Tonically Balancing Intracortical Excitation and Inhibition by GABAergic Gliotransmission

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For sensory cortices to respond reliably to feature stimuli, the balancing of neuronal excitation and inhibition is crucial. A typical example might be the balancing of phasic excitation within cell assemblies and phasic inhibition between cell assemblies. The former controls the gain of the latter and the tuning of neuronal responses. A change in ambient GABA concentration might affect the dynamic behavior of neurons in a tonic manner. For instance, an increase in ambient GABA concentration enhances the activation of extrasynaptic receptors, augments an inhibitory current, and thus inhibits neurons. When a decrease in ambient GABA concentration occurs, the tonic inhibitory current is reduced, and thus the neurons are relatively excited. We simulated a neural network model in order to examine whether and how such a tonic excitatory-inhibitory mechanism could work for sensory information processing. The network consists of cell assemblies. Each cell assembly, comprising principal cells (P), GABAergic interneurons (Ia, Ib), and glial cells (glia), responds to one particular feature stimulus. GABA transporters, embedded in glial plasma membranes, regulate ambient GABA levels. Hypothetical neuron-glia signaling via inhibitory (Ia-to-glia) and excitatory (P-to-glia) synaptic contacts was assumed. The former let transporters...
import (remove) GABA from the extracellular space and excited stimulus-relevant P cells. The latter let them export GABA into the extracellular space and inhibited stimulus-irrelevant P cells. The main finding was that the glial membrane transporter gave a combinatorial excitatory-inhibitory effect on P cells in a tonic manner, thereby improving the gain and tuning of neuronal responses. Interestingly, it worked cooperatively with the conventional, phasic excitatory-inhibitory mechanism. We suggest that the GABAergic gliotransmission mechanism may provide balanced intracortical excitation and inhibition so that the best perceptual performance of the cortex can be achieved.

1 Introduction

Sensory cortices are known to form cell assemblies called feature columns in order to detect specific feature stimuli such as the orientation of a bar in vision, the frequency of a sound in audition, and the sensation of a body surface in somatosensation (for review, see Mountcastle, 1997). For feature columns to respond reliably to sensory stimuli, the balancing of neuronal excitation and inhibition is essential (Moore, Nelson, & Sur, 1999; Zhang, Tan, Schreiner, & Merzenich, 2003; Wehr & Zador, 2003; Tan, Zhang, Merzenich, & Schreiner, 2004; Marino et al., 2005; Okun & Lampl, 2008). A typical example might be the balancing of phasic excitation within cell assemblies and phasic inhibition between cell assemblies. The former controls the gain and the latter the tuning of neuronal responses.

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter and mediates inhibition in a phasic manner by activating intrasynaptic GABA receptors, that is, GABA receptors in the synaptic cleft. So-called tonic inhibition occurs when extrasynaptic GABA activates receptors located on membranes outside synapses (Semyanov, Walker, Kullmann, & Silver, 2004; Farrant & Nusser, 2005; Ortinski et al., 2006). GABA molecules in extracellular space and GABA receptors on extrasynaptic membrane regions are referred to as ambient GABA and extrasynaptic GABA receptor, respectively. Extrasynaptic GABA$_a$ receptors have been found in the cerebellum (Somogyi, Takagi, Richards, & Mohler, 1989; Nusser, Roberts, Baude, Richards, & Somogyi, 1995; Brickley, Cull-Candy, & Farrant, 1996; Soltesz & Nusser, 2001) and in the cortex (Drasbek & Jensen, 2006; Scimemi et al., 2006).

In the brain, intrasynaptic GABA rises to a millimolar level triggered by a presynaptic action potential (Maconochie, Zempel, & Steinbach, 1994; Jones & Westbrook, 1995). In contrast, ambient GABA changes within the submicromolar-micromolar range (Lerma, Herranz, Herreras, Abraira, & Martin, 1986; Tossman, Jonsson, & Ungerstedt, 1986; Scimemi, Semyanov, Sperk, Kullmann, & Walker, 2005). The lower ambient GABA level is sufficient to activate extrasynaptic but not intrasynaptic GABA$_a$ receptors.
GABA_A receptors containing the δ subunit have been found in extrasynaptic membrane regions (Somogyi et al., 1989; Nusser et al., 1995; Brickley et al., 1996; Soltesz & Nusser, 2001), which are known to have high affinity for GABA (Saxena & Macdonald, 1996; Brown, Kerby, Bonnert, Whiting, & Wafford, 2002) and little desensitization to continuous activation by GABA (Bianchi, Haas, & Macdonald, 2001, 2002). This leads to tonic inhibition of neurons even at lower ambient GABA levels.

As to the maintenance of ambient GABA levels, Richerson and colleagues (Wu, Wang, & Richerson, 2001; Richerson & Wu, 2003; Richerson, 2004; Wu, Wang, Diez-Sampedro, & Richerson, 2007) made an interesting suggestion. A GABA transporter such as GAT-1 is crucial not only for importing (removing) GABA from but also for exporting it into the extracellular space. Transporters, embedded in membranes of glial cells (and interneurons), can regulate ambient GABA levels. They are near equilibrium under normal physiological conditions and will reverse with a small increase or decrease in membrane potential.

A change in ambient GABA concentration might affect the dynamic behavior of neurons in a tonic manner. For instance, an increase in ambient GABA concentration enhances the activation of extrasynaptic receptors, augments an inhibitory current, and thus inhibits neurons. When a decrease in ambient GABA concentration occurs, the tonic inhibitory current is reduced, and thus the neurons are relatively excited. The purpose of this study is to examine whether and how such a tonic excitatory-inhibitory mechanism could work for perceptual information processing. We simulate a neural network model that consists of cell assemblies. Each cell assembly, comprising principal cells (P), GABAergic interneurons (Ia, Ib), and glial cells (glia), responds to one particular feature stimulus.

