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RESEARCH REPORT

Insufficient augmentation of ambient GABA responsible for age-related cognitive deficit

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Abstract Age-related degeneration of intracortical inhibition could underlie declines in cognitive function during senescence. Based on a hypothesis that a decrease in basal concentration of ambient (extrasynaptic) GABA with aging leads to depressing intracortical inhibition, we investigated how the basal concentration affects stimulus-evoked activity (as signal), ongoing-spontaneous activity (as noise) of neurons and their (signal-to-noise) ratio S/N. We simulated a neural network model equipped with a GABA transport system that regulates ambient GABA concentration in a neuronal activity-dependent manner. An increase in basal concentration augmented ambient GABA, increased GABA-mediated inhibitory current, and depressed ongoing-spontaneous activity while still keeping stimulus-evoked activity. This led to S/N improvement, for which it was necessary for the reversal potential of GABA transporter to be close to the resting potential of neurons. Above the resting potential, ongoing-spontaneous activity was predominantly enhanced due to excessive GABA-uptake from the extracellular space by transporters. Below the resting potential, stimulus-evoked activity was predominantly depressed, caused by excessive GABA-release. We suggest that the insufficient augmentation of ambient GABA due to a decrease in its basal concentration may be one of the possible causes of cognitive deficit with aging, increasing ongoing-spontaneous neuronal activity as noise. GABA transporter may contribute to improving S/N, provided that its reversal potential is close to the resting potential.

Keywords Neural network model · Ambient GABA · Ongoing-spontaneous neuronal activity · Noise reduction · Age-related cognitive decline · Signal-to-noise ratio

Introduction

In general, cognitive performance is age-related (Craik and Bialystok 2006). For instance, the processing speed of cognitive tasks (e.g., letter comparison and pattern comparison) and their acuity decrease from young adulthood towards old age (Salthouse 1996, 1999; Baltes and Lindenberger 1997). Although little is known about the underlying neuronal mechanisms of difficulties in processing cognitive information in old animals, recent studies have provided some insight into it. Schmolesky and colleagues (Schmolesky et al. 2000) demonstrated that old macaque monkeys exhibited decreased orientation selectivity and direction selectivity in the primary visual cortex (V1).

The researchers suggested that age-related degeneration of intracortical inhibition could underlie declines in cognitive function during senescence. Similar results were reported for the frequency selectivity of neurons of the primary auditory cortex (Manunta and Edeline 1997, 1998). A follow-up study (Leventhal et al. 2003) demonstrated that administration of GABA enhanced signal-to-noise ratio

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(S/N), when a reduction in ongoing-spontaneous activity of V1 cells as noise was greater than that in stimulus-evoked activity as signal. One important question that still remains to be answered is: What is the underlying neuronal mechanism for the predominant noise reduction, compared to the signal reduction?

A decrease in basal concentration of ambient (extrasynaptic) GABA in the brain might be responsible for age-related cognitive decline. Taurine, which is structurally similar to GABA, is known not only to work as GABAa receptor agonist but also to enhance GABA synthesis (El Idrissi et al. 2003; El Idrissi and Trenkner 2004; El Idrissi 2008). Mice fed with taurine in drinking water (0.05% for 4 weeks) increased the expression of glutamate acid decarboxylase (GAD), which is a GABA synthesizing enzyme, accompanied by an increase in basal concentration of ambient GABA in the brain. Interestingly, supplementation of taurine to aged mice significantly improved cognitive performance. It was suggested that taurine might protect against age-related cognitive decline by augmenting the basal concentaraion of ambient GABA.

In relation to ambient GABA concentration, Richerson and colleagues (Richerson and Wu 2003; Wu et al. 2003, 2007; Richerson 2004) made an interesting suggestion. Transporter such as GAT-1, located on the axon terminals of GABAergic interneurons and on glia, is crucial not only for removing GABA from but also for releasing it into the extracellular space. The transporter can clamp ambient GABA at a certain level: within a submicromolar range at rest. The transporter is near equilibrium under normal physiological conditions and will reverse with a relatively small increase in membrane potential. The researchers demonstrated that GABAergic transmission was prevented not by blocking vesicular GABA release but by GABA transporter antagonists. In the cortex, a variety of GABAergic interneurons have been identified, including basket cells, nest basket cells, chandelier cells, martinotti cells and so on (Markram et al. 2004).

It is well known that ambient GABA, even though its concentration is low, acts on extrasynaptic GABAa receptors and provides neurons with the so-called tonic inhibitory current. Many experiments have identified extrasynaptic GABAa receptors, mostly in cerebellum and hippocampus (Nusser et al. 1998; Wei et al. 2003; Mody and Pearce 2004). Recent experiments (Drasbek and Jensen 2006; Scimemi et al. 2006) have identified them as well in the cortex for humans and rats.

Inspired by these studies, we hypothesized that the depression of intracortical inhibition due to a decrease in basal concentration of ambient GABA might cause cognitive deficit in old (healthy) adult animals. To examine our hypothesis, we simulate a neural network model equipped with a GABA transport system that regulates ambient GABA concentration in a neuronal activity-dependent manner. The network, comprising principal cells and GABAergic interneurons, detects elemental sensory features as primary sensory cortices do. Ambient GABA is recognized by extrasynaptic GABAa receptors on principal cells and interneurons, and provides them with tonic inhibitory currents. We investigate whether and how the basal concentration of ambient GABA affects stimulus-evoked activity (as signal), ongoing-spontaneous activity (as noise) of neurons and their (signal-to-noise) ratio S/N.

