Effect of cortical extracellular GABA on motor response

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Abstract
To elucidate how the flattening of sensory tuning due to a deficit in tonic inhibition slows motor responses, we simulated a neural network model in which a sensory cortical network (NS) and a motor cortical network (NM) are reciprocally connected, and the NM projects to spinal motoneurons (Mns). The NS was presented with a feature stimulus and the reaction time of Mns was measured. The flattening of sensory tuning in NS caused by decreasing the concentration of gamma-aminobutyric acid (GABA) in extracellular space resulted in a decrease in the stimulus-sensitive NM pyramidal cell activity while increasing the stimulus-insensitive NM pyramidal cell activity, thereby prolonging the reaction time of Mns to the applied feature stimulus. We suggest that a reduction in extracellular GABA concentration in sensory cortex may interfere with selective activation in motor cortex, leading to slowing the activation of spinal motoneurons and therefore to slowing motor responses.

Keywords Sensory tuning · Motor cortex · Cortical GABA · Selective activation · Motor response

1 Introduction

Both in humans and animals, sensory functions such as vision, audition and somatosensation decline with aging (Craik & Bialystok, 2006). Notably, such sensory degradation takes place even at early sensory cortical stages, e.g., primary visual cortex (V1) (Schmolesky et al., 2000; Leventhal et al., 2003). These studies compared the orientation tuning of V1 neurons between young and old (healthy) macaque monkeys, and indicated a significant degradation in the old monkeys. Interestingly, gamma-aminobutyric acid (GABA) or its agonists dosed into old monkeys’ V1 improved their orientation tuning, which was comparable to that of young monkeys. These results suggest that impairment in intracortical inhibition might be a key factor for the age-related degradation of sensory information processing.

In the human primary somatosensory cortex (S1), tactile tuning was associated with cortical GABAergic tone (Kolasinski et al., 2017). To elucidate the correlations of GABA concentration to tactile tuning and to perceptual acuity, the researchers applied a combination of fMRI, magnetic resonance spectroscopy (MRS), and psychophysics. Their study demonstrated that higher GABA concentration was associated with sharper sensory tuning, which resulted in enhancement of sensory perception. It was suggested that MRS GABA signals are likely to reflect extracellular GABA, pointing to the possibility that a kind of non-synaptic intracortical inhibition might work to enhance sensory tuning; namely, tonic inhibition functions when extracellular GABA molecules activate extrasynaptic GABA receptors.

MRS is a noninvasive method for measuring the brain content of selected metabolites, including GABA. MRS detects radiofrequency signals that arise from hydrogen nuclear spins within metabolites, and these signals have chemically specific frequencies. Thus, MRS signals are separated in the MR spectrum along chemical lines: N-acetyl aspartate (NAA), creatine-containing compounds (Cr), choline-containing compounds (Cho), Myoinositol (Myo), glutamate (Glu), glutamine (Gln) and GABA. GABA concentration can be determined by separating GABA signals from the rest of the spectrum; for details see a review (Puts & Edden, 2012).

The flattening of sensory tuning in V1 in senescent monkeys is considered responsible for their poor detection...
performance (Schmoesky et al., 2000). Psychophysical experiments (Yordanova et al., 2004; Falkenstein et al., 2006) demonstrated age-related slowing in sensory detection tasks. They recorded event-related potentials (ERPs) over the primary motor cortex (M1). Younger (mean 22 years) and older (mean 58 years) subjects were instructed to respond sensory (visual and auditory) stimuli (letters) as quickly as possible. They found that this behavioral slowing was not due to delays in stimulus processing as reflected by latencies of early ERP components. Instead, the behavioral slowing was due to an alteration of movement-related components, particularly prolongation of the motor-related potential in the motor cortex. It was suggested that the overt response requires a higher activation in older subjects. This extra-activation needs time and hence prolongs reaction time with aging.

These studies motivated us to elucidate how the flattening of sensory tuning due to a deficit in tonic inhibition slows motor responses. To address this issue, we simulate a neural network model. In the network model, a sensory cortical network (NS) and a motor cortical network (NM) are reciprocally connected, and the NM sends projections to spinal motoneurons (Mns). The NS is presented with a feature stimulus and the reaction time of Mns is measured. This hierarchical model structure was assumed based on the following findings of studies. The primary motor cortex is known to control voluntary movement; however, it also exhibits responses to sensory stimuli such as vision and somatosensation (Hatsopoulos & Suminski, 2011). Sachidhanandam and colleagues (Sachidhanandam et al., 2013) investigated the relationship between membrane potential and perceptual judgment. In their experiment, a mouse was trained to detect a single brief whisker stimulus and obtained a reward when detecting the stimulus. Recordings 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 long-range reciprocal projections between motor and somatosensory cortices, and demonstrated that recurrent input to sensory cortex was essential for accurate perceptual judgments.

A circuit model for sensorimotor associative learning was proposed (Makino et al., 2016). In their model, dopamine-dependent plasticity initially strengthens corticothalamic synapses in the basal ganglia carrying specific sensory information. This pathway then drives specific motor responses via prefrontal cortex (PFC) and the basal ganglia output to PFC 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 creates the direct sensory-motor cortical pathway via coincidental activation-dependent synaptic plasticity. An experiment (Zach et al., 2008) demonstrated that neurons of primary motor cortex in macaques became sensitive to visual feature stimuli such as colors after associative learning of specific colors with distinctive reaching movements.

