ON and OFF inhibition as mechanisms for forward masking in the inferior colliculus: a modeling study

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Gai Y. ON and OFF inhibition as mechanisms for forward masking in the inferior colliculus: a modeling study. J Neurophysiol 115: 2485–2500, 2016. First published February 24, 2016; doi:10.1152/jn.00892.2015.—Masking effects of a preceding stimulus on the detection or perception of a signal have been found in several sensory systems in mammals, including humans and rodents. In the auditory system, it has been hypothesized that a central “OFF-inhibitory” mechanism, which is generated by neurons that respond after a sound is terminated, may contribute to the observed psychophysics. The present study constructed a systems model for the inferior colliculus that includes major ascending monaural and binaural auditory pathways. The fundamental characteristics of several neuron types along the pathways were captured by Hodgkin-Huxley models with specific membrane and synaptic properties. OFF responses were reproduced with a model of the superior paraolivary nucleus containing a hyperpolarization-activated h current and a T-type calcium current. When the gap between the end of the masker and the onset of the signal was large, e.g., >5 ms, OFF inhibition generated strong suppressive effects on the signal response. For smaller gaps, an additional inhibitory source, which was modeled as ON inhibition from the contralateral dorsal nucleus of the lateral lemniscus, showed the potential of explaining the psychophysics. Meanwhile, the effect of a forward masker on the binaural sensitivity to a low-frequency signal was examined, which was consistent with previous psychophysical findings related to sound localization.

forward masking; inferior colliculus; SPON; MSO; ITD; DMPO

Forward masking is a robust psychophysical phenomenon that can be found in the auditory (e.g., Deatherage and Evans 1969), visual (e.g., Wilding 1982), and somatosensory (e.g., Kirman 1984) systems. The masking reflects the limit of a system in separating nonsimultaneous sensory events. In audition, a preceding masker can generate adverse effects on the detection or perception of a subsequent sound. The masking effect is especially prominent in hearing-impaired listeners (Reed et al. 2009). A better understanding of the underlying neural mechanisms may potentially lead to improvements of prosthetic devices.

The masking effect is normally measured as an increment in the detection threshold of a signal due to the addition of a preceding masker (e.g., Deatherage and Evans 1969; Kollmeier and Gilkey 1990; Smiarowski and Carhart 1975; Waltzman and Levitt 1978; Weber and Moore 1981). The elevation of threshold is smaller when a silent gap is introduced between the end of the masker and the onset of the signal. The masking effect systematically weakens as the interstimulus gap increases (Fig. 1A) and may last over 100 ms (Smiarowski and Carhart 1975; Weber and Moore 1981).

Physiological studies have demonstrated suppressive effects of a preceding sound on neural responses to the subsequent signal at multiple centers of the auditory pathway [auditory nerve (AN): Relkin and Turner 1988; Smith 1977; inferior colliculus (IC): Al’tman et al. 1997; Brosch and Schreiner 1997; Faure et al. 2003; Nelson et al. 2009; Singheiser et al. 2012; cortex: Zhou and Wang 2014; IC and inferior cortex: Bekhterev et al. 2002]. It is likely that substantial inhibition at central stages, such as the IC, contributes to the prominent masking effect over a wide dynamic range (Nelson et al. 2009).

The IC receives inhibitory input from various sources. In particular, inhibitory neurons that respond only after a sound is terminated, referred to here as “OFF neurons,” have the potential of generating suppression on a subsequent signal. OFF neurons have been recorded in the rodent superior paralavulary nucleus (SPON) (Behrend et al. 2002; Dehmel et al. 2002; Felix et al. 2011; Kopp-Scheinflug et al. 2011; Kulesza et al. 2003), a subnucleus of the superior olivary complex (SOC). The SPON sends dense GABAergic projections to the ipsilateral IC (Kulesza et al. 2007; Saldaña et al. 2009). In cats and rabbits, OFF responses have been reported in the dorsomedial periolivary nucleus (DMPO) (Guinan et al. 1972a, 1972b; Kuwada and Batra 1999). The input and output projections of the DMPO are similar but not entirely equivalent to projections of the rodent SPON (Elverland 1977), and the type of neurotransmitters of DMPO projections has not been explicitly identified.

OFF neurons in the SPON/DMPO display precisely timed OFF responses. Figure 1 shows three examples of previously published OFF neurons in the form of poststimulus time histograms (PSTHs) (Dehmel et al. 2002; Felix et al. 2011; Kuwada and Batra 1999). The duration of the OFF response can be short (Fig. 1B), intermediate (Fig. 1C), or long (Fig. 1D). This duration, in part, increases with stimulus level (Kuwada and Batra 1999). Such neurons may serve as one type of neural mechanism for the compromised detection of a signal following a masker. To account for the psychophysical finding that forward masking can last up to 100 ms, the goal of the present study was to develop a model of OFF neurons that had a long-duration OFF response such as those in Fig. 1, C and D.

Although cellular models have been developed to explain in vitro responses of the SPON (Kopp-Scheinflug et al. 2011), there are no systems-level models to simulate sound-elicited OFF response in the SPON or DMPO. The SPON receives excitatory input from octopus and multipolar cells in the ipsilateral ventral cochlear nucleus (VCN) and inhibitory input from the ipsilateral medial nucleus of the trapezoid body.
Inhibitory input from the dorsal nucleus of the lateral lemniscus and excitatory input from the medial superior olive (MSO) and lateral superior olive (LSO) have been studied by Cai et al. (1998) and Xia et al. (2010), which has implications for forward masking. Previous studies have shown that forward masking is affected by interaural time differences (ITDs) and affects the localization for low-frequency signals, but not for higher-frequency signals (Gai et al. 2013). We found that the forward masker mostly affected the localization for low-frequency signals, but not for high-frequency signals. Because the forward masker is interaural time difference (ITD) different from that of the signal's, less masking is observed when the ITD is different from that of the signal's. Inhibition triggered by inhibitory, rather than excitatory, postsynaptic potentials (PSPs) was demonstrated that the OFF response was triggered by inhibitory, rather than excitatory, postsynaptic potentials. The SPON model developed here combined the OFF- and ON-inhibitory pathways to explain forward masking. The simulations presented here show that this was true only when a gap longer than 5 ms existed between the masker and the signal; for shorter gaps, delayed ON inhibition may serve as a possible source to create the desired forward suppression.

**Methods**

**General structure.** The model was based on the conventional IC model with an additional inhibitory circuit containing the SPON (Fig. 2, red). The conventional IC model was developed by Cai et al. (1998) based on anatomical and physiological evidence showing that IC neurons receive excitatory input from the ipsilateral MSO and GABAergic inhibitory input from the contralateral DNLL (Fig. 2, black and green) (Adams and Mugnaini 1984; Henkel and Spangler 1983; Shneiderman et al. 1993). This model generates appropriate binaural responses to tones, binaural beats, and clicks. Intuitively, inhibitory inputs from the DNLL and ventral nucleus of the lateral lemniscus (VNLL) should not contribute much to forward masking, because they occur mostly during stimulus presentation. Therefore, we will first examine the role of inhibition from OFF neurons in the SPON (Fig. 2, red) that show long-lasting responses after sound is turned off. However, as will be shown later, certain conditions seem to call for additional types of inhibitory inputs. In that case, we added the input from the contralateral DNLL (Fig. 2, green), according to the Cai et al. (1998) model. Possible roles of other mechanisms will be reviewed in the DISCUSSION.

