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Reducing variability in motor cortex activity at a resting state by extracellular GABA for reliable perceptual decision-making

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Abstract

Interaction between sensory and motor cortices is crucial for perceptual decision-making, in which intracortical inhibition might have an important role. We simulated a neural network model consisting of a sensory network (N_S) and a motor network (N_M) to elucidate the significance of their interaction in perceptual decision-making in association with the level of GABA in extracellular space: extracellular GABA concentration. Extracellular GABA molecules acted on extrasynaptic receptors embedded in membranes of pyramidal cells and suppressed them. A reduction in extracellular GABA concentration either in N_S or N_M increased the rate of errors in perceptual decision-making, for which an increase in ongoing-spontaneous fluctuations in subthreshold neuronal activity in N_M prior to sensory stimulation was responsible. Feedback (N_M-to-N_S) signaling enhanced selective neuronal responses in N_S, which in turn increased stimulus-evoked neuronal activity in N_M. We suggest that GABA in extracellular space contributes to reducing variability in motor cortex activity at a resting state and thereby the motor cortex can respond correctly to a subsequent sensory stimulus. Feedback signaling from the motor cortex improves the selective responsiveness of the sensory cortex, which ensures the fidelity of information transmission to the motor cortex, leading to reliable perceptual decision-making.

Keywords Sensory cortex · Motor cortex · Sensory perception · Cortical GABA

1 Introduction

Intracortical inhibition mediated by GABA is crucial for selective neuronal responses to meaningful stimuli, which might have a great impact on behavioral performance such as perceptual decision-making. Orientation selectivity in primary visual cortex (V1) and orientation discrimination performance depended on GABAergic inhibition (Edden et al. 2009), in which a positive correlation between task performance and GABA concentration was indicated. Sandberg and colleagues (Sandberg et al. 2014) measured GABA levels in human early visual cortex by magnetic resonance spectroscopy (MRS), and indicated a negative correlation between GABA concentration and perceptual error rate. MRS cannot not distinguish extracellular GABA from that in cellular compartments but nevertheless reveals changes in global GABA levels in the cortex (Gonzalez-Burgos et al. 2011). It was suggested (Hasler et al. 2007; Stagg et al. 2011) that MRS-determined GABA concentration is likely to correlate with extracellular GABA concentration.

Human subjects with greater perceptual abilities in a tactile judgment task showed more selective neuronal activity in primary somatosensory cortex (S1), which was significantly correlated with greater GABA concentration (Kolasinski et al. 2017). The researchers suggested that the observed S1 activity was likely composed of both ascending somatosensory afferents from the hand as well as efferent information from the primary motor cortex (M1). Interestingly, M1 is considered to be a dynamic modulator of S1 during not only movement but also non-movement (Zagha et al. 2013). Reciprocal connections between the sensory and motor cortices were evidenced (Matyas et al.

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2010; Mao et al. 2011), inferring intimate interaction between the sensory and motor cortices.

Several experimental studies suggested that GABA concentration in the motor cortex might be correlated with task performance. Puts and colleagues (Puts et al. 2011) demonstrated that tactile discrimination performance was significantly correlated with GABA concentration in the motor cortex but less in the visual cortex. Sumner and colleagues (Sumner et al. 2010) demonstrated that competitive action decisions such as shifting gaze to one stimulus rather than another could be predicted by GABA concentration in the frontal cortex, which was relevant to eye movements, but less in the visual cortex. Then, several important questions arise: what roles does GABA play in perceptual decision-making? How does the motor cortex modulate the selective neuronal activity in the sensory cortex, and how does it in turn affect the motor cortex activity?

To answer these questions, we simulate a neural network model that consists of a sensory network (N_S) and a motor network (N_M). Extracellular GABA molecules act on extrasynaptic receptors embedded in pyramidal cell membranes. Here we show that a reduction in extracellular GABA concentration either in N_S or N_M deteriorates perceptual performance (detection of a sensory stimulus), for which an increase in ongoing-spontaneous fluctuations in subthreshold neuronal activity in N_M prior to sensory stimulation is responsible. Feedback (N_M-to-N_S) signaling enhances selective neuronal responses in N_S, which in turn increases stimulus-evoked neuronal activity in N_M. We conclude that GABA in extracellular space contributes to reducing variability in motor cortex activity at a resting state and thereby the motor cortex can respond correctly to a subsequent sensory stimulus. Feedback signaling from the motor cortex improves the selective responsiveness of the sensory cortex, which ensures the fidelity of information transmission to the motor cortex, leading to reliable perceptual decision-making.

2 Methods

2.1 Model structure

Based on a previous study (Hoshino et al. 2018), we constructed a neural network model shown in Fig. 1. A sensory network (N_S) receives sensory input and a motor network (N_M) generates motor output. The N_S and N_M contain cell assemblies, with each comprising pyramidal cells (P) and basket cells (B). Within the same cell assembly (n), each P cell receives excitatory inputs from other P cells and inhibitory inputs from B cells. Each B cell receives excitatory inputs from P cells belonging to different cell

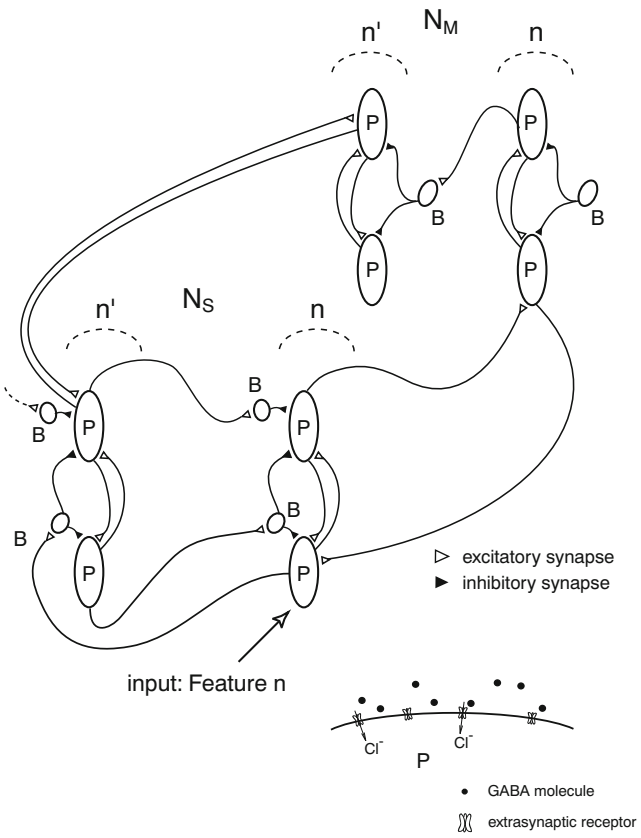

Fig. 1 Neuronal architecture. The neural network model consists of a sensory network (N_S) and a motor network (N_M), with each containing a set of cell assemblies ($1 \leq n \leq 8$). Each cell assembly comprises pyramidal (P) and basket (B) cells. The open and filled triangles denote excitatory and inhibitory synapses, respectively. An excitatory current is provided to N_S P cells belonging to cell assembly "n" when presented with feature stimulus "Feature n" as a sensory input. *Inset*: A schematic illustration of tonic inhibition. GABA molecules in extracellular space are accepted by extrasynaptic $GABA_A$ receptors and tonically inhibit a P cell

assemblies ($n' \neq n$). P cells are connected in an all-to-all fashion. Within N_S and N_M, different cell assemblies are only coupled through P-to-B synapses. N_S and N_M P cells are recurrently connected between corresponding (n) cell assemblies in an all-to-all fashion with a delay of 50 ms (Sachidhanandam et al. 2013; Manita et al. 2015).

The columnar organization of N_S and N_M is a widely accepted principle of structure observed in sensory (somatosensory, visual, auditory) and motor cortices (Mountcastle 1997). Pyramidal cells and non-pyramidal cells (interneurons) are clustered into columnar aggregates. Axon collaterals of pyramidal cells project to neighboring pyramidal cells, thereby providing recurrent excitation within neuronal columns. Lateral inhibition between neuronal columns is mediated by inhibitory interneurons to which pyramidal cell axon collaterals project. The lateral inhibitory mechanism allows pyramidal cells to be activated selectively to a certain feature stimulus in the primary

sensory cortex and to the planed direction of reaching movements in the primary motor cortex (deCharms and Zador 2000). To simply achieve such recurrent excitation and lateral inhibition respectively within and between neuronal columns or cell assemblies, we let the B cells receive inputs from P cells belonging to different cell assemblies but not from those belonging to the same cell assembly.

