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RESEARCH REPORT

# Dynamic modulation of an orientation preference map by GABA responsible for age-related cognitive performance

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**Abstract** Accumulating evidence suggests that cognitive declines in old (healthy) animals could arise from depression of intracortical inhibition, for which a decreased ability to produce GABA during senescence might be responsible. By simulating a neural network model of a primary visual cortical (V1) area, we investigated whether and how a lack of GABA affects cognitive performance of the network: detection of the orientation of a visual bar-stimulus. The network was composed of pyramidal (P) cells and GABAergic interneurons such as small (S) and large (L) basket cells. Intrasynaptic GABA-release from presynaptic S or L cells contributed to reducing ongoing-spontaneous (background) neuronal activity in a different manner. Namely, the former exerted feedback (S-to-P) inhibition and reduced the frequency (firing rate) of action potentials evoked in P cells. The latter reduced the number of saliently firing P cells through lateral (L-to-P) inhibition. Non-vesicular GABA-release, presumably from glia and/or neurons, into the extracellular space reduced the both, activating extrasynaptic GABAa receptors and providing P cells with tonic inhibitory currents. By this combinatorial, spatiotemporal inhibitory mechanism, the background activity as noise was significantly reduced, compared to the stimulus-evoked activity as signal, thereby improving signal-to-noise (S/N) ratio. Interestingly, GABA-spillover from the intrasynaptic cleft into the extracellular space was effective for improving orientation selectivity (orientation bias), especially when distractors interfered with detecting the bar-stimulus. These simulation results may provide some insight into how the depression of intracortical inhibition due to a reduction in GABA content in the brain leads to age-related cognitive decline.

**Keywords** Age-related cognitive decline · Neural network model · GABA-mediated intracortical inhibition · Orientation selectivity · Primary visual cortex

## Introduction

It is well known that aging adversely affects cognitive brain functions in humans. Namely, cognitive performance advances progressively from infancy to young adulthood and then declines toward old age. Salthouse (1996) provided clear evidence of age-related cognitive decline, in which the processing speed of perceptual tasks (e.g., letter comparison and pattern comparison) increased from infancy to young adulthood and then decreased toward old age. Deficit in memory recall is another common problem in aging (Cohen and Burke 1993). Old (healthy) subjects had difficulty in accessing stored information, or memories, even though there had been no decrease in memory performance in that they were able to retrieve information with better cues. Craik and Bialystok (2006) speculated that poor cognitive performance in infancy might be due to incomplete representation of information and that in old

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age might be associated with difficulties in accessing the information.

Although little is known about the underlying neuronal mechanism of age-related cognitive decline, experimental studies provided some insight into it. Schmolesky et al. (2000) demonstrated that old macaque monkeys exhibited decreased orientation selectivity and direction selectivity accompanied by a greater increase in ongoing-spontaneous activity than in stimulus-evoked activity in V1 (primary visual cortex) cells, resulting in a decrease in signal-to-noise (S/N) ratio. Their follow-up study (Leventhal et al. 2003) investigated how gamma-aminobutyric acid (GABA) affects responses of V1 cells to oriented bars presented to visual receptive fields. Administration of GABA enhanced S/N ratio, accompanied by a greater decrease in ongoing-spontaneous activity than in stimulus-evoked activity in V1 cells. The researchers suggested that age-related cognitive decline might arise from depression of intracortical inhibition, for which a decreased ability to produce GABA during senescence might be responsible. Important questions still unanswered are as follows: how is the depression of intracortical inhibition caused, and how does it lead to age-related cognitive decline?

Distinct modes of GABA-release into target regions might be responsible for intracortical inhibition, for example, (1) intrasynaptic release into the synaptic cleft triggered by a presynaptic action potential, (2) its spillover into the extracellular space, and iii) non-vesicular release, presumably from glia and/or neurons, into the extracellular space (Semyanov et al. 2004). The first type of GABA-release activates intrasynaptic GABAa receptors, while the second and third ones activate extrasynaptic GABAa receptors (Somogyi et al. 1989; Nusser et al. 1995; Brickley et al. 1996; Soltesz and Nusser 2001). Extrasynaptic GABAa receptors have been found in the cerebellum and cortex (Drasbek and Jensen 2006; Scimemi et al. 2006).

In the cortex, anatomical and physiological properties of GABAergic interneurons are markedly diverse (Gupta et al. 2000). Typical GABAergic interneurons found in the cortex include basket cells, bitufted cells, and martinotti cells. It is also well known that about 50 % of GABAergic cortical interneurons are basket cells (Markram et al. 2004). Basket cells tend to synapse on pyramidal cells (Somogyi et al. 1983), have diversity especially in their axonal arborizations, and are classified roughly into two subclasses: large and small basket cells (Wang et al. 2002). The large basket cells and small basket cells may correspond to wide arbor basket cells and local arbor basket cells, respectively (Krimer and Goldman-Rakic 2001), which have aspiny wide (up to $\sim$1000 μm) and narrow (up to $\sim$300 μm) axonal arbors, and synapse mostly on the somata of target cells.

In the primary visual cortex, a long range inhibitory system made of large basket cells provides broadband inhibition toward its target cells (Kisvarday et al. 1993). A single large basket cell provides input to regions representing the whole range of orientations, that is, to the iso-orientation ($\pm 30°$), oblique-orientation ($\pm[30 - 60]°$), and cross-orientation ($\pm[60 - 90]°$) columns (Kisvarday and Eysel 1993; Buzas et al. 2001). This implies that the large basket cells might have a lateral inhibitory effect on pyramidal cells via their long and wide axonal arbors and contribute to tuning to the orientations (angles) of bar-stimuli.

It is also well known that excitatory and inhibitory neurons frequently form reciprocal synaptic connections (Martin 2002). Zilberter (2000) has reported that 75 % ($n = 80$) of pairs of a pyramidal cell and an interneuron form reciprocal synaptic connections. The interneuron might be small basket cell or chandelier cell (Krimer and Goldman-Rakic 2001). Such reciprocal connections are likely to mediate feedback inhibition as the activity of pyramidal cells becomes greater.

Based on these experimental observations, we construct a neural network model of an orientation preference map, which is simple and functional but involves key neuronal elements. Orientation columns consist of cell units. A cell unit contains one pyramidal cell, one small basket cell, and one large basket cell. In the model, we assume three distinct modes of GABA-release into target regions as addressed previously, namely intrasynaptic release into the synaptic cleft, its spillover into the extracellular space, and non-vesicular release into the extracellular space. We investigate how these modes of GABA-supply affect the performance of the V1 network (signal-to-noise ratio, orientation selectivity, and reaction time), and how the depression of intracortical inhibition is caused and how it leads to age-related cognitive decline.

## Methods

A functional, minimal neural network model of an orientation preference map is schematically illustrated in Fig. 1a. Each domain ($\theta_n$: $0 \leq n \leq 7$), so-called orientation column, has a preference to one particular orientation, ranging from 0 to $7\pi/8$ (radian), and consists of cell units as shown in Fig. 1b ("gray oval"). A cell unit contains one pyramidal cell ("P"), one small basket cell ("S"), and one large basket cell ("L"). Within the same column, P cells receive excitatory projections from each other. Each P cell receives an inhibitory projection from its accompanying S cell and receives inhibitory projections from L cells that belong to other orientation columns. An excitatory current

