}$. Increasing inhibition makes the F1 vs. frequency tuning increasingly band pass. Peak amplitude of stimulus was 50 dB in all cases.
MF, peak $r_E(t)$ could decrease monotonically (1 Hz) or non-monotonically (4 Hz) with stimulus cycle.

**DISCUSSION**

We used a combination of experiments and simulations to characterize the cellular and synaptic properties that contribute to processing of auditory stimuli. Using whole cell recordings, we demonstrate for the first time in auditory cortex significant differences in the synaptic properties of RS pyramidal cells and FS interneurons. We used these experimental data to constrain a simple computational model in order to examine how FFI and synaptic dynamics affect cortical responses. We found that both FFI and synaptic depression alter the tuning of RS cells to time-varying stimuli that mimic sAM tones.

Comparison of FS and RS cells. The PSPs evoked in FS cells were significantly larger and depressed more than those evoked in RS cells after stimulation of MGv. These observations differ somewhat from previous studies using similar auditory TC slice preparations (Rose and Metherate 2005; Verbny et al. 2006; but see Lee and Sherman 2008 for qualitatively similar results). One study did not find a significant difference in threshold PSP amplitudes or a consistent difference in STD recorded in FS and RS cells (Rose and Metherate 2005). Part of the discrepancy might be due to the fact that in that study (Rose and Metherate 2005) the sample was smaller ($n = 5$ FS cells), the RS and FS cells were often recorded in separate slice preparations, and the mice were younger (P14–P16) and of a different genetic strain. In combination, these factors may have obscured differences between the two already variable cell populations (Table 2). Another previous in vitro study observed smaller PSP amplitudes in thalamorecipient interneurons compared with pyramidal cells (Verbny et al. 2006). However, that study did not specifically target FS cells in layers 3 and 4 and therefore may have overlooked this interneuron subpopulation known to receive particularly strong input from thalamus in other systems (Beierlein et al. 2003; Cruikshank et al. 2007; Gabernet et al. 2005; Markram et al. 2004; Ren et al. 1992; Staiger et al. 1996). In our model, FFI is reliably recruited because FS cells receive large-amplitude TC PSPs. This study represents the first in vitro evidence for larger-amplitude TC PSPs in FS cells in auditory cortex. As such, these data may present a physiological mechanism for the strong FFI seen in vivo and are similar to what has been documented in somatosensory cortex (Cruikshank et al. 2007; Gabernet et al. 2005; Inoue and Imoto 2006; Wehr and Zador 2003; Zhang et al. 2003).

The differences in PSP properties of RS and FS cells are unlikely to reflect bias or variability in experimental conditions (e.g., slicing procedure, stimulus intensity, electrode placement, etc.). These possibilities were effectively eliminated since FS and RS cells were recorded simultaneously and were located within 200 μm of one another; therefore both cell types should have been affected equally by experimental variables. Because experiments were performed in current rather than voltage clamp, it is possible that there may have been an inhibitory component of the threshold PSPs observed in RS cells that contributed to their smaller am-
Simulations. To assess the functional implications of thalamic synaptic dynamics and the FS-RS cell interactions, we constructed a model that incorporated the experimental data. To simplify analysis, we used a firing rate model (Wilson and Cowan 1972) rather than a spiking neuronal model. Rate models have fewer variables, which facilitates the interpretation of changes in model parameters on network behavior. The output of rate models may be viewed as the pooled response of a population of spiking neurons (Pinto et al. 1996) and is not intended to reproduce exactly the fine time scales of the spiking behavior of neurons. Another simplification we employed was to implement thalamic activity in response to AM stimuli as a smooth, rectified sinusoid that mirrored the stimulus (Eq. 4); thalamic activity in vivo shows more complex temporal profiles as well as diverse response tuning (Bartlett and Wang 2007; Creutzfeldt et al. 1980; Miller et al. 2002; Preuss and Muller-Preuss 1990). Nonetheless, the model provides insight into the qualitative effects that the modeled synaptic and intrinsic properties may have on cortical responses.

The two-population model lacked recurrent cortical connections and associated synaptic dynamics largely because of the absence of sufficient data generated in these experiments to constrain these parameters. However, the effects that inhibition, thalamic synaptic depression, and the differences in E and I population parameters had on the model behavior are expected to extend to any system (including spiking models or real neurons) in which the general relationships among the elements remain similar (de la Rocha et al. 2008; Pinto et al. 1996). Indeed, simulations that used a spiking neuronal model with synaptic conductances or that included recurrent E-to-E, E-to-I, and I-to-I connections and the associated synaptic dynamics produced qualitatively similar results for a relatively large parameter space provided that overall network activity generated sufficiently strong FFI to modify E cell responses (data not shown). One potential mechanism of reducing FFI that was not included in the model is powerful mutual inhibition of E and I cells (data not shown). One potential mechanism of reducing FFI that was not included in the model is powerful mutual inhibition of E and I cells (data not shown). One potential mechanism of reducing FFI that was not included in the model is powerful mutual inhibition of E and I cells (data not shown). One potential mechanism of reducing FFI that was not included in the model is powerful mutual inhibition of E and I cells (data not shown). One potential mechanism of reducing FFI that was not included in the model is powerful mutual inhibition of E and I cells (data not shown).
via disinhibition broadened the modeled receptive field over time.