To regulate ambient GABA levels, we construct a functional model of a glial plasma membrane transporter. Concerning neuron to glia signaling, a variety of types of neuron-glial circuits have been evidenced, including chemical (glutamate, GABA) synapses between presynaptic neurons and postsynaptic glial cells (for review, see Bezzi & Volterra, 2001; Fields & Stevens-Graham, 2002; Overstreet, 2005). We assume neuron-glial signaling via inhibitory Ia-to-glia and excitatory P-to-glia synaptic contacts. The former hyperpolarizes glial cells, thereby letting their transporters import (remove) GABA from the extracellular space and thus exciting P cells. In contrast, the latter depolarizes the glial cells, thereby letting their transporters export GABA into the extracellular space and thus inhibiting the P cells. Namely, the glial membrane transporter gives a combinatorial excitatory-inhibitory effect on P cells in a tonic manner. During exposure to a feature stimulus, neuronal activities (membrane potentials and spikes) are recorded. We examine whether and how the GABAergic gliotransmission mechanism works for balancing neuronal excitation and inhibition and investigate how it contributes to perceptual information processing.
Figure 1: The neural network model. Multiple cell assemblies constitute the network. Each cell assembly (0 ≤ n ≤ 7) comprises 20 cell units: one principal cell (P), two GABAergic interneurons (Ia, Ib), and one glial cell (glia). The open and filled triangles denote excitatory and inhibitory synapses, respectively. Constant excitatory current is applied to P cells as sensory input (see equations A.1 and A.5 in appendix A). Inset: A schematic illustration of GABA transport (Hoshino, 2012). P and Ia cells excite and inhibit a glial cell, respectively. Glial plasma membrane transporters import (remove) GABA from or export it into the extracellular space, depending on the membrane potential. Ambient GABA molecules are accepted by extrasynaptic GABA<sub>a</sub> receptors and tonically inhibit a P cell.

2 Neural Network Model

As shown in Figure 1, cell assemblies consist of principal cells (P), GABAergic interneurons (Ia, Ib), and glial cells (glia). Each cell assembly (0 ≤ n ≤ 7)
comprises 20 cell units (P, Ia, Ib, glia). Each P cell receives excitatory inputs from other P cells and inhibitory inputs from Ib cells, which receive excitatory inputs from P cells belonging to other cell assemblies. Each Ia cell receives an excitatory input from its accompanying P cell and synaptically connects to a glial cell. P cells synaptically connect to glial cells belonging to other cell assemblies. P cells receive an excitatory current as a sensory input when stimulated. A conductance-based, integrate-and-fire neuron model (Hoshino, 2007a, 2007b, 2008) is employed.

As schematically illustrated in Figure 1 (inset), a gliotransmission-mediated ambient GABA regulatory system is constructed based on our previous study (Hoshino, 2012). P and Ia cells synaptically excite and inhibit a glial cell, respectively. Transporters are distributed in the glial cell membrane, which import (remove) GABA from or export it into the extracellular space, depending on the membrane potential of the glial cell. Ambient GABA molecules are accepted by extrasynaptic GABA$_3$ receptors and tonically inhibit a P cell. The neural network model is described in appendixes A to C, whose parameters and their values are listed in Table 1.

As will be shown in later sections, the hypothetical P-glia and Ia-glia circuits play key roles in regulating ambient GABA concentration. The former has a role in increasing a level of ambient GABA around stimulus-irrelevant P cells, and the latter has a role in decreasing a level of ambient GABA around stimulus-relevant P cells. These circuits achieve combinatorial regulation of local ambient GABA levels, by which the neuronal gain and tuning to sensory input can be improved. To the best of our knowledge, these specific circuits between different (P, Ia) cells and glia have not been observed. They were assumed based on studies (Bezzi & Volterra, 2001; Fields & Stevens-Graham, 2002; Overstreet, 2005) that indicated a variety of glutamatergic and GABAergic neuron-glia projections.

3 Results

3.1 Dynamic Properties of Neuron and Ambient GABA Concentration. Figure 2 shows fundamental dynamic properties of principal (P) cells (see Figure 2A), ambient GABA concentrations around them (see Figure 2B), and glial cells (see Figure 2C) belonging to respective cell assemblies ($0 \leq n \leq 7$). When the network is presented with a feature stimulus ($f_3$), P cells relevant to the stimulus are activated (see $n = 3$ in Figure 2A). The ambient GABA concentration around P cells relevant to the stimulus is reduced (see the trace marked by $n = 3$ in Figure 2B). This leads to a decrease in tonic inhibitory current in the stimulus-relevant P cells and thus to their excitation. In contrast, ambient GABA concentrations around P cells irrelevant to the stimulus are increased (see the traces marked by $n \neq 3$), which leads to an increase in tonic inhibitory current and thus to their inhibition. These results indicate that the GABAergic gliotransmission mechanism balances
Table 1: List of Parameters and Their Values.