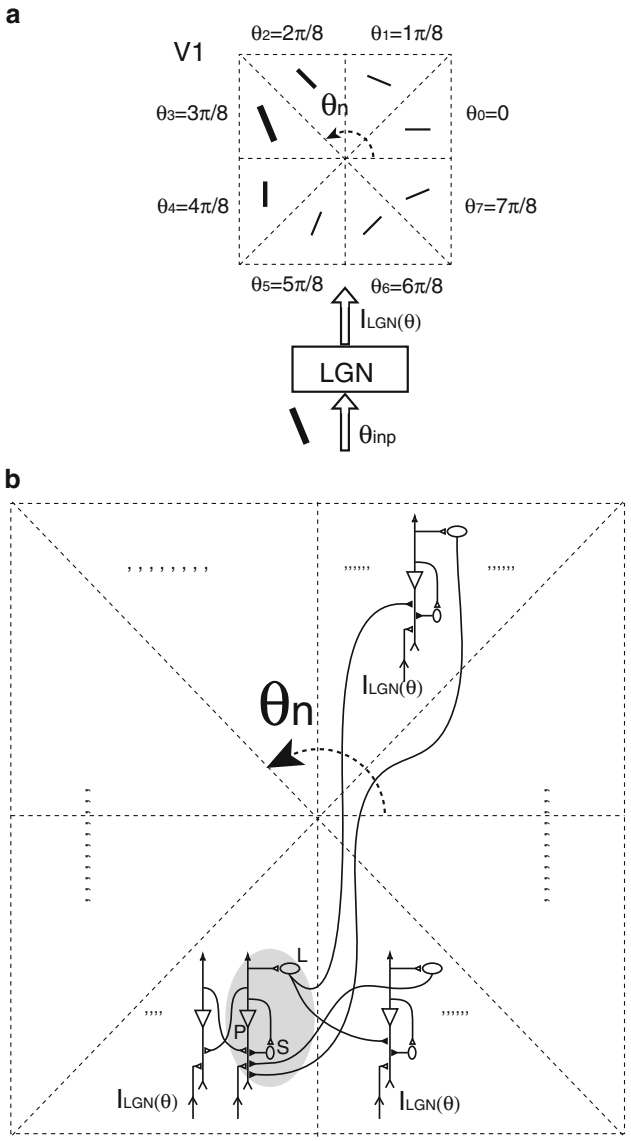


**Fig. 1** A neural network model of a primary visual cortical (V1) area. **a** Orientation columns organized functionally (but not anatomically), having orientation preferences ranging from 0 to $7\pi/8$ (radian). The V1 network receives input signals ($I_{\mathrm{LGN}}(\theta)$) from the lateral geniculate nucleus (LGN) to which an oriented bar-stimulus ($\theta_{\mathrm{inp}}$) is presented. **b** Each column consists of cell units ("gray oval"): one pyramidal cell ("P"), one small basket cell ("S"), and one large basket cell ("L")

($I_{\mathrm{LGN}}(\theta)$) is provided as a sensory input to the corresponding P cells when presented with a sensory stimulus ($\theta_{\mathrm{inp}}$). The S and L cells have narrow and wide axonal arbors and provide feedback and lateral inhibitory effects on P cells, respectively. Details of the network dynamics regulated by these interneurons have been reported in our previous studies (Hoshino 2006, 2008a; Totoki et al. 2010; Fujiwara et al. 2011; Miyamoto et al. 2012). For model descriptions, see Appendix.

## Results

### Neuronal responses to visual stimulation

In this section, we show how neurons respond to visual stimulation. Intra- and extrasynaptic (ambient) GABA concentrations are varied, mimicking young and old (healthy) subjects, in order to see whether and how they affect a simple perceptual task: detection of a visual bar-stimulus.

Figure 2a presents membrane potentials (top) and raster plots of action potentials (bottom) evoked in pyramidal (P) cells of the network assumed for a young subject, where an oriented ($\theta = 5\pi/8$) bar-stimulus was presented briefly (see the horizontal bar). Figure 2b presents those assumed for an old subject in which the amounts of intrasynaptic and non-vesicular GABA-release were reduced to half: $[\mathrm{GABA}]_j^K(\theta;\ t) = \mathrm{GABA}_K = 0.5$ mM (K = S, L) and $[\mathrm{GABA}]_0 = 0.5$ μM (see Eqs. 12, 14 in Appendix). In the old network, both the ongoing-spontaneous (background) and stimulus-evoked neuronal activities are increased.

Figure 3a presents the time course of ambient GABA concentration in the young (thick trace) or old (thin trace) network. The overall GABA concentration in the old network is lower than that in the young network. The transient increase in ambient GABA concentration, triggered by the stimulus, arises from GABA-spillover (from synaptic clefts) into the extracellular space. Figure 3b (left) presents firing rates ("circles") of a P cell, when presented with a series of orientations ($0 \le \theta \le 7\pi/8$). S/N ratio ("squares") is the ratio of the stimulus-evoked firing rate to the ongoing-spontaneous firing rate for the young (top-left) or old (bottom-left) network. These results indicate that the P cell has its orientation preference to $\theta = 5\pi/8$.

To quantitatively evaluate the orientation preference, we calculated orientation bias (OB), which is frequently used for visual systems such as the lateral geniculate nucleus (LGN) (Xu et al. 2002) and the primary visual cortex (Leventhal et al. 1995). We briefly explain it. Responses of a cell to different orientations (0, $\pi/8$, $2\pi/8$, $3\pi/8$, $4\pi/8$, $5\pi/8$, $6\pi/8$, $7\pi/8$) are stored as a series of vectors. The vectors are added and divided by the sum of the absolute values of the vectors. The angle and the length of the resultant vector provide, respectively, the preferred direction and the degree of orientation preference of the cell. The degree of orientation preference is termed "orientation bias (OB)." Note that since the periodicity of orientation is $\pi$, the angles of bar-stimuli are multiplied by a factor of two. As a result, OB ranges from 0 to 1.0, with 0 being completely insensitive to orientation and 1.0 responding to only one orientation. As shown in Fig. 3b, OB = 0.712 for the young network (top-right) and 0.583 for the old network (bottom-right) indicate that the orientation preference

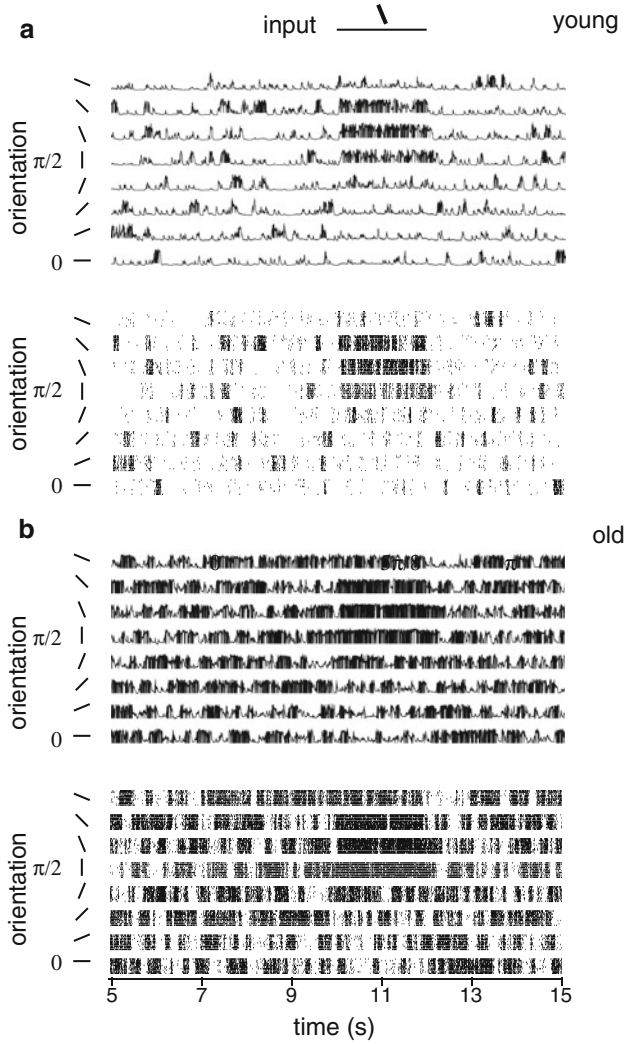


**Fig. 2** Ongoing-spontaneous and stimulus-evoked neuronal activities. **a** Membrane potentials (*top*) and raster plots of action potentials (*bottom*) evoked in P cells for each orientation column $\theta$ ($0 \leq \theta \leq 7\pi/8$). Intrasynaptic and basal GABA concentrations, assumed for a young subject, were $GABA_K$ = 1 mM (K = S, L) and $[GABA]_0$ = 1 μM (see Appendix), respectively. The *horizontal bar* indicates a time period of stimulation. **b** Membrane potentials (*top*) and raster plots (*bottom*) for $GABA_K$ = 0.5 mM (K = S, L) and $[GABA]_0$ = 0.5 μM, assumed for an old subject

