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Possible role of cooperative action of NMDA receptor and GABA function in developmental plasticity

Shigeru Kubota · Tatsuo Kitajima

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Abstract The maturation of cortical circuits is strongly influenced by sensory experience during a restricted critical period. The developmental alteration in the subunit composition of NMDA receptors (NMDARs) has been suggested to be involved in regulating the timing of such plasticity. However, this hypothesis does not explain the evidence that enhancing GABA inhibition triggers a critical period in the visual cortex. Here, to investigate how the NMDAR and GABA functions influence synaptic organization, we examine an spike-timing-dependent plasticity (STDP) model that incorporates the dynamic modulation of LTP, associated with the activity- and subunit-dependent desensitization of NMDARs, as well as the background inhibition by GABA. We show that the competitive interaction between correlated input groups, required for experience-dependent synaptic modifications, may emerge when both the NMDAR subunit expression and GABA inhibition reach a sufficiently mature state. This may suggest that the cooperative action of these two developmental mechanisms can contribute to embedding the spatiotemporal structure of input spikes in synaptic patterns and providing the trigger for experience-dependent cortical plasticity.

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S. Kubota (✉)
Department of Biomedical Information Engineering,
Yamagata University,
4-3-16 Jonan,
Yonezawa, Yamagata 992-8510, Japan
e-mail: kubota@yz.yamagata-u.ac.jp

T. Kitajima
Department of Bio-System Engineering, Yamagata University,
4-3-16 Jonan,
Yonezawa, Yamagata 992-8510, Japan

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1 Introduction

Sensory experience during postnatal critical period significantly affects synaptic transmission in developing cortical neurons (Wiesel 1982). Despite the importance of such plasticity for the maturation of functional circuits, its synaptic basis is unclear. A prevailing view is that the alteration in the subunit composition of NMDA receptors (NMDARs) is involved in the regulation of plasticity (Crair and Malenka 1995; Roberts and Ramoa 1999; Erisir and Harris 2003; Dumas 2005). Functional NMDARs are formed by the co-expression of obligatory NR1 subunits and variable NR2 (NR2A–D) subunits (Stephenson 2001). In the forebrain, the NR2B-containing NMDARs are predominant at birth, whereas the number of NR2A-containing NMDARs increases as development proceeds (Monyer et al. 1994; Flint et al. 1997; Quinlan et al. 1999a, b; Mierau et al. 2004). The time period during which the subunit expression changes nearly coincides with the critical period for experience-dependent plasticity (Roberts and Ramoa 1999; Erisir and Harris 2003; Daw et al. 2007) as well as for the induction of LTP and LTD (Crair and Malenka 1995; Feldman et al. 1998). These findings have lead to the hypothesis that the switch in the NMDAR subunit expression may control the timing of cortical plasticity.

However, the hypothesis based on NMDAR-dependent mechanisms cannot explain a line of evidence that the maturation of GABA inhibition controls the timing of the critical period for visual cortical plasticity (Hensch et al. 1998; Hanover et al. 1999; Huang et al. 1999; Fagiolini and

Hensch 2000; Hensch 2005). When the maturation of inhibitory transmission is prevented by the targeted deletion of an isoform of a GABA synthetic enzyme, glutamic acid decarboxylase (GAD65), the onset of ocular dominance plasticity is delayed until intracortical inhibition is pharmacologically restored (Hensch et al. 1998). Likewise, the critical period can be triggered prematurely by enhancing inhibition via the drug treatment (Fagiolini and Hensch 2000) or the overexpression of brain-derived neurotrophic factor (BDNF) (Hanover et al. 1999). The findings that the enhancement of GABA inhibition either does not affect (Hensch et al. 1998; Froemke and Dan 2002) or suppresses (Kirkwood and Bear 1994) long-term synaptic modifications in visual cortical slices suggest that it may be difficult to simply associate the mechanisms of *in vivo* plasticity with the LTP and LTD induction observed *in vitro*.

A key aspect of activity-dependent development is the involvement of competition among afferent inputs such that the strengthening of inputs from one eye to a visual cortical cell weakens the inputs from the other eye (Rauschecker and Singer 1979; Wiesel 1982; Shatz 1990; Gordon and Stryker 1996). Spike-timing-dependent plasticity (STDP), wherein changes in millisecond-scale timing of pre- and postsynaptic spikes determines the magnitude and sign of synaptic modification (e.g., Markram et al. 1997; Bi and Poo 1998; Feldman 2000; Froemke and Dan 2002; for a recent review, see Caporale and Dan (2008) and Morrison et al. (2008)), provides a biophysical mechanism that introduces competition when the magnitude of LTP and LTD in the learning curve is approximately balanced (Gerstner et al. 1996; Kempter et al. 1999; Song et al. 2000). Such competitive function is particularly important in early development, since it is considered to be responsible for the input selectivity that underlies the synaptic organization such as cortical maps and columnar architecture (Kepecs et al. 2002; Song and Abbott 2001).

Therefore, in order to address the issue of how two candidate mechanisms for developmental plasticity—NMDAR subunit expression and GABA inhibition—can influence early synaptic organization, we theoretically examine the effects of these two developmental mechanisms on the synaptic competition induced by STDP. We construct a conductance-based pyramidal neuron model that receives two groups of excitatory inputs, which are correlated within each group, and uncorrelated GABAergic inhibitory inputs. The excitatory synapses are modified by STDP incorporated with metaplastic regulation by the activity-dependent feedback (ADFB) mechanism (Kubota et al. 2009), wherein the subunit- and activity-dependent desensitization of NMDARs dynamically modulates LTP. We show that the competition between the groups of correlated inputs does not occur either when the ADFB function is weak due to the immature state of NMDAR subunit expression or when the level of GABA inhibition is low. However, when both the NMDAR expression and GABA inhibition reach a sufficiently mature state, the emergence of competitive interaction between the input groups permits the information regarding the sensory experience to be embedded in the synaptic efficacies, since which group wins the competition depends on the past input activities. This may suggest that the cooperation of NMDAR subunit and GABA functions may be responsible for introducing the competition between afferent inputs and thus for providing the trigger for critical period plasticity.

2 Methods

2.1 Conductance-based neuron model

We used a conductance-based pyramidal neuron consisting of two compartments representing a soma and a dendrite. Both compartments contain voltage-gated sodium and potassium currents (I_{Na} and I_K). Additionally, the dendrite contains high-threshold voltage-gated Ca^{2+} currents ($I_{ca,V}$) and Ca^{2+}-dependent K^+ currents (I_{AHP}) to reproduce spike frequency adaptation found in pyramidal cells (Ahmed et al. 1998). The somatic and dendritic membrane potentials V_s and V_d (in mV) obey the following equations (modified from Wang (1998)):

$$C_m \frac{dV_s}{dt} = -I_{leak} - I_{Na} - I_K + \frac{g_c}{p}(V_d - V_s) + I_{inj}, \quad (1)$$

$$C_m \frac{dV_d}{dt} = -I_{leak} - I_{Na} - I_K - I_{Ca,V} - I_{AHP} + \frac{g_c}{1-p} \times (V_s - V_d) - I_{syn}, \quad (2)$$

where C_m=1 μF/cm^2 is the specific membrane capacitance, $I_{leak} = g_{leak}(V - E_{leak})$ is the leak current, g_c=2 mS/cm^2 is the coupling conductance between the soma and dendrite, p=0.5 is the ratio of soma to total area (Wang 1998), I_{inj} is the injected current to the soma, and I_{syn} is the synaptic current to the dendrite. All the currents in our model have been expressed as densities with units of μA/cm^2.