Methods

A neural network model of a primary sensory cortical area is shown in Fig. 1a, whose neurons have a tuning property to a specific sensory feature f_n $(n = 0 - M)$. Activation of a population of neurons (dynamic cell assembly) encodes the information about a single feature. Cell assemblies comprise cell units (see the gray circle) that contain one principal cell (P) and two GABAergic interneurons (F and L).

Within cell assemblies, P cells are recurrently connected via excitatory synapses. An F cell receives an excitatory projection from a P cell and sends a feedback inhibitory projection to that P cell. An L cell receives excitatory projections from P cells belonging to other cell assemblies (n'), and sends inhibitory projections to P cells belonging to the same assembly $(n \neq n')$. This circuitry provides the so-called lateral inhibition between cell assemblies. A feature f_n is presented to the P cells of cell assembly n, for which we employ a graded stimulus. Namely, the cell assembly n receives the most intense input, its neighbors $(n - 1, n + 1)$ the second most, and so on, as schematically shown in Fig. 1b (see the arrows).

To regulate ambient GABA concentration, we employ a GABA transport system that has been proposed in a previous paper (Hoshino 2009). We briefly explain about the GABA transport system. As suggested by Richerson and colleagues (Richerson and Wu 2003; Wu et al. 2003, 2007; Richerson 2004), transporter such as GAT-1 is not simply a vacuum removing GABA from the extracellular space. Instead, it operates in an ion-coupled manner, pursuing an equilibrium point that is determined by the stoichiometry of transporter, the concentration gradients of substrates and the membrane potential. Under normal physiological conditions, a thermodynamic reaction cycle involves coupled translocation of two Na^+ ions, one Cl^- ion and one uncharged GABA molecule. The co-transported molecules

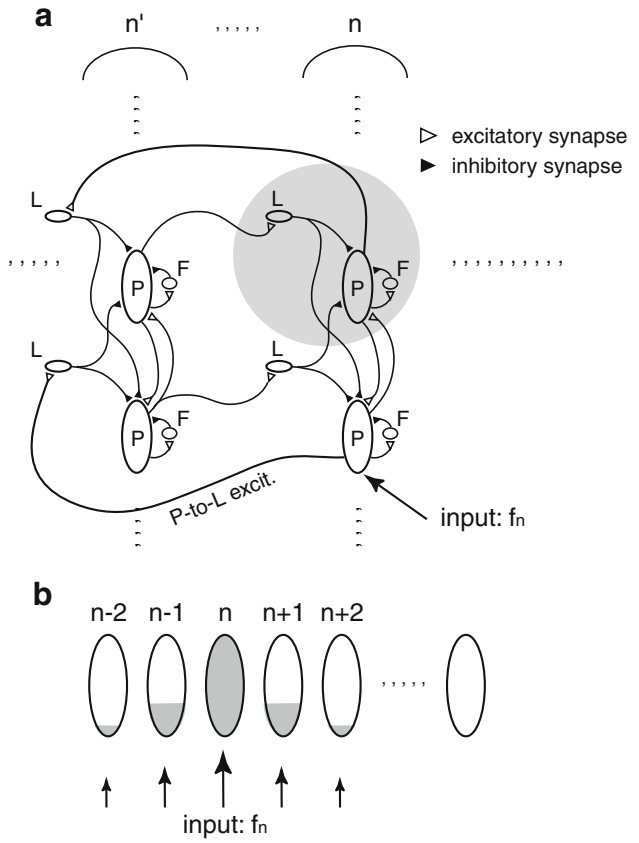

Fig. 1 A neural network model. **a** The network consists of cell assemblies ($n = 0 - M$), which comprise cell units (see the *gray circle*). Each cell unit contains one principal cell (P) and two inhibitory cells (F, L). Input is applied to P cells. **b** Cell assemblies receive graded input, whose intensity is schematically indicated by the *size of arrows*

($2Na^+$, Cl^-, GABA) cross the membrane together. The driving force for the coupled transport is the electrochemical potential, which is the sum of the electropotential and the chemical potential.

The reversal potential of transporter is the equilibrium membrane voltage at which the value of electrochemical potential is equal to 0. Under the normal condition, the reversal potential is close to the resting potential of neurons. At membrane potentials below the reversal potential, net influx of GABA, called forward transport or GABA-uptake, takes place. In contrast, at membrane potentials above the reversal potential, net efflux of GABA, called reverse transport or GABA-release, takes place.

A conductance-based, integrate-and-fire neuron model is employed (Hoshino 2006, 2008). GABA transporters, located on the axon terminals of F and L cells, regulate ambient GABA concentration. Depending on ambient GABA concentration, tonic inhibitory currents flow in P, F and L cells via extrasynaptic GABAa receptors (Hoshino 2009). Model definition is provided in electronic supplementary material (Appendices A–C).

Results

Influences of the basal concentration of ambient GABA on S/N

In this section, we show how the basal concentration of ambient GABA influences signal-to-noise ratio (S/N). As mathematically defined (see $[GABA]^0_{ext}$ of Eq. 17 of Appendix C in electronic supplementary material), the basal concentration is a steady-state concentration, when the membrane potentials of GABAergic interneurons (F, L) become equal to their reversal potentials (u^F_{rev}, u^L_{rev}).