**AN model.** The auditory periphery was simulated by a phenomenological model (Zilany et al. 2009, 2014), which converts sound input to AN spiking activity. This model simulates the basilar-membrane compressive nonlinearity, transduction, and membrane properties of the inner hair cell, the IHC-AN synapse, and AN discharge times based on a nonhomogeneous Poisson process modified by refractoriness. The model can accurately predict a wide range of the neuron was 3.1 kHz. The tone duration was 100 ms. [Figures from Felix et al. 2011, Kuwada and Batra 1999, and Dehmel et al. 2002 with permission.]
of AN properties, such as responses to amplitude modulation, long-term adaptation, and adaptation to increments and decrements. In the present study, the ratio of AN fibers with high, medium, and low spontaneous rates was 3:1:1 to coarsely match the physiological distribution (Kiang et al. 1965; Liberman 1978). We included all spontaneous groups in the simulation because both bushy and chopper cells exhibit a wide range of spontaneous firing rates.

**Model of bushy cells in the cochlear nucleus.** Recordings in the low-frequency region (<700 Hz) of the VCN reveal that low-frequency bushy cells phase lock more strongly to CF tones than do AN properties, such as responses to amplitude modulation, long-term adaptation, and adaptation to increments and decrements. In the present study, the ratio of AN fibers with high, medium, and low spontaneous rates was 3:1:1 to coarsely match the physiological distribution (Kiang et al. 1965; Liberman 1978). We included all spontaneous groups in the simulation because both bushy and chopper cells exhibit a wide range of spontaneous firing rates.

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The MSO model neuron (CFB) (Fig. 4) has ITD tuning curve (expressed as which serves to enhance coincidence detection and decrease action-inactivated sodium current (Scott et al. 2010; Svirskis et al. 2004), feature of MSO neurons that is not captured by this model is the (Colburn et al. 2009; Gai et al. 2009; Zhou et al. 2005). However, a Eq. 1 model (tuning properties due to inhibition. The type II cochlear-nucleus IC model, although the two model neurons could have different ITD response to a 500-Hz, 25-ms tone at 60-dB SPL presented 1,000 times. The AN model showed phase locking to the tone frequency, whereas the chopper model showed a slow chopping pattern.

[Fig. 3. PSTHs of the AN model input (A) and the target chopper model (B) in response to a 500-Hz, 25-ms tone at 60-dB SPL presented 1,000 times. The horizontal bar in B represents the signal duration. The AN model CF was 500 Hz. The AN model showed phase locking to the tone frequency, whereas the chopper model showed a slow chopping pattern.]

The MSO model. The MSO model provided binaural sensitivity to the IC model, although the two model neurons could have different ITD tuning properties due to inhibition. The type II cochlear-nucleus model (Eq. 1) has been used as a point-neuron model for the MSO (Colburn et al. 2009; Gai et al. 2009; Zhou et al. 2005). However, a feature of MSO neurons that is not captured by this model is the inactivated sodium current (Scott et al. 2010; Svirskis et al. 2004), which serves to enhance coincidence detection and decrease action-potential sizes.

In Rothman and Manis (2003), the sodium inactivation function is expressed as

\[ h_s = \left[ 1 + \exp\left( \frac{V - (-65)}{6} \right) \right]^{-1} \]  

Here the half-activation point was shifted from −65 mV to −70 mV, so that the sodium channels of the MSO model cell were more inactivated at the resting membrane potential compared with the bushy cells. The other parameters were identical to those of the type II model listed for Eq. 1. Each model MSO neuron received 10 inputs from bushy cells in the ipsilateral VCN and 10 from the contralateral VCN (Gai et al. 2009; Zhou et al. 2005). The excitatory synaptic time constant was 0.1 ms (Table 2; Cai et al. 1998).

The majority of MSO neurons have non-zero best ITDs, called “best delays,” which favor sound coming from the contralateral hemifield (Yin and Chan 1990). Here we generated best delays according to the “cochlear disparities” theory (Joris et al. 2006; Shamma et al. 1989). Specifically, the MSO model neuron received ascending inputs with CFs that differed between the ipsilateral and contralateral sides. Because traveling waves along the cochlea create frequency-dependent delays, this frequency mismatch can serve as a source of interaural delays. Figure 4A shows a representative ITD curve in response to a 500-Hz tone [60-dB sound pressure level (SPL)] with mismatched input CFs (ipsilateral CF = 518 Hz; contralateral CF = 483 Hz). The ITD tuning properties and firing rates were similar to in vivo measurement in the MSO (Yin and Chan 1990). A clear shift of the best delay toward the contralateral side (200 μs) was observed. Here the variation of the firing rate (the error bars) resulted from the built-in stochastic nature of the AN model. Throughout the study, we fixed the ipsilateral and contralateral CFs to the values stated above.

Figure 4B shows the frequency tuning curve of the MSO model obtained with a 15-ms tone at various levels and frequencies. Although the two groups of excitatory inputs differ slightly in their CFs, the CF of the MSO model was still near 500 Hz.

SPON/DMPO model. Modeling and physiological studies have shown that the postinhibitory rebounds in SPON neurons are co-created by a hyperpolarization-activated h current and a T-type calcium current (Felix et al. 2011; Kopp-Scheinflug et al. 2011). Here, the following equation was used to model SPON neurons.

\[ C_m \frac{dV}{dt} = -I_{Na} - I_{KHT} - I_{Ca} - I_h - I_{ex} - I_{in} = S_G \cdot \left[ -g_{Na} \cdot m \cdot h \cdot (V - E_{Na}) - g_{KHT} \cdot (\varphi^2 + (1 - \varphi)p) \cdot \left( V - E_K \right) - g_{Ca} \cdot (V - E_C) - g_{h} \cdot (V - E_h) - g_{ex} \cdot (V - E_{ex}) - g_{in} \cdot (V - E_{in}) \right] \]  

where \( C_m = 12 \, \text{pF/cm}^2 \) and \( E_{ex} = 120 \, \text{mV} \) (Wang et al. 1991). \( I_{KHT}, I_{Na}, I_h, \) and \( I_{ex} \) were modeled in the same way as the bushy-cell model. \( I_{Na} \) is the inhibitory synaptic current, and \( I_{Ca} \) is the calcium current. \( I_{KHT} \) was not simulated because it has not been reported for SPON neurons. \( g_{Na} = 10 \, \text{nS}, g_{Ca} = 20 \, \text{nS}, \) and \( g_{h} = 2 \) or 2.5 nS (Table 1; the choices are justified below); other parameter values were the same as for the type II model (Eq. 1). The resulting resting membrane potential was −58 mV. Note that, although \( g_{h} \) was larger than \( g_{Na}, \) the actual \( h \) current after membrane hyperpolarization was larger than the calcium current, which agrees with the measurements of Felix et al. (2011).