Voltage-gated currents are described by Hodgkin-Huxley-type equations. The sodium current is expressed as $I_{Na} = g_{Na} m_\infty^3(V) h (V - E_{Na})$, where $m_\infty(V) = \alpha_m(V)/(\alpha_m(V) + \beta_m(V))$, $\alpha_m(V) = -0.1(V+23)/\{\exp[-0.1(V+23)] - 1\}$, $\beta_m(V) = 4\exp[-(V+48)/12]$, $dh/dt = \phi_h[\alpha_h(V)(1-h) - \beta_h(V)h]$, $\alpha_h(V) = 0.07\exp[-(V+40)/10]$, and $\beta_h(V) = 1/\{\exp[-0.1(V+10)] + 1\}$. The potassium current is expressed as $I_K = g_K n^4 (V - E_K)$, where $dn/dt = \phi_n[\alpha_n(V)(1-n) - \beta_n(V)n]$, $\alpha_n(V) = -0.01(V+24)/\{\exp[-0.1(V+24)] - 1\}$, and $\beta_n(V) = 0.125\exp[-(V+34)/25]$. The

voltage-gated calcium current is $I_{Ca,V} = g_{Ca,V} m_{Ca,\infty}^2(V)(V - E_{Ca})$, where $m_{Ca,\infty}(V) = 1/\{1 + \exp[-(V + 20)/9]\}$. The calcium-dependent potassium current is $I_{AHP} = g_{AHP}\left[[Ca]_d/\left([Ca]_d + K_D\right)\right]\ (V - E_K)$, where K_D=30 μM. The calcium concentration $[Ca]_d$ in the dendrite obeys the following equation: $d[Ca]_d/dt = -[Ca]_d/\tau_d - \alpha_d I_{Ca,V}$, where the time constant τ_d=80 ms and α_d=0.002 μM cm^2 (ms μA)$^{-1}$ (Wang 1998). The conductances associated with these currents are as follows: g_{leak}=0.04; g_{Na}=45 (soma), 2 (dendrite); g_K=24 (soma), 0.01 (dendrite); $g_{Ca,v}$=1; and g_{AHP}=5 (in mS/cm^2). The reversal potentials are E_{leak}=–75, E_{Na}=55, E_K=–80, and E_{Ca}=120 (in mV), and the temperature factors are ϕ_h=ϕ_n=4. The parameter values for the voltage-dependent currents and I_{AHP} were selected such that the initial and adapted *f-I* curves (obtained by changing the input current I_{inj}) approximately agree with those of neocortical pyramidal cells (Ahmed et al. 1998). The value of I_{inj} is set to 0 in all figures.

2.2 Synaptic inputs

The dendritic compartment receives inputs, generated by Poisson processes, from 4000 excitatory and 800 inhibitory synapses (Kubota and Kitajima 2008). The excitatory inputs are comprised of NMDAR-and AMPA receptor (AMPAR)-mediated currents, while inhibitory inputs are mediated by GABA currents. The equation for each synaptic current takes the following form: $I_s = G_s(t)(V - E_s)$ (s=AMPA, NMDA, or GABA). AMPA conductance follows an alpha function

$$G_{AMPA}(t) = w\, g_{AMPA}\,(e/t_{AMPA})\, t \exp(-t/t_{AMPA}), \tag{3}$$

where w is the synaptic weight, the peak conductance g_{AMPA}= 2.5 μS/cm^2, and t_{AMPA}=1.5 ms (Zador et al. 1990). The weight w is dynamically changed by STDP (see below). NMDAR conductance follows the equation that depends on the membrane voltage at the present time (Jahr and Stevens 1990):

$$G_{NMDA}(t) = g_{NMDA}\frac{\exp\left(-t/\tau_{decay}^{NMDA}\right) - \exp\left(-t/\tau_{rise}^{NMDA}\right)}{1 + 0.33\exp(-0.06V(t))}, \tag{4}$$

where g_{NMDA}=1 μS/cm^2 is the peak conductance, τ_{decay}^{NMDA} = 140ms and $\tau_{rise}^{NMDA} = 0.67$ms are the decay and rise time constants, respectively (Mierau et al. 2004; Koch 1999). The GABA conductance follows the equation

$$G_{GABA}(t) = g_{GABA}\,(e/t_{GABA})\, t \exp(-t/t_{GABA}), \tag{5}$$

where g_{GABA} is the peak conductance and t_{GABA}=10 ms (Bernander et al. 1991). The reversal potentials for these currents are $E_{AMPA} = E_{NMDA} = 0$mV and E_{GABA}=–70 mV. The synaptic conductances evoked by the past presynaptic inputs are linearly summed for calculating the synaptic conductance at the present time.

The excitatory synapses are activated by two groups of correlated spike trains, while inhibitory synapses are activated by uncorrelated spike trains. The uncorrelated inputs were generated using independent Poisson spike trains of 3 Hz. The input correlation was introduced by the method similar to Song and Abbott (2001) as follows. The excitatory synapses were assumed to consist of two equally sized groups (2000 synapses each). We divided time into intervals obtained from an exponential distribution with a mean interval of τ_c. For every interval, we generated a random number y from a Gaussian distribution with mean 0 and standard deviation 1. The firing rate of the Poisson spikes of input neurons was set to $r(1+0.3y)$ (in Hz) and was fixed at this value until the start of the next interval. We selected independent interval start times and independent y values for the two groups so that they were uncorrelated with each other. We set the mean presynaptic rate r=3 Hz, unless otherwise stated. Given the low success rate of synaptic transmission in developing neurons (~10%; Hessler et al. 1993), the input rate of 3 Hz corresponds to a presynaptic firing rate of ~30 Hz, which is within the physiological range of the sensory-evoked responses of neocortical cells (Ahmed et al. 1998). The correlation time τ_c=10 ms was selected such that the correlated inputs in the same group that fire at similar times can contribute to rapidly evoking a postsynaptic spike (Song and Abbott 2001).

2.3 Synaptic modification by STDP

The synaptic weight change Δw is determined as a function of the interspike interval (ISI) $\Delta t = t_{post} - t_{pre}$ between the pre- and postsynaptic events (e.g., Song et al. 2000):

$$\Delta w = \begin{cases} A_+ \exp(-\Delta t/\tau_+), & \text{for } \Delta t > 0, \\ -A_- \exp(\Delta t/\tau_-), & \text{for } \Delta t < 0, \end{cases} \tag{6}$$

Here, A_+ (> 0 ; see below) and A_- (= 0.004) denote the magnitude of LTP and LTD, respectively, and $\tau_+ = \tau_- =$ 20ms decides the width of the temporal window in STDP (Kubota et al. 2009). Recent experimental findings have revealed that in some cortical synapses, LTP and LTD in STDP may involve distinct signaling pathways that function as coincidence detectors of pre- and postsynaptic activity: the activation of postsynaptic NMDARs for LTP and that of other signaling receptors, such as metabotropic glutamate receptors (mGluRs), for LTD (Bender et al. 2006; Egger et al. 1999; Nevian and Sakmann 2006; Caporale and Dan 2008). Therefore, when the firing activity augments the postsynaptic Ca^{2+} level via the repetitive opening of voltage-gated Ca^{2+} channels (Helmchen et al. 1996;

Svoboda et al. 1997), the induction of LTP (but not LTD) can be suppressed through the Ca^{2+}-dependent desensitization of postsynaptic NMDARs (Legendre et al. 1993; Medina et al. 1999; Rosenmund et al. 1995). Furthermore, experimental evidence indicates that NR2A- but not NR2B-containing NMDARs exhibit Ca^{2+}-dependent desensitization (Krupp et al. 1996), suggesting that the activity-dependent desensitization of NMDARs will be strengthened by the developmental increase in the NR2A subunits. To incorporate these observations, we used our previously proposed STDP model including ADFB mechanism (Kubota et al. 2009), wherein the magnitude of LTP A_+ is suppressed by the feedback of postsynaptic firing rate f_{post} with the gain dependent on the state of NMDAR subunit expression:

$$A_+ = A_+^0 - k_{\max}\rho f_{post}. \tag{7}$$

Here, $A_+^0 = 0.008$ is the amplitude of LTP for single spike pairs (i.e., f_{post}=0) and k_{max}=0.068 ms represents the maximum gain provided by the mature state of NMDARs (Kubota et al. 2009). The non-dimensional parameter ρ ($0 \le \rho \le 1$) is used to represent the developmental stage associated with the NMDAR subunit expression: ρ=0 corresponds to the very early stage, wherein the NMDARs are composed of NR1 and NR2B subunits, whereas ρ=1 denotes the late stage, wherein the NMDARs comprise many NR2A subunits. Thus, at earlier stages (smaller ρ), the postsynaptic activity hardly affects the value of A_+, whereas, as development proceeds (larger ρ), the increased postsynaptic activity will significantly decrease this value. The postsynaptic firing rate f_{post} was estimated by the following equation:

$$f_{post}(t) = \int_0^\infty \lambda \exp(-\lambda\tau) S_{post}(t-\tau) d\tau, \tag{8}$$

where $S_{post}(t) = \sum_f \delta\left(t - t_{post}^f\right)$ denotes the output spike train (Tanabe and Pakdaman 2001). In Eq. (8), the temporal range over which the postsynaptic activity is averaged depends on the inverse of λ; therefore, the value of λ^{-1} determines the time scale of the rate of changes in A_+ via the activity-dependent desensitization of NMDARs (Eq. (7)). Experimental data suggests that the recovery from Ca^{2+}-dependent desensitization of NMDARs is very slow, with a time constant of as long as ~10 s, while its onset is as slow as or a little faster than the recovery (Legendre et al. 1993; Medina et al. 1999). Therefore, we set the value of λ to be 0.1 /s (λ^{-1}=10 s) so that the accumulation of the effects of successive action potentials gradually strengthens the level of desensitization.