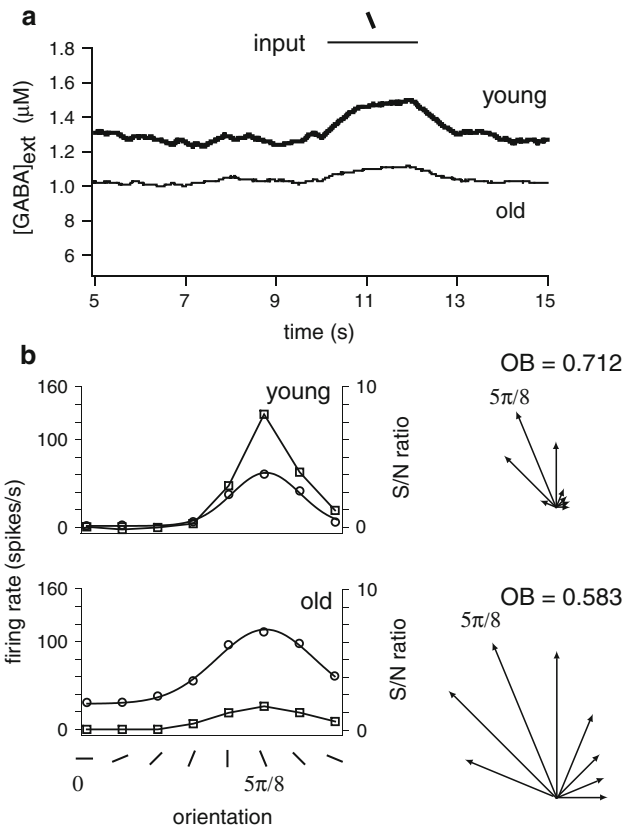


**Fig. 3** Perceptual performance of the network. **a** Time courses of ambient GABA concentrations in the "young" and "old" networks shown in Fig. 2. **b** *Left* firing rates of a P cell during the stimulus-presentation time period (*circles*) for young (*top-left*) and old (*bottom-left*) networks. The network was stimulated with a series of orientations ($0 \leq \theta \leq 7\pi/8$). Signal-to-noise (S/N) ratios (*squares*) are shown. *Right* orientation bias (*OB*). Responses (firing rates) of the P cell are expressed in vectors. For the details of S/N and OB, see the text

is deteriorated in the old network. Experimental studies (Schmolesky et al. 2000; Leventhal et al. 2003) reported a similar tendency.

Next, we investigated how intrasynaptic GABA molecules supplied by small (S) and large (L) basket cells ($[GABA]_j^S(\theta; t) = GABA_S$ and $[GABA]_j^L(\theta; t) = GABA_L$; see Eq. 12 in Appendix) and ambient (extrasynaptic) GABA molecules supplied by non-vesicular release ($[GABA]_0$; see Eq. 14 in Appendix) affect the network performance. Figure 4a (left) presents firing rates of a P cell during the ongoing-spontaneous ("triangles") and stimulus-presentation ("circles") time periods, S/N ratio ("squares"), and OB (right) as a function of $GABA_S$. Figure 4b, c are those for $GABA_L$ and $[GABA]_0$, respectively. We found that these (intrasynaptic and non-vesicular) GABA-release modes can improve S/N ratio, when neuronal suppression is greater in ongoing-spontaneous (background) activity than in stimulus-evoked activity. Note that the L cells contribute to responding selectively to the applied stimulus, that is, to improving OB (Fig. 4b; right).

## Influences of intrasynaptic and non-vesicular GABA-release on ongoing-spontaneous neuronal activity

As has been shown in the previous section, the reduction in ongoing-spontaneous neuronal activity is essential for improving S/N ratio. In this section, we show how the intrasynaptic and non-vesicular GABA-release modes affect the ongoing-spontaneous neuronal activity.

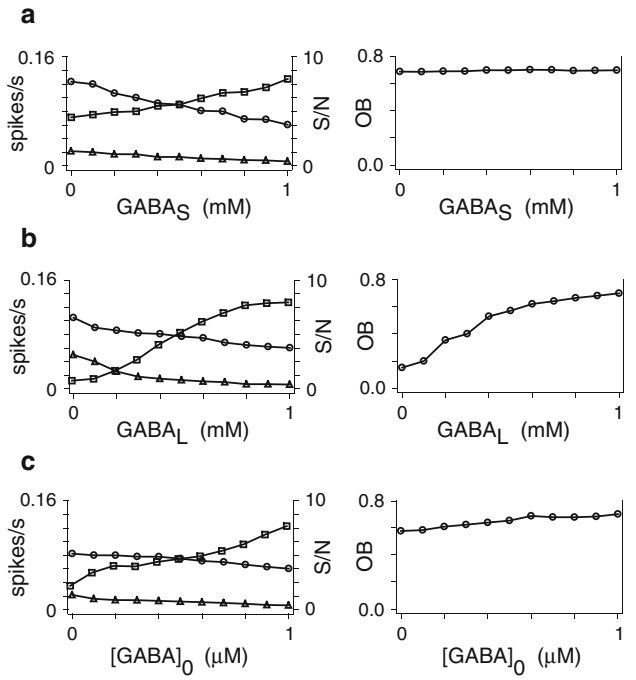


**Fig. 4** Influences of intrasynaptic and non-vesicular GABA-release modes on ongoing-spontaneous neuronal activity. **a** Firing rates of a P cell during the ongoing-spontaneous (*triangles*) and stimulus-presentation (*circles*) time periods, S/N ratio (*squares*) and OB (*right*) as a function of intrasynaptic GABA concentration ($GABA_S$) supplied by presynaptic S cells. **b** Those for the intrasynaptic GABA concentration ($GABA_L$) supplied by presynaptic L cells. **c** Those for the basal (ambient GABA) concentration ($[GABA]_0$) supplied by non-vesicular GABA-release

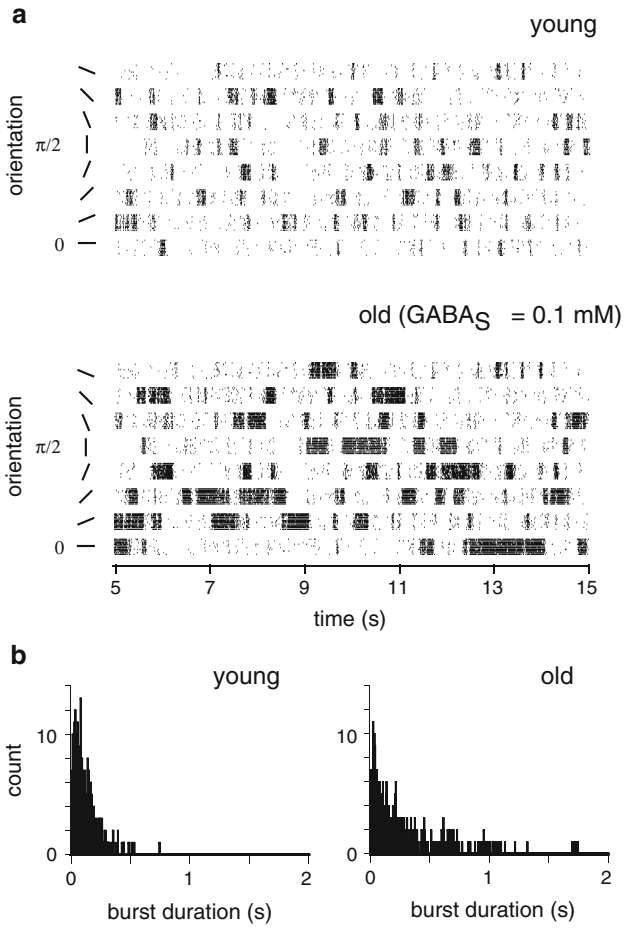


**Fig. 5** Dependence of ongoing-spontaneous neuronal activity on intrasynaptic GABA concentration supplied by presynaptic S cells. **a** Raster plots of action potentials evoked in P cells for the young (*top*) or old (*bottom*) network in which the intrasynaptic GABA concentration was reduced to $GABA_S = 0.1$ mM. **b** Histograms of burst durations for the young (*left*) and old (*right*) networks shown in **a**