In previous experiments using a similar model, we explored the effects of FFI on cortical processing of static stimuli (de la Rocha et al. 2008). Here we show that an additional effect of FFI is to alter the response properties of the E population to time-varying stimuli. When time-varying stimuli of different MFs were delivered to the network with strong FFI, the E population response became high pass for F0 amplitude and band pass for F1 amplitude as a result of selective suppression of responses at low MFs (Fig. 6). This change in tuning resulted from cortical mechanisms alone, specifically delayed inhibition. The model therefore provides a simple cellular mechanism as the basis of receptive field differences between thalamus and cortex. Synaptic depression tempered the effects of FFI: Depression of thalamic input acts to disinhibit E population firing by reducing the synaptic currents that drive FFI (Fig. 8). The effect of disinhibition was qualitatively similar for a range of $\Delta t_{ij}$. The degree of disinhibition was correlated with the strength of $\Delta t_{ij}$ and the attendant suppression of E population responses by FFI (data not shown). Disinhibition can cause the E cell population activity to increase over the course of the stimulus (Fig. 8B), suggesting that the enhancement of cortical responses observed in vivo may be due to disinhibition rather than facilitation of thalamic inputs (Fig. 8, A and B; Bartlett and Wang 2005; Brosch and Schreiner 2000; Wehr and Zador 2005).

In the model, disinhibition produces a relatively modest absolute effect on response amplitude in the E population (Fig. 8). However, the firing rates of AI cells in vivo in the anesthetized animal are often quite low (DeWeese et al. 2003), and therefore small-magnitude changes in firing rate can produce relatively large effects on response tuning. As shown in Fig. 8, C and D, the modest absolute changes in E population responses caused by disinhibition produce a rather dramatic change in tuning of E responses from band pass to more low pass when the responses are normalized to their peak amplitude. One reason that we chose to normalize the tuning curves was precisely to highlight the relative changes in tuning under the different simulated conditions.

The synaptic depression measured in vitro strongly suppressed thalamic input and in our model resulted in disinhibition of cortical responses. However, synaptic depression observed in vivo may differ from that observed in vitro for a variety of reasons including effects of age, spontaneous activity, and presence of neuromodulators (Castro-Alamancos and Connors 1997). If the degree of depression is mild, depression will have a less profound effect on cell activity and disinhibition will be less prominent (data not shown).

Comparison to in vivo studies in auditory cortex. In general, the in vitro and modeling results are in accord with those obtained in vivo with acoustic stimuli. The large PSPs evoked in FS cells (Fig. 2, Table 2) may provide the substrate for powerful FFI in vivo (Wehr and Zador 2003; Zhang et al. 2003). Moreover, the time constant of recovery from depression of PSPs that we observe in vitro is similar to that documented in vivo (Asari and Zador 2009; Wehr and Zador 2005). In addition, a substantial fraction of cells recorded in vivo respond to the second click of a pair with greater suppression of inhibitory than excitatory conductances as predicted by our model (Fig. 8; Wehr and Zador 2005). Finally, several in vivo studies have shown that auditory cortical neurons respond to paired stimuli with long-lasting response enhancement that develops over time (Bartlett and Wang 2005; Brosch et al. 1999; Brosch and Schreiner 2000), similar to the effects of disinhibition predicted by the model (Fig. 8).

The stimuli used in our simulations are analogous to sAM tones and were chosen for several reasons. In most sensory systems, natural stimuli are often time varying rather than transient or constant. Moreover, in the auditory system, amplitude modulation envelopes are key components of biologically relevant natural sounds such as species-specific vocalizations. sAM tones are also expected to fully engage the dynamics imparted to the network by FFI and synaptic depression. Finally, the response properties of auditory cortical neurons to AM stimuli are well characterized.