The weight updating rule is assumed to be additive, i.e., the magnitude of plasticity is independent of the synaptic strength, and the effects of all the spike pairs are linearly summed. When a pre- or postsynaptic event occurs, the synaptic weights w are updated stepwise by STDP. Upper and lower bounds were imposed such that $w \in [0, w_{max}]$ (w_{max}=2) to stabilize the learning dynamics. The modification in synaptic weights was reflected in the peak conductance of AMPA synapses as shown in Eq. (3). For all the figures, we set the initial weights to their upper limit, which can produce high firing rate and thus facilitate the learning processes. The timing of the postsynaptic spike of the conductance-based neuron was defined as the instant when the somatic potential exceeds 0 mV.

2.4 Numerical simulation

All models were implemented in the C programming language and integrated using the fourth-order Runge-Kutta method with a time-step size of 0.05 ms. The duration of simulation was set to be sufficiently long so that we can reliably ensure the convergence of synaptic weights to a stable stationary distribution. Typical simulation time was 1,000,000 s (~12 days), which corresponds to ~20 h in real time on the Intel Core 2 Duo personal computer (2.4 GHz). Since the average weight among the synapses, as well as the weight distribution, fluctuate even at the equilibrium, we have taken their temporal average over a sufficiently long period (≥ 20,000 s).

3 Results

3.1 Synaptic distribution regulated by NMDAR and GABA function

The computational properties of STDP that can detect coincidence of inputs and thereby introduce correlation-based competition have been suggested to play a role in developing functional cortical circuits (Gerstner et al. 1996; Kempter et al. 1999; Song et al. 2000). To investigate the dynamics of synaptic population emerging through such competition, we simulated a conductance-based neuron that receives random inputs from both excitatory synapses following STDP and non-plastic inhibitory synapses. We divided the excitatory inputs into two equally sized groups and introduced independent correlations of equal magnitude to both of them (Song and Abbott 2001). This is an example reminiscent of ocular dominance plasticity, which is driven by the interaction between correlated inputs from both the eyes (Rauschecker and Singer 1979; Wiesel 1982; Shatz 1990). The magnitude of LTP was dynamically modified by the ADFB mechanism (Eq. (7)), which models the subunit- and activity-dependent desensitization of NMDARs (Krupp et al. 1996; Legendre et al. 1993;

Medina et al. 1999) with the parameter ρ representing the level of maturation of their subunit expression.

Figure 1 shows the equilibrium properties of the model (i.e., the state at which the synaptic weight converges to a stationary distribution) for various values of ρ and the peak GABA conductance g_{GABA}. As shown in the previous studies (Kubota et al. 2009; Tegnér and Kepecs 2002), the ADFB modulation generates an approximate balance between LTP and LTD such that the temporal average of the A_+/A_- ratio converges to a value slightly smaller than 1 for relatively larger ρ values (ρ>~0.5) (Fig. 1a and b). Although further increase in ρ will act to reduce the LTP/LTD ratio (Eq. (7)), a small decrease in A_+/A_- significantly decreases the average synaptic weight and postsynaptic activity (Fig. 1c and d) (Song et al. 2000). Therefore, the facilitation of ADFB by a further increase in ρ can be nearly compensated for by the reduction in the firing activity, decreasing the temporal average of A_+/A_- very gradually (Fig. 1; Kubota et al. 2009). Additionally, in the presence of the approximate balance in LTP and LTD,

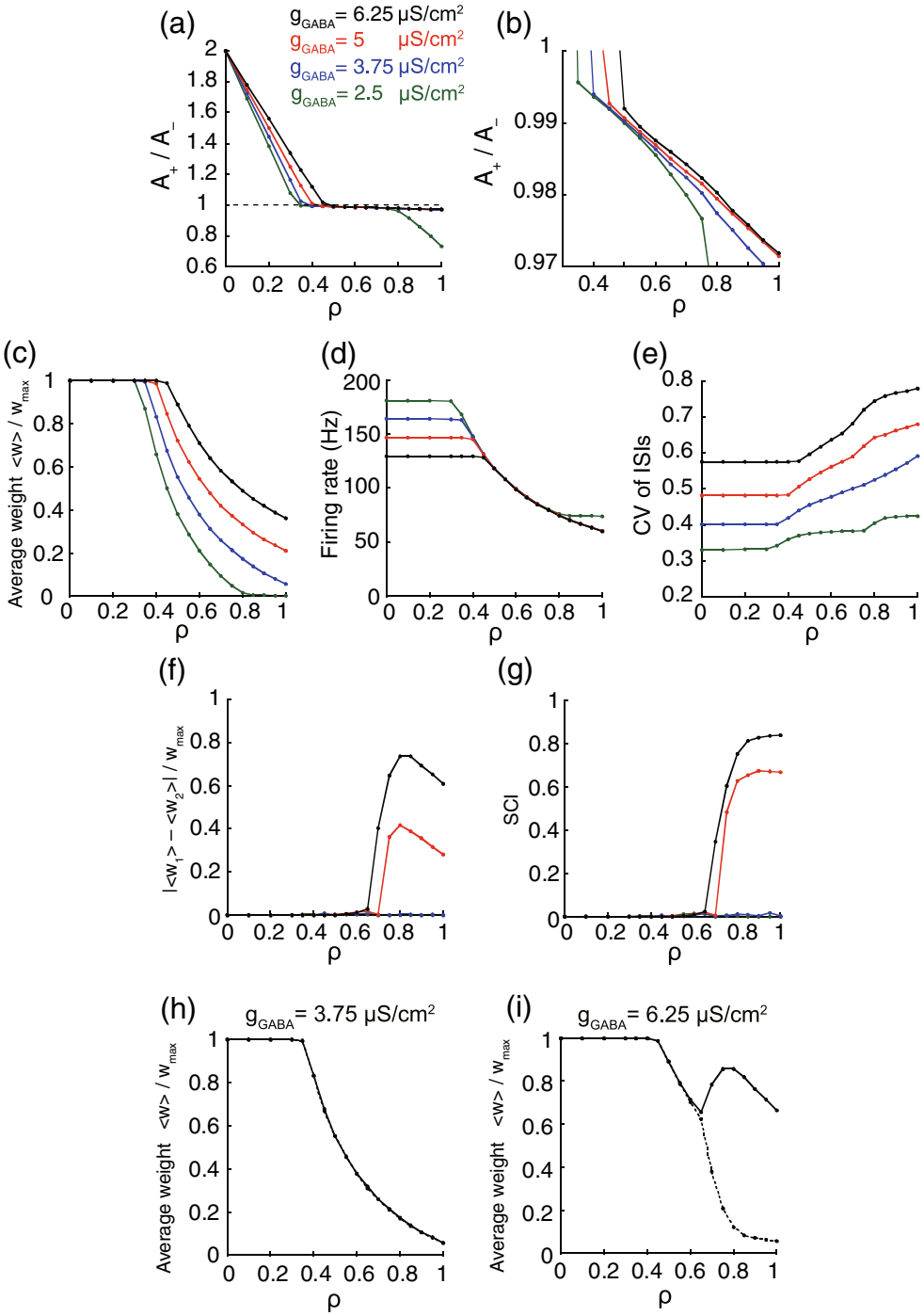

Fig. 1 Equilibrium properties of STDP incorporating ADFB mechanism in the presence of two groups of correlated inputs. (**a**–**g**) The changes in the A_+/A_- ratio (temporally averaged value) (**a** and **b**), the average weight over all the synapses (**c**) the firing rate (**d**), the CV of ISIs (**e**), the difference in average weights between the two groups (**f**), and SCI (**g**) are plotted for various values of ρ and g_{GABA} (g_{GABA}=2.5 (green), 3.75 (blue), 5 (red), or 6.25 μS/cm^2 (black)). (**b**) shows the higher magnification of the A_+/A_- ratio in (**a**). For the case of ρ>~0.8 and g_{GABA}=2.5 μS/cm^2, the saturation of synaptic weights to their lower limit (**c**) acts to increase the firing rate (**d**) and decrease the A_+/A_- ratio (**a**). Even in cases where the weights decrease to very low level, the postsynaptic activity occurs due to the activation of NMDAR currents (Eq. (4)) (**c** and **d**). The occurrence of competition between the different groups requires both larger ρ and g_{GABA} (**f** and **g**). (**h** and **i**) Average synaptic weights of the two groups as a function of ρ, where g_{GABA}=3.75 (**h**) or 6.25 μS/cm^2 (**i**). Both groups have the same average weight for all ρ in (**h**), while they segregate into strong (*solid*) and weak (*dashed*) ones for larger ρ in (**i**)

larger g_{GABA} tends to strengthen the synaptic weights through a slight increase in A_+/A_- (Fig. 1b and c) while keeping the postsynaptic firing rate almost constant (Fig. 1d) (Kubota et al. 2009). This implies the existence of a regulatory function that maintains the balance between excitation and inhibition via a precise control of that between LTP and LTD. Only in the case of sufficiently large ρ and small g_{GABA} (ρ>~0.8 and g_{GABA}<~2.5 μS/cm^2), the synaptic weights are saturated at their lower boundary (w=0) (Fig. 1c), producing the increase in the postsynaptic activity and the resultant decrease in the A_+/A_- ratio, compared to those for the cases of larger g_{GABA} values (Fig. 1a and d). The coefficient of variation (CV) of ISIs was found to increase with both ρ and g_{GABA} (Fig. 1e), as in the previous study (Kubota et al. 2009).