<table>
<thead>
<tr>
<th>Description</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane capacitance of type Y (Y = P, Ia, Ib, glia) cell</td>
<td>$c_m^Y$</td>
<td>$c_m^P = 500 \ pF$, $c_m^{Ia} = 200 \ pF$, $c_m^{Ib} = 600 \ pF$, $c_m^{Gl} = 45 \ pF$</td>
</tr>
<tr>
<td>Membrane conductance</td>
<td>$g_m^Y$</td>
<td>$g_m^P = 25 \ nS$, $g_m^{Ia} = 20 \ nS$, $g_m^{Ib} = 15 \ nS$, $g_m^{Gl} = 9 \ nS$</td>
</tr>
<tr>
<td>Resting potential</td>
<td>$u_{rest}^Y$</td>
<td>$u_{rest}^P = -65 \ mV$</td>
</tr>
<tr>
<td>Maximal conductance for type Z (Z = AMPA, GABA) receptor</td>
<td>$\hat{g}_Z$</td>
<td>$\hat{g}<em>{AMPA} = 0.5 \ nS$, $\hat{g}</em>{GABA} = 0.7 \ nS$</td>
</tr>
<tr>
<td>Reversal potential</td>
<td>$u_{rev}^Z$</td>
<td>$u_{rev}^{AMPA} = 0 \ mV$, $u_{rev}^{GABA} = -80 \ mV$</td>
</tr>
<tr>
<td>Number of cell units within cell assemblies</td>
<td>$N$</td>
<td>20</td>
</tr>
<tr>
<td>Number of cell assemblies</td>
<td>$M$</td>
<td>7</td>
</tr>
<tr>
<td>Synaptic weight (strength) from j to i th P cell</td>
<td>$w_{ij}^{P,P}$</td>
<td>6</td>
</tr>
<tr>
<td>Synaptic weight from jth Ib to ith P cell</td>
<td>$w_{ij}^{P,Ib}$</td>
<td>1.6</td>
</tr>
<tr>
<td>Synaptic weight from ith P to Ia cell</td>
<td>$w_{i}^{Ia,P}$</td>
<td>30</td>
</tr>
<tr>
<td>Synaptic weight from ith P to Ib cell between different (n' ≠ n) cell assemblies</td>
<td>$w_{i}^{Ib,P,(n, n')}$</td>
<td>1.6</td>
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<tr>
<td>Synaptic weight from ith P to glial cell</td>
<td>$w_{i}^{Gl,P,(n, n')}$</td>
<td>5</td>
</tr>
<tr>
<td>Synaptic weight from ith Ia to glial cell</td>
<td>$w_{i}^{Gl,Ia}$</td>
<td>5</td>
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<tr>
<td>Amount of extrasynaptic GABA$_a$ receptors on P cell</td>
<td>$\delta_P$</td>
<td>$6 \times 10^3$</td>
</tr>
<tr>
<td>Input current</td>
<td>$\alpha_P$</td>
<td>150 \ pA</td>
</tr>
<tr>
<td>Broadness of input</td>
<td>$\tau_P$</td>
<td>2.6</td>
</tr>
<tr>
<td>Channel opening rate for type Z (Z = AMPA, GABA) receptor</td>
<td>$\alpha_Z$</td>
<td>$\alpha_{AMPA} = 1.1 \times 10^6$, $\alpha_{GABA} = 5 \times 10^6$</td>
</tr>
<tr>
<td>Channel closing rate</td>
<td>$\beta_Z$</td>
<td>$\beta_{AMPA} = 190$, $\beta_{GABA} = 180$</td>
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<tr>
<td>Steepness of sigmoid function for type Y (Y = P, Ia, Ib) cell</td>
<td>$\eta_Y$</td>
<td>$\eta_P = 220$, $\eta_{Ia} = \eta_{Ib} = 180$</td>
</tr>
<tr>
<td>Threshold of sigmoid function</td>
<td>$\zeta_Y$</td>
<td>$\zeta_P = -35 \ mV$, $\zeta_{Ia} = \zeta_{Ib} = -38 \ mV$</td>
</tr>
<tr>
<td>Decay constant for ambient GABA concentration</td>
<td>$\gamma_{trn}$</td>
<td>0.2</td>
</tr>
<tr>
<td>Basal ambient GABA concentration</td>
<td>$[GABA]_{ext}^{Gl}$</td>
<td>0.1 \ mM</td>
</tr>
<tr>
<td>Maximal ambient GABA concentration</td>
<td>$GABA_{max}$</td>
<td>3.5 \ mM</td>
</tr>
<tr>
<td>Minimal ambient GABA concentration</td>
<td>$GABA_{min}$</td>
<td>0 \ mM</td>
</tr>
<tr>
<td>GABA transfer coefficient</td>
<td>$T_{Gl}$</td>
<td>$9 \times 10^{10}$</td>
</tr>
<tr>
<td>Reversal potential of GABA transporter</td>
<td>$u_{rev}^{Gl}$</td>
<td>-70 \ mV</td>
</tr>
</tbody>
</table>
intracortical excitation and inhibition in a tonic manner, thereby improving the selective responsiveness of the network to the applied feature stimulus.

Figure 2C indicates that stimulus-relevant glial cells are hyperpolarized (see the enlarged trace for $n = 3$), which let their transporters import GABA and thus leads to the decrease in ambient GABA concentration (see the trace marked by $n = 3$ in Figure 2B), whereas stimulus-irrelevant glial cells are depolarized (e.g., see the enlarged trace for $n = 4$), which let their transporters export GABA and thus leads to the increase in ambient GABA concentration.
concentration (see the traces marked by $n \neq 3$ in Figure 2B). Note that $u_{\text{rev}}^{\text{Gl}}$ is the reversal potential of the GABA transporter (see equation C.1 in appendix C).