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter, which mediates phasic inhibition by activating intrasynaptic GABA receptors and tonic inhibition by activating extrasynaptic GABA receptors (Semyanov et al. 2004; Farrant and Nusser 2005; Ortinski et al. 2006). Extrasynaptic $GABA_A$ receptors have been found in the cortex (Drasbek and Jensen 2006; Scimemi

Table 1 List of parameters and their values

Symbol	Description	Value	Unit
c_{m}^{α}	Membrane capacitance for cell type $\alpha(\alpha = \mathrm{P_S}, \mathrm{P_M}, \mathrm{B_S}, \mathrm{B_M})$	$c_{\mathrm{m}}^{\mathrm{P_S}} = c_{\mathrm{m}}^{\mathrm{P_M}} = 500, c_{\mathrm{m}}^{\mathrm{B_S}} = c_{\mathrm{m}}^{\mathrm{B_M}} = 115$	pF
g_{m}^{α}	Membrane conductance for cell type $\alpha(\alpha = \mathrm{P_S}, \mathrm{P_M}, \mathrm{B_S}, \mathrm{B_M})$	$g_{\mathrm{m}}^{\mathrm{P_S}} = g_{\mathrm{m}}^{\mathrm{P_M}} = 25, g_{\mathrm{m}}^{\mathrm{B_S}} = g_{\mathrm{m}}^{\mathrm{B_M}} = 8.2$	nS
$v_{\mathrm{rest}}^{\alpha}$	Resting potential for cell type $\alpha(\alpha = \mathrm{P}_S, \mathrm{P}_M, \mathrm{B}_S, \mathrm{B}_M)$	$v_{\mathrm{rest}}^{\mathrm{P_S}} = v_{\mathrm{rest}}^{\mathrm{P_M}} = -65, r_{\mathrm{rest}}^{\mathrm{B_S}} = v_{\mathrm{rest}}^{\mathrm{B_M}} = -70$	mV
g_{Z}	Maximal conductance for receptor type Z (Z = AMPA, GABA)	$g_{\mathrm{AMPA}} = 0.5, g_{\mathrm{GABA}} = 0.7$	nS
v_{Z}	Reversal potential for receptor type Z (Z = AMPA, GABA)	$v_{\mathrm{AMPA}} = 0, v_{\mathrm{GABA}} = -80$	mV
N	Number of cell-units within cell assemblies	20	*
M	Number of cell assemblies	8	*
$w_{n,ij}^{\mathrm{P_S P_S}}, w_{n,ij}^{\mathrm{P_M P_M}}$	Synaptic weight (strength) from j to ith P cell in cell assembly n	$w_{n,ij}^{\mathrm{P_S P_S}} = w_{n,ij}^{\mathrm{P_M P_M}} = 1$	*
$w_{n,ij}^{\mathrm{P_S B_S}}, w_{n,ij}^{\mathrm{P_M B_M}}$	Synaptic weight from jth B to ith P cell in cell assembly n	$w_{n,ij}^{\mathrm{P_S B_S}} = w_{n,ij}^{\mathrm{P_M B_M}} = 6$	*
$w_{n,ij}^{\mathrm{P_S P_M}}, w_{n,ij}^{\mathrm{P_M P_S}}$	Synaptic weight from jth $\mathrm{N_M}$ P cell to ith $\mathrm{N_S}$ P cell and vise versa between corresponding (n) cell assemblies	$w_{n,ij}^{\mathrm{P_S P_M}} = w_{n,ij}^{\mathrm{P_M P_S}} = 4.6$	*
$w_{n,ij}^{\mathrm{B_S P_S}}, w_{n,ij}^{\mathrm{B_M P_M}}$	Synaptic weight from ith P to B cell between different ($n' \neq n$) cell assemblies	$w_{n,ij}^{\mathrm{B_S P_S}} = w_{n,ij}^{\mathrm{B_M P_M}} = 1.2$	*
δ_{α}	Amount of extrasynaptic $GABA_A$ receptors on cell type $\alpha(\alpha = \mathrm{P_S}, \mathrm{P_M})$	$\delta_{\mathrm{P_S}} = \delta_{\mathrm{P_M}} = 200$	*
$\alpha_{\mathrm{P_S}}$	Sensory input current	600	pA
$\tau_{\mathrm{P_S}}$	Input broadness	14	*
α_{z}	Channel opening rate for receptor type Z (Z = AMPA, GABA)	$\alpha_{\mathrm{AMPA}} = 1.1 \times 10^6, \alpha_{\mathrm{GABA}} = 5 \times 10^6$	$\mathrm{M^{-1}s^{-1}}$
β_{Z}	Channel closing rate for receptor type Z (Z = AMPA, GABA)	$\beta_{\mathrm{AMPA}} = 190, \beta_{\mathrm{GABA}} = 180$	$\mathrm{s^{-1}}$
$Glu_{\mathrm{syn}}^{\alpha}$	Maximal intrasynaptic glutamate concentration released from cell type $\alpha(\alpha = \mathrm{P_S}, \mathrm{P_M})$	$Glu_{\mathrm{syn}}^{\mathrm{P_S}} = Glu_{\mathrm{syn}}^{\mathrm{P_M}} = 1$	mM
$GABA_{\mathrm{syn}}^{\alpha}$	Maximal intrasynaptic GABA concentration released from cell type $\alpha(\alpha = \mathrm{B_S}, \mathrm{B_M})$	$GABA_{\mathrm{syn}}^{\mathrm{B_S}} = GABA_{\mathrm{syn}}^{\mathrm{B_M}} = 1$	mM
η_{α}	Steepness of sigmoid function for cell type $\alpha(\alpha = \mathrm{P_S}, \mathrm{P_M}, \mathrm{B_S}, \mathrm{B_M})$	$\eta_{\mathrm{P_S}} = \eta_{\mathrm{P_M}} = 240, \eta_{\mathrm{B_S}} = \eta_{\mathrm{B_M}} = 300$	$\mathrm{mV^{-1}}$
θ_{α}	Threshold of sigmoid function for cell type $\alpha(\alpha = \mathrm{P_S}, \mathrm{P_M}, \mathrm{B_S}, \mathrm{B_M})$	$\theta_{\mathrm{P_S}} = \theta_{\mathrm{P_M}} = -33, \theta_{\mathrm{B_S}} = \theta_{\mathrm{B_M}} = -31$	mV
$[GABA]_{\mathrm{ext}}^{\mathrm{X}}$	Basal extracellular GABA concentration in network type $\mathrm{N_X}$ (X = S, M)	$[GABA]_{\mathrm{ext}}^{\mathrm{S}} = [GABA]_{\mathrm{ext}}^{\mathrm{M}} = 2$	μM

* unitless

et al. 2006). As illustrated in the inset of Fig. 1, extrasynaptic GABA receptors are embedded in P cell membranes. GABA molecules in extracellular space act on extrasynaptic $GABA_A$ receptors and provide P cells with tonic inhibitory current.

Inhibition through B cells suppresses P cells in a phasic manner, where spike generation in B cells is vital. In contrast, inhibition mediated by extracellular GABA suppresses P cells in a tonic manner, where spiking activity is unnecessary; namely, it persistently suppresses P cells during both ongoing-spontaneous and stimulus-presented periods. We did not introduce extracellular GABA-mediated inhibition of B cells, because it is unlikely to play any significant role in this study. The extracellular GABA-mediated inhibition will suppress B cells and presumably impair lateral inhibition of P cells, which, however, can be compensated by strengthening the P-to-B synaptic connection weight and thus we will reach the same conclusion.

Intrasynaptic GABA rises to a millimolar level triggered by a presynaptic action potential (Maconochie et al. 1994; Jones and Westbrook 1995), while extracellular GABA is maintained within a range of submicromolar to several micromolar levels (Lerma et al. 1986; Tossman et al. 1986; Scimemi et al. 2005). Extracellular GABA could originate from various sources such as spillover from synaptic clefts and non-synaptic release from neurons and glia (Semyanov et al. 2004). The lower extracellular GABA level is sufficient to activate extrasynaptic but not intrasynaptic $GABA_A$ receptors. Extrasynaptic $GABA_A$ receptors which contain the δ subunit (Somogyi et al. 1989; Nusser et al. 1995; Brickley et al. 1996; Soltesz and Nusser 2001) have high affinity for GABA (Saxena and Macdonald 1996; Brown et al. 2002) and little desensitization to continuous activation by GABA (Bianchim et al. 2001, 2002), leading to tonic inhibition of neurons even at lower extracellular GABA levels.

In numerical simulations, we used the Euler method to integrate model equations, which will be defined in Sections 2.1 and 2.2. C-language was used for programming. Time step size for numerical calculation was 100 microseconds. Parameter values are given in Table 1.

2.2 Sensory cortex

In the N_S, dynamic evolution of membrane potentials of the ith P and B cells that belong to cell assembly n is defined by

$$c_{\mathrm{m}}^{\mathrm{P_S}} \frac{d}{dt} v_{n,i}^{\mathrm{P_S}}(t) = -g_{\mathrm{m}}^{\mathrm{P_S}}(v_{n,i}^{\mathrm{P_S}}(t) - v_{\mathrm{rest}}^{\mathrm{P_S}}) + I_{n,i}^{\mathrm{P_S P_S}}(t) + I_{n,i}^{\mathrm{P_S B_S}}(t) + I_{n,i}^{\mathrm{P_S P_M}}(t) + I_{n,i}^{\mathrm{E_S}}(t) + I_n^{\xi}(t), \tag{1}$$

$$c_{\mathrm{m}}^{\mathrm{B_S}} \frac{d}{dt} v_{n,i}^{\mathrm{B_S}}(t) = -g_{\mathrm{m}}^{\mathrm{B_S}}(v_{n,i}^{\mathrm{B_S}}(t) - v_{\mathrm{rest}}^{\mathrm{B_S}}) + I_{n,i}^{\mathrm{B_S P_S}}(t), \tag{2}$$

$$I_{n,i}^{\mathrm{P_S P_S}}(t) = -g_{\mathrm{AMPA}}(v_{n,i}^{\mathrm{P_S}}(t) - v_{\mathrm{AMPA}}) \sum_{\substack{j=1 \\ j \neq i}}^{N} w_{n,ij}^{\mathrm{P_S P_S}} r_{n,j}^{\mathrm{P_S}}(t), \tag{3}$$