Importantly, whether the distributions of learned synaptic efficacies reflect the input correlation structure strongly depended on the strength of ADFB modulation as well as of GABA inhibition. When GABA activity was relatively weak (g_{GABA}=3.75 μS/cm^2; Fig. 1h), the two groups of synapses converged to the same average weight independent of ρ. However, when the GABA activity was increased (g_{GABA}=6.25 μS/cm^2; Fig. 1i), the synaptic efficacies segregated into the two input groups with the one winning the competition suppressing the other at sufficiently large ρ values (which group wins is random) (Song and Abbott 2001). This result was clarified by the steady-state weight distribution (Fig. 2). The figure indicates that when either ρ or g_{GABA} is relatively small, the two groups of synapses have identical distributions. The segregation of distributions occurs only when both ρ and g_{GABA} are increased sufficiently.

To quantify the level of competition between the different groups, we used two measures: the difference in average weights normalized by the maximum weight and the synaptic competition index (SCI), which are defined as $|<w_1>-<w_2>|/w_{\max}$ and $|<w_1>-<w_2>|/(<w_1>+<w_2>)$, respectively, where $<w_i>$ is the average weight over synapses in group i at the equilibrium state. The use of SCI was inspired by the physiological experiments of ocular dominance plasticity (e.g., Rittenhouse et al. 2006), which frequently employ an index analogous to SCI for testing the relative contributions of the two eyes to visual cell responses. An SCI of 0 means that the neuron is equally responsive to the two groups of inputs, while an SCI of 1 means that the cell response is dominated by either of the groups.

When either ρ or g_{GABA} is small, both measures of competition are 0 (Fig. 1f and g), indicating that both groups have the same average strength at the equilibrium. However, when both ρ and g_{GABA} are sufficiently large (ρ>~0.65 and g_{GABA}>~5 μS/cm^2), the two measures take positive values, indicating that the two groups segregate into the ones winning and losing the competition. The

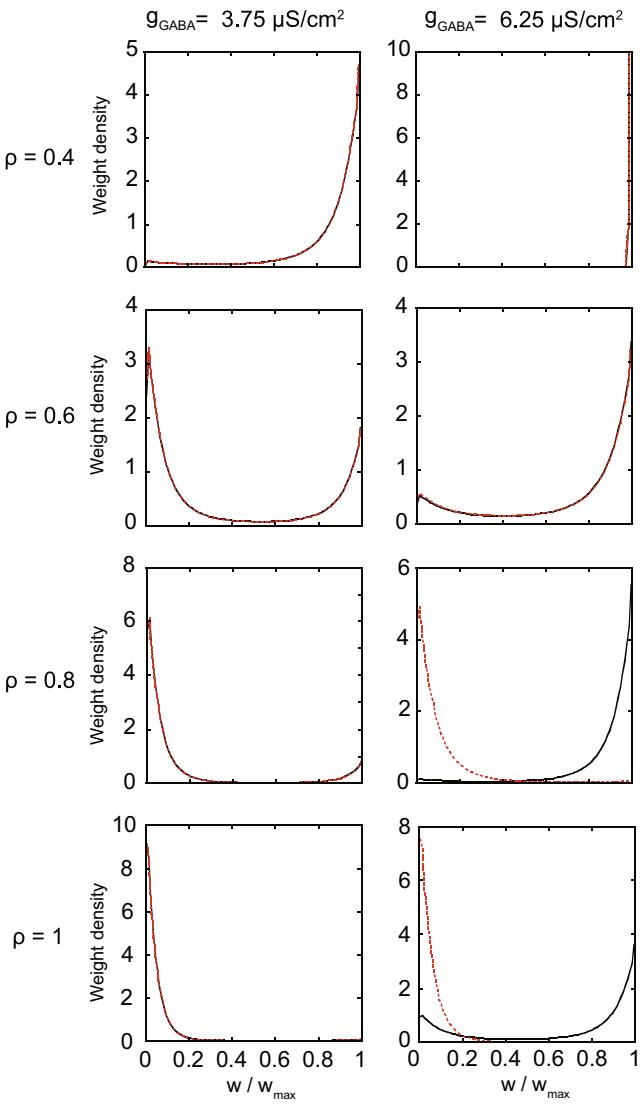

Fig. 2 Steady-state weight distribution obtained by STDP. The distributions of synapses for the two groups are shown by black solid and red dashed lines for various values of ρ and g_{GABA}. For lower GABA activity (g_{GABA}=3.75 μS/cm^2, left column), the weight distributions of both the groups are identical for all values of ρ. However, for higher GABA activity (g_{GABA}=6.25 μS/cm^2, right column), the competition between the different groups occurs for sufficiently large values of ρ (ρ=0.8 and 1) and the synaptic weights segregate into the two groups

results here suggest that the induction of the between-group competition may require both the strengthening of ADFB, provided by the mature state of NMDAR subunit expression (larger ρ), and the enhancement of GABA inhibition (larger g_{GABA}).

To explore the reason why the between-group competition requires the increase in both ρ and g_{GABA}, we investigated the firing statistics of the neuron. In Fig. 3, we plotted the cross-correlation function of pre- and postsynaptic action potentials (Gerstner and Kistler 2002)

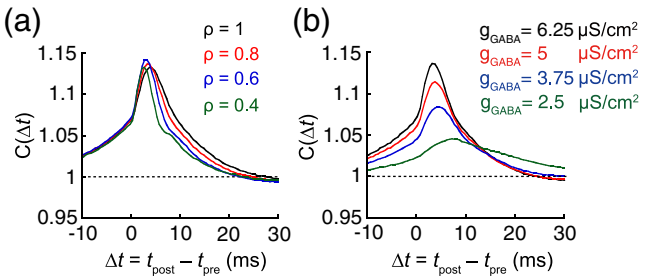

Fig. 3 Correlation function $C(\Delta t)$ (Eq. (9)) between the pre- and postsynaptic spike trains at the equilibrium state of STDP. (**a**) and (**b**) show the effects of changing ρ and g_{GABA}, respectively (ρ=0.4 (*green*), 0.6 (*blue*), 0.8 (*red*), or 1 (*black*), and g_{GABA}=6.25 μS/cm^2 in (**a**) g_{GABA}=2.5 (*green*), 3.75 (*blue*), 5 (*red*), or 6.25 μS/cm^2 (*black*), and ρ=0.8 in (**b**)). In the case of smaller g_{GABA} (g_{GABA}=2.5 μS/cm^2) in (**b**), the synaptic weights accumulate near their lower boundary (w=0) (Fig. 1c). In this case, the activation of NMDAR conductances (Eq. (4)) would be mainly involved in the regulation of firing pattern. Note that because there is temporal correlation among inputs within the same group (with correlation time τ_c=10 ms), the function $C(\Delta t)$ takes values greater than 1 even in cases where $\Delta t = t_{post} - t_{pre}$ is negative

at the equilibrium of STDP. The correlation function was normalized so that the value for pairings that are due solely to chance is 1 as follows:

$$C(\Delta t) = \frac{< S_{pre}(t - \Delta t) S_{post}(t) >_t}{< S_{pre}(t) >_t < S_{post}(t) >_t}. \quad (9)$$

Here, $S_{pre}(t) = \sum_f \delta(t - t^f_{pre})$ and $S_{post}(t) = \sum_f \delta(t - t^f_{post})$ denote the presynaptic (excitatory) and postsynaptic spike trains, respectively, and angular brackets with subscript t denote averaging over time. As expected, the activation of a given input, as well as the inputs correlated with it, can increase the probability of the occurrence of action potentials within a short period of time (Fig. 3). However, increasing ρ and g_{GABA} has distinct effects on the influence of the input spike on the firing probability: larger ρ primarily prolongs the duration of this influence almost without changing its peak (Fig. 3a), while larger g_{GABA} considerably increases the peak amplitude (Fig. 3b). Similar changes in the peak and duration of the correlation function were found in the absence of input correlation (data not shown), i.e., under homogeneous inputs (as in Kubota et al. 2009), implying that these changes are not attributable to the occurrence of the between-group competition. Although the detailed mechanism that modifies the input-output correlation function is beyond the scope of this study, the effect of larger g_{GABA} to increase its peak value seems considerably attributable to the increased synaptic efficacies (Fig. 1c). While larger ρ weakens synapses (Fig. 1c), this effect may be overcome by decreasing the postsynaptic activity (Fig. 1d): since, at lower firing rates, a neuron spends more time near the threshold, its responsiveness to synaptic inputs would be enhanced (Rubin et al. 2001). In addition, these changes in the correlation function (Fig. 3) could be in line with the finding that larger ρ and g_{GABA} cause the increase in the firing variability (Fig. 1e), which may permit a neuron to respond to weak fluctuations in input activity (Shadlen and Newsome, 1994; Destexhe et al. 2001; Wolfart et al. 2005). For STDP to reflect the correlation structure among inputs, it would be important that the presynaptic spike has a strong influence on the statistics of postsynaptic firing and, moreover, that this influence has a prolonged duration as compared to the correlation time (τ_c=10 ms) (Kempter et al. 1999, 2001; Song and Abbott 2001; Gerstner and Kistler 2002; also see Discussion). Therefore, the concurrence of larger ρ and g_{GABA} would be required to produce both strong and prolonged influence of input spikes on the output firing statistics.