### 3.2 Improvement of Neuronal Gain Function by GABAergic Gliotransmission

In this section, we show how the GABAergic gliotransmission mechanism contributes to the improvement of neuronal gain function. Figure 3 presents spikes evoked in P cells (see Figure 3A), ambient GABA concentrations (see Figure 3B), and membrane potentials recorded from glial cells (see Figure 3C) belonging to respective cell assemblies, where the Ia-to-glia projection was cut. Due to the impaired Ia-to-glia projection, stimulus-relevant glial cells are not hyperpolarized, and thus the ambient GABA concentration is not to be reduced (see the solid trace marked by $n = 3$). This results in a failure to elevate stimulus-related P cell activity (compare Figures 2A and 3A), which is quantitatively shown in Figure 3D. $u_{i}^{\text{Gl,la}} = 0$ corresponds to the impairment of Ia-to-glia projection (see equation A.12 in appendix A). We found that increasing the Ia-to-glia connection weight elevates the stimulus-evoked neuronal activity. These results indicate that the GABAergic gliotransmission-mediated tonic excitation enhances the neuronal responsiveness.

As shown in Figure 4A (top), phasic excitation by P cells (see $w_{i}^{P,P}$ in equation A.2) per se (i.e., even without Ia-to-glia signaling) can improve the neuronal gain function. Beyond the maximal connection weight ($w_{i}^{P,P} > 6$, see the circles), P cells continued firing even after the termination of the stimulus (not shown). We refer to this as “invalid.” Figure 4A (bottom) shows the dependence of the gain function on Ia-to-glia connection weight. Interestingly, the gain function achieved at the maximal connection weight $w_{i}^{P,P} = 6$ (see the open circles) could be improved by the GABAergic gliotransmission-mediated tonic excitatory mechanism (bottom; see the filled circles), being able to respond to weaker stimuli.

Figure 4B shows how the tonic (nonsynaptic) and phasic (synaptic) excitatory mechanisms cooperatively work. As addressed above, the network operates in the valid but not invalid condition (left). Figure 4B (right) presents minimal input currents at which a population response to the stimulus can take place in P cells. We found that the GABAergic gliotransmission-mediated tonic excitatory mechanism enables the network to respond to weaker sensory stimuli. These results indicate that the neuronal gain function ensured by the conventional phasic excitatory mechanism can be improved by the GABAergic gliotransmission-mediated tonic excitatory mechanism.

### 3.3 Improvement of Sensory Tuning by GABAergic Gliotransmission

In this section, we show how the GABAergic gliotransmission mechanism contributes to the improvement of sensory tuning performance. Figure 5
Figure 3: Responses to a feature stimulus without GABAergic gliotransmission-mediated tonic excitation via Ia-to-glia signaling. (A) Raster plots of action potentials evoked in principal (P) cells. (B) Ambient GABA concentrations. (C) Membrane potentials recorded from glial cells. (D) Stimulus-evoked activity (firing rate) as a function of Ia-to-glia connection weight.

(top) presents spikes evoked in P cells, where the P-to-glia projection was cut. Stimulus-irrelevant P cells tend to generate trains of spikes (see n = 2 and n = 4), which worsens the sensory tuning. Figure 5 (middle) presents phasic (Ib-to-P) inhibitory current in a stimulus-irrelevant (n = 5) P cell. The frequent, transient reduction in inhibitory current during the stimulation period (see the enlarged trace) would give the stimulus-irrelevant
Figure 4: Improvement of neuronal gain function by GABAergic gliotransmission-mediated tonic excitation. (Top) Stimulus-evoked activity (firing rate) as a function of input intensity (excitatory current) without GABAergic gliotransmission-mediated tonic excitation via Ia-to-glia signaling. The weight of recurrent connections between P cells ($w_{ij}^{P,P}$) was strengthened from 0 (inverted triangles) to 4 (diamonds), 5 (squares), 5.5 (triangles), or 6 (circles). (Bottom) Stimulus-evoked activity as a function of input intensity, where $w_{ij}^{P,P} = 6$. The Ia-to-glia connection weight was strengthened from 0 (open circles) to 1 (triangles), 2 (squares), 3 (diamonds), or 5 (filled circles). Note that the top and bottom open circles are identical. (B) Cooperation of GABAergic gliotransmission-mediated tonic (nonsynaptic) excitation and conventional phasic (synaptic) excitation in order to achieve the best neuronal gain function. (Left) Neuronal responses. $w_{i}^{Gl,Ia}$ and $w_{ij}^{P,P}$ are Ia-to-glia and P-to-P connection weights, respectively. Beyond the maximal recurrent connection weight ($w_{ij}^{P,P} > 6$), P cells continued firing even after the termination of the stimulus (not shown). We refer to this as invalid. (Right) Minimal input currents at which a population response to the stimulus can take place in P cells.
Figure 5: Relevance of phasic inhibition in neuronal responsiveness. (Top) Raster plots of action potentials evoked in principal (P) cells without GABAergic gliotransmission-mediated tonic inhibition via P-to-glia signaling. (Middle) Phasic (Ib-to-P) inhibitory current recorded from a stimulus-irrelevant ($n = 5$) P cell. (Bottom) GABAergic gliotransmission-mediated tonic inhibitory current recorded from the same P cell.

(evenly the neighboring $n = 2$ and $n = 4$) P cells a chance of activation because they receive a small but significant amount of excitatory current arising from the graded sensory input (see $\tau_p = 2.6$ in equation A.5 and Table 1). Figure 5 (bottom) evidences no GABAergic gliotransmission-mediated tonic inhibitory current due to the deletion of P-to-glia projection.