As to intracortical inhibition, it is well known that GABA mediates phasic inhibition by activating intrasynaptic GABA receptors (i.e., GABA receptors in the synaptic cleft) and tonic inhibition by activating extrasynaptic receptors (Semyanov et al., 2004; Farrant & Nusser, 2005; Ortinski et al., 2006). To provide tonic inhibitory current to pyramidal cells, we assumed extrasynaptic GABA receptors in their membranes, on which extracellular GABA (i.e., ambient GABA) molecules act. In general, intrasynaptic GABA rises to a millimolar level triggered by a presynaptic action potential (Maconochie et al., 1994; Jones & Westbrook, 1995), whereas ambient GABA is in a submicromolar to several micromolar range (Lerma et al., 1986; Tossman et al., 1986; Scimemi et al., 2005). Such lower ambient GABA concentration is enough to activate extrasynaptic but not intrasynaptic GABA_A receptors. Extrasynaptic GABA_A receptors that contain the δ subunit (Somogyi et al., 1989; Nusser et al., 1995; Brickley et al., 1996; Soltesz & Nusser, 2001) are known to have high affinity for GABA (Saxena & Macdonald, 1996; Brown et al., 2002) and little desensitization to continuous GABA application (Bianchini et al., 2002). This allows neurons to be inhibited by GABA at low concentrations.

Here we show that the flattening of sensory tuning in NS caused by decreasing GABA concentration in extracellular space results in a decrease in the stimulus-sensitive NM_pyramidal cell activity while increasing the stimulus-insensitive NM_pyramidal cell activity, thereby prolonging the reaction time of Mns to the applied feature stimulus. We conclude that a reduction in extracellular GABA concentration in sensory cortex may interfere with selective activation in motor cortex, leading to slowing the activation of spinal motoneurons and therefore to slowing motor responses.

2 Methods

2.1 Model structure

Based on a previous study (Hoshino et al., 2019), we constructed a neural network model, schematically shown in Fig. 1. The sensory network (NS) and the motor network (NM) contain cell assemblies with each comprising pyramidal (P) and basket (B) cells. The NS and NM are reciprocally connected by P cells. Within the same cell assembly (n),
each P cell receives excitatory and inhibitory inputs from P and B cells, respectively, and each B cell receives excitatory inputs from P cells belonging to different cell assemblies \((n' \neq n)\). When a sensory stimulus (Feature \(n\)) is presented to the NS, excitatory current is provided to corresponding \((n)\) NS P cells, whose activation is transmitted to corresponding \((n)\) NM P cells and then to a population of corresponding \((n)\) spinal motoneurons (Mns). Mns are reciprocally connected via excitatory synapses.

Each layer (NS, NM, spinal cord) consists of eight cell assemblies with each comprising twenty cell units. Each cell unit consists of one P cell and one B cell in the NS and NM, and of one Mn in the spinal cord. This is a general model that could explain fundamental mechanisms of age-related slowing of motor responses. It is well known that the age-related slowing of motor responses has been confirmed in different sensory systems: vision and audition (Yordanova et al., 2004; Falkenstein et al., 2006) and somatosensation (Zhang et al., 2011).

We assumed a columnar organization for the NS and NM, which is a widely accepted principle of structure for sensory cortices (e.g., barrel columns in somatosensory cortex, orientation columns in visual cortex, and frequency columns in auditory cortex) and the motor cortex (Mountcastle, 1997). In these cortices, pyramidal cells and interneurons are clustered into columnar aggregates and axon collaterals of pyramidal cells project to neighboring pyramidal cells, which provides recurrent excitation within neuronal columns. Pyramidal cell axon collaterals project to interneurons, which mediates lateral inhibition between neuronal columns. Such lateral inhibition allows a population of

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**Fig. 1** Neuronal architecture. The sensory network (NS) and the motor network (NM) contain cell assemblies with each comprising pyramidal (P) and basket (B) cells. The NS and NM are reciprocally connected by P cells. An excitatory current as a sensory input is provided to NS P cells, whose activation is transmitted to NM P cells and then to a population of spinal motoneurons (Mns). The open and filled triangles denote excitatory and inhibitory synaptic connections, respectively. Inset: Tonic inhibitory current flowing into a P cell through extrasynaptic GABA receptors.
pyramidal cells to respond to a specific feature stimulus in the sensory cortex and to a planned direction of reaching movement in the motor cortex (deCharms & Zador, 2000).

Although the details of columnar organization established by sensory and motor cortices are different, we modeled here the sensory and motor cortices to have the same structure. A difference in anatomical structure may cause a difference in the sensory and motor cortices to have the same structure. A planned direction of reaching movement is calculated DR by the mean ± standard deviation.

Behavioral outputs, such as reaction to sensory stimuli (e.g., to an oriented bar or a single frequency tone) by pressing a button, are completed by muscle contraction when spinal motor neurons send action potentials to muscle fibers. In this respect, parameter values are presented in Table 1. We measured firing rate (FR), reaction time (RT), feature bias (FB), and detection rate (DR); mean ± standard deviation (ten trials for FR, RT, and FB; see Eq. (27)). To calculate DR, we applied a sensory stimulus and observed the response of spinal motor neurons (Mns) in one trial. The response is regarded as correct if the stimulus-sensitive Mns are selectively activated otherwise as incorrect. We implemented twenty trials and calculated DR by dividing the number of correct responses by twenty (the number of trials). One session was composed of twenty trials, and we implemented ten sessions and expressed DR by the mean ± standard deviation.