Figure 5a presents the dependence of ongoing-spontaneous neuronal activity on intrasynaptic (S-to-P) GABA concentration. A reduction in intrasynaptic GABA concentration (bottom; $GABA_S = 0.1$ mM) results in greater action potential generation. A notable finding is that the lower GABA concentration makes P cells generate action potentials in a dense manner in "time," emitting longer bursts, which are quantitatively shown in Fig. 5b (right). The longer bursts arise from depressed feedback inhibition due to a decrease in intrasynaptic GABA-release from presynaptic S cells.

Figure 6 presents the dependence of ongoing-spontaneous neuronal activity on intrasynaptic (L-to-P) GABA concentration. A reduction in intrasynaptic GABA concentration (bottom; $GABA_L = 0.1$ mM) results in greater action potential generation. A notable finding is that the lower GABA concentration makes P cells generate action potentials in a dense manner in "space," where multiple dynamic cell assemblies are allowed to emerge at the same time. This overlapping neuronal behavior arises from depressed lateral inhibition due to a decrease in intrasynaptic GABA-release from presynaptic L cells.

Figure 7a presents the dependence of ongoing-spontaneous neuronal activity on basal concentration that is supplied by non-vesicular GABA-release: $[GABA]_0$. Its reduction (bottom; $[GABA]_0 = 0.1$ μM) results in greater action potential generation, in which P cells generate action potentials in a dense manner in both "time" and "space." The lower ambient GABA concentration increases the overall neuronal activity (firing rate) as shown in Fig. 7b (see the solid trace).

These results indicate that the intrasynaptic and non-vesicular GABA-release modes contribute to reducing ongoing-spontaneous (background) neuronal activity in different manners. Namely, the intrasynaptic feedback inhibition by presynaptic S cells reduces the frequency (firing rate) of action potentials, the intrasynaptic lateral inhibition by presynaptic L cells reduces the number of saliently firing neurons, and the non-vesicular GABA-release

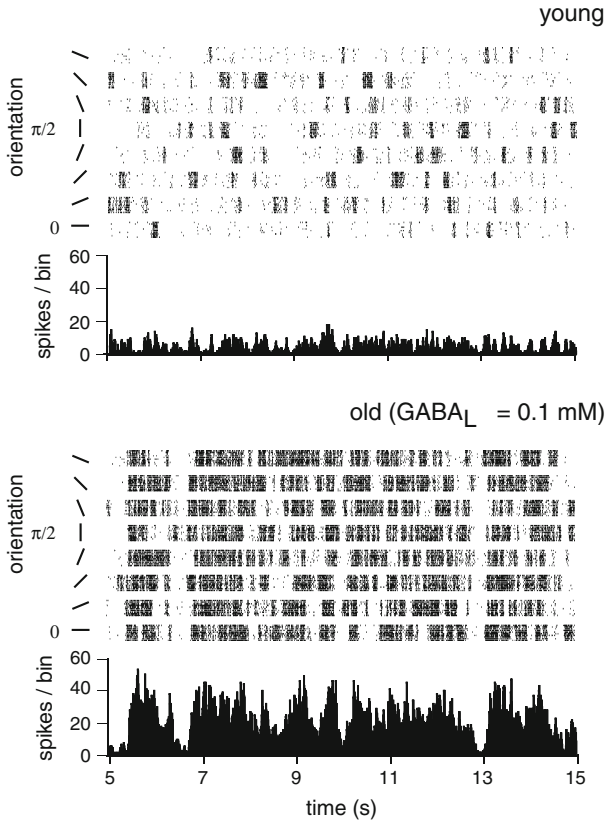


**Fig. 6** Dependence of ongoing-spontaneous neuronal activity on intrasynaptic GABA concentration supplied by presynaptic L cells. Raster plots of action potentials evoked in P cells together with the number of spikes observed within a time-window (bin = 5 ms) for the young (*top*) or old (*bottom*) network in which the intrasynaptic GABA concentration was reduced to $GABA_L$ = 0.1 mM

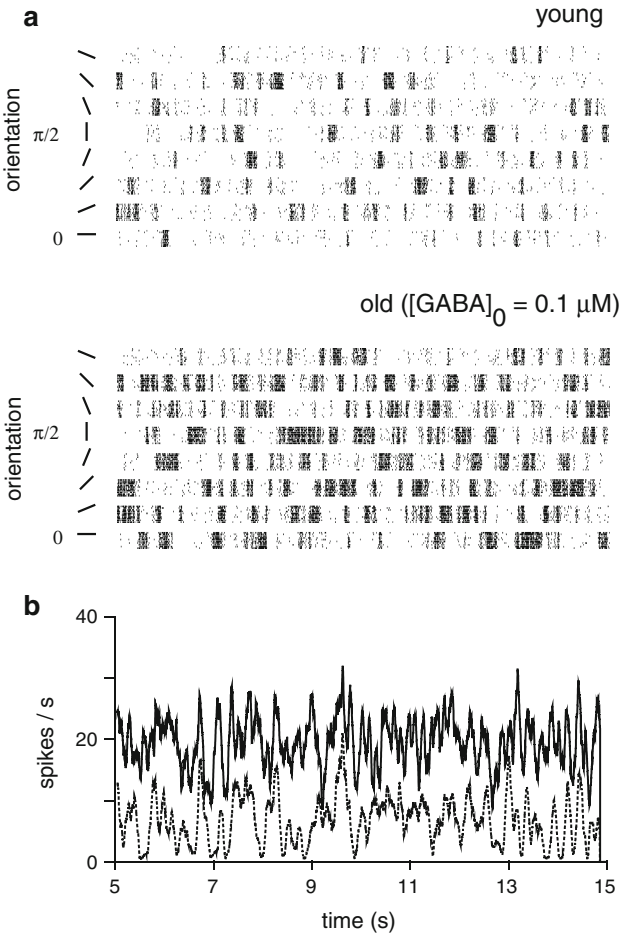


**Fig. 7** Dependence of ongoing-spontaneous neuronal activity on basal (ambient GABA) concentration. **a** Raster plots of action potentials evoked in P cells for the young (*top*) or old (*bottom*) network in which the basal concentration supplied by non-vesicular GABA-release was reduced to $[GABA]_0$ = 0.1 μM. **b** Firing rates of a P cell for the young (*dashed trace*) and old (*solid trace*) networks shown in **a**

mode reduces the both. By this combinatorial, spatiotemporal inhibitory mechanism, the background activity as noise can be significantly reduced, compared to the stimulus-evoked activity as signal, thereby improving the S/N ratio.

## Significance of GABA-spillover for sensory information processing

In this section, we show whether and how GABA-spillover from synaptic clefts into the extracellular space affects the network performance, if the perception of a bar is interfered with distractors.

Figure 8a presents the dependence of orientation bias (OB) on the ratio of stimulus ($\theta_2$) to distractor ($\theta_n$: $n \neq 2$) intensity, indicating that GABA-spillover works for OB enhancement ("change in OB"), when the fraction of distractors increases ("circles"). As shown in Fig. 8b, the distractors accelerate the intrasynaptic GABA-release from presynaptic S and L cells and thus enhance GABA-spillover, thereby increasing the ambient GABA concentration (see the upper arrows).