Figure 2a presents the raster plots of action potentials of P cells, where n ($0 - 7$) denotes a single cell assembly that has a tuning property to feature f_n. When the network is stimulated with feature f_3 (see the horizontal bar), corresponding P cells generate action potentials (see $n = 3$). Note that the network model shows ongoing-spontaneous activity, which is defined as neuronal activity in the absence of sensory stimulation. As shown in Fig. 2b, ambient GABA concentration in each cell assembly ($n = 0 - 7$) varies depending on neuronal activity.

Figure 2c (left) presents stimulus-evoked (see the open rectangles) and ongoing-spontaneous (see the filled rectangles) activities of P cells, which are expressed as firing rates. Figure 2c (right) presents average ambient GABA concentration in each cell assembly for the stimulus-presentation (see the open rectangles) or ongoing-spontaneous (see the filled rectangles) time period. The greater ambient GABA augmentation in the stimulus-relevant cell assembly (see $n = 3$) arises from the excitation of F cells (see $n = 3$ at the left of Fig. 2d) by their accompanying P cells (see $n = 3$ at the left of Fig. 2c) through P-to-F excitation (see Fig. 1a). The frequent membrane depolarization of F cells ($u^F_j(3;t) > u^F_{rev}$, see Eq. 17 of Appendix C in electronic supplementary material) leads to releasing GABA into the extracellular space and therefore to elevating ambient GABA concentration. The augmentation of ambient GABA in its neighboring cell assemblies (see the open rectangles at the right of Fig. 2c) arises from the excitation of L cells (see the open rectangles at the right of Fig. 2d) by the stimulus-relevant P cells through P-to-L excitation (see "P-to-L excit." in Fig. 1a). This excitation makes the L cells frequently cross their reversal potential ($> u^L_{rev}$) and therefore release GABA into the extracellular space.

Figure 3 (top-left) shows how the basal concentration affects S/N. Signal is stimulus-evoked activity (see the top-right) and noise is ongoing-spontaneous activity (see the bottom-left), which are expressed as firing rates. Their changes are shown (see the bottom-right), indicating that S/N could be improved by increasing the basal concentration (see the circles). The improvement of S/N arises from the predominant reduction in noise (see the