$$I_{n,i}^{\mathrm{P_S B_S}}(t) = -g_{\mathrm{GABA}}(v_{n,i}^{\mathrm{P_S}}(t) - v_{\mathrm{GABA}}) \sum_{j=1}^{N} w_{n,ij}^{\mathrm{P_S B_S}} r_{n,j}^{\mathrm{B_S}}(t), \tag{4}$$

$$I_{n,i}^{\mathrm{P_S P_M}}(t) = -g_{\mathrm{AMPA}}(v_{n,i}^{\mathrm{P_S}}(t) - v_{\mathrm{AMPA}}) \sum_{j=1}^{N} w_{n,ij}^{\mathrm{P_S P_M}} r_{n,j}^{\mathrm{P_M}}(t), \tag{5}$$

$$I_{n,i}^{\mathrm{E_S}}(t) = -g_{\mathrm{GABA}}(v_{n,i}^{\mathrm{P_S}}(t) - v_{\mathrm{GABA}}) \delta_{\mathrm{P_S}} r_{n,i}^{\mathrm{E_S}}(t), \tag{6}$$

$$I_n^{\xi}(t) = \alpha_{\mathrm{P_S}} \exp(-\frac{|n-\xi|}{\tau_{\mathrm{P_S}}}), (\xi \in \{1, 2, 3, ..., n, ..., M\}) \tag{7}$$

$$I_{n,i}^{\mathrm{B_S P_S}}(t) = -g_{\mathrm{AMPA}}(v_{n,i}^{\mathrm{B_S}}(t) - v_{\mathrm{AMPA}}) \sum_{\substack{n'=1 \\ n' \neq n}}^{M} w_{nn',i}^{\mathrm{B_S P_S}} r_{n',i}^{\mathrm{P_S}}(t). \tag{8}$$

In these equations, $I_{n,i}^{\mathrm{P_S P_S}}(t)$ is an excitatory synaptic current from other P cells, $I_{n,i}^{\mathrm{P_S B_S}}(t)$ an inhibitory synaptic current from B cells, $I_{n,i}^{\mathrm{P_S P_M}}(t)$ an excitatory synaptic current from N_M P cells, $I_{n,i}^{\mathrm{E_S}}(t)$ an inhibitory nonsynaptic current mediated by extracellular GABA via extrasynaptic receptors, and $I_n^{\xi}(t)$ an excitatory input current when presented with a sensory stimulus: Feature ξ. $I_{n,i}^{\mathrm{B_S P_S}}(t)$ is an excitatory synaptic current from P cells. $w_{n,ij}^{\mathrm{P_S P_S}}$, $w_{n,ij}^{\mathrm{P_S B_S}}$, $w_{n,ij}^{\mathrm{P_S P_M}}$ and $w_{nn',i}^{\mathrm{B_S P_S}}$

are P-to-P, B-to-P, P(N_M)-to-P(N_S) and P-to-B synaptic connection weights, respectively. $r^{P_S}_{n,j}(t)$ and $r^{P_M}_{n,j}(t)$ are the fractions of AMPA receptors in the open state triggered by presynaptic action potentials of the jth N_S and N_M P cells, respectively. $r^{B_S}_{n,j}(t)$ is the fraction of intrasynaptic $GABA_A$ receptors in the open state triggered by presynaptic action potentials of the jth B cell. $r^{E_S}_{n,i}(t)$ is the fraction of extrasynaptic $GABA_A$ receptors, located on the ith P cell, in the open state provoked by extracellular GABA. δ_{P_S} expresses the amount of extrasynaptic $GABA_A$ receptors embedded in P cell membrane (Hoshino 2009, 2012, 2014). $c^{P_S}_m$, $c^{B_S}_m$, $g^{P_S}_m$, $g^{B_S}_m$, $v^{P_S}_{rest}$, $v^{B_S}_{rest}$, g_{AMPA}, g_{GABA}, v_{AMPA}, v_{GABA}, α_{P_S} and τ_{P_S} are constants defined in Table 1.

Receptor dynamics in current equations are defined by

$$\frac{d}{dt}r^{P_S}_{n,j}(t) = \alpha_{AMPA}[Glu]^{P_S}_{n,j}(t)(1 - r^{P_S}_{n,j}(t)) - \beta_{AMPA}r^{P_S}_{n,j}(t), \tag{9}$$

$$\frac{d}{dt}r^{B_S}_{n,j}(t) = \alpha_{GABA}\,[GABA]^{B_S}_{n,j}\,(t)(1 - r^{B_S(t)}_{n,j} - \beta_{GABA}r^{B_S}_{n,j}(t), \tag{10}$$

$$\frac{d}{dt}r^{E_S}_{n,j}(t) = \alpha_{GABA}\,[GABA]^{S}_{ext}\,(1 - r^{E_S}_{n,j}(t)) - \beta_{GABA}r^{E_S}_{n,j}(t), \tag{11}$$

where $[Glu]^{P_S}_{n,j}(t)$ and $[GABA]^{B_S}_{n,j}\,(t)$ denote glutamate and GABA concentrations released from the jth P and B cells into synaptic clefts, respectively. $[GABA]^{S}_{ext}$ denotes the basal extracellular GABA concentration. α_{AMPA}, α_{GABA}, β_{AMPA} and β_{GABA} are constants defined in Table 1.

Probability of neuronal firing is defied by

$$PF^{\alpha}_{n,j} = \frac{1}{1 + \exp(-\eta_{\alpha}(v^{\alpha}_{n,j}(t) - \theta_{\alpha}))}.(\alpha = P_S, B_S) \tag{12}$$

When a cell generates an action potential, its membrane potential is depolarized to v_{act} (10 mV), kept for 1 ms, and then reset to the resting potential. η_{α} and θ_{α} are constants defined in Table 1.

An action potential triggers a release of glutamate or GABA into the synaptic cleft. Intrasynaptic neurotransmitter concentrations are defined by

$$[Glu]^{P_S}_{n,j}(t) = Glu^{P_S}_{syn}H(v^{P_S}_{n,i}(t) - v_{act}), \tag{13}$$

$$[GABA]^{B_S}_{n,j}\,(t) = GABA^{B_S}_{syn}H(v^{B_S}_{n,i}(t) - v_{act}), \tag{14}$$

where $Glu^{P_S}_{syn}$ and $GABA^{B_S}_{syn}$ are quantal discharges of neurotransmitters. H is a Heaviside function that is nonzero only during the brief window of an action potential: 1 ms.

2.3 Motor cortex

In the N_M, dynamic evolution of membrane potentials of the ith P and B cells that belong to cell assembly n is defined by

$$c^{P_M}_m\frac{d}{dt}v^{P_M}_{n,i}(t) = -g^{P_M}_m(v^{P_M}_{n,i}(t) - v^{P_M}_{rest}) + I^{P_MP_M}_{n,i}(t) + I^{P_MB_M}_{n,i}(t) + I^{P_MP_S}_{n,i}(t) + I^{E_M}_{n,i}(t), \tag{15}$$

$$c^{B_M}_m\frac{d}{dt}v^{B_M}_{n,i}(t) = -g^{B_M}_m(v^{B_M}_{n,i}(t) - v^{B_M}_{rest}) + I^{B_MP_M}_{n,i}(t), \tag{16}$$

$$I^{P_MP_M}_{n,i}(t) = -g_{AMPA}(v^{P_M}_{n,i}(t) - v_{AMPA})\sum_{\substack{j=1\\ j\neq i}}^{N} w^{P_MP_M}_{n,ij}r^{P_M}_{n,j}(t), \tag{17}$$

$$I^{P_MB_M}_{n,i}(t) = -g_{GABA}(v^{P_M}_{n,i}(t) - v_{GABA})\sum_{j=1}^{N} w^{P_MB_M}_{n,ij}r^{B_M}_{n,j}(t), \tag{18}$$

$$I^{P_MP_S}_{n,i}(t) = -g_{AMPA}(v^{P}_{n,i}(t) - v_{AMPA})\sum_{j=1}^{N} w^{P_MP_S}_{n,ij}r^{P_S}_{n,j}(t), \tag{19}$$

$$I^{E_M}_{n,i}(t) = -g_{GABA}(v^{P_M}_{n,i}(t) - v_{GABA})\delta_{P_M}r^{E_M}_{n,i}(t), \tag{20}$$

$$I^{B_MP_M}_{n,i}(t) = -g_{AMPA}(v^{B_M}_{n,i}(t) - v_{AMPA})\sum_{\substack{n'=1\\ n'\neq n}}^{M} w^{B_MP_M}_{nn',i}r^{P_M}_{n',i}(t), \tag{21}$$

In these equations, $I^{P_MP_M}_{n,i}(t)$ is an excitatory synaptic current from other P cells, $I^{P_MB_M}_{n,i}(t)$ an inhibitory synaptic current from B cells, $I^{P_MP_S}_{n,i}(t)$ an inhibitory synaptic current from N_S P cells, $I^{E_M}_{n,i}(t)$ an inhibitory nonsynaptic

current mediated by extracellular GABA via extrasynaptic receptors, and $I_{n,i}^{\mathrm{B_M P_M}}(t)$ an excitatory synaptic current from P cells. $w_{n,ij}^{\mathrm{P_M P_M}}$, $w_{n,ij}^{\mathrm{P_M B_M}}$, $w_{n,ij}^{\mathrm{P_M P_S}}$ and $w_{nn',i}^{\mathrm{B_M P_M}}$ are P-to-P, B-to-P, P(N_S)-to-P(N_M) and P-to-B synaptic connection weights, respectively. $c_{\mathrm{m}}^{\mathrm{P_M}}$, $c_{\mathrm{m}}^{\mathrm{B_M}}$, $g_{\mathrm{m}}^{\mathrm{P_M}}$, $g_{\mathrm{m}}^{\mathrm{B_M}}$, $v_{\mathrm{rest}}^{\mathrm{P_M}}$, $v_{\mathrm{rest}}^{\mathrm{B_M}}$ and $\delta_{\mathrm{P_M}}$ are constants defined in Table 1.