As shown in Fig. 9a, we compared reaction time of P cells to the stimulus between these two cases: with (top) or without (middle) GABA-spillover. Profiles of ambient GABA concentrations are shown at the bottom. Note that the maximal ambient GABA concentrations were adjusted to the same value (bottom), by which we could obtain almost identical OB values for these two cases. As shown in Fig. 9a (middle) and will be quantitatively shown in Fig. 10a (right), the ongoing-spontaneous membrane potentials of P cells tend to hyperpolarize, if the GABA-spillover does not take place. This membrane hyperpolarization results in prolonging the reaction time to the stimulus as shown in Fig. 9b (bottom). Figure 10a presents distributions of ongoing-spontaneous membrane potentials of a P cell with (left) and without (right) GABA-spillover, respectively, indicating that the

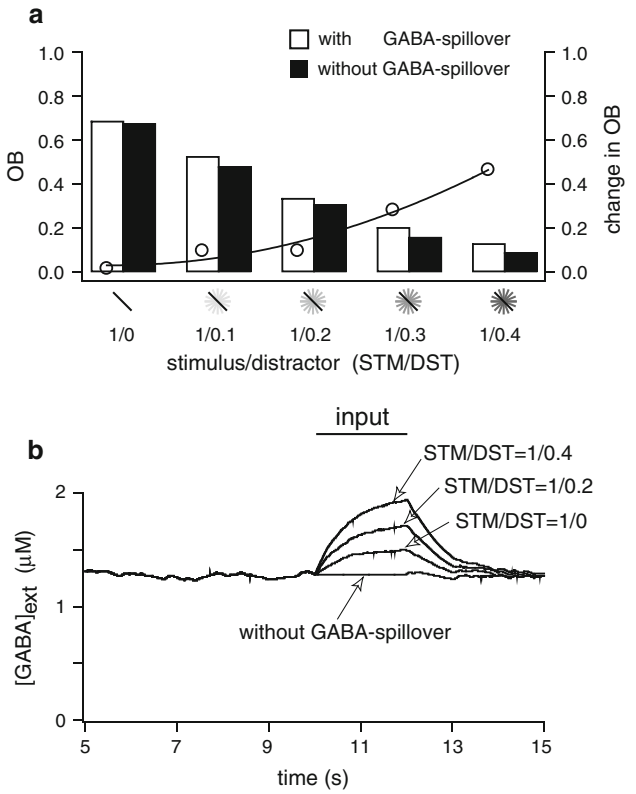


**Fig. 8** Dependence of orientation bias (*OB*) on the ratio of stimulus-intensity to distractor-intensity. **a** OB when stimulated (see the *single black bar* on the abscissa) together with distractors (see the *multiple gray scale bars* superimposed on the abscissa). *Open* and *filled rectangles* denote OBs with and without GABA-spillover, respectively. OB can be significantly enhanced ("change in OB"), provided that the GABA-spillover mechanism works (*circles*). **b** Dependence of ambient GABA concentration on the ratio of stimulus-intensity to distractor-intensity

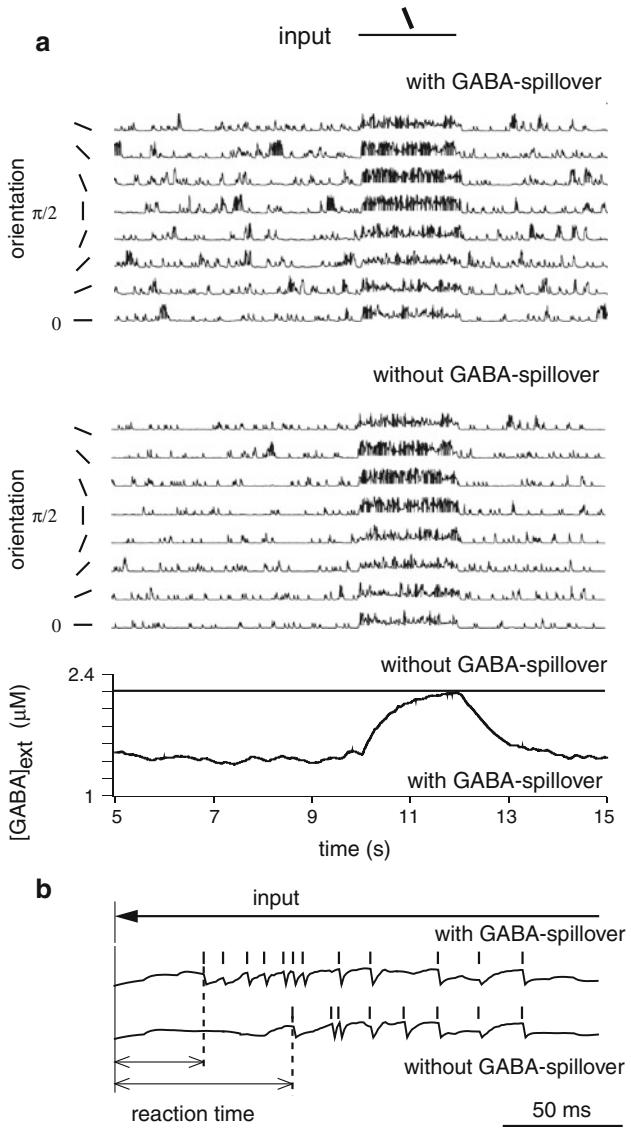


**Fig. 9** Dependence of ongoing-spontaneous neuronal activity on GABA-spillover. **a** Membrane potentials with (*top*) or without (*middle*) GABA-spillover and ambient GABA concentrations (*bottom*). Note that the same maximal ambient GABA concentration (~2.2 μM) yielded almost identical OB values (not shown). **b** Reaction time of a stimulus-relevant P cell to the stimulus: input. Neuronal spikes are overlaid on the membrane potentials. The reaction speed can be significantly accelerated by GABA-spillover (*top-trace*), compared to that without GABA-spillover (*bottom-trace*)

GABA-spillover mechanism allows the P cell to depolarize below firing threshold (left).

As a ready state for sensory input, the ongoing-spontaneous activity has a great impact on subsequent neuronal information processing (Hoshino 2008b, 2009, 2010, 2011a). Figure 10b shows a relationship between the reaction time of a P cell and its ongoing-spontaneous membrane potential just (1 msec) before the stimulus onset. The same stimulus was presented repeatedly and arbitrary in time. We found that the greater the membrane depolarization, the shorter the reaction time. This result indicates that the ongoing-spontaneous subthreshold neuronal state, achieved by the GABA-spillover mechanism, allows the network to respond rapidly to subsequent sensory stimulation.

## Discussion

Accumulating evidence suggests that age-related cognitive decline could arise from depression of intracortical inhibition, for which a decreased ability to produce GABA during senescence might be responsible. By simulating a neural network model of a primary visual cortical (V1) area, we investigated whether and how a lack of GABA affects perceptual performance of the network: detection of the orientation of a visual bar-stimulus. The network was composed of pyramidal (P) cells, small basket (S) cells, and large basket (L) cells. To exert intracortical inhibition, the network was supplied with GABA in three distinct