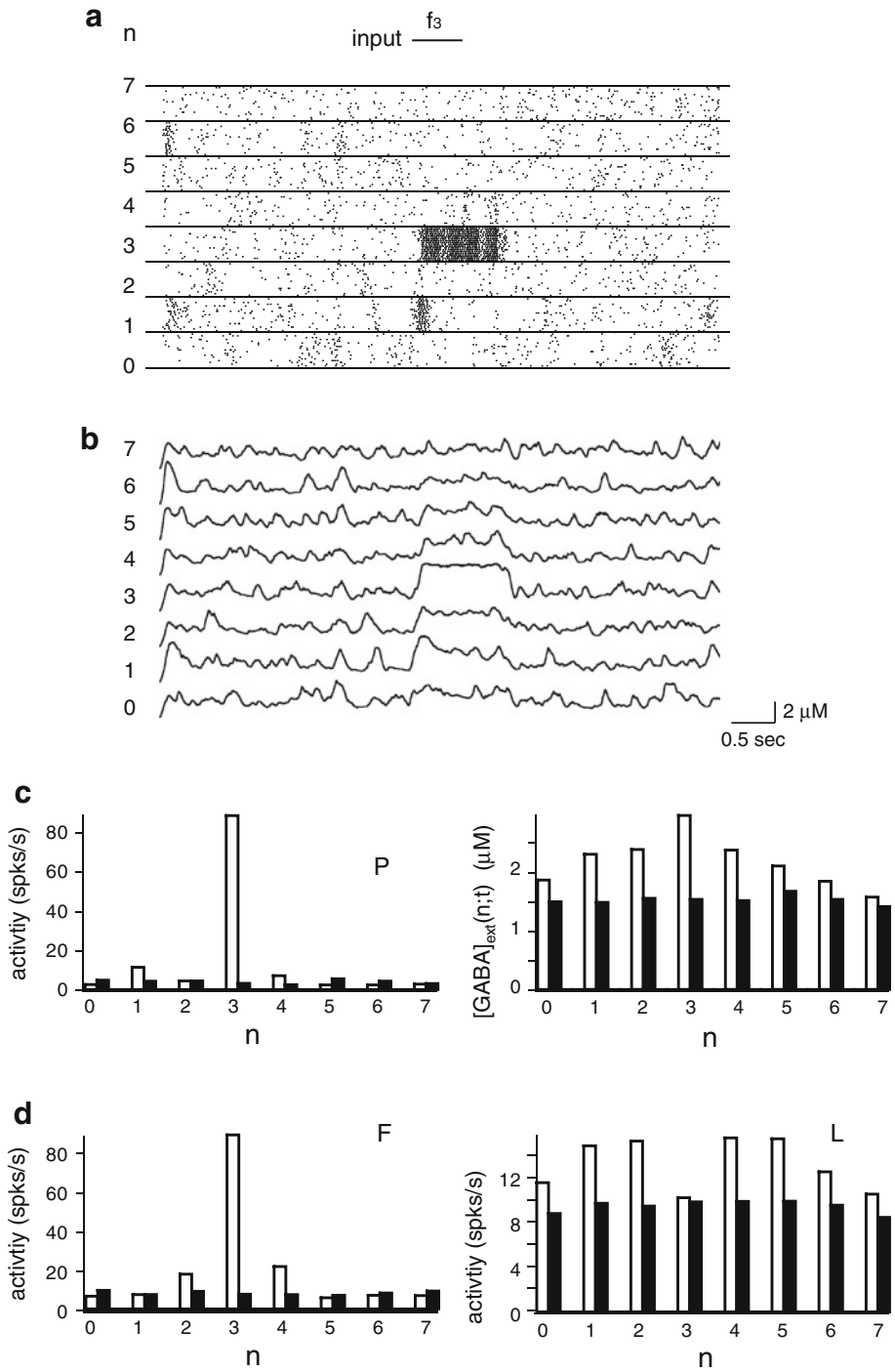

Fig. 2 Dynamic property of the network. **a** Raster plots of action potentials of P cells, when stimulated with feature f_3 (see the *horizontal bar*). **b** Ambient GABA concentration in each cell assembly. **c** *Left* Stimulus-evoked (see the *open rectangles*) and ongoing-spontaneous (see the *filled rectangles*) activities of P cells (firing rates). *Right* Average ambient GABA concentrations for the stimulus-presentation (see the *open rectangles*) or ongoing-spontaneous (see the *filled rectangles*) time period. **d** Stimulus-evoked (see the *open rectangles*) and ongoing-spontaneous (see the *filled rectangles*) activities of F (*left*) and L (*right*) cells

squares). Note that the signal change is small (see the triangles).

Influences of basal concentration on GABA-mediated tonic inhibition

In this section, we show how the basal concentration influences GABA-mediated tonic inhibition. Figure 4a presents inhibitory currents flowing in a stimulus-relevant P cell. It is enhanced as basal concentration increases ($[GABA]^0_{ext}$: 0.1→0.5→1.0 μM) for both ongoing-spontaneous and stimulus-presentation time periods (see the insets). The enhancement of inhibitory current arises largely from the augmentation of ambient GABA, as shown in Fig. 4b. We confirmed the same tendency for a large value of parameter $GABA_{max}$ (e.g., see the bottom traces) that defines a dynamic range of ambient GABA concentration (see Eq. 17 of Appendix C in electronic supplementary material).

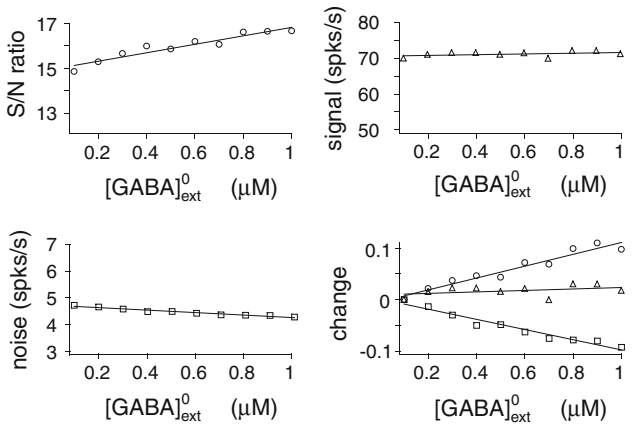

Fig. 3 Influences of the basal concentration of ambient GABA on neuronal activity. *Top-left* signal-to-noise ratio (S/N). *Top-right* stimulus-evoked activity (firing rate) as signal. *Bottom-left* ongoing-spontaneous activity as noise. *Bottom-right* Their changes

A transient decrease in concentration during the stimulation period (e.g., see the open arrow) is due to ceasing firing in P cells (not shown), which is caused by strong ambient GABA-mediated inhibition. The depression of spiking activity in P cells, leads to ceasing firing in their accompanying F cells and thus to a decrease in GABA-release, as reflected in the transient reduction in ambient GABA concentration (see the open arrow).

As address in the "Methods" section, we assumed that the reversal potential for GABA transporter (GAT-1) is close to the resting potential of neurons, which is based on the experimental and theoretical studies by Wu and colleagues (Wu et al. 2003, 2007). We made an investigation about how the reversal potential affects S/N. Figure 5 shows changes in noise activity (ongoing-spontaneous), signal activity (stimulus-evoked) and their ratio S/N as a function of basal concentration. The reversal potential was varied between −60 mV and −80 mV. We found that S/N could be improved, if the reversal potential is close to the resting potential −70 mV (see the filled circles). Note that we obtained the best improvement in S/N, when the reversal potential was equal to −71 mV. Above −60 mV, ongoing-spontaneous activity was predominantly enhanced, i.e., noise was increased (not shown). This was due to excessive reduction in ambient GABA concentration, caused by exclusive GABA-uptake. Below −80 mV, stimulus-evoked activity was predominantly depressed, i.e., signal was reduced. This was due to excessive augmentation of ambient GABA concentration, caused by exclusive GABA-release.