$r_{n,j}^{\mathrm{P_M}}(t)$ and $r_{n,j}^{\mathrm{B_M}}(t)$ were similarly defined as in N_S, and $r_{n,i}^{\mathrm{E_M}}(t)$ is defined by

$$\frac{d}{dt} r_{n,i}^{\mathrm{E_M}}(t) = \alpha_{\mathrm{GABA}} \, [GABA]_{\mathrm{ext}}^{\mathrm{M}} \, (1 - r_{n,i}^{\mathrm{E_M}}(t)) - \beta_{\mathrm{GABA}} r_{n,i}^{\mathrm{E_M}}(t), \quad (22)$$

where $[GABA]_{\mathrm{ext}}^{\mathrm{M}}$ denotes the basal extracellular GABA concentration. Probability of neuronal firing and neurotransmitter concentrations were similarly defined as in N_S.

3 Results

3.1 Influence of extracellular GABA on perceptual decision-making

To assess how the level of extracellular GABA affects perceptual decision-making that takes place in N_M, we ran three simulations: the control condition, the level of extracellular GABA in N_S ($[GABA]_{\mathrm{ext}}^{\mathrm{S}}$; see Eq. 11) or N_M ($[GABA]_{\mathrm{ext}}^{\mathrm{M}}$; see Eq. 22) was decreased from 2 μM to 0 μM. As shown in Fig. 2a (*bottom*), stimulus-sensitive (n = 4) N_M P cells can respond correctly to a feature stimulus: Feature 4 ($\xi = 4$; see Eq. 7). This corresponds to a successful perceptual decision. However, as shown in Fig. 2b, stimulus-insensitive (n = 3) P cells happen to respond wrongly to the stimulus if the level of extracellular GABA is decreased in the N_S (*left*) or N_M (*right*). These perceptual errors arise largely from a large $\tau_{\mathrm{P_S}}$ value (14; see Table 1 and Eq. 7) and indicate that intracortical tonic inhibition is crucial for reliable perceptual decision-making.

To investigate in more detail how the level of extracellular GABA affects the perceptual decision-making, we measured the rate of perceptual errors. As shown in Fig. 3a, the reduction of extracellular GABA concentration in N_M ($[GABA]_{\mathrm{ext}}^{\mathrm{M}}$) fatally increases the error rate, almost irrespective of the GABA level in N_S ($[GABA]_{\mathrm{ext}}^{\mathrm{S}}$). Decreasing $[GABA]_{\mathrm{ext}}^{\mathrm{S}}$ increases the error rate if $[GABA]_{\mathrm{ext}}^{\mathrm{M}}$ is less than 1.5 μM (e.g., see the circled 1 to 3). Interestingly, the increase of the error rate by decreasing $[GABA]_{\mathrm{ext}}^{\mathrm{S}}$ is not so significant if $[GABA]_{\mathrm{ext}}^{\mathrm{M}}$ is greater than 1.5 μM. This result may explain why tactile discrimination performance was significantly correlated with GABA concentration in the motor cortex but less in the visual cortex (Puts et al. 2011).

To elucidate possible roles of extracellular GABA in perceptual decision-making, we investigated whether and how the level of extracellular GABA affects the variability of neuronal activity. This was motivated by a study (Fox et al. 2007) that demonstrated that blood oxygen level-dependent (BOLD) responses in the somatomotor cortex were correlated with perception and behavior in human subjects and suggested that ongoing-spontaneous fluctuations in neuronal activity might account for variability in human behavior, e.g., the force of button press. Figure 3b shows ongoing-spontaneous membrane potentials recorded from N_M P cells under the three extracellular GABA level conditions (circled 1, 2 and 3 which correspond to those in panel a). Their means and variances are shown in Fig. 3c, indicating that a reduction in extracellular GABA concentration depolarizes the membrane potentials and increases their fluctuations (see the solid traces) from those of the initial condition (see the dashed traces which correspond to the circled 1).

Figure 4a shows their dependence (time-averaged for Fig. 3c) on extracellular GABA level, from which we derived the relation between the mean and the variance as shown in Fig. 4b (*left*). This result indicates that the membrane hyperpolarization by increasing the level of extracellular GABA contributes to reducing the variability in subthreshold neuronal activity in N_M at the resting state (see the squares). Interestingly, we found a clear positive correlation between the variance and the error rate as shown in Fig. 4b (*right*). This result supports the conclusion: ongoing-spontaneous fluctuation in motor cortex neuronal activity accounts for variability in human behavior (Fox et al. 2007).

3.2 Feedback influence of motor cortex on selective neuronal responses in sensory cortex

As has been addressed in Section 1, the primary motor cortex (M1) is considered to be a dynamic modulator of the somatosensory cortex (S1) during not only movement but also non-movement (Zagha et al. 2013). Reciprocal connections between the sensory and motor cortices (Matyas et al. 2010; Mao et al. 2011) infer intimate interaction between them. To see how the feedback signaling from N_M affects the selective responsiveness of N_S, we increased the synaptic connection weight from N_M to N_S P cells ($w_{n,ij}^{\mathrm{P_S P_M}}$, see Eq. 5). As shown in Fig. 5a, an increase in feedback signaling by strengthening the weight from 3 (*left*) to 5 (*right*) enhances the selective responsiveness of N_S P cells (*top-right, n = 4*) and the stimulus-evoked responses of N_M P cells (*bottom-right, n = 4*). In Fig. 5b, the top-left (*open circles, triangles, squares, asterisks*) and top-right panels show the dependence of firing rate of N_S P cells on the synaptic connection weight, indicating that the increase of feedback signaling sharpens the sensory tuning of the N_S to the applied feature stimulus.

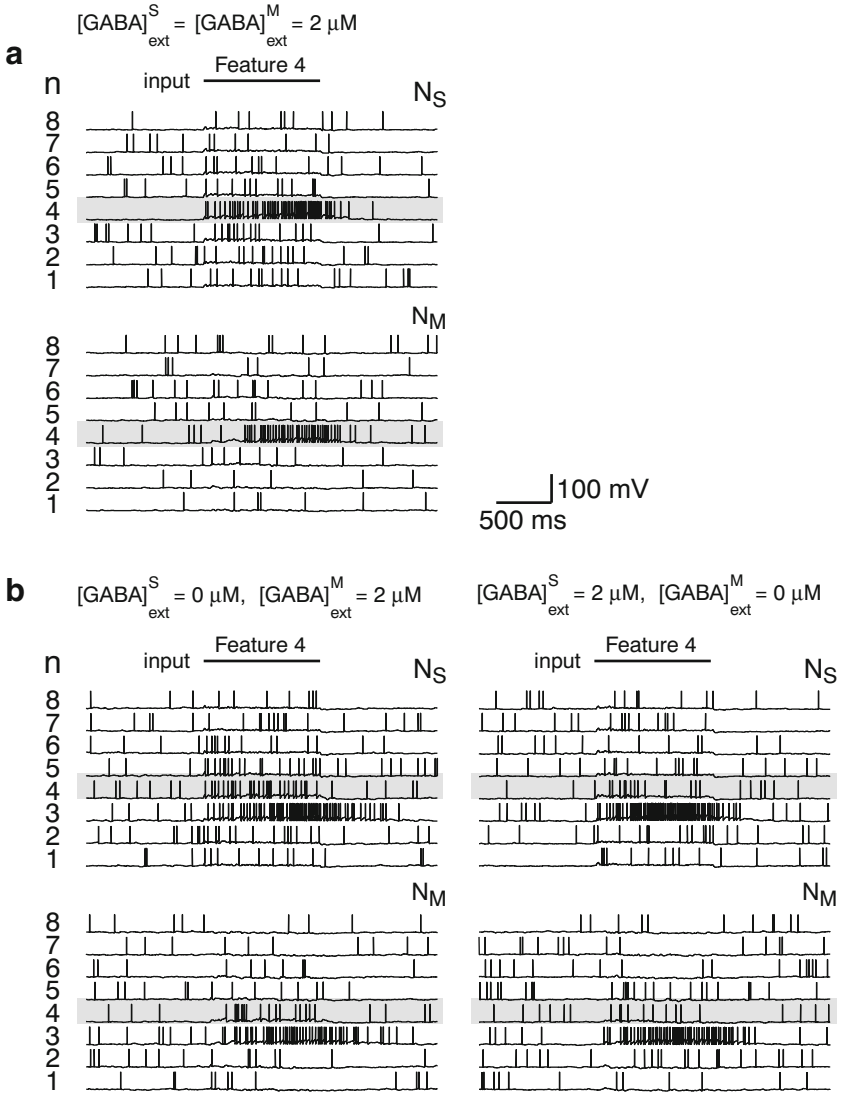

Fig. 2 Network behavior. **a** Responses (action potentials) of N_S (*top*) and N_M (*bottom*) P cells to a sensory stimulus (Feature 4). A horizontal bar indicates a stimulus presentation period. **b** Responses recorded under a condition in which the level of extracellular GABA in N_S ($[GABA]^S_{ext}, left$) or in N_M ($[GABA]^M_{ext}, right$) was decreased to 0 μM

To evaluate the selective responsiveness (i.e., the tuning performance) of the N_S, we measured "feature bias", which is defined by

$$FB = \frac{|\sum_{k=1}^{8} R(k) exp(i2\pi(k-1)/8)|}{\sum_{k} R(k)}. \quad (23)$$

$R(k)$ is the firing rate of a P cell when presented with a sensory stimulus (Feature k) ($1 \leq k \leq 8$). FB is a measure similar to orientation bias (OB) that is used for visual systems such as lateral geniculate nucleus (Xu et al. 2002) and primary visual cortex (Leventhal et al. 1995). We summarize how to measure OB. Responses of a cell to different orientations (angles) of a bar-stimulus $\{e.g., 0, \pi/8, 2\pi/8, 3\pi/8, 4\pi/8, 5\pi/8, 6\pi/8, 7\pi/8\}$ 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 that cell. The degree of orientation preference is termed "orientation bias (OB)". Since the periodicity of orientation is π, these angles are multiplied by a factor of two. As a consequence, OB ranges from 0 to 1.0, with 0 being completely insensitive to any orientation and 1.0 responding to only one orientation.