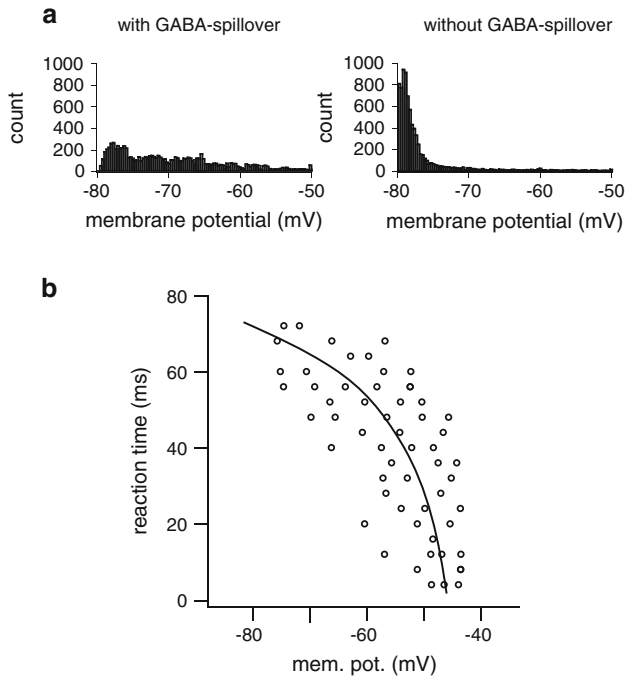


**Fig. 10** Dependence of ongoing-spontaneous membrane potential and reaction time on GABA-spillover. **a** Distributions of ongoing-spontaneous membrane potentials, where the GABA-spillover mechanism worked (*left*) or not (*right*). These membrane potentials were recorded from a P cell for 10 s in an interval of 1 ms. Bin for the counts was 0.1 mV. **b** Reaction time versus ongoing-spontaneous membrane potential of the P cell for **a** (*left*), in which the membrane potentials were recorded just (1 ms) before stimulus onset. The same stimulus was presented repeatedly and arbitrary in time

manners: (1) intrasynaptic release into synaptic clefts, (2) non-vesicular release, presumably from glia and/or neurons, into the extracellular space, and iii) spillover from synaptic clefts into the extracellular space. By simulating the network model, we investigated how GABA affects signal-to-noise (S/N) ratio, orientation bias (OB), and reaction time.

Intrasynaptic GABA-release from presynaptic S or L cells contributed to reducing ongoing-spontaneous (background) neuronal activity in a different manner. Namely, the former exerted feedback (S-to-P) inhibition and reduced the frequency (firing rate) of action potentials evoked in P cells. The latter reduced the number of saliently firing P cells through lateral (L-to-P) inhibition. Non-vesicular GABA-release into the extracellular space reduced the both, activating extrasynaptic GABAa receptors and providing P cells with tonic inhibitory currents. By this combinatorial, spatiotemporal inhibitory mechanism, the background activity as noise was significantly reduced, compared to the stimulus-evoked activity as signal, thereby improving the signal-to-noise (S/N) ratio. Interestingly, GABA-spillover from the synaptic cleft into the extracellular space was effective for improving the stimulus selectivity (orientation bias), especially when distractors interfered with detecting the bar-stimulus. These simulation results may provide some insight into how the depression of intracortical inhibition due to a reduction in GABA content in the brain leads to age-related cognitive decline.

In general, if neuronal activity, for any reason, happens to be increased (e.g., by noise from external environments or by irrelevant bombardment from other brain areas), ongoing-spontaneous neuronal activity would be increased and thus S/N ratio worsened. This problem can be overcome, provided that the GABA-spillover mechanism works. Namely, the greater the ongoing-spontaneous activity is, the greater the GABA spills over into the extracellular space, and therefore the greater the suppression of ongoing-spontaneous neuronal activity. This "self-inhibitory" system, mediated by the neuronal activity-dependent GABA-spillover mechanism, may contribute to maintaining the background neuronal activity at a low level and, therefore, to keeping S/N ratio relatively high.

The neuronal activity-dependent GABA-spillover mechanism was also effective in order to keep P cells oscillating near firing threshold (see Fig. 10), by which the reaction speed to sensory stimulation was accelerated. We suggest that the ongoing-spontaneous subthreshold neuronal state, achieved through GABA-spillover, may work as a ready state preparing for subsequent sensory input.

As discussed in detail by Leventhal et al. (2003), the depression of intracortical inhibition could result from diminished transmitter-release, diminished transmitter-production, and/or degraded transmitter-receptors. The researchers could not point to which is deteriorated in old animals, but they clearly demonstrated that administration of GABA facilitated visual function in old monkeys. Therefore, it was tempting to speculate that a decreased ability to produce GABA in the cortex might be responsible for age-related cognitive decline. The reduction in intrasynaptic and extrasynaptic (ambient) GABA levels, assumed for the old network, was a simple functional representation based on their speculation.

To examine whether and how GABAergic inhibition contributes to stimulus selectivity and competition among superimposed stimuli (bars with different orientations), Katzner et al. (2011) recorded spiking activity in primary visual cortical (V1) neurons after local iontophoresis of gabazine, a GABAa receptor antagonist. Gabazine broadened the orientation tuning curves of V1 neurons, by raising their responses to all orientations. Gabazine did not affect cross-orientation suppression, the competition seen when stimuli of different orientations are superimposed. They concluded that GABAergic inhibition in V1 enhances stimulus selectivity but is not responsible for competition among superimposed stimuli.

The latter conclusion contradicts our finding: GABAergic inhibition affected the competition among superimposed stimuli, increasing orientation bias (OB: see Fig. 8a). We showed that the GABAergic inhibition arising from GABA-spillover (see Fig. 8b) was responsible for that competition. In our simulation, even without the GABA-spillover, the extrasynaptic GABAa receptor still worked because of the basal ambient GABA concentration (see the trace marked by "without GABA-spillover" in Fig. 8b).

In their experiment (Katzner et al. 2011), gabazine presumably abolishes the whole GABAa receptor-mediated current in which a current arising from GABA-spillover would be involved. Our simulation result may reflect a unique impact of GABA-spillover on the competition between the presented stimulus and distractors, which we hope will be evidenced by future experiments.

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## Appendix

### The neural network model

Dynamic evolution of the membrane potential of the $i$th pyramidal (P) cell that belongs to orientation column $\theta$ is defined by

$$c_m^P \frac{du_i^P(\theta;t)}{dt} = -g_m^P(u_i^P(\theta;t) - u_{\text{rest}}^P) + I_{i,\text{rec}}^{\text{ex}}(\theta;t) + I_{i,\text{fed}}^{ih}(\theta;t) + I_{i,\text{lat}}^{ih}(\theta;t) + I_{\text{ext}}^{ih}(t) + I_{\text{LGN}}(\theta), \quad (1)$$

where $I_{i,\text{rec}}^{\text{ex}}(\theta;\ t)$ is a recurrent excitatory postsynaptic current within orientation columns, $I_{i,\text{fed}}^{ih}(\theta;\ t)$ a feedback inhibitory postsynaptic current, $I_{i,\text{lat}}^{ih}(\theta;\ t)$ a lateral inhibitory postsynaptic current, $I_{\text{ext}}^{ih}(t)$ an inhibitory non-postsynaptic current caused by GABA-spillover from synaptic clefts and non-vesicular GABA-release into the extracellular space, and $I_{\text{LGN}}(\theta)$ an excitatory input current triggered by an oriented bar-stimulus ($\theta_{\text{inp}}$). These currents are defined by

$$I_{i,\text{rec}}^{\text{ex}}(\theta;t) = -\hat{g}_{\text{AMPA}}(u_i^P(\theta;t) - u_{rev}^{\text{AMPA}}) \sum_{j=1}^{N_\theta} w_{ij,\text{rec}}^{\text{ex}}(\theta) r_j^P(\theta;t), \quad (2)$$

$$I_{i,\text{fed}}^{ih}(\theta;t) = -\hat{g}_{\text{GABA}}(u_i^P(\theta;t) - u_{\text{rev}}^{\text{GABA}}) w_{i,\text{fed}}^{ih}(\theta) r_i^S(\theta;t), \quad (3)$$

$$I_{i,\text{lat}}^{ih}(\theta;t) = -\hat{g}_{\text{GABA}}(u_i^P(\theta;t) - u_{\text{rev}}^{\text{GABA}}) \sum_{\theta'=0(\theta'\neq\theta)}^{7\pi/8} \sum_{j=1}^{N_\theta} w_{ij,\text{lat}}^{ih}(\theta,\theta') r_j^L(\theta';t), \quad (4)$$

$$I_{\text{ext}}^{ih}(t) = -\hat{g}_{\text{GABA}}(u_i^P(\theta;t) - u_{rev}^{\text{GABA}}) \delta r_{\text{ext}}^{\text{GABA}}(t), \quad (5)$$

$$I_{\text{LGN}}(\theta) = c_0 \times \{c_1 + cos[2(\theta - \theta_{\text{inp}})]\}. \quad (6)$$