These results indicate that GABA transporter contributes to improving S/N, provided that its reversal potential is close to the resting potential. Under normal physiological conditions, a small change in membrane potential relative

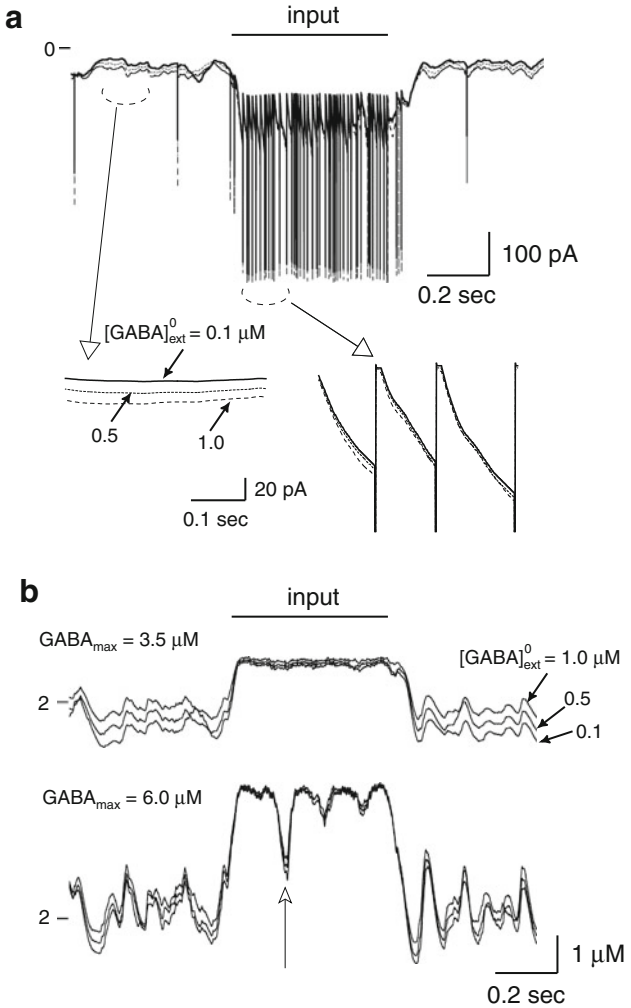

Fig. 4 Influences of basal concentration on ambient GABA concentrations. **a** Inhibitory currents flowing in a stimulus-relevant P cell. **b** Ambient GABA concentrations. Basal concentration was changed ($[GABA]^0_{ext}$: 0.1→0.5→1.0 μM). Maximal ambient GABA concentration ($GABA_{max}$) was 3.5 μM (*top*) or 6.0 μM (*bottom*)

to the resting potential is enough to release GABA into or remove it from the extracellular space. This may lead to well regulating ambient GABA concentrations, thereby improving S/N ratio. The assumption that the reversal potential is close to the resting potential will be discussed in the "Discussion" section.

Determination of an optimal ambient GABA regulatory condition

We tried to find an optimal ambient GABA regulatory condition by varying $GABA_{max}$, which is a critical parameter for the dynamics of ambient GABA concentrations (see Eq. 17 of Appendix C in electronic supplementary material). Note that the dynamic range of ambient GABA concentration expands as $GABA_{max}$ increases. As shown in

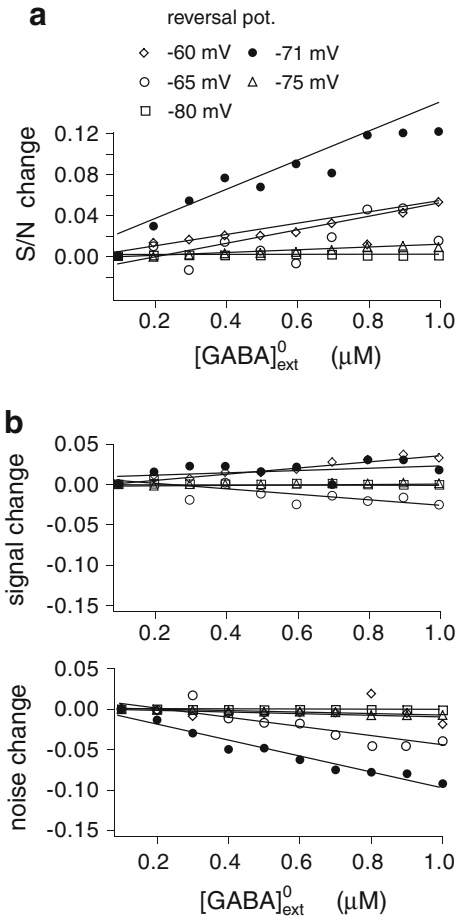

Fig. 5 Influences of the reversal potential of transporter on S/N. **a** Changes of S/N as a function of basal concentration. The reversal potential was varied between −60 mV and −80 mV. **b** Changes of stimulus-evoked (*top*) and ongoing-spontaneous (*bottom*) neuronal activities, respectively as signal and noise