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the reaction time should be measured as muscle activation; however, we measured here the initiation time of motoneuron activation instead of muscle activation as reaction time.

### 2.2 Modeling of sensory cortex

In the NS, membrane potential dynamics of the \(i\)th P and B cells that belong to cell assembly \(n\) are defined by

\[
\frac{dV_{n,i}^P}{dt} = \left( -\frac{g^{AMPA}}{C_{m}} (v_{n,i}^P(t) - v_{\text{rest}}^P) + I_{n,i}^{P,n_i} + I_{n,i}^{B,n_i} \right) + I_{n,i}^{P,n_i} + I_{n,i}^{E,n_i} + I_{n,i}^{n_i}(t),
\]

\[
\frac{dV_{n,i}^B}{dt} = \left( -\frac{g^{GABA}}{C_{m}} (v_{n,i}^B(t) - v_{\text{rest}}^B) + I_{n,i}^{B,n_i} \right),
\]

\[
I_{n,i}^{P,n_i} = -g^{AMPA} (v_{n,i}^P(t) - v_{\text{rest}}^P) \sum_{j=1}^{N} u_{n,j} w_{n,n_i} P_{n_j}^P (t),
\]

\[
I_{n,i}^{B,n_i} = -g^{GABA} (v_{n,i}^B(t) - v_{\text{rest}}^B) \sum_{j=1}^{N} u_{n,j} w_{n,n_i} B_{n_j}^B (t),
\]

\[
I_{n,i}^{P,M} = -g^{AMPA} (v_{n,i}^P(t) - v_{\text{rest}}^P) \sum_{j=1}^{N} u_{n,j} w_{n,n_i} P_{n_j}^M (t),
\]

\[
I_{n,i}^{E} = -g^{GABA} (v_{n,i}^B(t) - v_{\text{rest}}^B) \delta_{p,s} E_{n_i}^S(t),
\]

\[
I_{n,i}^{n_i}(t) = \alpha_{p,s} \exp\left(-\frac{n - \xi}{\tau_{p,s}}\right), (\xi \in \{1, 2, 3, \ldots, M\})
\]

\[
I_{n,i}^{B,n_i}(t) = -g^{AMPA} (v_{n,i}^B(t) - v_{\text{rest}}^B) \sum_{j'=1}^{M} u_{n,j'} w_{n,n_i} P_{n_j}^B (t),
\]

where \(\delta_{p,s}\) is the fraction of AMPA receptors in the open state triggered by presynaptic action potentials of the \(j\)th B cell. \(r_{n_i}^{E,j}(t)\) is the fraction of extrasynaptic GABA\(_A\) receptors in the open state. \(\delta_{p,s}\) expresses the amount of extrasynaptic GABA\(_A\) receptors embedded in P cell membrane (Hoshino, 2009, 2012, 2014). \(c_m, g_{m-n}, g_{m-n}, C_{m-n}, C_{m-n}, v_{\text{rest}}, \alpha_{p,s}, \tau_{p,s}, N, M, s, t\) and \(\eta_{Y}\) are constants (see Table 1). 

Receptor dynamics in current equations are defined by

\[
\frac{dP_{n,i}^P(t)}{dt} = \alpha_{AMPA}[\text{Glu}](v_{n,i}^P(t)) (1 - r_{n_i}^{E,j}(t)) - \beta_{AMPA} P_{n_i}^P(t),
\]

\[
\frac{dP_{n,i}^B(t)}{dt} = \alpha_{GABA}[\text{GABA}](v_{n,i}^B(t)) (1 - r_{n_i}^{E,j}(t)) - \beta_{GABA} P_{n_i}^B(t),
\]

\[
\frac{dE_{n_i}^S(t)}{dt} = \alpha_{GABA}[\text{GABA}](v_{n,i}^B(t)) (1 - r_{n_i}^{E,j}(t)) - \beta_{GABA} E_{n_i}^S(t),
\]

where \([\text{Glu}]_{n_i}^P(t)\) and \([\text{GABA}]_{n_i}^B(t)\) denote glutamate and GABA concentrations released from the \(j\)th P and B cells into synaptic clefts, respectively. \([\text{GABA}]_{n_i}^S\) denotes the basal ambient GABA concentration. \(\alpha_{AMPA}, \alpha_{GABA}, \beta_{AMPA}\) and \(\beta_{GABA}\) are constants (see Table 1). 

The probability of neuronal firing is defined by

\[
P_{F_{Y, n_i}^Y}(t) = \frac{1}{1 + \exp(-\eta_{Y}(v_{n_i}^Y(t) - \theta_{Y}))}, (Y = P_s, B_s)
\]

When a cell generates an action potential, its membrane potential is depolarized to \(v_{\text{act}}\) (10 mV), kept for 1 ms, and then reset to the resting potential. We implemented the probability function of neuronal firing at each discrete time step: 100 microseconds. \(\eta_{Y}\) and \(\theta_{Y}\) are constants (see Table 1).

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

\[
[\text{Glu}]_{n_j}^P(t) = \text{Glu}_{syn}^P H(v_{n_j}^P(t) - v_{\text{act}}),
\]

\[
[\text{GABA}]_{n_j}^B(t) = \text{GABA}_{syn}^B H(v_{n_j}^B(t) - v_{\text{act}}),
\]

where \(\text{Glu}_{syn}^P\) and \(\text{GABA}_{syn}^B\) are quantal discharges of neurotransmitters. \(H\) is a Heaviside function that is nonzero only during the brief window of an action potential: 1 ms.