Dynamic evolution of the membrane potentials of small basket (S) cells and large basket (L) cells is defined by

$$c_m^S \frac{du_i^S(\theta;t)}{dt} = -g_m^S(u_i^S(\theta;t) - u_{\text{rest}}^S) + I_i^S(\theta;t), \quad (7)$$

$$c_m^L \frac{du_i^L(\theta;t)}{dt} = -g_m^L(u_i^L(\theta;t) - u_{\text{rest}}^L) + I_i^L(\theta;t), \quad (8)$$

where $I_i^S(\theta;\ t)$ and $I_i^L(\theta;\ t)$ are excitatory postsynaptic currents and defined by

$$I_i^S(\theta;t) = -\hat{g}_{\text{AMPA}}(u_i^S(\theta;t) - u_{rev}^{\text{AMPA}}) w_i^S(\theta) r_i^P(\theta;t), \quad (9)$$

$$I_i^L(\theta;t) = -\hat{g}_{\text{AMPA}}(u_i^L(\theta;t) - u_{\text{rev}}^{\text{AMPA}}) w_i^L(\theta) r_i^P(\theta;t). \quad (10)$$

In these equations, $c_m^Y$ is the membrane capacitance of Y (Y = P, S, L) cell, $u_i^Y(\theta;\ t)$ the membrane potential of the $i$th Y cell of $\theta$ column at time $t$, $g_m^Y$ the membrane conductance of Y cell, and $u_{\text{rest}}^Y$ the resting potential. $\hat{g}_Z$ and $u_{\text{rev}}^Z$ (Z = AMPA or GABA) are, respectively, the maximal conductance and the reversal potential for the current mediated through Z-type receptor. $N_\theta$ is the number of cell units constituting each orientation column. $w_{ij,\text{rec}}^{\text{ex}}(\theta)$ and $w_{i,\text{fed}}^{ih}(\theta)$ are, respectively, the excitatory synaptic strength from the $j$th to the $i$th P cell and the inhibitory synaptic strength from S-to-P cell of unit $i$ within columns. $w_{ij,\text{lat}}^{ih}(\theta,\ \theta')$ is the inhibitory synaptic strength from the $j$th L cell of $\theta'$ column to the $i$th P cell of $\theta$ column ($\theta' \neq \theta$). $w_i^S(\theta)$ and $w_i^L(\theta)$ are, respectively, the excitatory synaptic strengths from P to S cell and to L cell within unit $i$. $\theta_{\text{inp}}$ in Eq. 6 denotes the orientation (angle) of an input stimulus (a bar).

$r_j^P(\theta;t)$ is the fraction of AMPA-receptors in the open state induced by a presynaptic action potential of the $j$th P cell belonging to $\theta$ column, and $r_j^Y(\theta;\ t)$ is that of GABAa receptors induced by the $j$th presynaptic S cell (Y = S) or by the $j$th presynaptic L cell (Y = L). $r_{\text{ext}}^{\text{GABA}}(t)$ is the fraction of GABAa receptors in the open state, which are located on extrasynaptic membrane regions of P cells. $\delta$ denotes a relative amount of extrasynaptic GABAa receptors. Dynamics of these receptors are described by Destexhe et al. (1998)

$$\frac{dr_j^P(\theta;t)}{dt} = \alpha_{\text{AMPA}}[\text{Glut}]_j^P(\theta;t)(1 - r_j^P(\theta;t)) - \beta_{\text{AMPA}} r_j^P(\theta;t), \quad (11)$$

$$\frac{dr_j^K(\theta;t)}{dt} = \alpha_{\text{GABA}}[\text{GABA}]_j^K(\theta;t)(1 - r_j^K(\theta;t)) - \beta_{\text{GABA}} r_j^K(\theta;t), \quad (K = S, L) \quad (12)$$

$$\frac{dr_{ext}^{\text{GABA}}(t)}{dt} = \alpha_{\text{GABA}}[\text{GABA}]_{\text{ext}}(t)(1 - r_{\text{ext}}^{\text{GABA}}(t)) - \beta_{\text{GABA}} r_{\text{ext}}^{\text{GABA}}(t), \quad (13)$$

where $\alpha_z$ and $\beta_z$ (z = AMPA or GABA) are positive constants. $[T]_j^Y(\theta;\ t)$ (T = Glut or GABA) is the concentration of glutamate or GABA in the synaptic cleft. $[T]_j^Y(\theta;\ t) = T_Y$ for 1 ms when the $j$th presynaptic Y cell fires, and 0 otherwise. $[\mathrm{GABA}]_{\mathrm{ext}}(t)$ is ambient (extrasynaptic) GABA concentration and defined by

$$\frac{d[\mathrm{GABA}]_{\mathrm{ext}}(t)}{dt} = \frac{1}{\tau_{\mathrm{ext}}}([\mathrm{GABA}]_{\mathrm{ext}}(t) - [\mathrm{GABA}]_0) + \sum_{\theta'=0}^{7\pi/8}\sum_{j=1}^{N_\theta}\int_{-\infty}^{t} C_{\mathrm{ext}} e^{\frac{-(t-t')}{\tau_{\mathrm{dec}}}}\{[\mathrm{GABA}]_j^S(\theta';t') + [\mathrm{GABA}]_j^L(\theta';t')\}dt', \tag{14}$$

where $\tau_{\mathrm{ext}}$ is a time constant for ambient GABA concentration, and $[\mathrm{GABA}]_0$ is a basal (resting GABA) concentration determined by non-vesicular GABA-release. The second term (on the right-hand side of Eq. 14) describes a relative amount of GABA-spillover from the synaptic clefts of presynaptic S and L cells. $C_{\mathrm{ext}}$ is a positive constant, and $\tau_{\mathrm{dec}}$ determines a degree of contribution of previously released 1 ms pulses of $\mathrm{GABA}_K$ (K = S, L). We assume that GABA molecules diffuse rapidly across the network.

Probability of firing of the $j$th Y cell belonging to $\theta$ column is defied by

$$Prob[Y_j(\theta;t);\mathrm{firing}] = \frac{1}{1+e^{-\eta_Y(u_j^Y(\theta;t)-\zeta_Y)}}, \tag{15}$$

where $\eta_Y$ and $\zeta_Y$ are, respectively, the steepness and the threshold of the sigmoid function. After firing, the membrane potential is reset to the resting potential.

Unless otherwise stated, $c_m^P = 0.5$ nF, $c_m^S = 0.2$ nF, $c_m^L = 0.5$ nF, $g_m^P = 25$ nS, $g_m^S = 20$ nS, $g_m^L = 25$ nS, $u_{\mathrm{rest}}^P = -65$ mV, and $u_{\mathrm{rest}}^S = u_{\mathrm{rest}}^L = -70$ mV (Koch 1999; McCormick et al. 1985; Kawaguchi and Shindou 1998). $\hat{g}_{\mathrm{AMPA}} = 0.5$ nS, $\hat{g}_{\mathrm{GABA}} = 0.7$ nS, $u_{\mathrm{rev}}^{\mathrm{AMPA}} = 0$ mV, and $u_{\mathrm{rev}}^{\mathrm{GABA}} = -80$ mV. Each orientation column consists of ten cell units: $N_\theta = 10$. $w_{ij,\mathrm{rec}}^{\mathrm{ex}}(\theta) = 5.0$, $w_{i,\mathrm{fed}}^{ih}(\theta) = w_{ij,\mathrm{lat}}^{ih}(\theta,\ \theta') = 1.0$, $w_i^S(\theta) = w_i^L(\theta) = 10.0$. $\delta = 1000.0$, $c_0 = 5.0 \times 10^{-10}$, $c_1 = 1.0$. $\alpha_{\mathrm{AMPA}} = 1.1 \times 10^6$, $\alpha_{\mathrm{GABA}} = 5.0 \times 10^5$, $\beta_{\mathrm{AMPA}} = 190.0$, $\beta_{\mathrm{GABA}} = 180.0$, $\mathrm{Glut}_P = \mathrm{GABA}_S = \mathrm{GABA}_L = 1.0$ mM, $\tau_{\mathrm{ext}} = 1.0$, $[\mathrm{GABA}]_0 = 1$ μM, $C_{\mathrm{ext}} = 0.2$, $\tau_{\mathrm{dec}} = 10.0$, $\eta_P = \eta_S = \eta_L = 350.0$, and $\zeta_P = \zeta_S = \zeta_L = -50$ mV. For these values, see our previous studies (Hoshino 2006, 2008a, b, 2009, 2010, 2011a, b).