Temporal coding of repetitive acoustic stimuli is often evaluated with the use of modulation transfer functions (MTFs), which assess the cell responses to repetitive stimuli. We calculated the frequency modulated (F1) and unmodulated (F0) components of E cell responses to compare to temporal and rate modulation transfer functions (tMTFs and rMTFs), respectively, obtained from in vivo recordings (Liang et al. 2002; Miller et al. 2002; Preuss and Muller-Preuss 1990). The model predicts that band-pass tMTFs and high-pass rMTFs, similar to what is observed for many cells in vivo (Liang et al. 2002; Miller et al. 2002), are a product of strong FFI (Fig. 6). Cells that have low-pass tMTF (Eggermont 2002; Liang et al. 2002; Miller et al. 2002) are predicted to result from low levels of FFI (Fig. 6); such limited inhibition could be due to weak inhibitory synaptic strength, low levels of I population activity, spontaneous firing in the thalamic population, or disinhibition produced by thalamic synaptic depression.

The model makes further testable predictions of the mechanisms that underlie the tuning of cortical responses. For cells whose inputs are dominated by FFI, the model predicts that neural responses will be more transient than tonic, be phase advanced for a periodic stimuli, show nonmonotonic rate-level functions (data not shown; see de la Rocha et al. 2008), exhibit band-pass tMTF and high-pass rMTF, respond more robustly to rapidly changing stimuli, and exhibit changes in tuning over repetitions of a stimulus. The model also provides a possible explanation for the increased responsiveness of auditory cortical cells observed in awake versus anesthetized animals. In the awake animal, there is likely to be sufficient spontaneous thalamic activity to produce chronic depression of TC and inhibitory synapses, thus reducing FFI and allowing for more tonic responses to auditory stimuli (Wang et al. 2005).

One of the best-documented TC transformations in the auditory system is the decrease in the high-frequency cutoff of temporal MTFs between thalamus and cortex (Creutzfeldt et al. 1980; Miller et al. 2002). To assess the contribution of cortical mechanisms to the MTF, we explored the effect of thalamic inputs with untuned tMTFs (similar results were found with tuned thalamic tMTF; data not shown). The modeling results provide evidence that FFI and synaptic depression play a major role in determining the high-frequency cutoff of cortical cells’ tMTFs. This finding is in line with in vivo studies demonstrating that cortical tMTF is independent of the tuning of their thalamic inputs (Creutzfeldt et al. 1980; Miller et al. 2002).

The significant heterogeneity in MTF tuning of neurons recorded in vivo (Liang et al. 2002; Wang et al. 2008) is
postulated to reflect differences in the tuning of thalamic afferents onto these cells. On the other hand, the simulations indicate that such heterogeneity may reflect differences in the levels of inhibition or synaptic depression that drive cortical responses. Both FFI and synaptic depression can be altered by neuromodulation and long-term synaptic plasticity (Gil et al. 1997; Kruglikov and Rudy 2008; Maffei et al. 2004), thereby providing a potential mechanism for adaptive tuning of cortical responses (Kilgard and Merzenich 1998).

Comparison to studies performed in somatosensory cortex. In general, the in vitro and modeling results reported here agree with similar studies in the somatosensory cortex (Beierlein et al. 2003; Cruikshank et al. 2007; Gabernet et al. 2005; Pinto et al. 1996, 2003). In vitro studies in somatosensory TC slices have demonstrated that FS cells receive larger-amplitude TC inputs that exhibit greater STD compared with RS cells (Beierlein et al. 2003; Cruikshank et al. 2007; Gabernet et al. 2005). In vivo and modeling studies of somatosensory cortex have also demonstrated that FFI can act as a high-pass filter on thalamic inputs (Fig. 7, A and B; Pinto et al. 1996, 2003).

One potentially important difference between the auditory and somatosensory systems is that the amplitudes of TC PSPs onto FS and RS cells reported here are smaller and more variable than those generally reported in somatosensory slices (Beierlein et al. 2003; Cruikshank et al. 2007; Gabernet et al. 2005). These differences may reflect variation in slice connectivity, slice health, or stimulation conditions between studies and/or slice preparations or more significantly reflect genuine divergence in TC processing across the two modalities. The heterogeneous and complex sprectrometemporal receptive fields of auditory cortical neurons (Miller et al. 2002) may reflect the diversity of thalamic input strength to both RS and FS cells. Nonetheless, the differences in the biophysical and synaptic properties of RS and FS cells appear to represent a cardinal feature of primary sensory cortices. Consequently, the modeling results describing the relationship of cellular properties to the tuning of response properties to dynamic stimuli are likely to generalize across modalities.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: M.L.S. and A.D.R. conception and design of research; M.L.S. performed experiments; M.L.S. analyzed data; M.L.S. and A.D.R. interpreted results of experiments; M.L.S. and A.D.R. prepared figures; M.L.S. drafted manuscript; M.L.S. and A.D.R. edited and revised manuscript; M.L.S. and A.D.R. approved final version of manuscript.

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