Additionally, to examine whether the temporal fluctuation in the learning curve itself is also involved in the mechanism for regulating the competition, we investigated the cases where A_+ was fixed to a time-invariant value, without ADFB modulation (i.e., ρ=0 in Eq. (7)), within a range of $A_+/A_- \sim 1$ (Fig. 4). When the GABA inhibition was relatively weak (g_{GABA}=3.75 μS/cm^2), the two groups of synapses converged to the same average strength independent of the A_+/A_- ratio (Fig. 4a, closed circles). However, for the increased inhibition level (g_{GABA}= 6.25 μS/cm^2), the synaptic weights segregated into the two input groups for smaller values of A_+/A_- (Fig. 4b, closed circles). These results suggest that in the absence of ADFB function, a combination of a relatively small LTP/LTD ratio and large GABA inhibition can induce the competition between the different groups. Furthermore, to compare the results in the presence and absence of the ADFB mechanism, we plotted in Fig. 4 (*open circles*) the relationship between the average weights of the two groups vs. the temporal average of the A_+/A_- ratio, obtained by the previous simulations that incorporate ADFB (Fig. 1). Figure 4a and b indicate that the results of using ADFB (open circles) show good agreement with those of not using ADFB (closed circles) (also compare Fig. 4 with Fig. 1h and i). The results here imply that it may not be so critical in our model to dynamically alter the shape of the learning curve with time. Instead, the control of the competition property involves the ability of ADFB mechanism to precisely regulate the balance between LTP and LTD in STDP through the modulation of the strength of feedback effect (Kubota et al. 2009).

3.2 Experience-dependent synaptic modification induced by competition

To investigate the functional consequences of the synaptic competition, we examined the learning dynamics when the

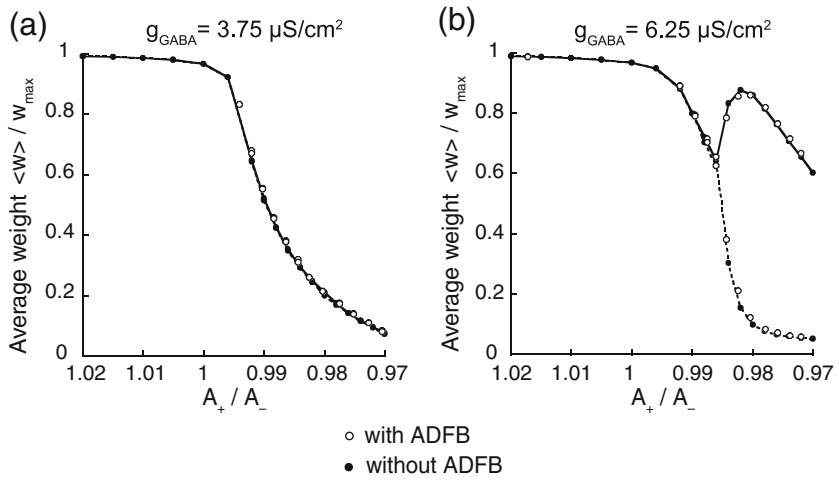

Fig. 4 The comparison of the equilibrium state of STDP in the presence and absence of ADFB mechanism. The solid and dashed lines (with closed circles) show the average weights of the two input groups, obtained by STDP without ADFB modulation (i.e., ρ=0 in Eq. (7)), as function of the A_+/A_- ratio. The open circles represent the relationship between the average weights of both the groups and the temporal mean of A_+/A_-, which is calculated by the STDP model with ADFB by using various values of ρ (as in Fig. 1). (**a**) and (**b**) show the results for two different values of the GABA conductance (g_{GABA}=3.75 μS/cm^2 in (**a**) and 6.25 μS/cm^2 in (**b**)). In both (**a**) and (**b**), good agreement is found between the cases of using and not using the ADFB function. When GABA activity is relatively weak (**a**), the average weights of the two groups are almost identical for all the cases. However, for stronger GABA activity (**b**), the competition takes place for smaller values of A_+/A_- and the synaptic efficacies segregate into the two input groups

input activity for either one group was transiently decreased as in the case of monocular deprivation (Rittenhouse et al. 1999). Figure 5 shows the time course of the average weights (left column) and the final weight distribution (right column) of the two groups, in cases where sufficiently large values of ρ and g_{GABA} generate a competitive situation. After the mean input frequency for the synapses of both groups was maintained at 3 Hz, the frequency for the group winning (Fig. 5a and c) or losing (Fig. 5b and d) the competition was decreased to $3(1-c_r)$ Hz for 200,000 s (denoted by gray bar), and then again restored to 3 Hz. The parameter c_r is used to represent the level of input modification, and the examples using two different values of c_r are illustrated (c_r=0.5 for Fig. 5a and b and 0.2 for Fig. 5c and d). The presynaptic firing rate is altered stepwise, so that the decrease (increase) in the total afferent activity rapidly increases (decreases) the A_+/A_- ratio through the ADFB modulation. Therefore, the weights of the two groups tend to be strengthened and weakened abruptly at the onset and end of the period of input modification, respectively. Importantly, only when the input activity of the winning group is suppressed (Fig. 5a and c), the dominant group is switched into the one that has been losing before the input frequency is altered. The time required for the switching was found to depend on the strength of input suppression such that the switching occurred much faster by larger c_r (compare Fig. 5a vs. c); however, once the dominant group was replaced, the final weight distribution did not depend on the level of input suppression. Consequently, the final synaptic pattern can reflect the information regarding which between the two input groups has received the activity modification, i.e., the group that has not been suppressed dominates over the one that has been suppressed, regardless of which group receives the suppression (Fig. 5, right column). This is reminiscent of the observations in ocular dominance plasticity, wherein the response of the visual cells is dominated by the non-deprived eye following the monocular deprivation (Wiesel 1982; Gordon and Stryker 1996).

Furthermore, it is important that such input experience-dependent synaptic modification does not occur when the competitive interaction is absent because of lower ρ and/or g_{GABA}, as shown in the example of Fig. 6. In this case, the two groups converge to an identical weight distribution independent of the past history of inputs (Fig. 6, right column); therefore, the final synaptic pattern cannot retain the information regarding which group was suppressed. The findings here indicate that the competitive interaction between the input groups elicited by larger ρ and g_{GABA} can contribute to embedding the information about the past sensory experience in the synaptic efficacies.

4 Discussion

4.1 NMDAR and GABA functions in developmental plasticity

In this study, we have examined the synaptic dynamics arising from STDP incorporated with ADFB mechanism,