Figure 5b (*bottom-left*) indicates that the feedback signaling from the N_M contributes to sharpening the sensory tuning of the N_S. It may be noted that to ensure the selective responsiveness (FB > 0.5; see the open arrow), minimal N_M P cell activity as feedback signaling is required (see the open arrow in the top-left panel). Based on these results, we derived the relation between the FB score and the firing rate of stimulus-sensitive N_M P cells as shown in the bottom-right panel, indicating a positive correlation between them. This result suggests that the feedback signaling from the N_M

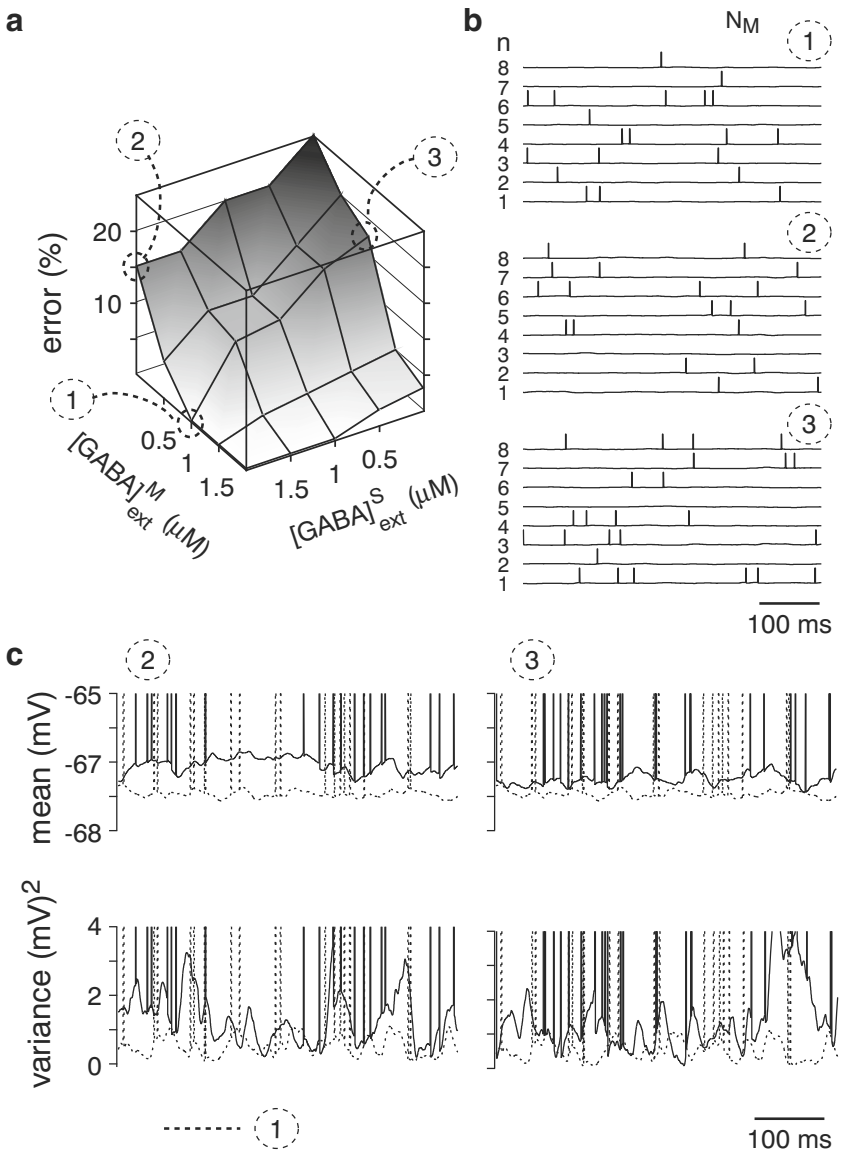

Fig. 3 Influence of extracellular GABA on perceptual decision-making. **a** Dependence of perceptual error rate on extracellular GABA concentrations in N_S ($[GABA]^S_{ext}$) and N_M ($[GABA]^M_{ext}$). **b** Ongoing-spontaneous membrane potentials recorded from N_M P cells under the three extracellular GABA level conditions; see the circled 1, 2 and 3 in panel a. **c** Modulation of ongoing-spontaneous membrane activity by extracellular GABA. The solid traces denote the means (*top*) and variances (*bottom*) of ongoing-spontaneous N_M P cell membrane potentials where ($[GABA]^M_{ext}$) (*left*) or $[GABA]^S_{ext}$ (*right*) was decreased to 0 μM. The dashed traces denote those obtained under the initial condition: ($[GABA]^M_{ext}$, $[GABA]^S_{ext}$) = (1 μM, 2 μM)

contributes to enhancing the selective responsiveness of the N_S.

To elucidate how the feedback signaling affects the perceptual decision-making performance, we investigated the dependence of the error rate on the intensity of feedback signaling; i.e., on $w^{P_S P_M}_{n,ij}$. As shown in Fig. 5c (*left*), too intense feedback signaling increases errors in decision-making ($w^{P_S P_M}_{n,ij} > 6$). Figure 5c (*right*) shows the relation between the error rate and the firing rate of stimulus-sensitive N_M P cells. This result indicates that too strong N_M activation ($>\sim$50 Hz) deteriorates the perceptual decision-making performance and suggests that the connection weight ($w^{P_S P_M}_{n,ij}$) should be limited up to 5 (see the filled up-arrow in the top-left panel of Fig. 5b) for the improvement of sensory tuning performance (see the bottom-left panel of Fig. 5b).

As has been address in Section 1, inhibitory tone correlates with the tuning performance of the sensory cortex. So we investigated how the level of extracellular GABA affects the FB score. Figure 6a (*top*) shows FBs, indicating that an increase in extracellular GABA concentration in N_S ($[GABA]^S_{ext}$) leads to an increase in selective responsiveness, which is remarkable if the intensity of feedback signaling is sufficient (*squares*). The middle panel shows the firing rate of stimulus-sensitive N_M P cells, based on which we derived its relation to the FB score shown in the bottom panel, indicating a positive correlation between them.

Then, we investigated how the level of extracellular GABA in N_M affects the FB score. As shown in Fig. 6b (*top*), we found that the ability of sensory tuning could be ensured if $[GABA]^M_{ext}$ is less than $\sim$2 μM. This result

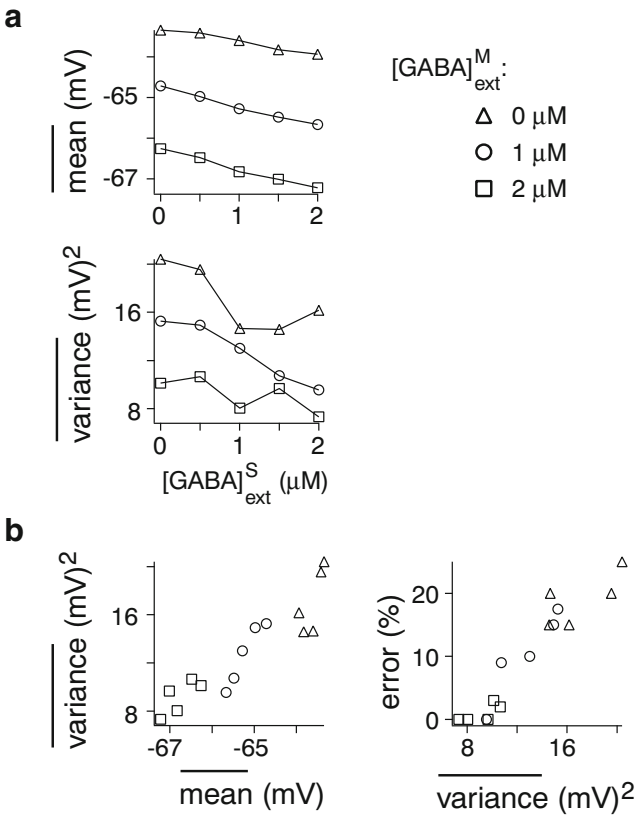

Fig. 4 Correlation between neuronal variability and perceptual performance. **a** Dependence of the mean (*top*) and variance (*bottom*) of ongoing-spontaneous N_M P cell membrane potentials on extracellular GABA level. The means and variances were time-averaged representations of those in Fig. 3**c**. **b** Relations between the mean and the variance (*left*) and between the error rate and the variance (*right*)

suggests that although the higher the GABA level in N_M, the lower the error rate (see Fig. 3a), it should be limited (up to $\sim$2 μM). Otherwise, the tuning performance of the N_S is to be deteriorated. The bottom panel indicates a clear positive correlation between the FB score and the firing rate of stimulus-sensitive N_M P cells. These results suggest that cortical extracellular GABA has crucial roles in tuning to sensory stimuli.