To see how the GABAergic gliotransmission-mediated tonic inhibitory mechanism contributes to the sensory tuning, we cut the Ib-to-P projection. Namely, the neuronal suppression is processed solely by tonic inhibition. As shown in Figure 6 (top), the stimulus-irrelevant P cells (see $n = 2, 4,$ and 5) transiently respond at the onset of sensory input. It takes 1 second or so for the network to tune to the stimulus, when these stimulus-irrelevant P
Figure 6: Relevance of GABAergic gliotransmission-mediated tonic inhibition in neuronal responsiveness. (Top) Raster plots of action potentials evoked in principal (P) cells without phasic (Ib-to-P) inhibition. (Middle) Phasic (Ib-to-P) inhibitory current recorded from a stimulus-irrelevant (n = 5) P cell. (Bottom) GABAergic gliotransmission-mediated tonic inhibitory current recorded from the same P cell.

cells cease firing (see the dashed line). Figure 6 (middle) evidences no phasic (Ib-to-P) inhibitory current due to the deletion of Ib-to-P projection. As shown in Figure 6 (bottom), the GABAergic gliotransmission-mediated inhibitory current is gradually increased when stimulated. This slow increase in inhibitory current would give the stimulus-irrelevant P cells a chance to activate at the stimulus onset (top: see n = 2, 4, and 5). The stimulus-irrelevant neuronal activities disappear when the tonic inhibitory current reaches a certain level and the network has finally tuned to the stimulus (top: see the dashed line).

Figure 7 shows how the tonic (nonsynaptic) and phasic (synaptic) inhibitory mechanisms cooperatively work in order to achieve the best sensory tuning performance (top). The rapid inhibition due to a sudden increase in phasic inhibitory current at the stimulus onset (see the middle)
compensates for the insufficient tonic inhibitory current (see the open arrow). The GABAergic gliotransmission-mediated tonic inhibition (see the bottom) compensates for the transient reduction in phasic inhibitory current that frequently takes place during the stimulation period (see the middle) when it reaches a certain level (see the filled arrow). Their cooperation achieves the reliable sensory tuning (see Figure 7, top).

The poor sensory tuning due to the P-to-glia circuitry impairment (see Figure 8A, same as Figure 5) might be overcome if the inhibitory (Ib-to-P) connection weight ($w_{ij}^{P,Ib}$ in equation A.3) is strengthened. However, as shown in Figure 8B, this causes a fatal problem: the reaction speed to the stimulus is decelerated (compare the two dashed lines). The poor reaction performance is due largely to hyperpolarization in ongoing-spontaneous membrane potential, as shown in Figure 8C (see the dashed trace). Since

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**Figure 7:** Relevance of the combinatorial (phasic and tonic) inhibition in sensory tuning. (Top) Raster plots of action potentials evoked in principal (P) cells. (Middle) Phasic (Ib-to-P) inhibitory current recorded from a stimulus-irrelevant ($n = 5$) P cell. (Bottom) GABAergic gliotransmission-mediated tonic inhibitory current recorded from the same P cell. The open and filled arrows roughly indicate insufficient and sufficient tonic inhibitory currents, respectively.
membrane hyperpolarization corresponds functionally to an increase in firing threshold, it will lead to a delay in sensory reaction. Our previous studies (Hoshino, 2008, 2009) indicated a close relationship between reaction speed and ongoing-spontaneous membrane potential. We suggested that an ongoing-spontaneous neuronal state, in which neurons oscillated at a
subthreshold for firing, might be one of the crucial factors for rapid neuronal responses to sensory input. Figure 8D indicates that the ongoing-spontaneous membrane potential is hyperpolarized as the connection weight increases.

Figure 9 presents how the tonic (nonsynaptic) and phasic (synaptic) inhibitory mechanisms cooperatively work in order to achieve the best sensory tuning performance. In Figure 9 (left), the circles represent successful tuning: a population response is evoked only in stimulus-relevant P cells. The crosses represent unsuccessful tuning: a population response is evoked not only in stimulus-relevant P cells but also in stimulus-irrelevant P cells. Figure 9 (right) shows average ongoing-spontaneous membrane potentials. The best sensory tuning performance is achieved, provided that the weights of P-to-glia and Ib-to-P connections are properly chosen (e.g., see the double circle). Namely, the detection of the stimulus is successfully made with ongoing-spontaneous membrane potential less hyperpolarized.

3.4 Robustness Testing. In an additional simulation, we carried out a robustness test. Figure 10 shows the dependence of neuronal responsiveness on sensory input broadness (bottom: see $\tau_p$ in equation A.5). The top and middle panels show stimulus ($f_3$) evoked neuronal (P cell) activities and gain functions, respectively. These results indicate that the neural network model proposed here is robust, ensuring stable and reliable responses to a variety of sensory input stimuli: salient (small $\tau_p$ values) to unsalient (large $\tau_p$ values) sensory information available for the network.
Figure 10: Dependence of neuronal responsiveness on sensory input broadness (see $\tau_p$ in equation A.5). (Top) Stimulus ($f_i$) evoked neuronal (P cell) activities. (Middle) Gain functions. (Bottom) Narrow ($\tau_p = 0.01$) to broad ($\tau_p = 2.6$) sensory input profiles.