The initial condition for the receptor activation was

\[
r_{n_i}^{P,j}(t = 0) = r_{n_i}^{B,j}(t = 0) = r_{n_i}^{E,j}(t = 0) = 0\) (see Eqs. (9)-(11)).

Figure 2a (top) shows how the intrasynaptic glutamate-receptor activation (solid trace) and the intrasynaptic GABA-receptor activation (dashed trace) reach their steady-state values when each intrasynaptic neurotransmitter is released into the synaptic cleft (bottom; see \(t = 2\) ms). Figure 2b (top) shows how the extrasynaptic
Fig. 2 Receptor dynamics. a Intrasyaptic glutamate-receptor activation (top: solid trace) and intrasyaptic GABA-receptor activation (top: dashed trace) when each intrasyaptic neurotransmitter is released into the synaptic cleft (bottom). b Extrasynaptic GABA-receptor activation (top) where the basal ambient GABA concentration was set to 1 μM (middle). The steady-state value of the extrasynaptic GABA-receptor activation is roughly linear when plotted as a function of the basal ambient GABA concentration (bottom).

GABA-receptor activation reaches its steady-state value where the basal ambient GABA concentration ([GABA]_0) was set to 1 μM (middle). Figure 2b (bottom) shows the steady-state value of the extrasynaptic GABA-receptor activation as a function of the basal ambient GABA concentration: $r_{n,i}^{E_G}(t \to \infty) = \alpha_{GABA}[GABA]^0_0/(\alpha_{GABA}[GABA]^0_0 + \beta_{GABA})$. The steady-state value of extrasynaptic GABA-receptor activation is roughly linear when plotted as a function of the basal ambient GABA concentration for the parameters used in this study.

2.3 Modeling of motor cortex

In the $N_M$-membrane potential dynamics of the $i$th P and B cells that belong to cell assembly $n$ are defined by

$$c_m \frac{d}{dt} v_{n,i}^P(t) = -S_m (v_{n,i}^P(t) - v_{rest}^P) + I_{n,i}^{P_m P_m}(t) + I_{n,i}^{P_m B_m}(t) + I_{n,i}^{P_m E_m}(t),$$

$$c_m \frac{d}{dt} v_{n,i}^B(t) = -S_m (v_{n,i}^B(t) - v_{rest}^B) + I_{n,i}^{B_m P_m}(t),$$

$$I_{n,i}^{P_m P_m}(t) = -g_{AMPA}(v_{n,i}^P(t) - v_{AMPA}) \sum_{j=1}^{N} w_{n,j}^{P_m P_m} r_{n,j}^{P_m}(t),$$

$$I_{n,i}^{P_m B_m}(t) = -g_{GABA}(v_{n,i}^P(t) - v_{GABA}) \sum_{j=1}^{N} w_{n,j}^{P_m B_m} r_{n,j}^{B_m}(t),$$

$$I_{n,i}^{P_m E_m}(t) = -g_{AMPA}(v_{n,i}^P(t) - v_{AMPA}) \sum_{j=1}^{N} w_{n,j}^{P_m E_m} r_{n,j}^{E_m}(t),$$

$$I_{n,i}^{B_m P_m}(t) = -g_{GABA}(v_{n,i}^B(t) - v_{GABA}) \delta_{P_m} r_{n,i}^{E_m}(t).$$

$$I_{n,i}^{B_m B_m}(t) = -g_{GABA}(v_{n,i}^B(t) - v_{GABA}) \sum_{n'=1}^{N} w_{n'^{i},i}^{B_m B_m} r_{n'^{i},j}^{E_m}(t).$$

In these equations, $I_{n,i}^{P_m P_m}(t)$ is an excitatory synaptic current from other P cells, $I_{n,i}^{P_m B_m}(t)$ an inhibitory synaptic current from B cells, $I_{n,i}^{P_m E_m}(t)$ an excitatory synaptic current from $N_S$ P cells,
\[ I_{\text{Em}}^{\text{NS}}(t) \] is an inhibitory nonsynaptic current mediated by ambient GABA via extrasynaptic receptors, and \[ I_{\text{Em}}^{\text{P-Mn}}(t) \] an excitatory synaptic current from P cells. \( w_{n,i}^{\text{P-Mn}} \) and \( w_{n,i}^{\text{P-Mn}} \) are P-to-P, B-to-P, P(\( N_{\text{M}} \))-to-P(\( N_{\text{M}} \)) and P-to-B synaptic connection weights, respectively. \( \beta_m^\text{r} \) and \( \beta_m^\text{o} \) are constants (see Table 1). \( i_{n,i}(t) \) and \( r_{n,j}(t) \) were similarly defined as in the \( N_S \), and \( E_{n,i}(t) \) is defined by

\[ \frac{d}{dt} E_{n,i}(t) = \alpha_{\text{GABA}} [\text{GABA}]_0^\text{M}(1 - i_{n,i}(t)) - \beta_{\text{GABA}} E_{n,i}(t), \quad (22) \]

where \([\text{GABA}]_0^\text{M}\) denotes the basal ambient GABA concentration. The probability of neuronal firing and neurotransmitter concentrations were similarly defined as in the \( N_S \).