The calcium current was modeled in analogy with the HH model’s fast sodium current, according to Coulter et al. (1989) and Wang et al. (1991). The two studies provided detailed mathematical descrip-
ions of channel kinetics for rodent thalamic neurons. The activation gate, \( v_a \), was modeled as

\[
\dot{v} = \frac{v_a - v}{\tau_v}
\]

(6a)

where

\[
v_a = \left[ 1 + e^{-(V+63)/7.8} \right]^{-1}
\]

(6b)

and

\[
\tau_v = \left[ 1.7 + e^{-(V+28.8)/13.5} \right] \left[ 1 + e^{-(V+63)/7.8} \right]^{-1}
\]

(6c)

The inactivation gate, \( f \), was modeled as

\[
\dot{f} = \alpha_1 (1 - f - d) - \alpha_1 Kf
\]

(7a)

\[
d = \alpha_2 K (1 - f - d) - \alpha_2 f
\]

(7b)

\[
\alpha_1 = e^{-(V+160.3)/17.8}
\]

(7c)

\[
\alpha_2 = \frac{1 + e^{(V+37.4)/30}}{240(1 + K)}
\]

(7d)

and

\[
K = \sqrt{0.25 + e^{(V+92.1)/6.3} - 0.5}
\]

(7e)

Note that the half-inactivation voltage for computing \( K \) was changed from \(-83.5 \text{ mV}\) to \(-92.1 \text{ mV}\) to match rodent SPON in vitro data (Felix et al. 2011).

The inhibitory synaptic conductance was simulated as

\[
g_i = \sum \beta_{i,j} \frac{t - t_j}{\tau_i} \exp \left( \frac{t - t_j}{\tau_i} \right)
\]

(8)

where \( \tau_i \) is the inhibitory postsynaptic time constant. The reversal potential of inhibitory synapses, \( E_i \), was \(-70 \text{ mV}\) (Purves et al. 2001).

The majority of SPON neurons recorded in vitro by Felix et al. (2011) exhibited one spike at the end of a hyperpolarizing step current. Eight of 55 neurons exhibited one prominent spike followed by several smaller spikes, and the number of spikes did not correlate to the strength of the calcium current. Figure 5 shows membrane potentials (middle and bottom) of the model SPON neuron to injected hyperpolarizing currents (top). By adjusting the channel conductance of the leakage current, \( \bar{g}_l \), both single (bottom) and multiple (middle) spiking patterns can be observed. Because the present study aimed to model long-lasting forward-masking effects at low frequencies, such as those shown in Fig. 1, and \( D \), we set \( \bar{g}_l = 2 \text{ nS} \) for the rest of the study to create multiple spikes. Note that Felix et al. (2011) reported that SPON neurons were not spontaneously active in vitro, which agrees with the model response (Fig. 5, middle and bottom). Nevertheless, OFF neurons can have low spontaneous activity in vivo (Felix et al. 2011; Kulesza et al. 2003; Kuwada and Batra 1999).

As mentioned earlier, the SPON receives excitatory input from octopus cells and choppers (i.e., multipolar cells) in the contralateral VCN and inhibitory input from the ipsilateral MNTB. Because octopus cells respond primarily at the sound’s onset and thus are unlikely to generate suppression in the target IC neurons at the offset, here the excitatory input came only from choppers (Fig. 2, red). The inhibitory MNTB neuron was treated as a relay of the VCN bushy cells, except that the signal was changed from excitatory to inhibitory with a 1-ms synaptic delay (Cai et al. 1998). Each SPON model neuron received five excitatory inputs from cochlear-nucleus choppers and five inhibitory inputs from the MNTB (Table 3).

**Table 3. Synaptic input for complex neurons**

<table>
<thead>
<tr>
<th></th>
<th>Excitatory</th>
<th>Inhibitory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. inputs</td>
<td>( \tau, \text{ms} )</td>
</tr>
<tr>
<td>SPON</td>
<td>5</td>
<td>0.1</td>
</tr>
<tr>
<td>IC</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
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Model parameters are shown for neurons that received both excitatory and inhibitory input.* The parameter value was varied as stated in the text; the value shown in the table is an example value used in the simulation. \( I_c \) inhibition from the SPON. \( I_{ms} \) inhibition from the contralateral DNLL.

### DNLL model.

The contralateral DNLL provides ipsilateral ascending input to the contralateral VCN and inhibitory input from the ipsilateral MNTB. Because octopus cells respond primarily at the sound’s onset and thus are unlikely to generate suppression in the target IC neurons at the offset, here the excitatory input came only from choppers (Figs. 2, red). The inhibitory MNTB neuron was treated as a relay of the VCN bushy cells, except that the signal was changed from excitatory to inhibitory with a 1-ms synaptic delay (Cai et al. 1998). Each DNLL model neuron received five excitatory inputs from cochlear-nucleus choppers and five inhibitory inputs from the MNTB.

### IC model.

Cai et al. (1998) and Xia et al. (2010) used a type II model (Rothman et al. 1993) to simulate IC neurons for simplicity. This model exhibits only one onset spike to step depolarization. In vitro studies have reported both onset (i.e., phasic) and sustained responses in the IC, but suggested that onset neurons may receive phase-locked input (Peruzzi et al. 2000). Here, we used the newer type II model (Rothman et al. 2003) to simulate phasic IC neurons (the choice of the model is justified in the DISCUSSION).

\[
C_m \frac{dV}{dt} = -I_{Na} - I_{KHT} - I_{KLT} - I_{h} - I_{l} - I_{ex} - I_{in}
\]

(9)

Most of the parameter values that determined intrinsic cellular properties were the same as values used for the bushy cells (Table 1). The previous IC models (Cai et al. 1998; Xia et al. 2010) set the excitatory postsynaptic time constant, \( \tau_e \), to 0.1 ms. With high-signal input from the MSO at 500 Hz, this parameter value yielded a vector strength of 0.91, which is much higher than physiological measurements in the IC (cat: Kuwada et al. 1984; rabbit: Kuwada et al. 2006). Therefore, we increased \( \tau_e \) to 0.5 ms (Table 3). Furthermore, because \( I_{KLT} \) enhances temporal precision and coincidence detection (Svirskis et al. 2004), the maximum channel conductance for the \( I_{KLT} \) was decreased from 200 to 20 nS (Table 1). Even with the smaller amount of \( I_{KLT} \), the model remained phasic, i.e., it responded only at the onset of a step
depolarization. With the above two adjustments, the vector strength to CF tones at 500 Hz was reduced to 0.62, which was in line with those measured in the IC.

We initially simulated the IC model neuron with 5 excitatory inputs from the MSO and 10 inhibitory inputs from the SPON, both of which were located on the ipsilateral side of the brain (Fig. 2). In later simulations, three inhibitory inputs from the contralateral DNLL were added to the model (Table 3).