Figure 11A presents changes in neuronal responses if the P-glia circuit was made in an unselective manner. Namely, the P-to-glia projection was made not only between but also within cell assemblies. The unselective P-to-glia projection leads to an increase in tonic inhibitory current in stimulus-relevant P cells and thus to depressing their activities (see the filled rectangle for $n = 3$). As shown in Figure 11B, this shifts the gain function (see the triangles). The specific network architecture was employed to achieve the
Figure 11: Dependence of neuronal responsiveness on P-glia circuitry architecture. (A) Stimulus \( \frac{f}{3} \) evoked neuronal (P cell) activities. (B) Gain functions. The P-to-glia projection was made not only between but also within cell assemblies (see the filled rectangles in panel A and triangles in panel B): an unselective circuitry condition. The open rectangles in panel A and circles in panel B represent those obtained under the original (selective) circuitry condition: The P-to-glia projection was made only between different cell assemblies.

optimal network performance (see the open rectangles in Figure 11A and circles in Figure 11B) by which we could clearly show how the GABAergic gliotransmission mechanism contributes to modulating the neuronal gain and tuning to sensory input.

4 Discussion

We simulated a neural network model in order to examine whether and how GABAergic gliotransmission balances intracortical excitation and inhibition, and investigated how it contributes to perceptual information processing: detection of feature stimuli. The network comprises principal cells (P), GABAergic interneurons (Ia, Ib), and glial cells (glia). GABA transporters, embedded in glial plasma membranes, regulated ambient GABA
levels. Hypothetical neuron-glia signaling via inhibitory (Ia-to-glia) and excitatory (P-to-glia) synaptic contacts was assumed. The former let transporters import (remove) GABA from the extracellular space and excited stimulus-relevant P cells. The latter let them export GABA into the extracellular space and inhibited stimulus-irrelevant P cells. The main finding was that the glial membrane transporter gave a combinatorial excitatory-inhibitory effect on P cells in a tonic manner, thereby improving the gain and tuning of neuronal responses. Interestingly, it worked cooperatively with the conventional, phasic excitatory-inhibitory mechanism. We suggest that the GABAergic gliotransmission mechanism may provide balanced intracortical excitation and inhibition so that the best perceptual performance of the cortex can be achieved.

Figure 12 might help in understanding the important conclusion derived from this study. Normal perceptual performance ensured by the conventional, phasic (synaptic) excitation and inhibition (see “normal perform.”) can be improved by the GABAergic gliotransmission-mediated, tonic (non-synaptic) excitation and inhibition (see “best perform.”). The GABAergic gliotransmission-mediated tonic excitation improves the neuronal gain
function (see the top arrow), and the GABAergic gliotransmission-mediated tonic inhibition improves the sensory tuning (see the left arrow). The GABAergic gliotransmission-mediated, tonic excitatory-inhibitory mechanism leads to the best perceptual performance (see the filled arrow). This study points to a new understanding that the GABAergic gliotransmission-mediated regulation of local ambient GABA levels may modulate the neuronal gain and tuning to sensory input. To the best of our knowledge, the new understanding has not yet been experimentally demonstrated, which we hope will be done in the near future.

Simulation studies (Nadkarni, Jung, & Levine, 2008; De Pitta et al., 2012; Fellin, Ellenbogen, De Pitta, Ben-Jacob, & Halassa, 2012) indicated that glia could modulate synaptic transmission by regulating chemical substances such as glutamate, GABA, D-serine, and ATP, which act on pre- and postsynaptic receptors. It was suggested that glia might regulate extracellular ion concentrations, such as $\text{Na}^+$, $\text{K}^+$, and $\text{Cl}^-$, in order to achieve proper functioning of neurons (Volman, Bazhenov, & Sejnowski, 2012; Cressman, Ullah, Ziburkus, Schiff, & Barreto, 2009). The gliotransmission mechanism contributed to modulating neuronal and network functions (i.e., gain and tuning), in which the combinatorial regulation of ambient GABA concentration by glial transporters played a key role. Our previous model (Hoshino, 2013) had transporters on axon terminals, from which GABA molecules were exported into (but not imported from) the extracellular space. The GABA export was enough to show how age-related changes in multistable perception could take place.

Volman, Levine, and Sejnowski (2010) simulated a neural network model and demonstrated that asynchronous release of glutamate from presynaptic terminals could modulate neuronal gain. The novel idea of our study was that the GABAergic gliotransmission mechanism could regulate ambient GABA concentration in a combinatorial manner: an increase around stimulus-irrelevant principal (P) cells and a decrease around stimulus-relevant P cells. The former modulated the tuning and the latter the gain of neuronal responses, thereby improving the network’s perceptual performance.

We employed two distinct interneurons: Ia and Ib. A variety of GABAergic interneurons have been found in the cortex, such as horizontal cells and large, medium, and small multipolar cells (for a survey, see Prieto, Peterson, & Winer, 1994). Large multipolar cells with their wide axonal arbors send signals to distant cells, while small multipolar cells with their narrow axonal arbors are limited to proximal cells. Based on their observations, we let the Ib cell (as large multipolar cell) project to all (nearby to distant) P cells within the same cell assembly and the Ia cell (as small multipolar cell) to its proximal glial cell.

The Ia and Ib cells may correspond to fast and late spiking cells (or regular spiking cells), which, respectively, have short and long membrane time constants: $8.8 \pm 2$ msec and $20.6 \pm 8$ (or $28.5 \pm 12.2$) msec (Kawaguchi, 1995;
Based on these observations, we set the values of membrane capacitance and conductance: $c_{Ia}^{m} = 200\ pF$, $c_{Ib}^{m} = 600\ pF$ and $g_{Ia}^{m} = 20\ nS$, $g_{Ib}^{m} = 15\ nS$ (see Table 1). To make a fast GABAergic gliotransmission-mediated modulatory effect on P cells, we assumed such a short membrane time constant for the Ia cell. If we employ a longer time constant, the reaction time of P cells to sensory input and their firing frequency will be somewhat delayed and decreased, respectively. Nonetheless, we would come to the same conclusion: the GABAergic gliotransmission mechanism can improve the gain and tuning of neuronal responses to sensory input.