### 2.4 Modeling of spinal motoneuron

In the spinal cord, we assumed recurrent excitatory synaptic connections between Mns based on the finding that mammalian spinal motoneurons release not only acetylcholine to excite muscles but also glutamate to excite motoneurons (Nishimaru et al., 2005). Bhumbra and Beato (2018) demonstrated that recurrent excitation between spinal motoneurons was glutamatergic, which was strong and maintained throughout development into maturity. AMPA and NMDA receptors mediated the recurrent excitation. The AMPA receptor kinematics is rapid with a rise time in the submillisecond range. In contrast, the NMDA receptor kinematics is slow with a rise time of about tens of milliseconds (Destexhe et al., 1998). We focused here on investigating how the recurrent excitation between spinal motoneurons affects their reaction time, in which we employed the AMPA but not the NMDA receptor. That is because the AMPA receptor alone worked well in regulating recurrent excitatory postsynaptic current. Including the NMDA receptor in the network model will enhance the recurrent excitation.

Based on the above, we define the membrane potential of the \( j \)th Mn that belongs to cell assembly \( n \) by

\[ c_m \frac{d}{dt} \text{Mn}_j^N(t) = -g_m \text{Mn}_j^N(t) - v_{\text{rest}} + I_{n,j}^{\text{MMn}}(t) + I_{n,j}^{\text{APM}}(t), \quad (23) \]

\[ I_{n,j}^{\text{MMn}}(t) = -g_{\text{AMP}} (v_{n,j}^N(t) - v_{\text{AMP}}) \sum_{j=1}^{N} w_{n,ij}^{\text{MMn}}(t), \quad (24) \]

\[ I_{n,j}^{\text{APM}}(t) = -g_{\text{AMP}} (v_{n,j}^N(t) - v_{\text{AMP}}) \sum_{j=1}^{N} w_{n,ij}^{\text{APM}}(t), \quad (25) \]

where \( I_{n,j}^{\text{MMn}}(t) \) is an excitatory synaptic current from other Mns, and \( I_{n,j}^{\text{APM}}(t) \) an excitatory synaptic current from \( N_M \) P cells. \( w_{n,ij}^{\text{MMn}} \) and \( w_{n,ij}^{\text{APM}} \) are Mn-to-Mn and P(\( N_{\text{M}} \))-to-Mn synaptic connection weights, respectively. \( c_m^\text{r} \), \( g_m^\text{r} \) and \( v_{\text{rest}} \) are constants (see Table 1), whose values were determined based on experimental studies (Gogliotti et al., 2012; Bhumbra & Beato, 2018).

\[ i_{n,j}(t) \text{is defined by} \]

\[ \frac{d}{dt} i_{n,j}(t) = \alpha_{\text{AMP}} [Glu]_{n,j}^M(t)(1 - i_{n,j}(t)) - \beta_{\text{AMP}} i_{n,j}(t), \quad (26) \]

where \([Glu]_{n,j}^M(t)\) denotes a concentration of glutamate released from the \( j \)th Mn. The probability of neuronal firing and intrasynaptic neurotransmitter concentration were similarly defined as in the \( N_S \).

### 3 Results

#### 3.1 Influence of sensory cortical tuning on reaction time of spinal motoneurons

We assessed the effect of sensory tuning in \( N_S \) on responses of Mns. Figure 3a (left) shows raster plots (spiking activities) of \( N_S \) (top), \( N_M \) (middle) P cells and Mns (bottom) when presented with a sensory stimulus: Feature 4 (\( \xi = 4 \); see Eq. (7)). Due to a broad input profile (\( \tau_p = 4 \); see Eq. (7)), it activates not only stimulus-sensitive (\( n = 4 \)) but also stimulus-insensitive (\( n \neq 4 \)) \( N_S \) P cells. Nevertheless, the stimulus-sensitive \( N_M \) P cells respond vigorously while those stimulus-insensitive are strongly suppressed. Namely, the \( N_M \) can respond selectively to the applied feature stimulus. This triggers activation of Mns. We recorded spiking activities of twenty Mns that are sensitive to the stimulus. The horizontal arrows point to the initiation of spike generation for each Mn. The filled horizontal arrow points to the initiation of spike generation for the Mn that responds with the longest time delay among the stimulus-sensitive Mns. Reaction time (RT) of Mns was defined by the time of the spike of the Mn with the longest delay (see the vertical arrow).