Overall strategy. Simulations were performed with MATLAB (MathWorks) at a sampling frequency of 100 kHz. Except for the simple illustration of Fig. 3, all simulations include two pools of AN responses with slightly mismatched frequencies (ipsilateral CF = 518 Hz; contralateral CF = 483 Hz). The CF of model neurons along the pathway was solely determined by their input CFs. For example, the MNTB and the SPON had CFs identical to the contralateral AN CF (483 Hz). As shown by Fig. 4B, the frequency mismatch was small enough to keep the MSO model CF at 500 Hz, the IC model CF inherited from the ascending MSO input.

As shown by Fig. 4A, this mismatch in the AN CFs creates a peak ITD of 200 μs in the MSO model. Within each pool, the simulated 100 AN responses for each class of spontaneous rates were statistically identical and independent. In every iteration, a subset of AN fibers was randomly selected as input to bushy or stellate cells with a ratio of 3:1:1 for fibers with high, medium, and low spontaneous rates, respectively.

RESULTS

OFF responses to sound can be created by postinhibitory rebound. First, we systematically varied the strengths of excitation ($\tilde{g}_e$) from cochlear-nucleus choppers and inhibition ($\tilde{g}_i$) from the MNTB to the SPON model neuron. The stimulus was a monaural contralateral 500-Hz tone. Figure 6A shows the part of the system simulated here. In general, the model responded mainly during sound presentation when the excitatory input was strong (Fig. 6B, bottom row). Inhibition tended to suppress responses during the sound presentation, while creating OFF responses at sound offset. Certain conditions generated responses that resembled the firing patterns obtained in previous in vivo recordings (Fig. 1). For example, with no excitatory input and weak inhibitory input (solid rectangle), the model exhibited a single peak after sound offset, which was similar to the neuron shown in Fig. 1B. With stronger excitation and inhibition (dotted rectangle), the OFF response showed a

Fig. 6. Model simulations of the SPON in response to a 500-Hz CF tone fixed at 50-dB SPL over 100 repetitions. A: the local circuit involved in the simulation. B: SPON model responses. The shaded area marks the duration of the tone presentation. The strengths of excitation and inhibition were systematically varied. The solid rectangle marks an example similar to the short OFF response shown in Fig. 1B. The dotted rectangle marks an example similar to the prolonged OFF responses in Fig. 1, C and D.
chopping pattern, which was similar to the examples in Fig. 1, C and D.

Because the chopper model received a mixture of high, medium, and low spontaneous-rate AN fibers as input, it was spontaneously active. Consequently, it could elicit spontaneous activity in the SPON model when the strength of excitation was high (Fig. 6B, the three rightmost columns). In the physiological examples shown in Fig. 1, OFF neurons either had little (B) or low spontaneous activity (C and D). Therefore, for Figs. 7 and 8, we chose the condition marked with the dotted rectangle (\(g_e = 1.4\) nS and \(g_i = 3.2\) nS), which generated multiple spikes as an OFF response with very low spontaneous activity.

Note that the beginning of the OFF response was clearly delayed relative to the end of the sound, as observed in the physiological data (Fig. 1, B and C). Here the inhibitory postsynaptic time constant, \(\tau_i\), was chosen as 1 ms, because longer values would further delay the OFF response. \(\tau_i\) shorter than 1 ms is generally not used when simulating inhibitory input (e.g., Nelson and Carney 2004; Xia et al. 2010) because inhibition is normally slower than excitation, such as the cases in the cochlear nucleus and the MSO (Smith et al. 2000; Xie and Manis 2014). The effect of the delay in the OFF response relative to the offset of the sound will be discussed in the next section. \(\tau_i\) was set to 0.1 ms. This parameter was varied from 0.1 to 0.5 ms and did not have a qualitative effect on the model response (with \(g_e\) adjusted accordingly).

Forward masking in the IC cannot be solely created by inhibition from the SPON. Before examining the masker’s effect on the signal-elicited activity, we first plotted the system’s responses to the masker or signal alone to speculate whether or not the proposed mechanism from the SPON was feasible. Figure 7A highlights the local circuit from which we
obtained the responses, but the simulation included all of the lower pathways (Fig. 2). When a 20-ms, 500-Hz contralateral signal was presented at 40-dB SPL (Fig. 7B), the ipsilateral MSO response occurred mostly during the signal presentation (shaded area), although slightly delayed at the onset with a first-spike latency of 5–6 ms.

Next, we examined model responses to the masker at three model stages. The masker was a frozen noise (0.2–2 kHz, 100 ms in duration) with a spectrum level of 30-dB SPL (overall level 62.6-dB SPL; ~47-dB SPL inside the critical band around 500 Hz). We chose a noise with a relatively broad frequency spectrum to match the cat behavioral study (Gai et al. 2013), but the model responded mostly in the 500-Hz frequency range, determined by its AN input (483 and 518 Hz). The same masker was used in all following simulations. Note that the noise waveforms after peripheral filtering would be somewhat different for the left and right sides due to the frequency mismatch, but the energies of the noise were similar. Here the masker was presented alone; its offset was aligned with the onset of the previous signal, although the signal was not presented. Responses of the VCN choppers (Fig. 7C, left) and the MNTB (middle) occurred during masker presentation, but also extended over the first half of the 20-ms interval during which the signal would be added in a masking paradigm (dotted rectangle). Because the MNTB neuron provided inhibitory input to the SPON, inhibitory rebounds were unlikely to occur until the end of the MNTB response plus extra membrane integration and spiking time. Consequently, the SPON model displayed an OFF response with a latency of 8 to 10 ms post-masker offset (Fig. 7C, right). In other words, even if the SPON responded only to the masker, it would be too late to entirely suppress the excitatory activity coming from the MSO (Fig. 7A). In addition, when the masker and signal formed a continuous sound (gap = 0), the OFF response would not occur until a few milliseconds post-signal offset. Therefore, OFF inhibition alone was unlikely to account for psychophysical forward masking observed for short gaps.

The limitation of OFF inhibition at short gaps was more obvious when examining model responses to both masker and signal presentations. Figure 8A shows representative PSTHs of the model IC neuron to the masker followed by the signal with different gaps (Fig. 8A, i–iv) or the signal alone (v). Here the inhibition was provided solely by the SPON. Again, we used a fixed noise for all gap values, so that changes in the masking effect were mainly caused by variation of the gap duration. The strength of the excitatory synapse from the ipsilateral MSO to the IC was \( g_e = 2.5 \) nS. The strength of inhibition from the SPON was \( g_i = 3.0 \) nS. The synaptic time constants were \( \tau_e = 0.5 \) ms and \( \tau_i = 5 \) ms. \( \tau_e \) was adjusted to yield the correct phase locking for IC neurons (see METHODS). \( \tau_i \) was selected as the medium value of Cai et al. (1998). The IC model responded robustly when the signal was presented alone (Fig. 8A, v). When the masker immediately preceded the signal (gap = 0), the model response to the signal was somewhat reduced (Fig. 8A, iv). This decrease was most likely due to a noninhibitory mechanism, e.g., adaptation, because, with gap = 0, the SPON model did not respond until the signal was terminated. When a 2.5-ms gap was introduced, the response to signal (Fig. 8A, iii) was similar to the gap = 0 condition (Fig. 8A, iv). At longer gaps, e.g., 10 ms, the response to the signal was largely absent (Fig. 8A, ii). At very long gaps, e.g., 50 ms, the response to the signal (Fig. 8A, i) was strong, albeit weaker than the signal-alone response (Fig. 8A, v).