## References


Brickley SG, Cull-Candy SG, Farrant M (1996) Development of a tonic form of synaptic inhibition in rat cerebellar granule cells resulting from persistent activation of GABAA receptors. J Physiol 497(3):753–759

Buzas P, Eysel UT, Adorjan P, Kisvarday ZF (2001) Axonal topography of cortical basket cells in relation to orientation, direction, and ocular dominance maps. J Comp Neurol 437:259–285

Cohen G, Burke DM (1993) Memory for proper names: a review. Memory 1:249–263

Craik FI, Bialystok E (2006) Cognition through the lifespan: mechanisms of change. Trends Cogn Sci 10:131–138

Destexhe A, Mainen ZF, Sejnowski TJ (1998) Kinetic models of synaptic transmission. In: Koch C, Segev I (eds) Methods in neuronal modeling. The MIT Press, Cambridge, pp 1–25

Drasbek KR, Jensen K (2006) THIP, a hypnotic and antinociceptive drug, enhances an extrasynaptic GABAA receptor-mediated conductance in mouse neocortex. Cereb Cortex 16:1134–1141

Fujiwara H, Zheng M, Miyamoto A, Hoshino O (2011) Insufficient augmentation of ambient GABA responsible for age-related cognitive deficit. Cogn Process 12:151–159

Gupta A, Wang Y, Markram H (2000) Organizing principles for a diversity of GABAergic interneurons and synapses in the neocortex. Science 287:273–278

Hoshino O (2006) Coherent ongoing subthreshold state of a cortical neural network regulated by slow- and fast-spiking interneurons. Netw Comput Neural Syst 17:351–371

Hoshino O (2008a) Extrasynaptic-GABA-mediated neuromodulation in a sensory cortical neural network. Netw Comput Neural Syst 19:95–117

Hoshino O (2008b) An ongoing subthreshold neuronal state established through dynamic coassembling of cortical cells. Neural Comput 20:3055–3086

Hoshino O (2009) GABA-transporter preserving ongoing-spontaneous neuronal activity at firing-subthreshold. Neural Comput 21:1683–1713

Hoshino O (2010) Alteration of ambient GABA by phasic and tonic neuronal activation. Neural Comput 22:1358–1382

Hoshino O (2011a) Neuronal responses below firing threshold for subthreshold cross-modal enhancement. Neural Comput 23:958–983

Hoshino O (2011b) Subthreshold membrane depolarization as memory trace for perceptual learning. Neural Comput 23:3205–3231

Katzner S, Busse L, Carandini M (2011) GABAA inhibition controls response gain in visual cortex. J Neurosci 31:5931–5941

Kawaguchi Y, Shindou T (1998) Noradrenergic excitation and inhibition of GABAergic cell types in rat frontal cortex. J Neurosci 18:6963–6976

Kisvarday ZF, Beaulieu C, Eysel UT (1993) Network of GABAergic large basket cells in cat visual cortex (area 18): implication for lateral disinhibition. J Comp Neurol 327:398–415

Kisvarday ZF, Eysel UT (1993) Functional and structural topography of horizontal inhibitory connections in cat visual cortex. Eur J Neurosci 5:1558–1572

Koch C (1999) Biophysics of computation. Oxford University Press, Oxford

Krimer LS, Goldman-Rakic PS (2001) Prefrontal microcircuits: membrane properties and excitatory input of local, medium, and wide arbor interneurons. J Neurosci 21:3788–3796

Leventhal AG, Thompson KG, Liu D, Zhou Y, Ault SJ (1995) Concomitant sensitivity to orientation, direction, and color of cells in layers 2, 3, and 4 of monkey striate cortex. J Neurosci 15:1808–1818

Leventhal AG, Wang Y, Pu M, Zhou Y, Ma Y (2003) GABA and its agonists improved visual cortical function in senescent monkeys. Science 300:812–815

Markram H, Toledo-Rodriguez M, Wang Y, Gupta A, Silberberg G, Wu C (2004) Interneurons of the neocortical inhibitory system. Nat Rev Neurosci 5:793–807

Martin KAC (2002) Microcircuits in visual cortex. Curr Opin Neurobiol 12:418–425

McCormick DA, Connors BW, Lighthall JW, Prince DA (1985) Comparative electrophysiology of pyramidal and sparsely spiny stellate neurons of the neocortex. J Neurophysiol 54:782–806

Miyamoto A, Hasegawa J, Zheng M, Hoshino O (2012) Diffusive feedback influences on hierarchical information processing. Neural Comput: 24:744–770

Nusser Z, Roberts JD, Baude A, Richards JG, Somogyi P (1995) Relative densities of synaptic and extrasynaptic GABAA receptors on cerebellar granule cells as determined by a quantitative immunogold method. J Neurosci 5:2948–2960

Salthouse TA (1996) The processing-speed theory of adult age differences in cognition. Psychol Rev 103:403–428

Schmolesky MT, Wang Y, Pu M, Leventhal AG (2000) Degradation of stimulus selectivity of visual cortical cells in senescent rhesus monkeys. Nat Neurosci 3:384–390

Scimemi A, Andersson A, Heeroma JH, Strandberg J, Rydenhag B, McEvoy AW, Thom M, Asztely F, Walker (2006) Tonic GABA(A) receptor-mediated currents in human brain. Eur J Neurosci 24:1157–1160

Semyanov A, Walker MC, Kullmann DM, Silver RA (2004) Tonically active GABA A receptors: modulating gain and maintaining the tone. Trends Neurosci 27:262–269

Soltesz I, Nusser Z (2001) Neurobiology. Background inhibition to the fore. Nature 409:24–25

Somogyi P, Kisvarday ZF, Martin KAC, Whitteridge D (1983) Synaptic connections of morphologically identified and physiologically characterized large basket cells in the striate cortex of cat. Neuroscience 10:261–294

Somogyi P, Takagi H, Richards JG, Mohler H (1989) Subcellular localization of benzodiazepine/GABAA receptors in the cerebellum of rat, cat, and monkey using monoclonal antibodies. J Neurosci 9:2197–2209

Totoki Y, Matsuo T, Zheng M, Hoshino O (2010) Local intracortical circuitry not only for feature binding but also for rapid neuronal responses. Cogn Process 11:347–357

Wang Y, Gupta A, Toledo-Rodoriguez M, Wu CZ, Markram H (2002) Anatomical, physiological, molecular and circuit properties of nest basket cells in the developing somatosensory cortex. Cereb Cortex 12:395–410

Xu X, Ichida J, Shostak Y, Bonds AB, Casagrande VA (2002) Are primate lateral geniculate nucleus (LGN) cells really sensitive to orientation or direction? Vis Neurosci 19:97–108

Zilberer Y (2000) Dendritic release of glutamate suppresses synaptic inhibition of pyramidal neurons in rat neocortex. J Physiol 538.3:489–496