Although discussed in detail in our previous study (Hoshino, 2012), we briefly address some important approximations and limitations of our model. A variety of neuron-glia circuits have been evidenced, including chemical (glutamate, GABA) synapses between presynaptic neurons and postsynaptic glial cells (for review, see Bezzi & Volterra, 2001; Fields & Stevens-Graham, 2002; Lin & Bergles, 2004; Overstreet, 2005). Based on their observations, we made the excitatory (P-to-glia) and inhibitory (Ia-to-glia) neuron-to-glia synaptic contacts. Neuron-glia signaling that we neglected here for simplicity might include GABA and glutamate signaling to glia through activation of metabotropic receptors (Verkhratsky, 2010; Velez-Fort, Audinat, & Angulo, 2012).

Glial cells might have a role in regulating extracellular concentrations of transmitters (GABA, glutamate), ions (potassium, hydrogen, calcium), and metabolites (D-serine, ATP) (Fields & Stevens-Graham, 2002; Newman, 2003; Hansson & Rönnbäck, 2003; Verkhratsky, 2010). In this study, we have focused on investigating how ambient GABA-mediated tonic inhibition affects the gain and tuning of neuronal responses. We could model a glial plasma membrane transporter that regulates an ambient GABA level, because the mechanism of GABA transport has been theoretically explained (Richerson & Wu, 2003; Wu, Wang, & Richerson, 2003; Richerson, 2004; Wu et al., 2007).

We did not model those that regulate extracellular levels of glutamate and potassium, because their transport mechanisms have not yet been theoretically explained. For instance, several lines of evidence indicate that a calcium-dependent exocytotic process can export glutamate; however, its neuronal mechanism is uncertain (for review, see Newman, 2003). Glial cells are probably the source of GABA responsible for extrasynaptic GABA$A_r$ receptor-mediated inhibitory current and can export different transmitters (Kozlov, Angulo, Audinat, & Charpak, 2006; Angulo, Le Meur, Kozlov, Charpak, & Audinat, 2008). The question remains: How could each of these different types of gliotransmission be controlled?

If the export of glutamate from glial cells into the extracellular space becomes greater or the import of extracellular potassium into glial cells does not take place, the tonic inhibitory mechanism would not work properly. Due to the limitation of our model (i.e., it was impossible to regulate
extracellular levels of glutamate and potassium as addressed above), we cannot declare that glial inhibitory effects are stronger than glial excitatory effects. We propose here a working hypothesis: GABAergic gliotransmission may prevail in intracortical tonic inhibitory processing, for which suitable spatial organization of glial cells would be required.

**Appendix A: The Neural Network Model**

Dynamic evolution of membrane potential of the $i$th P cell that belongs to cell assembly $n$ is defined by

$$c_m \frac{du^p_i(n; t)}{dt} = -S^p_m(u^p_i(n; t) - u^p_{rest}) + I^{P,P}_i(n; t) + I^{P,ib}_i(n; t) + I^{P}_{i,ext}(n; t) + I^{P}_{inp}(n; t), \quad (A.1)$$

where $I^{P,P}_i(n; t)$ is an excitatory synaptic current from other P cells, $I^{P,ib}_i(n; t)$ an inhibitory synaptic current from Ib cells, $I^{P}_{i,ext}(n; t)$ an inhibitory nonsynaptic current mediated by ambient GABA via extrasynaptic receptors, and $I^{P}_{inp}(n; t)$ an excitatory input current that is provided when presented with sensory feature $f_{inp}$: $inp \in \{0, 1, 2, 3, \ldots, n, \ldots, M\}$. These currents are defined by

$$I^{P,P}_i(n; t) = -\hat{g}_{AMPA}A(u^p_i(n; t) - u^p_{rev}) \sum_{j=1}^{N} w^P_{ij} r^P_j(n; t), \quad (A.2)$$

$$I^{P,ib}_i(n; t) = -\hat{g}_{GABA}(u^p_i(n; t) - u^{GABA}_{rev}) \sum_{j=1}^{N} w^{ib}_{ij} r^{ib}_j(n; t), \quad (A.3)$$

$$I^{P}_{i,ext}(n; t) = -\hat{g}_{GABA}(u^p_i(n; t) - u^{GABA}_{rev}) \delta_{P,i,ext}(n; t), \quad (A.4)$$

$$I^{P}_{inp}(n; t) = \alpha_pe^{-\frac{(n-inp)^2}{\tau^2}}. \quad (A.5)$$

Dynamic evolution of membrane potential of the $i$th Ia and Ib cells that belong to cell assembly $n$ is defined by

$$c_m \frac{du^{la}_i(n; t)}{dt} = -S^{la}_m(u^{la}_i(n; t) - u^{la}_{rest}) + I^{la,P}_i(n; t), \quad (A.6)$$

$$c_m \frac{du^{lb}_i(n; t)}{dt} = -S^{lb}_m(u^{lb}_i(n; t) - u^{lb}_{rest}) + I^{lb,P}_i(n; t), \quad (A.7)$$
where $I_{i}^{la,p}(n; t)$ and $I_{i}^{lb,p}(n; t)$ are excitatory synaptic currents from P cells. These currents are defined by

$$I_{i}^{la,p}(n; t) = -\tilde{g}_{\text{AMPA}}(u_{i}^{la}(n; t) - u_{\text{rev}}^{\text{AMPA}})w_{i}^{la,p}(n; t), \quad (A.8)$$

$$I_{i}^{lb,p}(n; t) = -\tilde{g}_{\text{AMPA}}(u_{i}^{lb}(n; t) - u_{\text{rev}}^{\text{AMPA}}) \sum_{n'=0(n' \neq n)}^{M} w_{i}^{lb,p}(n, n')r_{i}^{p}(n'; t). \quad (A.9)$$