Figure 8B summarizes the responses for all gap values tested. The average firing rate was measured between 4 ms post-signal onset, to exclude the spillover responses to the masker, and 15 ms post-signal offset. The means ± SD of the firing rate to signal alone are indicated by the dashed line and the shaded area, respectively. The addition of the masker to the signal significantly reduced the firing rate (\( P < 0.01; t \)-test with Bonferroni correction) for all gap values. However, there was not a monotonic increase of firing rate with increased gap length, which is required to explain psychophysical masking behavior based on an IC average rate metric. For short gaps, this nonmonotonicity was caused by the SPON not responding early enough to effectively suppress the signal. In addition, there was a large peak around 17.5 ms due to chopping activity of the SPON model (Fig. 6B).

Although previous studies suggested a role of auditory periphery in creating forward masking (Relklin and Turner 1988; Smith 1977), our simulation suggested that adaptation in the AN alone did not create a masking effect as strong as the central inhibition did. The AN model used here accurately simulated long-term adaptation and recovery in the auditory periphery that can last over seconds (Zilany et al. 2009). When the masker was introduced, the AN model showed significantly decreased (\( P < 0.01; t \)-test with Bonferroni correction) average firing rate for all gaps except 50 and 100 ms (Fig. 8C). However, the firing-rate reduction in the AN model was unable to explain the large reduction observed with the IC model. There can be other noninhibitory mechanisms that generate delayed suppression, such as the \( I_{KLT} \), often called a delayed rectifier. The assessment of the effect of \( I_{KLT} \) was difficult, because it was present in several stages of the model. In the last section of the RESULTS, we will provide insight on the overall effect of noninhibitory factors by comparing the MSO and IC responses.

Chopping patterns of the SPON. In the above simulations, the IC model neuron received multiple SPON input with the same chopping pattern, resulting in a nonmonotonic masking function for relatively large gaps. Various somatic and synaptic properties can cause heterogeneity in the response pattern. Figure 9A shows an example of varying the membrane capacitance, \( C_m \). An increase in \( C_m \) slows down the membrane time constant, \( \tau_m = R_m C_m \), and makes the cellular response more sluggish (\( R_m \) is the input resistance). The chopping patterns can thus be varied accordingly (Fig. 9A, left and middle). Here the SPON model received excitatory input from the choppers with \( g_e = 1.0 \) nS and inhibitory input from the MNTB with \( g_i = 3.5 \) nS. When averaging over 10 SPON responses with \( C_m \) uniformly distributed between 7 and 13.3 pF, the chopping pattern became more obscure (Fig. 9A, right). Thus the same configuration was applied to the simulations in Figs. 9 and 11.

Forward masking may be jointly created by inhibition from the SPON and DNLL. In Fig. 9B, we added three ON inhibitory projections from the contralateral DNLL with \( g_i = 3.5 \) nS. Because there were two inhibitory sources, the strength of each SPON inhibitory input was decreased from 3.0 to 2.0 nS (with a total of 10 projections). The number of inhibitory inputs was higher for the OFF than for the ON inhibition to compensate for the fact that the SPON model neuron responded at a much lower rate than the DNLL/MSO model neuron (Fig. 7).

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Inhibition from the DNLL occurred primarily during sound presentation, with a delay due to the peripheral latency and two synaptic properties. First, the peripheral response to sound, especially at low frequencies, always ended later than the stimulus offset, as reflected in Fig. 7. Second, the inhibitory time constant (5 ms) was slower than the excitatory time constant (0.5 ms). Third, the output of the contralateral MSO went through an extra synapse in the DNLL to become inhibitory. The DNLL synaptic delay was initially set to 1 ms.

In the model with both ON and OFF inhibition, a larger reduction of firing rate was observed for forward-masking stimuli with gaps of 0 (Fig. 9B) compared with the model that had only OFF inhibition (Fig. 8B). For the 2.5- and 5-ms gaps, however, the combined ON and OFF inhibition was still ineffective in suppressing the response. To enhance the effect of the ON inhibition, three parameters were considered: the inhibitory time constants, the synaptic strength, and delay of the ON inhibition. Increasing the time constants, \( \tau_i \), for both types of inhibitory sources from 5 to 10 ms was not adequate to suppress the responses to the stimulus with a 5-ms gap (not shown). Although the effect of ON inhibition could have been made stronger by further increasing its synaptic strength, this change would convert the sustained responses to the masker and signal into onset responses, which was not a desired outcome.

Increasing the synaptic delay of the DNLL model neuron from 1 to 5 ms, while keeping the same inhibitory strengths for the DNLL and SPON, resulted in forward-masking that was more effective and that varied monotonically with gap length (Fig. 9C), with a small bump at 17.5 ms due to the "dip" in the firing pattern of the SPON (Fig. 9A, right). Overall, the forward suppression jointly created by ON and OFF inhibition was robust for gap values up to 50 ms. This result was more in accord with psychophysical (Nelson et al. 2009) and behavioral (Weber and Moore 1981) results for forward masking. To better compare the result with human behaviors, the \( d' \) value...
variability is added. For example, as mentioned in the DISCUSSION, a small but significant reduction of response was sometimes observed for a gap of 100 ms (Figs. 8 and 9). A high $d'$ indicates a large reduction of firing rate by the masker. The IC model response receiving both types of inhibition with the 5-ms delay (Fig. 10, thick solid line) showed the largest change in $d'$ with gap and the most linear response that was similar to the psychophysical masking behavior (Fig. 1A).

It is worth pointing out that the inhibitory effect of the SPON, at least using the current model parameters, did not last more than 50 ms. A small but significant reduction of response rate was sometimes observed for a gap of 100 ms (Figs. 8B and 9B). This reduction at long delays was not robust (Fig. 9C) and did not originate from inhibition or variation in the average firing rate of the AN model (Fig. 8C). The occasional response reduction at long delays was likely caused by variation of spike times, to which the type II model (Eq. 1) used in several model stages was sensitive. Overall, the model $d'$ values were considerably higher than behavioral values normally used to determine detection thresholds. In reality, the proposed neural circuit is likely to yield worse performance when more internal variability is added. For example, as mentioned in the DISCUSSION, some SPON neurons do not generate OFF responses, and several omitted ascending inputs to the IC may also serve as noise sources.

Forward masker affected ITD sensitivity to the signal. In the above simulations, the signal and masker had zero ITDs, and the signal level was relatively low (40-dB SPL), because forward masking is traditionally assessed using detection thresholds (Fig. 1A). A recent behavioral study in our laboratory (Gai et al. 2013) showed that, even at high signal levels, the masker can significantly impair the localization of a low-frequency signal. Briefly, the signal location varied in the frontal hemisphere, while the masker was fixed at the front center. When the forward masker was presented, the accuracy of localizing a subsequent signal was significantly reduced.