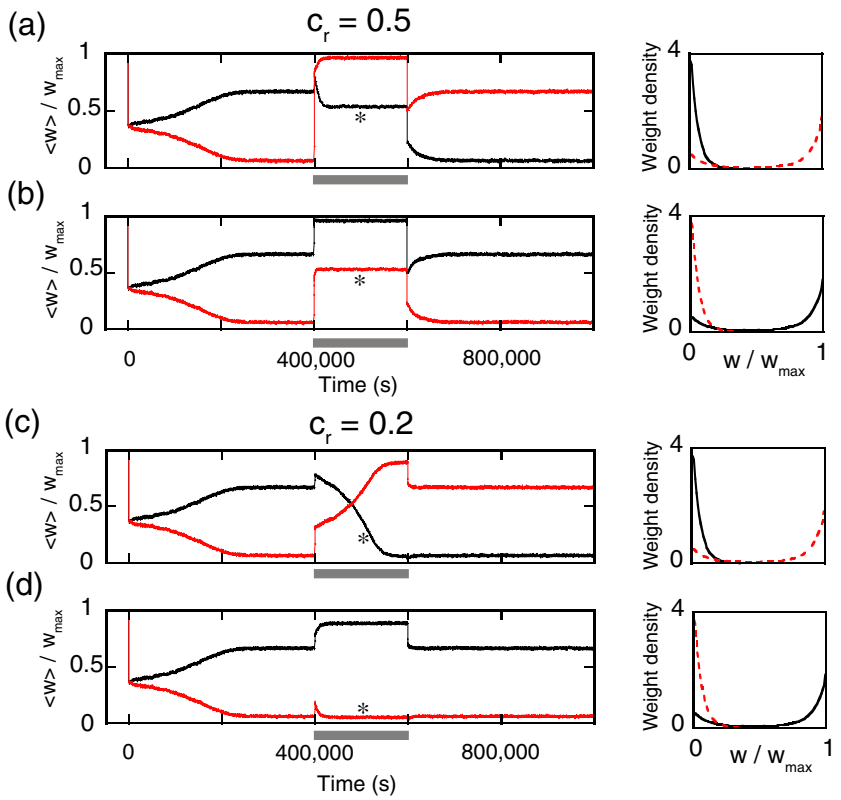

Fig. 5 Examples of experience-dependent synaptic modification induced by the between-group competition in the presence of both strong ADFB function and enhanced GABA inhibition (ρ=1 and g_{GABA}=6.25 μS/cm^2). Left column: the time course of the average weights of the two synaptic groups are shown by black and red lines. The mean input frequency for all synapses is initially maintained at 3 Hz. The activation frequency for either one group (denoted by "*"; a (black), b (red), c (black), and d (*red*)) is decreased to 3(1-c_r) Hz during the period of 400,000<t<600,000 (in s) (*gray bar*) and then returned to 3 Hz. The parameter c_r is used to determine the level of input modification and is set to 0.5 for (**a**) and (**b**) and 0.2 for (**c**) and (**d**). Right column: the final weight distributions for the two groups (with the line colors corresponding to those in the left column)

wherein the magnitude of LTP is dynamically modified through the activity-dependent desensitization of NMDARs. The firing activity of neuron has been driven by two groups of correlated inputs, similar to a visual cortical cell that receives input stimuli from both the eyes. It has been shown that the learning dynamics can be competitive such that one group dominates over the other at the equilibrium state, as in the previous studies (Song and Abbott 2001; Gütig et al. 2003; Yeung et al. 2004; Meffin et al. 2006). A novel feature of our model is that the occurrence of such competition has been shown to depend on the coexistence of two factors: the strengthening of ADFB modulation (larger ρ) and the enhancement of background GABA inhibition (larger g_{GABA}) (Fig. 1f and g). The strength of ADFB can be regulated by the developmental alteration in the NMDAR subunit expression, which increases the proportion of NR2A-containing NMDARs exhibiting Ca^{2+}-dependent desensitization (Monyer et al. 1994; Flint et al. 1997; Quinlan et al. 1999a, b; Mierau et al. 2004; Krupp et al. 1996). Therefore, the sensitivity of synaptic plasticity to the input correlation structure may be increased developmentally through the change in the NR2 subunits as well as the growth of GABA system.

Another important finding of our study is that in the presence, but not absence, of the between-group competition, the synaptic pattern has been shown to reflect the history of inputs such that the group winning the competition depends on the earlier input activities (Fig. 5 and 6). This result suggests the functional significance of competition: it can produce a "memory" of the past sensory stimuli (Angeli et al. 2004; Shpiro et al. 2007) and thereby provide the basis of sensory experience-dependent plasticity. In fact, the involvement of activity-dependent competition has been suggested by many experimental studies examining ocular dominance plasticity (Rauschecker and Singer 1979; Wiesel 1982; Shatz 1990; Gordon and Stryker 1996). Therefore, our findings may have intriguing implications for the possible mechanisms for regulating cortical plasticity: the onset of plasticity can be triggered by the cooperative action of the two developmental mechanisms that induce competition, i.e., the maturation of NMDAR subunit expression and GABA inhibition. This hypothesis may explain why many studies

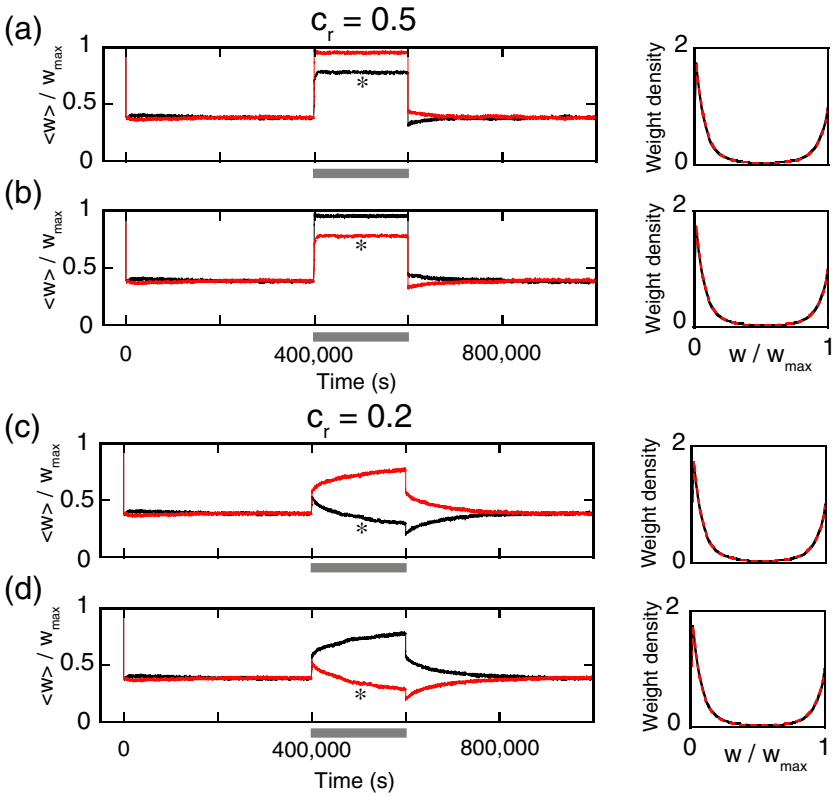

Fig. 6 Experience-dependent synaptic modification does not occur in the absence of competitive interaction. After the mean input frequency of all the synapses are maintained at 3 Hz, that of either one group (denoted by "*"; (**a**) (*black*), (**b**) (*red*), (**c**) (*black*), and (**d**) (*red*)) is transiently decreased to 3(1-c_r) Hz similar to Fig. 5, except that the strength of ADFB function and GABA inhibition is set at lower levels (ρ=0.5 and g_{GABA}=2.5 μS/cm^2). Left column: the time course of the average weights of the two input groups. The gray horizontal bar denotes the period at which the input frequency is modified (400,000 <t<600,000) (in s). c_r=0.5 (**a** and **b**) or 0.2 (**c** and **d**). Right column: the weight distributions of the two groups at the final state (*black solid* and *red dashed lines*) are identical

have reported the concurrence of the timing of critical period with the switching in the NMDAR subunit composition (Roberts and Ramoa 1999; Erisir and Harris 2003), as well as the regulation of this timing by GABA activity (Hensch et al. 1998; Fagiolini and Hensch 2000). Additionally, our hypothesis may give an experimentally verifiable prediction: manipulating either NMDAR subunit or GABA function in the direction that facilitates or suppresses competition can be counterbalanced by manipulating the other in the reverse direction. For example, increasing (decreasing) the NR2A/B ratio will facilitate (suppress) plasticity (Roberts and Ramoa 1999), while this effect may be canceled by decreasing (increasing) GABA activity (Hensch et al. 1998). This prediction appears to be basically similar to the observation that ocular dominance plasticity is weakened in NR2A knockout mice, while it is restored by enhancing inhibition (Fagiolini et al. 2003). Furthermore, our model is not the same but essentially similar to the local inhibitory circuit model of visual plasticity (Hensch 2005; Fagiolini et al. 2003), wherein the onset of plasticity requires the mechanism that enables STDP to embed information regarding correlated inputs in synaptic weights.

A limitation of our model is that it does not address the mechanism by which the cortical plasticity is terminated at the end of the critical period. The closing of the plastic period could be regulated by irreversible changes of intracortical circuitry, which may involve long-lasting facilitatory effects of GABA activity on itself (Iwai et al. 2003), although the detailed mechanism remains to be further explored. Additionally, our model does not explain the experiment by Ramoa et al. (1988) that suggests that the blockade of GABA activity disrupts the receptive field properties of visual cortical neurons and thereby suppresses the ocular dominance plasticity. In future work, it would be important to examine the effects of intracortical horizontal inhibition that refines the receptive field and thus can decrease the probability of the occurrence of correlation between the inputs from the two eyes (Ramoa et al. 1988).