As shown in Fig. 3a (right), decreasing the basal ambient GABA concentration in \( N_S \) ([GABA]_0^M, see Eq. (11)) from 1 μM to 0.1 μM flattens the sensory tuning (top), which interferes with the selective response in \( N_M \) activity (middle) and results in a delay in RT (bottom). This range (0.1–1 μM) was chosen based on experimental findings: GABA concentration in extracellular space is in a submicromolar to several micromolar range (Lerma et al., 1986; Tossman et al., 1986; Scimemi et al., 2005). Figure 3b shows firing profiles of \( N_S \) (top-left) and \( N_M \) (top-right) P cells belonging to different cell assemblies (\( 1 \leq n \leq 8 \))
Fig. 3  Dependence of network behavior on the level of GABA in extracellular space in sensory cortex. a Raster plots of $N_S$ (top), $N_M$ (middle) P cells, and Mns (bottom) for basal ambient GABA concentration in $N_S ([GABA]^S_0)$ equal to 1 μM (left) and 0.1 μM (right). b Firing profiles of $N_S$ (left) and $N_M$ (right) P cells belonging to different cell assemblies ($1 \leq n \leq 8$). $[GABA]^S_0$ equal to 1 μM (circles) and 0.1 μM (triangles). Sensory input profile (bottom).
where \( [\text{GABA}]_0^S = 1 \mu\text{M} \) (circles) or 0.1 \( \mu\text{M} \) (triangles). It may be noted that the sharpening of sensory tuning in \( N_5 \) by increasing \( [\text{GABA}]_0^S \) (left; see the circles) deactivates the stimulus-insensitive \( N_5 \) P cells (right; see the circles at \( n \neq 4 \)), thereby enhancing the activity of stimulus-sensitive \( N_5 \) P cells (right; see the circle at \( n = 4 \)) and thus accelerating the reaction speed of Mns (see the left vertical arrow in panel a). Figure 3b (bottom) shows the input profile: \( I_{in}^{\text{top}}(t) \) (see Eq. (7)). Such a small difference in input current between the stimulus-sensitive (\( n = 4 \)) \( N_5 \) P cell and its neighbors (\( n = 3 \) and \( 5 \)) gives a more chance of responding of the neighbors, thereby making the detection task difficult. This allowed us to clearly demonstrate how the sensory tuning affects the detection task.

Figure 4a shows the firing rates of P cells (top-left) and currents to P cells from B cells (i.e., lateral inhibitory currents) (bottom-left) as a function of \( [\text{GABA}]_0^S \). The symbols denote P cells belonging to different cell assemblies (\( 1 \leq n \leq 8 \)). An increase in basal ambient GABA concentration increases inhibition to all \( N_5 \) P cells, which is reflected by a decrease in their firing rate. Note that the stimulus-sensitive P cell is more active due to the external current (see the circles). With lower activity in P cells, B cells receive less excitation and therefore are less active too, and thus provide weaker inhibition to P cells (see the bottom-left of Fig. 4a). With higher ambient GABA concentration, the lateral inhibitory mechanism works well (e.g., see the currents at \( [\text{GABA}]_0^S = 1 \mu\text{M} \)). Namely, inhibitory currents into the stimulus-insensitive P cells (see the triangle, square, and asterisk) surpass those into the stimulus-sensitive P cells (see the circle), leading to an increase in tuning to the stimulus. In contrast, the lateral inhibitory mechanism does not work if the basal ambient GABA concentration is low. Namely, inhibitory currents into the stimulus-insensitive P cells do not surpass those into the stimulus-sensitive P cells (e.g., see the currents at \( [\text{GABA}]_0^S = 0.1 \mu\text{M} \)), leading to a decrease in tuning to the stimulus.

Figure 4a (top-right) shows that the activity of stimulus-sensitive (\( n = 4 \)) \( N_5 \) P cells can be enhanced by increasing \( [\text{GABA}]_0^S \) where those stimulus-insensitive (\( n \neq 4 \)) are strongly suppressed. Figure 4a (bottom-right) shows input current to an Mn from the stimulus-sensitive \( N_5 \) P cells.

To evaluate the sensory tuning performance of the \( N_5 \), we calculated “feature bias (FB)”:  
\[
FB = \left| \sum_{\xi=1}^{8} R(\xi) \exp(2\pi i (\xi - 1)/8) \right| / \sum_{\xi} R(\xi),
\]

where \( R(\xi) \) is the firing rate of a P cell when presented with a sensory stimulus (Feature \( \xi \): \( 1 \leq \xi \leq 8 \)). 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 \( \pi \), 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 4b shows relations of FB and RT to \( [\text{GABA}]_0^S \), indicating that the sensory tuning performance of the \( N_5 \) is improved by increasing \( [\text{GABA}]_0^S \) (left). The RT of Mns is shortened by increasing \( [\text{GABA}]_0^S \) (right). Note that the enhancement of stimulus-sensitive \( N_5 \) P cell activity (see the circles in the top-right panel of Fig. 4a) strongly drives Mns (see the bottom-right panel of Fig. 4a) and thus shortens their RTs. Figure 4c shows the relation between FB and RT. These results demonstrate that an increase in GABA concentration in \( N_5 \) enhances lateral inhibition, which is reflected by an increase in FB, activates \( N_5 \) P cells, and increases excitatory current into Mns, thereby decreasing RT.

To see in more detail, we assessed how the breadth of sensory input determined by \( \tau_{ps} \) (see Eq. (7)) affects the sensory tuning property of the \( N_5 \) in association with \( [\text{GABA}]_0^S \). Figure 5a and b show stimulus-evoked firing rates of \( N_5 \) (top) and \( N_5 \) (bottom) P cells where \( [\text{GABA}]_0^S \) was decreased from 1 \( \mu\text{M} \) (panel a) to 0.1 \( \mu\text{M} \) (panel b). The stimulus-sensitive P cell activity tends to decrease (see the circles) while the stimulus-insensitive P cell activity tends to increase (see the triangles, squares and asterisks) as the \( \tau_{ps} \) value increases. Figure 5c indicates that the elevation of \( [\text{GABA}]_0^S \) increases FB (see the circles), demonstrating that the augmentation of tonic inhibition improves the sensory tuning performance of the \( N_5 \), which is remarkable when applied with broad sensory input: e.g., \( \tau_{ps} > 3 \).