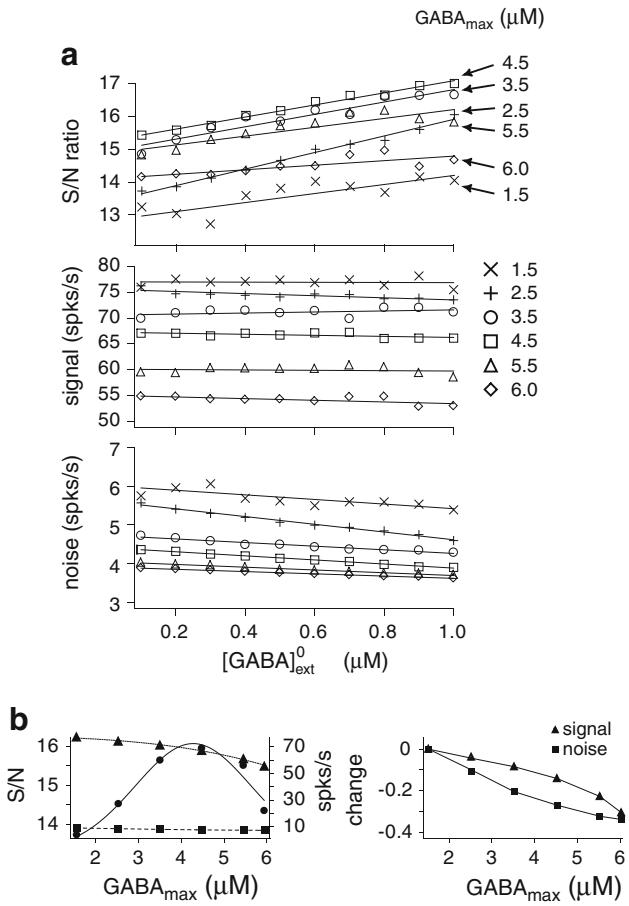

Fig. 6 Influences of maximal ambient GABA concentration ($GABA_{max}$) on S/N. **a** S/N (*top*), signal (*middle*) or noise (*bottom*) as a function of basal concentration ($[GABA]^0_{ext}$). $GABA_{max}$ was varied between 1.5-6.0 μM. **b** *Left* S/N (see the *circles*), signal (see the *triangles*) or noise (see the *squares*) as a function of $GABA_{max}$, where $[GABA]^0_{ext} = 0.5$ μM. *Right* Changes in signal and noise

Fig. 6a (top), we found a value for $GABA_{max}$ ($\sim$4.5 μM, see the squares), at which S/N reaches the highest. Larger $GABA_{max}$ values lead to excessive augmentation of ambient GABA and therefore to strong inhibition, resulting in the predominant depression of stimulus-evoked activity (see the diamonds among the middle traces), compared to that of ongoing-spontaneous activity (see the diamonds among the bottom traces).

Figure 6b (left) explains how the best S/N could be achieved, where the basal concentration was $[GABA]^0_{ext} = 0.5$ μM. S/N is expressed as a function of $GABA_{max}$ (see the circles: left axis). A peak in S/N is obtained at $GABA_{max} = 4.5$ μM. The stimulus-evoked activity (see the triangles) and the ongoing-spontaneous activity (see the squares) decrease monotonically (to the right axis) as $GABA_{max}$ increases. Figure 6b (right) presents their changes, indicating that the decrease of S/N for $GABA_{max} < 4.5$ μM is due to a marked reduction in noise, compared to that in signal, and vice versa for $GABA_{max} > 4.5$ μM.

According to Eq. 17 (see Appendix C in electronic supplementary material), ambient GABA concentration tends to converge toward the basal concentration ($[GABA]^0_{ext}$) at rest ($u^F_j(n;t) = u^F_{rest} = -70$ mV, $u^L_j(n;t) = u^L_{rest} = -70$ mV), because the reversal potentials of transporters are near the resting potentials of neurons ($u^F_{rev} = u^L_{rev} = -71$ mV) (Richerson and Wu 2003; Wu et al. 2003; Richerson 2004). Interestingly, neuronal activity is not silent even without stimulation. Namely, ongoing-spontaneous neuronal activity exists. Ongoing-spontaneous spikes in P cells activate F and L cells, by which they are slightly depolarized above the resting potential. This let their transporters release GABA into the extracellular space, leading ambient GABA concentration to be above the basal concentration: $[GABA]_{ext}(n;t) > [GABA]^0_{ext}$.

If the transporter does not work, by setting $T_F = T_L = 0$ (see Eq. 17 of Appendix C in electronic supplementary material), S/N worsens, as shown in Fig. 7 (see the

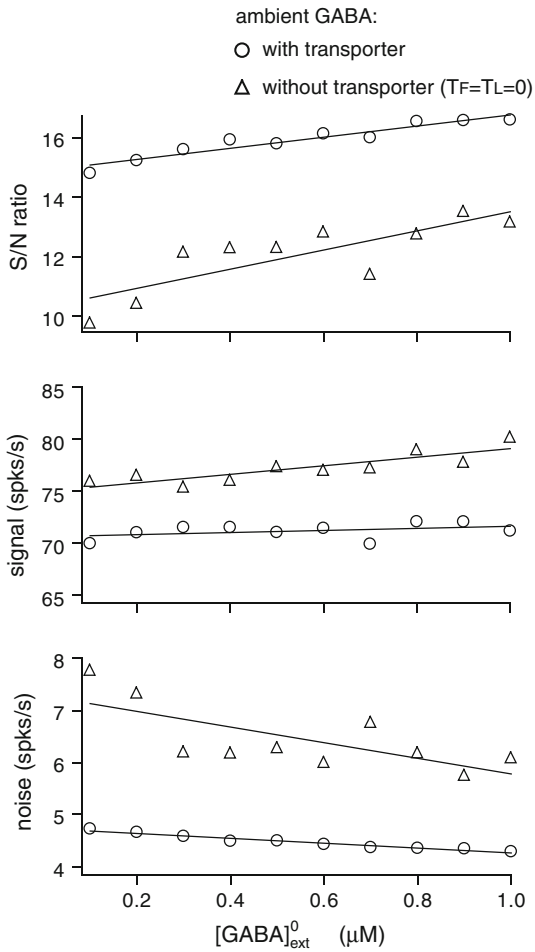

Fig. 7 Influences of GABA transport on S/N (*top*), signal (*middle*) or noise (*bottom*). Transporters worked (see the *circles*) or not (see the *triangles*)

triangles at the top), for which an insufficient reduction in noise is responsible (see the triangles at the bottom). This result indicates that the transporter may have a role in regulating ambient GABA concentration, by which the network can reduce ongoing-spontaneous activity while still keeping stimulus-evoked activity. Note that we assumed uniform ambient GABA concentration in each cell assembly. However, because GABA transport takes place at around axon terminal membranes, its target to modulate might be rather restricted to local regions. This would be advantageous for the brain to use a limited GABA resource, which will be discussed in the "Discussion" section.