3.3 Significance of reduction of variability in ongoing-spontaneous motor cortex activity by tonic inhibition

In Section 3.1, we showed that the tonic inhibition of N_M P cells by extracellular GABA was beneficial for the reduction of variability in ongoing-spontaneous neuronal activity, thereby decreasing errors in perceptual decision-making. In this section, we examined whether the intracortical phasic inhibition mediated by GABAergic interneurons (B cells) could reduce the neuronal variability and therefore decrease the error rate. As shown in Fig. 7a (*top-left*), strengthening B-to-P connection weights ($w_{n,ij}^{P_M B_M}$, *circles*) hyperpolarizes N_M P cells, whose tendency is similar to that obtained by the tonic inhibitory scheme (*triangles*). However, as shown in the right panel the variability in ongoing-spontaneous neuronal activity differs: the phasic inhibitory scheme (*circles*) can not reduce but rather increases the neuronal variability. Nevertheless, these (tonic and phasic) inhibitory schemes show similar ongoing-spontaneous firing activity, as shown in the bottom-left panel of Fig. 7a. The bottom-right panel of Fig. 7a indicates that an increase in phasic inhibitory tone results in an increase in perceptual error rate (*circles*).

As shown in Fig. 7b (*left*), we derived from these results the relation between the mean membrane potential and the neuronal variance, indicating that the hyperpolarization induced by tonic (*triangles*) but not by phasic (*circles*) inhibition can reduce the ongoing-spontaneous neuronal variability. The right panel of Fig. 7b indicates a positive correlation between the neuronal variance and the error rate for the tonic (*triangles*) and phasic (*circles*) inhibitory schemes. These results suggest that the tonic inhibitory scheme is beneficial for the reduction of variability in N_M activity at a resting state and thus for the reduction of perceptual errors (see the triangles).

To understand what accounts for the difference in ongoing-spontaneous neuronal variability between the tonic and phasic inhibitory schemes, we recorded membrane potentials and analyzed them. Figure 7c shows histograms of ongoing-spontaneous membrane potentials, where N_M P cells at an initial condition (thick solid trace) are hyperpolarized by tonic inhibition (dashed trace) or by phasic inhibition (thin solid trace). The narrow distribution around the mean ($\sim$-67 mV) indicates that the tonic inhibitory scheme can hyperpolarize N_M P cells with less membrane potential fluctuations. Whereas, the wide distribution around the mean ($\sim$-67 mV) indicates that the phasic inhibitory scheme results in greater membrane potential fluctuations. This results in an increase in neuronal variability at the resting state.

4 Discussion

Interaction between sensory and motor cortices is crucial for perceptual decision-making, in which intracortical inhibition might have an important role (Edden et al. 2009; Sandberg et al. 2014). We simulated a neural network model to elucidate the significance of interaction between sensory (N_S) and motor (N_M) cortices in perceptual decision-making in association with the level of GABA in extracellular space. Extracellular GABA molecules acted on extrasynaptic receptors embedded in membranes of

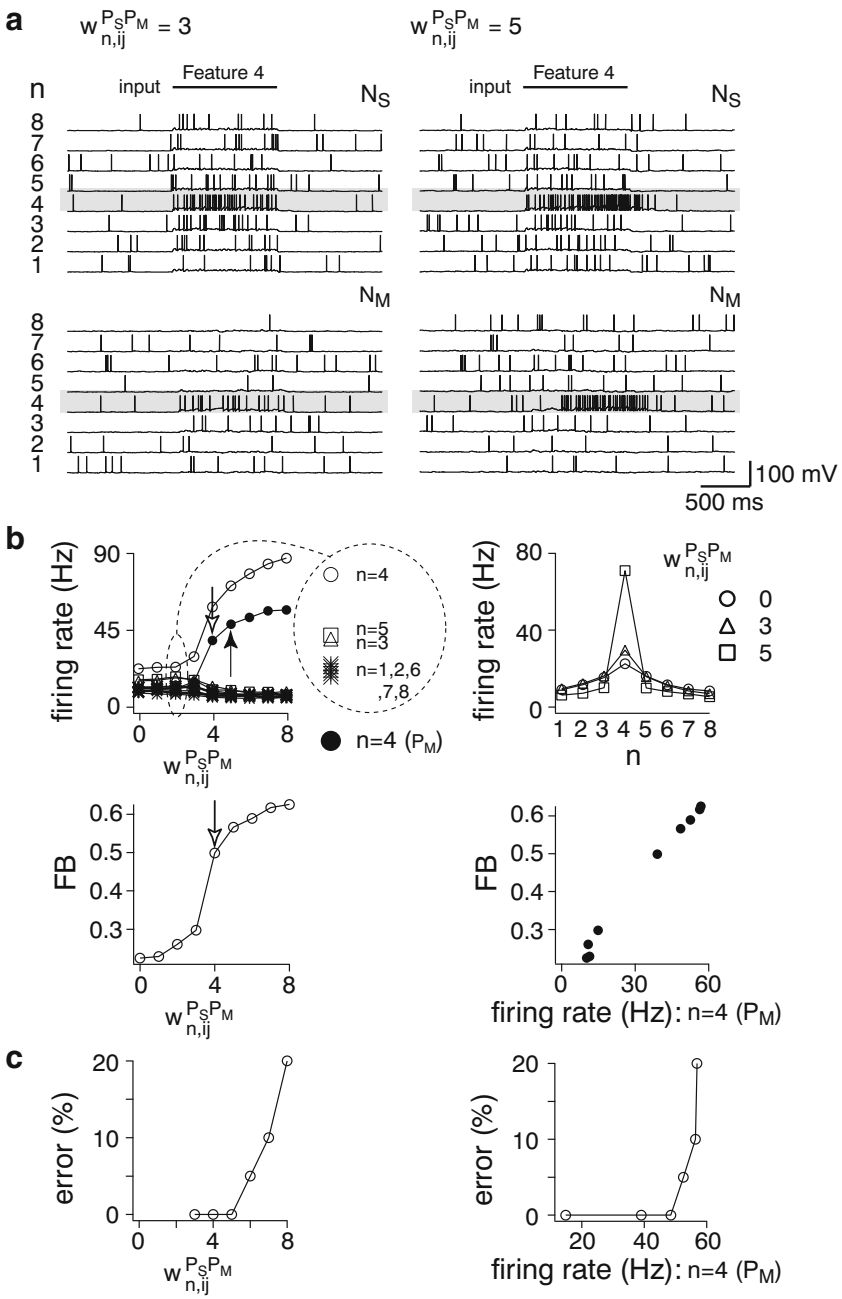

Fig. 5 Feedback influence of motor cortex on selective neuronal responsiveness in sensory cortex. **a** Responses of N_S (*top*) and N_M (*bottom*) P cells in which the synaptic connection weight from N_M to N_S P cells ($w^{P_S P_M}_{n,ij}$) was increased from 3 (*left*) to 5 (*right*). **b** Dependence of firing rate of N_S P cells (*top-left*) and their profiles (*top-right*) on $w^{P_S P_M}_{n,ij}$, and dependence of FB on $w^{P_S P_M}_{n,ij}$ (*bottom-left*) and on N_M P cell firing rate (*bottom-right*). **c** Dependence of perceptual error rate on $w^{P_S P_M}_{n,ij}$ (*left*) and on N_M P cell firing rate (*right*)

pyramidal (P) cells and suppressed them. A reduction in extracellular GABA concentration either in N_S or N_M increased the rate of errors in perceptual decision-making, for which an increase in ongoing-spontaneous fluctuations in subthreshold neuronal activity in N_M prior to sensory stimulation was responsible. Feedback (N_M-to-N_S) signaling enhanced selective neuronal responses in N_S, which in turn increased stimulus-evoked neuronal activity in N_M. We suggest that GABA in extracellular space contributes to reducing variability in motor cortex activity at a resting state and thereby the motor cortex can respond correctly to a subsequent sensory stimulus. Feedback signaling from the motor cortex improves the selective responsiveness of the sensory cortex, which ensures the fidelity of information transmission to the motor cortex, leading to reliable perceptual decision-making.