Here we explored the effect of the same noise masker (30-dB SPL spectrum level) on the ITD tuning of the model IC neuron in response to the signal, with the signal level increased to 70-dB SPL. The IC model received inhibition from both the SPON and the contralateral DNLL with the same parameter values as for Fig. 9C. The signal ITD was systematically varied. The masker ITD either covaried with the signal ($M_{\text{cov}}$) or was fixed at 0 ($M_{\text{fix}}$).

Figure 11 (black lines) shows the ITD tuning curves to the signal alone obtained in the ipsilateral MSO model (left, solid line), the contralateral DNLL (left, dotted line), and the IC model (right). As described earlier, with mismatched input CFs (ipsilateral CF = 518 Hz; contralateral CF = 483 Hz), the MSO model showed a best delay to the signal alone of $\sim 100 - 200$ ms (Fig. 11, left, black solid line). The best delay of the model IC neuron was increased to 400 ms (Fig. 11, right, black solid line) due to the ON inhibition from the contralateral DNLL (left, black dotted line), which had the same ITD tuning as the contralateral MSO. As mentioned earlier, the majority of MSO neurons respond more to contralateral-leading ITDs than to ipsilateral-leading ITDs. Therefore, for negative ITDs, the IC model neuron received stronger ON inhibition from the contralateral DNLL (left, black dotted line) and weaker excitation from the ipsilateral MSO (left, black solid line), compared with ITD = 0. In contrast, for large positive ITDs, the ON inhibition was weaker, and the excitation was stronger. As a result, the best delay of the IC in response to the signal alone was shifted more toward positive ITDs (Fig. 11, right, black solid line).

When a forward masker was introduced with a gap of 2 or 10 ms, there was small but significant ($P < 0.01$; $t$-test with Bonferroni correction) reduction near the peak in the MSO ITD curve for both $M_{\text{cov}}$ and $M_{\text{fix}}$ (Fig. 11, left, red and blue solid lines). In contrast, both types of forward maskers resulted in a large reduction of the response rate in the model IC neuron (Fig. 11, right, red and blue lines; $P < 0.01$, $t$-test with Bonferroni correction). For a gap of 2 ms, the inhibition generated by the $M_{\text{cov}}$ came mostly from the contralateral DNLL (Fig. 11, left, red dotted line), the ITD tuning of which was a mirror image of the ipsilateral MSO (Fig. 11, left, red solid line). Consequently, there was more reduction in the firing rate of the IC model on the ipsilateral side than on the contralateral side (Fig. 11A, right, red lines). For a gap of 10 ms, the OFF inhibition from the SPON played a major role in affecting the ITD curve of the IC. Because the SPON response was determined by the contralateral VCN and was not ITD sensitive (Fig. 2), it had a more uniform effect on the IC response across all the ITDs. A direct comparison of the two red curves (Fig. 11, right) can clearly demonstrate the different effects of the two inhibitory sources on ITD tuning of the IC model neuron. When the ITD of the masker was fixed to 0, the inhibition generated by the $M_{\text{fix}}$ did not vary with signal ITD. For both gap values, it had a strong and uniform suppression on the signal ITD tuning (Fig. 11, right, blue line).

Overall, these results show that a forward masker can have a strong suppressive effect on the IC model in response to a binaural signal, even when the signal had a high sound level (70-dB SPL). This finding agrees with the localization behavior in cats using loud signals (Gai et al. 2013). The suppression between the firing rates to the signal alone and the signal following the masker was computed as

\[ d = \frac{m_1 - m_2}{\sqrt{0.5(\text{Var}_1 + \text{Var}_2)}} \]  

(10)

Here $m_1$ and $m_2$ are the average firing rates, and $\text{Var}_1$ and $\text{Var}_2$ are the variances of the IC model in response to the signal alone and the signal following the masker, respectively. Figure 10 plots all the $d'$ functions for the above firing rates (Figs. 8 and 9). A high $d'$ indicates a large reduction of firing rate by the masker. The IC model response receiving both types of inhibition with the 5-ms delay (Fig. 10, thick solid line) showed the largest change in $d'$ with gap and the most linear response that was similar to the psychophysical masking behavior (Fig. 1A).

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was mostly created by ON and OFF inhibitions from the SPON and DNLL, rather than by noninhibitory mechanisms.

DISCUSSION

This study developed a model for SPON neurons and simulated the nonsimultaneous masking effect of a preceding noise on neural responses in the IC to low-frequency signals. Consistent with physiological findings (Kopp-Scheinpflug et al. 2011), the SPON model responses were shaped more by inhibitory input than by excitatory inputs. The model responses to simple sound resembled those recorded in vivo (Felix et al. 2011; Kopp-Scheinpflug et al. 2011; Kuwada and Batra 1999). The IC-model circuit included the ITD-sensitive pathway as its major excitatory input, as well as two sources of inhibition that each focused on a different type of response pattern. Unlike peripheral adaptation, these central inhibitory mechanisms generated substantial forward suppression, consistent with human psychophysical results (Smiarowski and Carhart 1975; Weber and Moore 1981). The binaural tuning of model neurons was in accord with previous physiological recordings (Kuwada et al. 2006; Yin and Chan 1990).

Physiological candidates for model neurons at several stages. Forward suppression has been reported at many levels of the auditory pathway, and it is unlikely that the overall masking effect can be explained at the auditory periphery. For example, dynamic ranges of neural masking and threshold shifts measured in the AN are much smaller than those observed psychophysically (Plack and Oxenham 1998; Relkin and Turner 1988). In contrast, responses in the IC have wide dynamic ranges that better match the psychophysics (Nelson et al. 2009). The physiological candidates for the IC neurons modeled here are type V neurons, which are found in the low-frequency regions of the IC. They receive excitatory input from neurons that are sensitive to ITDs (Ramachandran et al. 1999). Although there has been no direct evidence confirming that type V neurons receive projections from the SPON, it is known that the SPON project to all areas of the central IC in a topological manner (Saldaña et al. 2009).

A major source of the OFF inhibition is the rodent SPON or the nonrodent DMPO. Here we chose to model the SPON, rather than the DMPO, because more physiological studies have been performed in the SPON (Behrend et al. 2002; Dehmel et al. 2002; Felix et al. 2011; Kopp-Scheinpflug et al. 2011; Kulesza et al. 2003), and its ascending inputs are better understood. It is unclear how the DMPO may be different from the SPON. Note that, in both nuclei, a variety of response patterns have been reported, including a small percentage of ON responses that occurred during sound presentation (Dehmel et al. 2002; Guinan et al. 1972a, 1972b; Kulesza et al. 2003). Meanwhile, neurons other than the SPON and DMPO can also show OFF responses, such as the DNLL (Bajo et al. 1998; Guinan et al. 1972a, 1972b). In other words, there are no strict physiological correlates of the responses. Here the two types of inhibition were explored from a functional point of view, i.e., the possible contributions of the ON and OFF inhibitions to forward masking. Our construction of the DNLL and SPON models was one way to realize the ON and OFF inhibition. In reality, it is likely that both DNLL and SPON could contribute to forward-masking effects in a way different from the present report.