4.2 Synaptic competition induced by STDP with ADFB mechanism

STDP has been proposed to be a physiological mechanism that can automatically elicit synaptic competition to

stabilize neural activity, while maintaining the basic feature of Hebbian learning wherein temporally correlated inputs are preferentially strengthened (Song et al. 2000). However, the same and other theoretical studies also suggest that STDP does not always strengthen the correlated inputs (Song et al. 2000; Gütig et al. 2003; Song and Abbott 2001). For example, when the correlation time is longer as compared to the duration of EPSP or the width of the STDP window, the input correlation does not affect the learning dynamics (Song et al. 2000; Song and Abbott 2001). In such cases, once a group of inputs is strengthened and contributes to frequently evoking the postsynaptic spikes, the subsequent occurrence of the post-pre timing spike pairs causes depression (Song et al. 2000); therefore, it is difficult for the input group to maintain the control for the postsynaptic spike timings and continue to be potentiated. This also indicates that the prolongation of the impact of presynaptic spikes by increasing ρ value (Fig. 3a) would be quite effective to shorten the relative duration of the correlation time and therefore enhance the actual influence of the input correlation to induce competition.

Although, in our model, the correlation-based competition segregates two groups of synapses such that one group is potentiated while the other is depressed, the weight distribution does not necessarily reflect the correlation structure faithfully: in some cases, synapses within a winning or losing input group were divided into two subpopulations accumulating near the upper and lower boundaries (Fig. 2). Such unfaithful splitting would be a property inherent in the additive updating rule employed in our model (Gütig et al. 2003). It would be of interest to extend our study and investigate how the ability to represent the correlation structure can be enhanced when other higher-order rules of plasticity, such as the nonlinear weight dependence (Gütig et al. 2003; Meffin et al. 2006), are introduced in combination with the ADFB mechanism.

Another important extension of our model would be to take into account the dependence of the level of activity-dependent desensitization of NMDARs on the different synapses converging to the same neuron. Since the Ca^{2+} entry through synaptically activated NMDARs is sufficient to produce desensitization of the NMDARs themselves (Legendre et al. 1993; Rosenmund et al. 1995), the level of desensitization will vary depending on a recent history of presynaptic activity and thus the desensitization will be stronger for more frequently-activated inputs. Moreover, several evidence suggests that the expression pattern of distinct NR2 subunits may also be regulated depending on different input pathways to the same cortical neuron (Ito et al. 1997; Kumar and Huguenard 2003; Bellone and Nicoll 2007; see Köhr (2006) for a review). The observations that synaptic activity is involved in the replacement of NR2B with NR2A subunits (Barria and Malinow 2002) and that NR2A- but not NR2B-containing NMDARs exhibit Ca^{2+}-dependent inactivation (Krupp et al. 1996) imply that such input activity-dependent subunit expression could further strengthen the NMDAR desensitization for frequently-activated inputs. Therefore, based on the present results, it may be expected that among the synapses converging to the same postsynaptic neuron, the ones that have been recently and frequently activated will show LTP/LTD balance shifted toward LTD due to stronger desensitization of NMDARs (Fig. 1a and b). This effect will tend to weaken such synapses and thereby could be involved in preventing the excessive activity-dependent competition, wherein only a very small number of frequently-used inputs exclusively acquire the control of postsynaptic activity.

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References

Ahmed, B., Anderson, J. C., Douglas, R. J., Martin, K. A. C., & Whitteridge, D. (1998). Estimates of the net excitatory currents evoked by visual stimulation of identified neurons in cat visual cortex. *Cerebral Cortex, 8*, 462–476.

Angeli, D., Ferrell, J. E., & Sontag, E. D. (2004). Detection of multistability, bifurcations, and hysteresis in a large class of biological positive-feedback systems. *Proceedings of the National Academy of Sciences of the United States of America, 101*, 1822–1827.

Barria, A., & Malinow, R. (2002). Subunit-specific NMDA receptor trafficking to synapses. *Neuron, 35*, 345–353.

Bellone, C., & Nicoll, R. A. (2007). Rapid bidirectional switching of synaptic NMDA receptors. *Neuron, 55*, 779–785.

Bender, V. A., Bender, K. J., Brasier, D. J., & Feldman, D. E. (2006). Two coincidence detectors for spike timing-dependent plasticity in somatosensory cortex. *Journal of Neuroscience, 26*, 4166–4177.

Bernander, O., Douglas, R. J., Martin, K. A. C., & Koch, C. (1991). Synaptic background activity influences spatiotemporal integration in single pyramidal cells. *Proceedings of the National Academy of Sciences of the United States of America, 88*, 11569–11573.

Bi, G. Q., & Poo, M. M. (1998). Synaptic modifications in cultured hippocampal neurons: Dependence on spike timing, synaptic strength, and postsynaptic cell type. *Journal of Neuroscience, 18*, 10464–10472.

Caporale, N., & Dan, Y. (2008). Spike timing-dependent plasticity: A Hebbian learning rule. *Annual Review of Neuroscience, 31*, 25–46.

Crair, M. C., & Malenka, R. C. (1995). A critical period for long-term potentiation at thalamocortical synapses. *Nature, 375*, 325–328.

Daw, M. I., Scott, H. L., & Isaac, J. T. R. (2007). Developmental synaptic plasticity at the thalamocortical input to barrel cortex: Mechanisms and roles. *Molecular and Cellular Neuroscience, 34*, 493–502.

Destexhe, A., Rudolph, M., Fellous, J. M., & Sejnowski, T. J. (2001). Fluctuating synaptic conductances recreate *in vivo*-like activity in neocortical neurons. *Neuroscience, 107*, 13–24.

Dumas, T. C. (2005). Developmental regulation of cognitive abilities: Modified composition of a molecular switch turns on associative learning. *Progress in Neurobiology, 76*, 189–211.

Egger, V., Feldmeyer, D., & Sakmann, B. (1999). Coincidence detection and change of synaptic efficacy in spiny stellate neurons in rat barrel cortex. *Nature Neuroscience, 2*, 1098–1105.

Erisir, A., & Harris, J. L. (2003). Decline of the critical period of visual plasticity is concurrent with the reduction of NR2B subunit of the synaptic NMDA receptor in layer 4. *Journal of Neuroscience, 23*, 5208–5218.

Fagiolini, M., & Hensch, T. K. (2000). Inhibitory threshold for critical-period activation in primary visual cortex. *Nature, 404*, 183–186.

Fagiolini, M., Katagiri, H., Miyamoto, H., Mori, H., Grant, S. G. N., Mishina, M., et al. (2003). Separable features of visual cortical plasticity revealed by N-methyl-d-aspartate receptor 2A signaling. *Proceedings of the National Academy of Sciences of the United States of America, 100*, 2854–2859.

Feldman, D. E. (2000). Timing-based LTP and LTD at vertical inputs to layer II/III pyramidal cells in rat barrel cortex. *Neuron, 27*, 45–56.

Feldman, D. E., Nicoll, R. A., Malenka, R. C., & Isaac, J. T. R. (1998). Long-term depression at thalamocortical synapses in developing rat somatosensory cortex. *Neuron, 21*, 347–357.

Flint, A. C., Maisch, U. S., Weishaupt, J. H., Kriegstein, A. R., & Monyer, H. (1997). NR2A subunit expression shortens NMDA receptor synaptic currents in developing neocortex. *Journal of Neuroscience, 17*, 2469–2476.

Froemke, R. C., & Dan, Y. (2002). Spike-timing-dependent synaptic modification induced by natural spike trains. *Nature, 416*, 433–438.

Gerstner, W., Kempter, R., van Hemmen, J. L., & Wagner, H. (1996). A neuronal learning rule for sub-millisecond temporal coding. *Nature, 383*, 76–78.

Gerstner, W., & Kistler, W. M. (2002). *Spiking neuron models*. Cambridge: Cambridge University.

Gordon, J. A., & Stryker, M. P. (1996). Experience-dependent plasticity of binocular responses in the primary visual cortex of the mouse. *Journal of Neuroscience, 16*, 3274–3286.

Gütig, R., Aharonov, R., Rotter, S., & Sompolinsky, H. (2003). Learning input correlations though nonlinear temporally asymmetric Hebbian plasticity. *Journal of Neuroscience, 23*, 3697–3714.

Hanover, J. L., Huang, Z. J., Tonegawa, S., & Stryker, M. P. (1999). Brain-derived neurotrophic factor overexpression induces precocious critical period in mouse visual cortex. *Journal of Neuroscience, 19*, RC40.

Helmchen, F., Imoto, K., & Sakmann, B. (1996). Ca^{2+} buffering and action potential-evoked Ca^{2+} signaling in dendrites of pyramidal neurons. *Biophysical Journal, 70*, 1069–1081.

Hensch, T. K. (2005). Critical period plasticity in local cortical circuits. *Nature Reviews Neuroscience, 6*, 877–888.

Hensch, T. K., Fagiolini, M., Mataga, N., Stryker, M. P., Baekkeskov, S., & Kash, S. F. (1998). Local GABA circuit control of experience-dependent plasticity in developing visual cortex. *Science, 282*, 1504–1508.

Hessler, N. A., Shirke, A. M., & Malinow, R. (1993). The probability of transmitter release at a mammalian central synapse. *Nature, 366*, 569–572.