\( \tau_{ps} \) determines an input (current) profile provided by the preceding stage; e.g., lateral geniculate nucleus (LGN) and medial geniculate body (MGB), which are activated when retinal and cochlear neurons are stimulated visually and audibly, respectively. LGN neurons showed weak orientation tuning and it was much less selective for orientation compared with primary visual cortex (V1) neurons (Zaltsman
Fig. 4 Influence of the level of GABA in extracellular space in sensory cortex on sensory tuning and reaction time. 

a Dependence of firing rates of $N_S$ (top-left), $N_{NM}$ (top-right) P cells and $N_S$ B-to-P currents (bottom-left) belonging to different cell assemblies ($1 \leq n \leq 8$) on $[\text{GABA}]_S^0$. Input current to an Mn from the stimulus-sensitive $N_{NM}$ P cells as a function of $[\text{GABA}]_S^0$ (bottom-right).

b Dependence of sensory tuning in $N_S$ (FB: left) and reaction time (RT: right) of Mns on $[\text{GABA}]_S^0$. 

c Relationship between RT and FB.
et al., 2015). The reason why we changed the value of $\tau_{PS}$ is because we wanted to see how the LGN afferents, providing the broad tuning curves, could be subsequently sharpened by the inhibitory mechanisms in the sensory cortex, to see how the sharpening affects the motor cortex, and finally to see how it affects the reaction speed of spinal motoneurons.

The lateral phasic inhibition via B-to-P circuitry is supposed to make a major contribution to the sharpening of sensory tuning. As shown in Fig. 6, we confirmed that the enhancement of lateral inhibition by increasing the B-to-P synaptic connection weight ($w_{n,n,b}$, see Eq. (4)) from 1 (see the left of panel a) to 2 (see the right of panel a) sharpens the sensory tuning (see the circles in the left of panel b) and achieves the selective activation in $N_M$ (see the circles in the right of panel b), thereby shortening the RT of Mns (see the arrow in the right of panel a). A notable finding here is that tonic inhibition is another important factor that influences sensory tuning and thus motor responses.
3.2 Influence of GABA level in motor cortex extracellular space on motor response

Puts and colleagues (Puts et al., 2011) demonstrated that tactile discrimination performance was significantly correlated with GABA concentration in the motor 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, whose activation was relevant to eye movements. These studies led us to investigate how motor cortical GABA affects the output of spinal motoneurons; i.e., the motor response. Figure 7a shows stimulus-evoked firing rates of $N_s$ (top) and $N_m$ (bottom) P cells, and Fig. 7b shows those when the basal ambient GABA concentration in $N_s$ ($[GABA]_S^0$; see Eq. (22)) was decreased from 1 μM to 0.1 μM. We found no remarkable influence on $N_s$ and $N_m$ P cell activities. Figure 7c indicates that ambient
GABA in N_M does not affect the sensory tuning performance of the N_S.

However, as shown in Fig. 8a (left), we found a remarkable influence on motor responses when applied with a broad sensory input ($\tau_{PS}$ = 6) under the low ambient GABA level condition: $[\text{GABA}]_0^M = 0.1 \mu M$. Namely, the stimulus-sensitive ($n = 4$) Mns cannot respond to the stimulus (bottom). In contrast, they can respond under the sufficient ambient GABA level condition (right: $[\text{GABA}]_0^M = 1 \mu M$), though their reaction speed is decelerated (see the arrow and compare it with the arrow in the bottom-left of Fig. 3a). Figure 8b shows the relations of detection rate (DR, top-left) and RT (right) to $[\text{GABA}]_0^M$, indicating that although the RT is somewhat delayed, an increase in ambient GABA concentration in N_M ensures reliable motor responses. Figure 8b (bottom) shows the relationship between DR and RT.

A neuron receiving the strongest excitatory input depolarizes and reaches the threshold for spike generation. In contrast, neurons receiving weaker excitatory input cannot reach the threshold and therefore cannot respond. This phenomenon is called the “iceberg effect” (Carandini & Ferster, 2000; Rose & Blakemore, 1974). In the visual cortex, nonspecific inhibition
Fig. 8 Extracellular GABA in motor cortex contributes to reliable motor responses. 

**A** Raster plots of N_S (top), N_M (middle) P cells, and Mns (bottom) for \( \tau_{P_S} = 6 \). \([\text{GABA}]_0^M\) equal to 0.1 \(\mu\text{M}\) (left) and 1 \(\mu\text{M}\) (right). 

**B** Dependence of detection rate (DR: top-left) and RT (top-right) on \([\text{GABA}]_0^M\), and relationship between DR and RT (bottom).
could enhance the iceberg effect; i.e., suppress weaker responses to non-optimal orientations by preventing them from reaching the firing threshold (Vidyasagar & Volgushev, 1996). A reduction in tonic inhibition by decreasing ambient GABA concentration worsens the iceberg effect, which allows neurons receiving weaker excitatory input to reach the firing threshold and thus to respond, giving rise to drift on the activity of NM P cells (see the left of Fig. 8a).

These results demonstrate that a decrease in GABA concentration in NM activates P cells and increases excitatory current into Mns, thereby decreasing RT; however, the decreased GABA concentration allows for a drift on the activity of the NM P cell assemblies, resulting in a decrease in DR.