The IC model developed by Cai et al. (1998) receives inhibitory input from the contralateral DNLL (Fig. 2, green).
Later, Xia et al. (2010) added another inhibitory input from the ipsilateral DNLL (not shown), based on physiological findings by Adams and Mignaini (1984), to simulate two types of IC responses to binaural clicks. Meanwhile, the VNLL is known to provide inhibition to the ipsilateral IC (not shown; Benson and Cant 2008; Whitley and Henkel 1984). Here, the ON inhibition was modeled as the contralateral DNLL input. When an IC neuron receives inhibition from the ipsilateral DNLL, the ITD tuning of the inhibition should be more in line with the tuning of the excitation from the ipsilateral MSO. The ipsilateral VNLL receives input directly from the contralateral cochlear nucleus. Its inhibitory effect on the ITD tuning of the IC would be more or less uniform.

Simulating OFF responses in the SPON. Wang et al. (1991) simulated the T-type Ca$^{2+}$ current in thalamic neurons in a way similar to the fast Na$^+$ current of the Hodgkin and Huxley model. Their model using the Ca$^{2+}$ current and a leakage current generated small triangular action potentials at the offset of a hyperpolarizing current input. The present study added the h current and a regular spiking mechanism to their model. Kopp-Scheinflug et al. (2011) also constructed a cellular model for the SPON using the T-type Ca$^{2+}$ current, the h current, and a leak conductance with a reversal potential of −90 mV.

The SPON model presented here received excitatory input from contralateral cochlear-nucleus stellate cells and inhibitory input from the ipsilateral MNTB. The latter was modeled as contralateral VCN bushy cells with a synaptic delay. By varying the synaptic strengths of excitation and inhibition, the SPON response patterns were altered (Fig. 6B). The model was able to reproduce a single OFF peak, as well as more pronounced later activity. We chose the multiple-spike configuration to allow a sustained forward inhibition. In Felix et al. (2011), all of the 55 recorded SPON neurons showed OFF spikes to hyperpolarizing currents. Although only eight neurons showed prolonged spike patterns, i.e., multiple spikes, they were all restricted to the dorsolateral quadrant of the SPON corresponding to the low-frequency region, which was the simulation target of this study.

Because in most cases the chopping patterns lasted only slightly over 50 ms, the model was unable to generate suppressive effects longer than 50 ms. To produce a more sustained effect, such as the one shown in Fig. 1D, the SPON model properties must be modified. Since adaptation can usually last longer, it may also contribute to the masking effect by accumulating over multiple stages, which we did not explicitly simulate except at the level of the AN. It is also worth pointing out that the response patterns of the SPON model obtained with inhibitory input alone did not differ fundamentally from the patterns with inhibition plus weak excitation. The OFF response in the SPON was determined almost entirely by the inhibitory input from the MNTB, which is consistent with physiological finding (Kopp-Scheinflug et al. 2011). Although many neurons can exhibit postinhibitory rebounds, these neurons typically respond during sound presentation. The uniqueness of SPON neurons lies in the fact that its inhibitory input dominates its excitatory input.

In addition, by selectively blocking the h current and the Ca$^{2+}$ current, Felix et al. (2011) found that the h current is important for precise timing of the rebound, whereas the Ca$^{2+}$ current serves mostly to enhance the spiking. When we removed the Ca$^{2+}$ current from the simulation (not shown), the SPON model fired only one action potential for the multiple-spike condition in Fig. 5, middle, and no action potential for the single-spike condition in Fig. 5, bottom, suggesting that the role of the Ca$^{2+}$ current was properly simulated with $g_T = 20$ nS and $g_h = 10$ nS.

Forward masking jointly created by the SPON and DNLL. Sound-duration selectivity in the bat IC has been shown to relate to well-timed excitation and inhibition (Faure et al. 2003). Wang et al. (2007) showed that weak noise can generate forward suppression in the mouse IC through GABAergic inhibition, and Ayala et al. (2016) showed that blocking GABAergic inhibition can extend the IC response for over 50 ms. Both the DNLL and SPON send GABAergic projections to the IC and can thus serve as potential candidates for the mechanism. Intuitively, a strong suppressive effect of a masker on a subsequent signal is most likely produced by inhibition that occurs after the masker is turned off (Nelson et al. 2009). The present study showed that this is true for relatively long gaps, but not for short or no gaps. When the masker and the signal form a continuous sound, as long as both occurred in the response area of the SPON, there will not be an OFF response until after the signal is terminated. When the gap between the end of the masker and the beginning of the signal was short (e.g., ≤5 ms), even though there may be an OFF response elicited by the masker offset, it is too late to suppress the onset activity to the signal.

The present study showed that an important source of ON inhibition to the IC coming from the contralateral DNLL with a synaptic delay was able to suppress a short signal that immediately followed the masker. This mechanism was especially effective when the synaptic delay was 5 ms, rather than 1 ms. Physiologically, this delay may be implemented by slow time constants of the cell membrane and/or the synaptic input. As mentioned above, the ON inhibition does not necessarily come from the DNLL. Certain neurons in the SOC with chopping patterns showed latencies up to 10 ms later than other SOC neurons (Guinan et al. 1972a). These neurons, if inhibitory, can serve as candidates for the delayed ON inhibition.

We should point out that the combination of ON and OFF inhibition is probably one of the many mechanisms that jointly contribute to psychophysical forward masking. Besides inhibition from lower levels, it is also likely that certain local circuits within the IC or feedback from higher levels may generate forward masking. Theoretically, any inhibitory or suppressive mechanism with a delay of several to tens of milliseconds may contribute to the psychophysically observed masking behavior. The role of the proposed inhibition from lower pathways can only be verified by physiological studies that create a lesion in the inhibitory pathways while measuring IC responses or animal behavior.

The model’s ITD tuning to a high-level, low-frequency signal was considerably affected by the presence of a forward masker. The firing rate was reduced significantly when the ITD of the forward masker covaried with the signal ITD, and even more when the ITD of the masker was fixed to 0. In the covarying condition, the reduction of firing rate was stronger in response to stimuli on the ipsilateral side for short gaps and more or less uniform for long gaps. This effect of gap duration was due to the lack of spatial sensitivity of the model SPON, whereas the model contralateral DNLL had ITD tuning as a
mirror image of the ipsilateral MSO. Kuwada et al. (2006) compared ITD tuning in the SOC, the DNLL, the IC, and the thalamus. They found that the tuning sharpened along the ascending pathway, most likely due to inhibitory mechanisms.

When the preceding masker and the signal have different ITDs, forward masking can be reduced (Bekhterev et al. 2002; Deathager and Evans 1969; Kollmeier and Gilkey 1990; Zwicker and Zwicker 1984). Here there was no attempt to explain the binaural release from forward masking, which may involve a population of IC neurons with different best delays and tuning properties. For example, when the masker is located at the front center and the signal is off-center, spatial release from masking would make it easier to perceive the signal. In the above simulations, when the masker ITD was fixed to 0, the ITD tuning curve showed very little activity for a signal with a large ITD. This seeming contradiction indicates that population coding is likely to be involved in explaining the spatial-release effect.