Discussion

Based on a hypothesis that a decrease in basal concentration of ambient (extrasynaptic) GABA with aging leads to depressing intracortical inhibition, we investigated how the basal concentration affects ongoing-spontaneous activity (as noise), stimulus-evoked activity (as signal) of principal cells and their (signal-to-noise) ratio S/N. We simulated a neural network model equipped with a GABA transport system that regulates ambient GABA concentration in a neuronal activity-dependent manner. An increase in basal concentration augmented ambient GABA, increased GABA-mediated inhibitory current, and depressed ongoing-spontaneous activity while still keeping stimulus-evoked activity. This led to S/N improvement, for which it was necessary for the reversal potential of GABA transporter to be close to the resting potential of neurons. We suggest that the insufficient augmentation of ambient GABA due to a decrease in its basal concentration in the brain may be one of the possible causes of cognitive deficit with aging, increasing ongoing-spontaneous neuronal activity, namely, noise levels.

For simplicity, we assumed that ambient GABA concentration in each cell assembly is uniform. However, it might be unnecessary for the brain to modulate the region of whole space inside the cell assembly. Because GABA transport takes place at around axon terminal membranes (see the arrows in Fig. 8) (Richerson and Wu 2003; Wu et al. 2003; Richerson 2004), its target to modulate may be rather restricted to local regions, which might be advantageous for the brain to use a limited GABA resource. In this regard, ambient GABA may be modulated based on its basal concentration. The amount of modulation is to be added to or subtracted from the basal concentration, by which ambient GABA concentrations in local regions around a target cell are transiently altered (see the gray areas in Fig. 8).

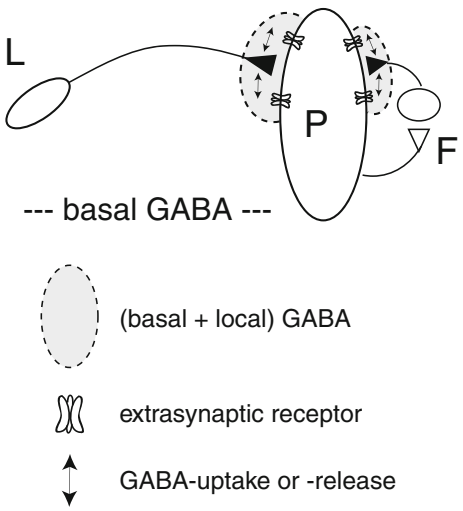

Fig. 8 A schematic illustration for hypothetical modulation of local ambient GABA. Ambient GABA concentration is locally altered based on basal concentration: (basal+local) GABA. The gray areas point to restricted local regions for the transient modulation of ambient GABA. For details, see the text

In brain areas (including sensory cortices) of old adult animals, basal concentrations of GABA are lower (−20 to −30 %) than those for young adults (Banay-Schwartz et al. 1989, Caspary et al. 1990, 1995, 1999). Basal concentration could be estimated to be in the range of 0.1-1 μM (Hagberg et al. 1985; Lerma et al. 1986; Tossman et al. 1986; Phillis et al. 1994; Cavelier et al. 2005; Santhakumar et al. 2006), which was employed in the present study. Note that the ambient GABA concentration fluctuated around the basal concentration (e.g., see Fig. 2b) up to 3.5 μM (maximal concentration). This may reflect a cognitive task-relevant, transient change of GABA concentration in a local extrasynaptic space, triggered by presynaptic neuronal activity.

Leventhal and colleagues (Schmolesky et al. 2000; Leventhal et al. 1995, 2003) hypothesized that a reduction in GABA-mediated intracortical inhibition might cause the degradation of cortical function for old adult animals. This motivated us to investigate whether and how the age-related reduction in basal concentration of ambient GABA affects cognitive information processing. Other plausible age-related factors might include diminished release of GABA into synaptic clefts, diminished production of GABA, degeneration of GABAa receptors and so on. A neural network model that considers these factors would allow us to see in more detail about age-related cognitive decline.

The assumption that the reversal potential for GABA transporter (GAT-1) is close to the resting potential of neurons is based on the experimental and theoretical studies by Wu and colleagues (2003, 2007). The researches made patch-clamp recordings from a pair of CHO cells, one transfected with subunits of GABAa receptor (called sniffer cell) and the other with GAT-1 (called GAT-1 cell). Concentrations of Na^+, Cl^- and GABA were systematically controlled in the inside (Na^+=15 mM, Cl^-=10 mM, GABA=2 mM) and on the outside (Na^+=151 mM, Cl^-=135 mM, GABA=100 nM) of the GAT-1 cell. These concentrations were within ranges reported for some adult mammalian neurons.

A slow ramp depolarization was applied to the GAT-1 cell and the current induced in the sniffer cell was plotted. The voltage in the GAT-1 cell at which an increase in inward current was first detected in the sniffer cell (i.e., when ambient GABA first began to rise) was estimated to be the reversal potential for GAT-1. The reversal potential determined by this method was −69.5 mV. The proposed method using the CHO cell assay has several advantages: (i) It is highly sensitive for detecting reversal of GABA transport, (ii) there is good control of membrane potential and substrate concentrations in the inside and on the outside of the membrane, and (iii) the CHO cells do not have synaptic vesicles, by which GAT-1-mediated GABA release can be detected in isolation. We hope this reversal potential will be confirmed for cortical neurons in the very near future.