Dynamic evolution of membrane potential of the $i$th glial cell that belongs to cell assembly $n$ is defined by

$$c_{m}^{Gl} \frac{d u_{Gl}^{Gl}(n; t)}{d t} = -g_{n}^{Gl}(u_{Gl}^{Gl}(n; t) - u_{\text{rest}}^{Gl}) + I_{i}^{Gl,p}(n; t) + I_{i}^{Gl,la}(n; t), \quad (A.10)$$

where $I_{i}^{Gl,p}(n; t)$ and $I_{i}^{Gl,la}(n; t)$ are excitatory and inhibitory synaptic currents from P and la cells, respectively. These currents are defined by

$$I_{i}^{Gl,p}(n; t) = -\tilde{g}_{\text{AMPA}}(u_{i}^{Gl}(n; t) - u_{\text{rev}}^{\text{AMPA}}) \sum_{n'=0(n' \neq n)}^{M} w_{i}^{Gl,p}(n, n')r_{i}^{p}(n'; t), \quad (A.11)$$

$$I_{i}^{Gl,la}(n; t) = -\tilde{g}_{\text{GABA}}(u_{i}^{Gl}(n; t) - u_{\text{rev}}^{\text{GABA}})w_{i}^{Gl,la}r_{i}^{la}(n; t). \quad (A.12)$$

In these equations, $r_{j}^{p}(n; t)$ is the fraction of AMPA receptors in the open state triggered by presynaptic action potentials of the $j$th P cell. $r_{j}^{lb}(n; t)$ and $r_{j}^{la}(n; t)$ are the fractions of intrasynaptic GABA$_a$ receptors in the open state triggered by presynaptic action potentials of the $j$th Ib cell and la cell, respectively. $r_{i,ext}^{p}(n; t)$ is the fraction of extrasynaptic GABA$_a$ receptors, located on the $i$th P cell, in the open state provoked by ambient GABA. The receptor dynamics and ambient GABA concentration dynamics are defined in Appendixes B and C. For model parameters and their values, see Table 1.

**Appendix B: Receptor Dynamics and Action Potential Generation**

Receptor dynamics is based on a study (Destexhe, Mainen, & Sejnowski, 1998) and described as

$$\frac{d r_{j}^{p}(n; t)}{d t} = \alpha_{\text{AMPA}}[\text{Glut}]_{j}(n; t)(1 - r_{j}^{p}(n; t)) - \beta_{\text{AMPA}}r_{j}^{p}(n; t), \quad (B.1)$$
\[ \frac{d r^X_j(n; t)}{dt} = \alpha_{GABA}[GABA]^X_j(n; t)(1 - r^X_j(n; t)) - \beta_{GABA}^X_j(n; t), \]
\( (X = Ia, Ib) \)  
(B.2)

\[ \frac{d r^P_{i,ext}(n; t)}{dt} = \alpha_{GABA}[GABA]^P_{i,ext}(n; t)(1 - r^P_{i,ext}(n; t)) - \beta_{GABA}^P_{i,ext}(n; t). \]
(B.3)

where \([Glut]^X_j(n; t)\) and \([GABA]^X_j(n; t)\) are concentrations of glutamate and GABA in synaptic clefts, respectively. \([Glut]^X_j(n; t) = 1\) mM and \([GABA]^X_j(n; t) = 1\) mM for 1 msec when the presynaptic \(j\)th P cell and type X cell fire, respectively. Otherwise, \([Glut]^X_j(n; t) = 0\) and \([GABA]^X_j(n; t) = 0\). Concentration of ambient GABA, \([GABA]^P_{i,ext}(n; t)\), is defined in Appendix C.

The probability of neuronal firing is defined by

\[ \text{Prob}[Y_j(n; t); \text{firing}] = \frac{1}{1 + e^{-\eta_{Y_j}(u_{Y_j}(n; t) - \zeta_{Y_j})}}. \]
\( (Y = P, Ia, Ib) \)  
(B.4)

When a cell fires, its membrane potential is depolarized to \(-10\) mV, which is kept for 1 msec and then reset to the resting potential. For model parameters and their values, see Table 1.

**Appendix C: Dynamics of Ambient GABA Concentration**

Concentration of ambient GABA around the \(i\)th P cell that belongs to cell assembly \(n\) is defined by

\[ \frac{d[GABA]^P_{i,ext}(n; t)}{dt} = -\gamma_{in}(GABA)^P_{i,ext}(n; t) - [GABA]^0_{ext} + T_{Gl}(\text{GABA}_{\text{max}} - [GABA]^P_{i,ext}(n; t))[GABA]^P_{i,ext}(n; t) - [GABA]^P_{i,ext}(n; t) - \text{GABA}_{\text{min}} \times (u_{Gl}^i(n; t) - u_{Gl}^i(n; t)). \]
(C.1)

For the details of model parameters and their values, see Table 1 and our previous studies (Hoshino, 2009, 2010, 2011a, 2011b, 2012, 2013).

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References


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