The circuit model naturally incorporated other forward-suppressive mechanisms, such as long-term adaptation in the AN and the delayed rectifier created by the low-threshold potassium current at various stages. Our simulations showed that these noninhibitory mechanisms can exhibit a forward-suppressive effect at certain auditory stages, but, overall, noninhibitory effects were not as sustained or prominent as the inhibitory effects. Our finding agrees with the AN study by Relkin and Turner (1988), which showed that the threshold shift due to forward masking in the AN could not account for the shift of behavioral threshold. Nevertheless, forward-masking behaviors are most likely to be jointly created by multiple mechanisms, including inhibition, as well as build-ups of adaptation and delayed rectification over multiple stages.

In addition, changes in forward-masking behavior associated with hearing loss have been thought to reflect changes in peripheral compression (e.g., Wojtczak and Oxenham 2010). However, it has been shown that hearing loss can lead to alteration of inhibition at the central auditory system (review: Caspary et al. 2008). Based on our simulation results, we caution against the approach of using forward masking as an assessment of peripheral hearing loss.

Comparisons with other forward-masking models. Two types of mathematical models have been proposed to explain forward-masking behavior. The first is based on neural adaptation that can happen both in the AN and at higher levels of the pathway (Oxenham 2001; Smith 1977). Adaptation is modeled as a low gain immediately after the masker offset and an increased gain as the time from the offset increases. The second model implements a temporal-integrator, which blends responses to the masker and the signal over a period of time (Moore et al. 1988; Oxenham and Moore 1994). Although the temporal-integration model is more acceptable with certain forward-masking behavior, that model has various limitations (Oxenham 2001).

Here, the AN model included short- and long-term adaptation, and the $K_{1.1}$ at various model stages can serve as a type of adaptation to ongoing sound. When there was no gap, the model result showed that, without either type of inhibition, adaptation from the above-mentioned sources was unable to generate large firing-rate reduction to the signal (Fig. 9A, iv). However, in reality, it is impossible to distinguish inhibitory suppression from ongoing adaptation based on a neuron’s output response, and we may have missed other types of adaptation in the simulation of the proposed model. Meanwhile, the temporal-integration mechanism more or less played a role in the proposed IC model because of the long membrane time constant.

Simulation choices and simplifications. The proposed model circuit included multiple ascending pathways, and certain simplifications were made with the assumption that they did not alter the major conclusions. Those mentioned in the earlier part of the DISCUSSION will not be repeated here.

First, similar to previous studies (e.g., Xia et al. 2010), inhibitory projections to the MSO coming from the MNTB and the LNTB were neglected. The role of inhibition in the MSO has long been under debate. Some studies proposed that inhibition shifts the best delays for MSO neurons (Brand et al. 2002; Zhou et al. 2005). Other studies have claimed that the best delay was solely determined by excitatory input to the MSO (van der Heijden et al. 2013), and the strength of inhibition covaries with the $I_{KLT}$ to maintain ITD consistency across frequencies (Roberts et al. 2013). Meanwhile, noninhibitory mechanisms have also been proposed to account for the best delays (Jercog et al. 2010; Joris et al. 2006). Here, the best delay was created by binaural mismatches in the CFs of the ascending input (Benichoux et al. 2015; Day and Semple 2011; Joris et al. 2006; Shamma et al. 1989). A difference of 0.1 octave in the CFs (a 35-Hz difference around 500 Hz) generated a best delay of $\sim 200 \mu s$ for MSO neurons. This best delay was magnified at the level of the IC due to inhibition from the contralateral DNLL (Fig. 11). Whether or not inhibition to the MSO changes the best delay, the focus of this study was to examine the effect of a preceding masker on the detection and localization of the signal. Thus the omission should not affect the conclusions of this study in a significant way. Meanwhile, because a significant proportion of IC neurons showed input frequency mismatches of $<0.1$ octave (Davis et al. 1999), it is likely that more than one mechanism, such as the above-mentioned hypotheses, as well as the delay lines proposed by Jeffress (1948), jointly contribute to the best delays.

Second, the MNTB and the DNLL were treated as relay stations with artificial synaptic delays. Because the major synapse in the MNTB, the calyx of Held, is believed to convey information in a secured one-to-one manner (Guinan and Li 1990), this simplification should not have affected our results. Kuwada et al. (2006) indicated that substantial signal processing can occur in the DNLL, such as sharper ITD tuning and weaker phase locking compared with the MSO. Therefore, it is likely that our model simulation has missed certain signal processing in the DNLL that is important for forward masking.

Third, similar to previous studies (Cai et al. 1998; Xia et al. 2010), a type II model for bushy cells was used to simulate IC neurons with an adjustment of the amount of $I_{KLT}$ to yield a reasonable vector strength for IC phasic neurons, i.e., neurons that fire a single spike in response to steady current depolarization. By far, there are three known mechanisms to create phasic-firing properties, namely the $I_{KLT}$ sodium inactivation (Svirskis et al. 2004), and a modification of the $I_{KHT}$ nonlinearity in the original HH equations (Clay et al. 2008). Because $K_{1.1}$ is known to exist in the IC (Grigg et al. 2000; Karcz et al. 2012; Rosenberger et al. 2003), we believe that the general type II model structure is reasonable to be used to model IC
neurons. However, future modeling studies should refine or revise the model to better represent IC responses.

Fourth, overall, we tried to set model parameter values according to physiological measurements when possible. When such a measurement was unavailable, such as the number of excitatory and inhibitory inputs to the IC, the values we chose were within the range used by other modeling studies. We believe that the variation in input numbers in a point neuron model, as opposed to a multicompartment model, should not cause a large effect, as long as the strength of channel conductance can be adjusted accordingly.

Last, similar to previous modeling studies (Cai et al. 1998; Xia et al. 2010), the present IC circuit omitted an important ascending pathway, the lateral superior olive (LSO). It has been hypothesized that the type I units in the IC receive input from the LSO (Ramachandran et al. 1999). In vivo physiological recordings in the IC showed that the best frequencies of the type V neurons range from 0.3 to 3 kHz, whereas the best frequencies of the type I neurons range from 1 to 60 kHz (Ramachandran et al. 1999). Because the above simulation was confined to the low-frequency region around 500 Hz, the omission of type I neurons and the LSO should not have made a major difference. Nevertheless, future modeling studies should incorporate the LSO pathway in the simulation of forward masking, especially at high frequencies. We expect the inhibitory effect from the monaural SPON to be similar; the effect from the DNLL is harder to predict, as the DNLL receives major excitatory input from the MSO, which changes its ITD properties at high frequencies. In addition, sound responses from other omitted ascending inputs to the IC, such as projections from the cochlear nucleus choppers and the VNLL, may serve as noise sources, even though they may not account for forward masking.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

Author contributions: Y.G. conception and design of research; Y.G. performed experiments; Y.G. analyzed data; Y.G. interpreted results of experiments; Y.G. prepared figures; Y.G. drafted manuscript; Y.G. edited and revised manuscript; Y.G. approved final version of manuscript.

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