The primary motor cortex is known to control voluntary movement; however, it also exhibits responses to various sensory stimuli: vision and somatosensation (Hatsopoulos and Suminski 2011). An experimental study (Sachidhanandam et al. 2013) investigated the link between membrane potential and perceptual judgment. A mouse was trained to detect single brief whisker stimuli and to report perceived stimuli by licking to obtain a reward. Whole-cell recordings

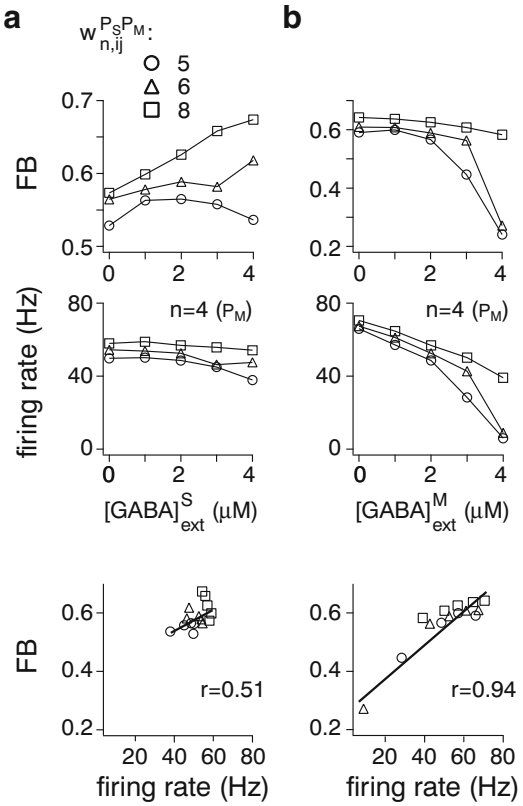

Fig. 6 Influence of extracellular GABA level on sensory tuning performance. **a** Dependence of FB (*top*) and N_M P cell firing rate (*middle*) on extracellular GABA level in N_S, and the relation between the FB score and the firing rate (*bottom*). The intensity of feedback signaling was changed by varying the synaptic connection weight ($w^{P_S P_M}_{n,ij}$): 5 (*circles*), 6 (*triangles*), 8 (*squares*). **b** Dependence of FB (*top*) and N_M P cell firing rate (*middle*) on extracellular GABA level in N_M, and the relation between the FB score and the firing rate (*bottom*)

from barrel cortex neurons revealed that membrane potential correlated with perceptual judgments. Whisker deflection evoked an early (less than 50 ms) and a late (50-400 ms) depolarization. The researchers found that the late depolarization component was enhanced on hit trials but not on miss trials. They concluded that the late membrane activity contributes to driving perceptual judgments, and suggested that internal command from the motor cortex could provide a top-down source for the late membrane response in the sensory cortex. Manita and colleagues (Manita et al. 2015) identified a neural circuit consisted of long-range reciprocal projections between motor and somatosensory cortices, and demonstrated that the recurrent input to the sensory cortex was essential for accurate perceptual judgments. The flattening of sensory tuning in V1 observed in old animals was considered responsible for their poor detection performance (Schmolesky et al. 2000). Our study indicates the importance of the motor to sensory cortex feedback signaling for tuning to external stimuli, leading to reliable decision-making.

Makino and colleagues (Makino et al. 2016) proposed a circuit model of sensorimotor associative learning. In their model, sensorimotor association is initially executed by dopamine-dependent plasticity to strengthen corticostriatal synapses in the basal ganglia carrying specific sensory information. This pathway drives specific motor responses via prefrontal cortex (PFC). The basal ganglia output to PFC also strengthens sensory input synapses in PFC, which subsequently forms a pathway from sensory cortex to PFC and to motor cortex, bypassing the basal ganglia. Further training can create the direct sensory-motor cortical pathway via coincidental activation-dependent synaptic plasticity. Zach and colleagues (Zach et al. 2008) demonstrated that primary motor cortex neurons of macaques became sensitive to the visual features of stimuli such as colors after learning to associate different colors with different reaching movements. In our neural network model, the coordinated wiring between N_S and N_M P cells was assumed as a result of sensorimotor associative learning.

We showed that a reduction of variability in ongoing-spontaneous membrane potential in the motor cortex decreased the perceptual error rate. A study (Fox et al. 2007) indicated a close correlation between blood oxygen level-dependent (BOLD) response in the somatomotor cortex and perception and behavior in human subjects, and suggested that fluctuation in ongoing-spontaneous membrane potential might account for variability in human behavior. Our study points to a possible strategy employed by the brain for the reduction of neuronal variability in the motor cortex so as to improve behavioral performance: tonic inhibition of motor cortex by extracellular GABA.

To reduce the neuronal variability in the motor cortex, we employed the extracellular GABA-mediated inhibitory mechanism. Homeostatic scaling may be another possible mechanism. Homeostatic scaling operates as a compensatory negative feedback mechanism to maintain neural network stability. It normalizes all synaptic connections by decreasing the strength of each synapse by the same factor (Turrigiano and Nelson 2000; Siddoway et al. 2014). Homeostatic scaling of P cells may work to reduce the neuronal variability in the motor cortex.

Sandberg and colleagues (Sandberg et al. 2014) measured GABA levels in human early visual cortex by magnetic resonance spectroscopy (MRS), and indicated a negative correlation between GABA concentration and perceptual error rate. Another study (Puts et al. 2011) demonstrated that tactile discrimination performance was significantly correlated with GABA concentration in the motor cortex but less in the visual cortex. These contradictory results could be explained by our study. Namely, a reduction of extracellular GABA concentration in N_S increases

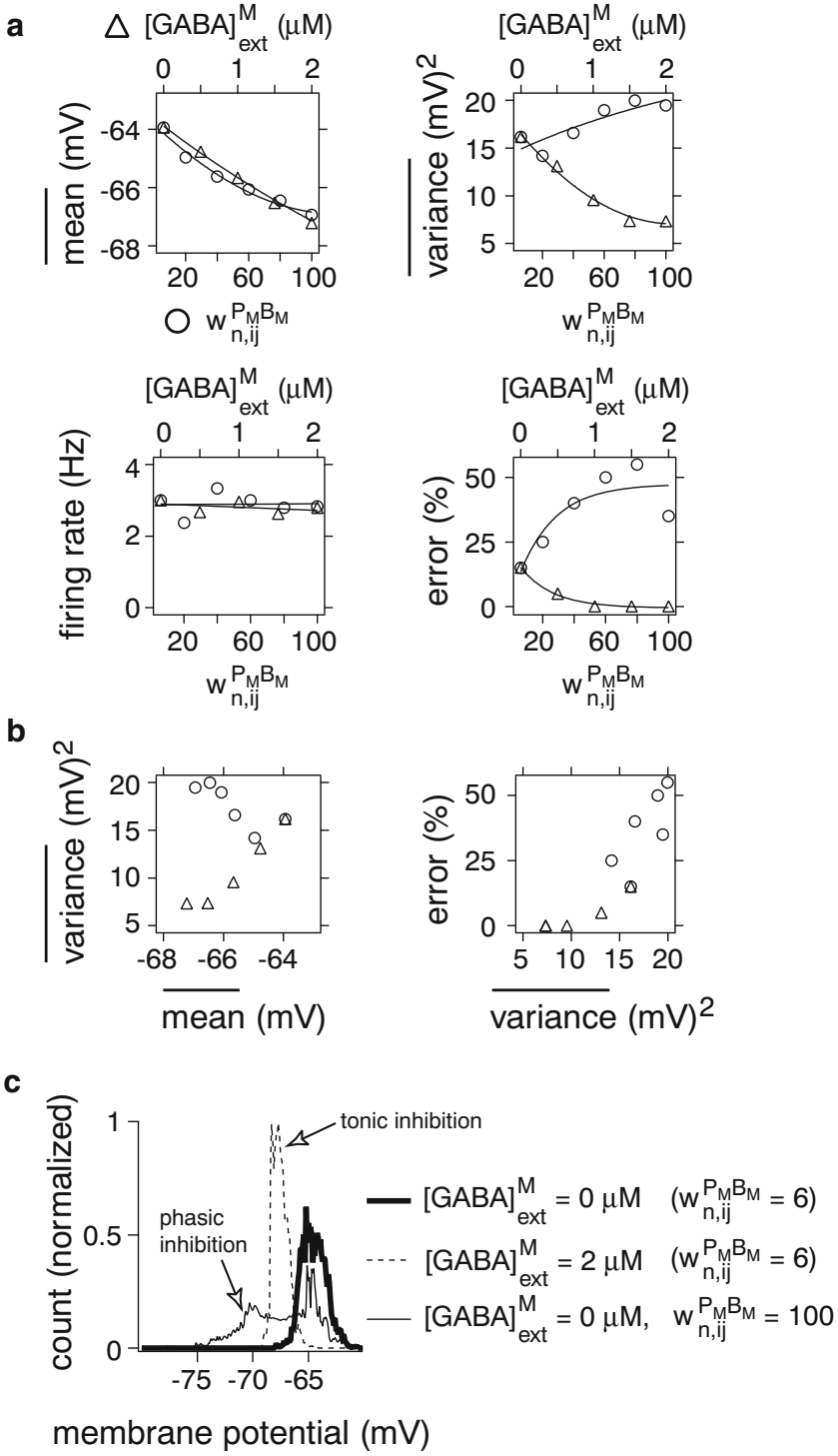

Fig. 7 Influence of phasic inhibition on variability in ongoing-spontaneous neuronal activity. **a** Dependence of mean (*top-left, circles*) and variance (*top-right, circles*) of ongoing-spontaneous N_M P cell membrane potentials on B-to-P connection weight ($w_{n,ij}^{P_M B_M}$), and dependence of firing rate (*bottom-left, circles*) and perceptual error rate (*bottom-right, circles*) on $w_{n,ij}^{P_M B_M}$. The triangles denote those obtained by the tonic inhibitory scheme. **b** Relations between the mean and the variance (*left*) and between the error rate and the variance (*right*). **c** Histograms of ongoing-spontaneous membrane potentials, where N_M P cells at an initial condition (thick solid trace) were hyperpolarized by tonic inhibition (dashed trace) or by phasic inhibition (thin solid trace)

the error rate if the extracellular GABA level in N_M is insufficient (see Fig. 3a,$[GABA]_{ext}^{M} < 1.5\mu$M). In contrast, a reduction of extracellular GABA concentration in N_S does not significantly increase the error rate if the extracellular GABA level in N_M is sufficient (see Fig. 3a,$[GABA]_{ext}^{M} > 1.5\mu$M). Notably, the reduction of extracellular GABA levels in N_M fatally increases the error rate, almost irrespective of extracellular GABA levels in N_S (see Fig. 3a,$0\mu\text{M} < [GABA]_{ext}^{S} < 2\mu$M). Our previous study (Hoshino et al. 2018) demonstrated that transient reduction of extracellular GABA concentration in the sensory cortex, which was mediated by gliotransmission, accelerated the reaction speed of the motor cortex to sensory stimulation. These studies may provide insights into possible roles of extracellular GABA-mediated inhibition of sensory and motor cortices in perceptual decision-making.