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References

Baltes PB, Lindenberger U (1997) Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? Psychol Aging 12:12–21

Banay-Schwartz M, Lajtha A, Palkovits M (1989) Changes with aging in the levels of amino acids in rat CNS structural elements. I. Glutamate and related amino acids. Neurochem Res 14:555–562

Caspary DM, Holder TM, Hughes LF, Milbrandt JC, McKernan RM, Naritoku DK (1999) Age-related changes in GABA(A) receptor subunit composition and function in rat auditory system. Neuroscience 93:307–312

Caspary DM, Milbrandt JC, Helfert RH (1995) Central auditory aging: GABA changes in the inferior colliculus. Exp Gerontol 30:349–360

Caspary DM, Raza A, Lawhorn Armour BA, Pippin J, Arneric SP (1990) Immunocytochemical and neurochemical evidence for age-related loss of GABA in the inferior colliculus: implications for neural presbycusis. J Neurosci 10:2363–2372

Cavelier P, Hamann M, Rossi D, Mobbs P, Attwell D (2005) Tonic excitation and inhibition of neurons: ambient transmitter sources and computational consequences. Prog Biophys Mol Biol 87:3–16

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

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

El Idrissi A (2008) Taurine improves learning and retention in aged mice. Neurosci Lett 436:19–22

El Idrissi A, Trenkner E (2004) Taurine as a modulator of excitatory and inhibitory neurotransmission. Neurochem Res 29:189–197

El Idrissi A, Messing J, Scalia J, Trenkner E (2003) Prevention of epileptic seizures by taurine. Adv Exp Med Biol 526:515–525

Hagberg H, Lehmann A, Sandberg M, Nystrom B, Jacobson I, Hamberger A (1985) Ischemia-induced shift of inhibitory and excitatory amino acids from intra- to extracellular compartments. J Cereb Blood Flow Metab 5:413–419

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

Hoshino O (2008) 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

Lerma J, Herranz AS, Herreras O, Abraira V, Martin dR (1986) In vivo determination of extracellular concentration of amino acids in the rat hippocampus. A method based on brain dialysis and computerized analysis. Brain Res 384:145–155

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
Manunta Y, Edeline JM (1997) Effects of noradrenaline on frequency tuning of rat auditory cortex neurons. Eur J Neurosci 9:833–847
Manunta Y, Edeline JM (1998) Effects of noradrenaline on rate-level function of auditory cortex neurons: is there a "gating" effect of noradrenaline? Exp Brain Res 118:361–372
Markram H, Toledo-Rodriguez M, Wang Y, Gupta A, Silberberg G, Wu C (2004) Interneurons of the neocortical inhibitory system. Nature Rev Neurosci 5:793–807
Mody I, Pearce RA (2004) Diversity of inhibitory neurotransmission through GABA(A) receptors. Trends Neurosci 27:569–575
Nusser Z, Sieghart W, Somogyi P (1998) Segregation of different GABAA receptors to synaptic and extrasynaptic membranes of cerebellar granule cells. J Neurosci 8:1693–1703
Phillis JW, Smith-Barbour M, Perkins LM, O'Regan MH (1994) Characterization of glutamate, aspartate, and GABA release from ischemic rat cerebral cortex. Brain Res Bull 34:457–466
Richerson GB (2004) Looking for GABA in all the wrong places: the relevance of extrasynaptic GABA(A) receptors to epilepsy. Epilepsy Curr 4:239–242
Richerson GB, Wu Y (2003) Dynamic equilibrium of neurotransmitter transporters: not just for reuptake anymore. J Neurophysiol 90:1363–1374
Salthouse TA (1996) The processing-speed theory of adult age differences in cognition. Psychol Rev 103:403–428
Salthouse TA (1999) Step toward the explanation of adult age differences in cognition. In: Perfect TJ, Mylor EA (eds) Models of cognitive aging. Oxford University Press, New York, pp 19–49
Santhakumar V, Hanchar HJ, Wallner M, Olsen RW, Otis TS (2006) Contributions of the GABAA receptor alpha6 subunit to phasic and tonic inhibition revealed by a naturally occurring polymorphism in the alpha6 gene. J Neurosci 26:3357–3364
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 MC (2006) Tonic GABA(A) receptor-mediated currents in human brain. Eur J Neurosci 24:1157–1160
Tossman U, Jonsson G, Ungerstedt U (1986) Regional distribution and extracellular levels of amino acids in rat central nervous system. Acta Physiol Scand 127:533–545
Wei W, Zhang N, Peng Z, Houser CR, Mody I (2003) Perisynaptic localization of delta subunit-containing GABA(A) receptors and their activation by GABA spillover in the mouse dentate gyrus. J Neurosci 23:10650–10661
Wu Y, Wang W, Diez-Sampedro A, Richerson GB (2007) Nonvesicular inhibitory neurotransmission via reversal of the GABA transporter GAT-1. Neuron 56:851–865
Wu Y, Wang W, Richerson GB (2003) Vigabatrin induces tonic inhibition via GABA transporter reversal without increasing vesicular GABA release. J Neurophysiol 89:2021–2034