3.3 Influence of feedback signaling from motor to sensory cortex on motor response

Zagha and colleagues (Zagha et al., 2013) considered that the primary motor cortex could be a dynamic modulator of the primary sensory cortex (somatosensation) during not only movement but also non-movement. Reciprocal connections between sensory and motor cortices were evidenced (Matyas et al., 2010; Mao et al., 2011), inferring intimate interactions between them. To see whether the NM affects the activity of the NS, which then in turn affects the NM itself and the responses of Mns, we varied the intensity of feedforward sensory (visual and auditory) stimuli while increasing the strength of the recurrent excitation (PM cell activity). The results demonstrated that RT is sensitive to parameter choices regarding these quantities, while DR and FB are robust. The motor cortex to spinal cord excitation and the recurrent excitation between spinal motoneurons contribute to accelerating the reaction speed of the spinal motoneurons.

The motor cortex to spinal cord excitation drives the membrane potentials of spinal motoneurons toward their firing threshold. The stronger the spinal cord excitation, the faster the membrane potentials cross the firing threshold, accelerating the reaction speed of the spinal motoneurons. Similarly, the recurrent excitation between spinal motoneurons drives their membrane potential toward the firing threshold. The stronger the recurrent excitation, the faster the membrane potentials cross the firing threshold, accelerating the reaction speed of the spinal motoneurons.

4 Discussion

To elucidate how the flattening of sensory tuning due to a deficit in tonic inhibition slows motor responses, we simulated a neural network model in which a sensory cortical network (NS) and a motor cortical network (NM) are reciprocally connected, and the NM projects to spinal motoneurons (Mns). The NS was presented with a feature stimulus and the reaction time of Mns was measured. The flattening of sensory tuning in NS caused by decreasing GABA concentration in extracellular space resulted in a decrease in the stimulus-sensitive NM Pyramidal cell activity while increasing the stimulus-insensitive NM Pyramidal cell activity, thereby prolonging the reaction time of Mns to the applied feature stimulus. We suggest that a reduction in extracellular GABA concentration in sensory cortex may interfere with selective activation in motor cortex, leading to slowing the activation of spinal motoneurons and therefore to slowing motor responses.

Psychophysical experiments (Yordanova et al., 2004; Falkenstein et al., 2006) demonstrated age-related slowing in sensory detection tasks, in which subjects were instructed to respond sensory (visual and auditory) stimuli as quickly as possible. Significant age-related slowing in these tasks was observed and it was suggested that the slowing of motor responses originates from the slowing of activation of the motor cortex. We speculate that age-related slowing of motor responses may arise from a deficit in selective motor cortical activation, for which the flattening of sensory cortical tuning due to a reduction in extracellular GABA concentration is responsible.
We showed that a deficit in selective activation in $N_M$ slowed the activation of $MNs$. An experimental study (Hasegawa et al., 2017) investigated how preparatory activity is related to motor performance of a mouse by evaluating reaction time to execute a movement. Motor preparation is manifested by a shorter reaction time: when reaction time is short, the mouse is regarded as well prepared. They found that when the mice were well prepared, the cortical circuit exhibited the suppression of extra activity other than essential activity that is required for signal processing. The extra and essential activity may correspond to the stimulus-insensitive and stimulus-sensitive activity, respectively.

It was demonstrated (Puts et al., 2011) that tactile discrimination performance was significantly correlated with GABA concentration in the motor cortex. Competitive action decisions such as shifting gaze to one stimulus rather than another could be predicted by GABA concentration in the frontal cortex, whose activation was relevant to eye movements (Sumner et al., 2010). We confirmed that decision-making could be predicted by extracellular GABA.
concentration; namely, the more GABA in motor cortex the more reliable was the sensory detection performance (see the top-left panel of Fig. 8b).

To the best of our knowledge, the relation between GABA concentration and reaction time is our novel finding that has not been demonstrated experimentally. That is, this relationship is our prediction to be tested in the future. Other our predictions include the relationships of GABA concentration to stimulus-evoked firing rate of pyramidal cells, to feature bias, and to detection rate of sensory stimuli. To investigate how the broad sensory input from the preceding stage is sharpened in the sensory cortex in association with GABA concentration, we changed the value of $P/2$. To our knowledge no such attempt has been undertaken yet.

The effect of extracellular GABA on motor response can only be seen for a particular set of parameters (connectivity strength, spiking threshold, etc.). We hypothesize that synaptic (such as excitatory and inhibitory synaptic connection weights) and intrinsic (such as spiking thresholds) plasticity that occurs as a result of learning through task-dependent training may optimize these parameters in the brain’s circuity. As addressed in Sect. 1, we assumed the specific hierarchical neuronal circuity as a result of somatosensorimotor associative learning. Buonomano and Merzenich (1998) suggested that changes in cortical map organization occur as a result of learning through task-dependent training that produces specific patterns of activity in identical cortical regions. Froemke and colleagues (Froemke et al., 2013) demonstrated that the modification of cortical inputs led to synaptic changes, which were related to enhanced behavioral performance. Cudmore and Turrigiano (2004) demonstrated that a brief period of neuronal firing induced long-lasting potentiation (LTP) in layer V neocortical pyramidal neurons. A reduction in the threshold for action potential generation accompanied this LTP.

We showed that an increase in ambient GABA concentration in $N_S$ enhanced lateral inhibition, which was reflected by an increase in FB, activated $N_M$ P cells and increased excitatory current into Mns, thereby decreasing RT. However, the notion of a sharpened tuning curve (i.e., an increase in FB) alone does not necessarily improve sensory coding performance in the context of a population of neurons (Seriès et al., 2004). Butts and Goldman, (2006) suggested that broader tuning curves produce either worse or better performance depending on task and noise conditions.

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Declarations

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

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