Huang, Z. J., Kirkwood, A., Pizzorusso, T., Porciatti, V., Morales, B., Bear, M. F., et al. (1999). BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. *Cell, 98*, 739–755.

Ito, I., Futai, K., Katagiri, H., Watanabe, M., Sakimura, K., Mishina, M., et al. (1997). Synapse-selective impairment of NMDA receptor functions in mice lacking NMDA receptor epsilon 1 or epsilon 2 subunit. *Journal of Physiology (London), 500*(2), 401–408.

Iwai, Y., Fagiolini, M., Obata, K., & Hensch, T. K. (2003). Rapid critical period induction by tonic inhibition in visual cortex. *Journal of Neuroscience, 23*, 6695–6702.

Jahr, C. E., & Stevens, C. F. (1990). Voltage dependence of NMDA-activated macroscopic conductances predicted by single-channel kinetics. *Journal of Neuroscience, 10*, 3178–3182.

Kempter, R., Gerstner, W., & van Hemmen, J. L. (1999). Hebbian learning and spiking neurons. *Physical Review E, 59*, 4498–4514.

Kempter, R., Gerstner, W., & van Hemmen, J. L. (2001). Intrinsic stabilization of output rates by spike-based Hebbian learning. *Neural Computation, 13*, 2709–2741.

Kepecs, A., van Rossum, M. C. W., Song, S., & Tegner, J. (2002). Spike-timing-dependent plasticity: Common themes and divergent vistas. *Biological Cybernetics, 87*, 446–458.

Kirkwood, A., & Bear, M. F. (1994). Hebbian synapses in visual cortex. *Journal of Neuroscience, 14*, 1634–1645.

Koch, C. (1999). *Biophysics of computation*. New York: Oxford University.

Köhr, G. (2006). NMDA receptor function: subunit composition versus spatial distribution. *Cell and Tissue Research, 326*, 439–446.

Krupp, J. J., Vissel, B., Heinemann, S. F., & Westbrook, G. L. (1996). Calcium-dependent inactivation of recombinant N-methyl-d-aspartate receptors is NR2 subunit specific. *Molecular Pharmacology, 50*, 1680–1688.

Kubota, S., & Kitajima, T. (2008). A model for synaptic development regulated by NMDA receptor subunit expression. *Journal of Computational Neuroscience, 24*, 1–20.

Kubota, S., Rubin, J., & Kitajima, T. (2009). Modulation of LTP/LTD balance in STDP by an activity-dependent feedback mechanism. *Neural Networks, 22*, 527–535.

Kumar, S. S., & Huguenard, J. R. (2003). Pathway-specific differences in subunit composition of synaptic NMDA receptors on pyramidal neurons in neocortex. *Journal of Neuroscience, 23*, 10074–10083.

Legendre, P., Rosenmund, C., & Westbrook, G. L. (1993). Inactivation of NMDA channels in cultured hippocampal neurons by intracellular calcium. *Journal of Neuroscience, 13*, 674–684.

Markram, H., Lubke, J., Frotscher, M., & Sakmann, B. (1997). Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science, 275*, 213–215.

Medina, I., Leinekugel, X., & Ben-Ari, Y. (1999). Calcium-dependent inactivation of the monosynaptic NMDA EPSCs in rat hippocampal neurons in culture. *European Journal of Neuroscience, 11*, 2422–2430.

Meffin, H., Besson, J., Burkitt, A. N., & Grayden, D. B. (2006). Learning the structure of correlated synaptic subgroups using stable and competitive spike-timing-dependent plasticity. *Physical Review E, 73*, 041911.

Mierau, S. B., Meredith, R. M., Upton, A. L., & Paulsen, O. (2004). Dissociation of experience-dependent and -independent changes in excitatory synaptic transmission during development of barrel cortex. *Proceedings of the National Academy of Sciences of the United States of America, 101*, 15518–15523.

Monyer, H., Burnashev, N., Laurie, D. J., Sakmann, B., & Seeburg, P. H. (1994). Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. *Neuron, 12*, 529–540.

Morrison, A., Diesmann, M., & Gerstner, W. (2008). Phenomenological models of synaptic plasticity based on spike timing. *Biological Cybernetics, 98*, 459–478.

Nevian, T., & Sakmann, B. (2006). Spine Ca^{2+} signaling in spike-timing-dependent plasticity. *Journal of Neuroscience, 26*, 11001–11013.

Quinlan, E. M., Olstein, D. H., & Bear, M. F. (1999a). Bidirectional, experience-dependent regulation of N-methyl-d-aspartate receptor subunit composition in the rat visual cortex during postnatal development. *Proceedings of the National Academy of Sciences of the United States of America, 96*, 12876–12880.

Quinlan, E. M., Philpot, B. D., Huganir, R. L., & Bear, M. F. (1999b). Rapid, experience-dependent expression of synaptic NMDA receptors in visual cortex *in vivo*. *Nature Neuroscience, 2*, 352–357.

Ramoa, A. S., Paradiso, M. A., & Freeman, R. D. (1988). Blockade of intracortical inhibition in kitten striate cortex: Effects on receptive field properties and associated loss of ocular dominance plasticity. *Experimental Brain Research, 73*, 285–296.

Rauschecker, J. P., & Singer, W. (1979). Changes in the circuitry of the kitten visual cortex are gated by postsynaptic activity. *Nature, 280*, 58–60.

Rittenhouse, C. D., Shouval, H. Z., Paradiso, M. A., & Bear, M. F. (1999). Monocular deprivation induces homosynaptic long-term depression in visual cortex. *Nature, 397*, 347–350.

Rittenhouse, C. D., Siegler, B. A., Voelker, C. A., Shouval, H. Z., Paradiso, M. A., & Bear, M. F. (2006). Stimulus for rapid ocular dominance plasticity in visual cortex. *Journal of Neurophysiology, 95*, 2947–2950.

Roberts, E. B., & Ramoa, A. S. (1999). Enhanced NR2A subunit expression and decreased NMDA receptor decay time at the onset of ocular dominance plasticity in the ferret. *Journal of Neurophysiology, 81*, 2587–2591.

Rosenmund, C., Feltz, A., & Westbrook, G. L. (1995). Calcium-dependent inactivation of synaptic NMDA receptors in hippocampal neurons. *Journal of Neurophysiology, 73*, 427–430.

Rubin, J., Lee, D. D., & Sompolinsky, H. (2001). Equilibrium properties of temporally asymmetric Hebbian plasticity. *Physical Review Letters, 86*, 364–367.

Shadlen, M. N., & Newsome, W. T. (1994). Noise, neural codes and cortical organization. *Current Opinion in Neurobiology, 4*, 569–579.

Shatz, C. J. (1990). Impulse activity and the patterning of connections during CNS development. *Neuron, 5*, 745–756.

Shpiro, A., Curtu, R., Rinzel, J., & Rubin, N. (2007). Dynamical characteristics common to neuronal competition models. *Journal of Neurophysiology, 97*, 462–473.

Song, S., & Abbott, L. F. (2001). Cortical development and remapping through spike timing-dependent plasticity. *Neuron, 32*, 339–350.

Song, S., Miller, K. D., & Abbott, L. F. (2000). Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. *Nature Neuroscience, 3*, 919–926.

Stephenson, F. A. (2001). Subunit characterization of NMDA receptors. *Current Drug Targets, 2*, 233–239.

Svoboda, K., Denk, W., Kleinfeld, D., & Tank, D. W. (1997). *in vivo* dendritic calcium dynamics in neocortical pyramidal neurons. *Nature, 385*, 161–165.

Tanabe, S., & Pakdaman, K. (2001). Noise-enhanced neuronal reliability. *Physical Review E, 64*, 041904.

Tegnér, J., & Kepecs, Á. (2002). Why neuronal dynamics should control synaptic learning rules. *Advances in Neural Information Processing Systems, 14*, 285–292.

Wang, X. J. (1998). Calcium coding and adaptive temporal computation in cortical pyramidal neurons. *Journal of Neurophysiology, 79*, 1549–1566.

Wiesel, T. N. (1982). Postnatal development of the visual cortex and the influence of environment. *Nature, 299*, 583–591.

Wolfart, J., Debay, D., Masson, G. L., Destexhe, A., & Bal, T. (2005). Synaptic background activity controls spike transfer from thalamus to cortex. *Nature Neuroscience, 8*, 1760–1767.

Yeung, L. C., Shouval, H. Z., Blais, B. S., & Cooper, L. N. (2004). Synaptic homeostasis and input selectivity follow from a calcium-dependent plasticity model. *Proceedings of the National Academy of Sciences of the United States of America, 101*, 14943–14948.

Zador, A., Koch, C., & Brown, T. H. (1990). Biophysical model of a Hebbian synapse. *Proceedings of the National Academy of Sciences of the United States of America, 87*, 6718–6722.