Compliance with Ethical Standards

Conflict of interests The authors declare that they have no conflict of interest.

References

Bianchim, M.T., Haas, K.F., Macdonald, R.L. (2001). Structural determinants of fast desensitization and desensitization-deactivation coupling in GABAa receptors. *J. Neurosci.*, *21*, 1127–36.

Bianchim, M.T., Haas, K.F., Macdonald, R.L. (2002). Alpha1 and alpha6 subunits specify distinct desensitization, deactivation and neurosteroid modulation of GABA(A) receptors containing the delta subunit. *Neuropharmacology*, *43*, 492–502.

Brickley, S.G., Cull-Candy, S.G., 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.

Brown, N., Kerby, J., Bonnert, T.P., Whiting, P.J., Wafford, K.A. (2002). Pharmacological characterization of a novel cell line expressing human alpha(4)beta(3)delta GABA(A) receptors. *Br. J. Pharmacol.*, *136*, 965–974.

deCharms, R.C., & Zador, A. (2000). Neural representation and the cortical code. *Annu. Rev. Neurosci.*, *23*, 613–647.

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

Edden, R.A., Muthukumaraswamy, S.D., Freeman, T.C., Singh, K.D. (2009). Orientation discrimination performance is predicted by GABA concentration and gamma oscillation frequency in human primary visual cortex. *J. Neurosci.*, *29*, 15721–15726.

Farrant, M., & Nusser, Z. (2005). Variations on an inhibitory theme: phasic and tonic activation of GABA(A) receptors. *Nat. Rev. Neurosci.*, *6*, 215–229.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Raichle, M.E. (2007). Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. *Neuron*, *56*, 171–184.

Gonzalez-Burgos, G., Fish, K.N., Lewis, D.A. (2011). GABA Neuron alterations, cortical circuit dysfunction and cognitive deficits in schizophrenia. *Neural Plasticity*, *2011*, 723184.

Hasler, G., van der Veen, J.W., Tumonis, T., Meyers, N., Shen, J., Drevets, W.C. (2007). Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. *Arch. Gen. Psychiatry*, *64*, 193–200.

Hatsopoulos, N.G., & Suminski, A.J. (2011). Sensing with the motor cortex. *Neuron*, *72*, 477–487.

Hoshino, O. (2009). GABA Transporter preserving ongoing spontaneous neuronal activity at firing subthreshold. *Neural Comput.*, *21*, 1683–1713.

Hoshino, O. (2012). Regulation of ambient GABA levels by neuron-glia signaling for reliable perception of multisensory events. *Neural Comput.*, *24*, 2964–2993.

Hoshino, O. (2014). Balanced crossmodal excitation and inhibition essential for maximizing multisensory gain. *Neural Comput.*, *26*, 1362–1385.

Hoshino, O., Zheng, M., Watanabe, K. (2018). Perceptual judgments via sensory-motor interaction assisted by cortical GABA. *J. Comput. Neurosci.*, *44*, 233–251.

Jones, M.V., & Westbrook, G.L. (1995). Desensitized states prolong GABAA channel responses to brief agonist pulses. *Neuron*, *15*, 181–91.

Kolasinski, J., Logan, J.P., Hinson, E.L., Manners, D., Divanbeighi, Z.A.P., Makin, T.R., Emir, U.E., Stagg, C.J. (2017). A mechanistic link from GABA to cortical architecture and perception. *Current Biology*, *27*, 1685–1691.

Lerma, J., Herranz, A.S., Herreras, O., Abraira, V., Martin, D.R. (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, A.G., Thompson, K.G., Liu, D., Zhou, Y., Ault, S.J. (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.

Maconochie, D.J., Zempel, J.M., Steinbach, J.H. (1994). How quickly can GABAA receptors open?. *Neuron*, *12*, 61–71.

Makino, H., Hwang, E.J., Hedrick, N.G., Komiyama, T. (2016). Circuit Mechanisms of Sensorimotor Learning. *Neuron*, *92*, 705–721.

Manita, S., Suzuki, T., Homma, C., Matsumoto, T., Odagawa, M., Yamada, K., Ota, K., Matsubara, V., Inutsuka, A., Sato, M., Ohkura, M., Yamanaka, A., Yanagawa, Y., Nakai, J., Hayashi, Y., Larkum, M.E., Murayama, M. (2015). A Top-Down Cortical Circuit for Accurate Sensory Perception. *Neuron*, *86*, 1304–1316.

Mao, T., Kusefoglu, D., Hooks, B.M., Huber, D., Petreanu, L., Svoboda, K. (2011). Long-range neuronal circuits underlying the interaction betweeN$_S$sory and motor cortex. *Neuron*, *72*, 111–123.

Matyas, F., Sreenivasan, V., Marbach, F., Wacongne, C., Barsy, B., Mateo, C., Aronoff, R., Petersen, C.C. (2010). Motor control by sensory cortex. *Science*, *330*, 1240–1243.

Mountcastle, V.B. (1997). The columnar organization of the neocortex. *Brain: A Journal of Neurology*, *120*, 701–722.

Nusser, Z., Roberts, J.D., Baude, A., Richards, J.G., Somogyi, P. (1995). Relative densities of synaptic and extrasynaptic GABAA receptors on cerebellar granule cells as determined by a quantitative immunogold method. *The Journal of Neuroscience*, *5*, 2948–2960.

Ortinski, P.I., Turner, J.R., Barberis, A., Motamedi, G., Yasuda, R.P., Wolfe, B.B., Kellar, K.J., Vicini, S. (2006). Deletion of the GABA(a) receptor alpha1 subunit increases tonic GABA(a) receptor current: a role for GABA uptake transporters. *The Journal of Neuroscience*, *26*, 9323–9331.

Puts, N.A., Edden, R.A., Evans, C.J., McGlone, F., McGonigle, D.J. (2011). Regionally specific human GABA concentration correlates with tactile discrimination thresholds. *J. Neurosci.*, *31*, 16556–16560.

Sachidhanandam, S., Sreenivasan, V., Kyriakatos, A., Kremer, Y., Petersen, C.C. (2013). Membrane potential correlates of sensory perception in mouse barrel cortex. *Nature Neuroscience*, *16*, 1671–1677.

Sandberg, K., Blicher, J.U., Dong, M.Y., Rees, G., Near, J., Kanai, R. (2014). Occipital GABA correlates with cognitive failures in daily life. *Neuroimage*, *87*, 55–60.

Saxena, N.C., & Macdonald, R.L. (1996). Properties of putative cerebellar gamma-aminobutyric acidA receptor isoforms. *Mol. Pharmacol.*, *49*, 567–579.

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

Scimemi, A., Semyanov, A., Sperk, G., Kullmann, D.M., Walker, M.C. (2005). Multiple and plastic receptors mediate tonic GABAA receptor currents in the hippocampus. *J. Neurosci.*, *25*, 10016–10024.

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

Semyanov, A., Walker, M.C., Kullmann, D.M., Silver, R.A. (2004). Tonically active GABA A receptors: modulating gain and maintaining the tone. *Trends Neurosci.*, *27*, 262–269.

Siddoway, B., Hou, H., Xia, H. (2014). Molecular mechanisms of homeostatic synaptic downscaling. *Neuropharmacology*, *78*, 38–44.

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

Somogyi, P., Takagi, H., Richards, J.G., 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.

Stagg, C.J., Bestmann, S., Constantinescu, A.O., Moreno, L.M., Allman, C., Mekle, R., Woolrich, M., Near, J., Johan-Berg, H., Rothwell, J.C. (2011). Relationship between physiological measures of excitability and levels of glutamate and GABA in the human motor cortex. *J. Physiol.*, *589*, 5845–5855.

Sumner, P., Edden, R.A., Bompas, A., Evans, C.J., Singh, K.D. (2010). More GABA, less distraction: a neurochemical predictor of motor decision speed. *Nat. Neurosci.*, *13*, 825–827.

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.

Turrigiano, G.G., & Nelson, S.B. (2000). Hebb and homeostasis in neuronal plasticity. *Curr. Opin. Neurobiol.*, *10*, 358–364.

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

Zach, N., Inbar, D., Grinvald, Y., Bergman, H., Vaadia, E. (2008). Emergence of novel representations in primary motor cortex and premotor neurons during associative learning. *J. Neurosci.*, *28*, 9545–9556.

Zagha, E., Casale, A.E., Sachdev, R.N., McGinley, M.J., McCormick, D.A. (2013). Motor cortex feedback influences sensory processing by modulating network state. *Neuron*, *79*, 567–578.