Neurocomputing 143 (2014) 261–268

Contents lists available at ScienceDirect

Neurocomputing

journal homepage: www.elsevier.com/locate/neucom

The onset and closure of critical period plasticity regulated by feedforward inhibition

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ARTICLE INFO

Article history:
Received 9 December 2013
Received in revised form
15 April 2014
Accepted 1 June 2014
Communicated by: Shuiwang Ji
Available online 12 June 2014

Keywords:
STDP
Synaptic competition
Critical period
Visual cortex

ABSTRACT

Synaptic circuits are highly sensitive to sensory experience during a critical period in early development. The maturation of GABA inhibition in the visual cortex is suggested to be required for both the onset and closure of the critical period for ocular dominance (OD) plasticity, although the underlying mechanism is unclear. This study examines a model of a visual cortical cell to investigate the mechanism by which inhibitory pathway regulates OD plasticity, through the competition between the groups of correlated inputs from two eyes. We show that when feedforward inhibition is at a low level, the activity-dependent competition does not arise. In the lack of competition, synaptic dynamics are monostable, which prevents the sensory experience to be embedded into synaptic weights. When the feedforward inhibition becomes greater than a threshold, the competitive interaction segregates the input groups into dominant and recessive ones. In this case, the synaptic dynamics become bistable, which provides the synaptic pattern with the ability to reflect sensory experience, opening the critical period. When the feedforward inhibition is further increased, a strong stability of synaptic patterns makes it difficult to change according to input stimuli. Therefore, it becomes difficult again for the synaptic weights to reflect the information about sensory stimuli, closing the critical period. Our hypothesis suggests that the start and end of critical period plasticity may be explained by the competitive dynamics of synapses, which is modulated by the feedforward inhibition.

1. Introduction

The brain is organized by receiving sensory experience during a restricted critical period [1]. Well-known examples are the effects of modulating visual experience on the developing visual cortex [1]. The deprivation of vision from one eye during a critical period shifts the response of visual cortical cells to favor the inputs from the open eye. In contrast, monocular deprivation (MD) before or after the critical period does not significantly affect the response of the neurons.

Many studies have suggested that the timing of critical period is regulated by the maturation of GABA inhibition [2–7] ([7] for review). When the maturation of inhibition is suppressed by the targeted deletion of an isoform of the GABA synthetic enzyme, glutamic acid decarboxylase (GAD65), the onset of ocular dominance (OD) plasticity is delayed until the inhibition level is pharmacologically recovered [2]. Similarly, OD plasticity can be prematurely induced by pharmacologically enhancing GABA function [3], suggesting the existence of a threshold level of GABA to start visual plasticity. Furthermore, recent experiments have shown that enhanced GABA inhibition not only can trigger the opening of critical period but also contribute to its closure [8–12]. Suppression of GABA through the infusion of an inhibitor of GABA synthesis mercaptopropionic acid, at doses which do not affect the responsiveness of visual cortical cells, can reactivate OD plasticity in the adult rats [9,10]. In addition, exposure to enriched environment or treatment with a serotonin reuptake inhibitor fluoxetine, which reduces intracortical GABA inhibition, can recover plasticity [11,12]. These findings suggest that there may exist two threshold levels of inhibition: a lower threshold above which OD plasticity is expressed and a higher threshold above which the ability of plasticity is suppressed [10].

Several studies using computational models have proposed a role of GABA in regulating the onset of OD plasticity. A recent study [13] suggests that GABA activity preferentially decreases the synaptic efficacy of less coherent inputs, which contributes to inducing an OD shift toward more coherent inputs. A study on subplate circuits [14] also indicates that higher inhibition levels may be necessary to induce an OD shift toward the non-deprived eye during MD. Although these research proposes mechanisms inducing the onset of OD plasticity in response to MD, it appears difficult to extend the same mechanisms to explain the closure of OD plasticity. One possibility is that the closure of critical period may result from a gradual decline in neuronal activity through

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http://dx.doi.org/10.1016/j.neucom.2014.06.002
0925-2312/

GABA maturation, which will act to prevent long-term potentiation (LTP) and long-term depression (LTD) at cortical synapses [15,16]. However, recent findings suggest that both LTP and LTD occur in the adult visual cortex *in vivo* [17], implying that the suppressive effect of GABA on OD plasticity seems difficult to be simply explained by the reduction in the activity level.

In this study, we examine a simplified model of a visual cortical cell to explain the mechanism by which GABA controls both the onset and closure of the critical period of OD plasticity. In our model, we hypothesized that the level of feedforward inhibition corresponds to the level of GABAergic development. The model neuron receives two groups of excitatory inputs conveying correlated activities, as in a visual cortical cell receiving inputs from two eyes, and feedforward inhibition mediated by GABA. The synaptic weights of the two input groups are modulated by spike-timing-dependent plasticity (STDP) [18,19], where the weight change depends on the precise timing of pre- and postsynaptic spikes. We particularly investigate the synaptic dynamics regulated by competition between the input groups, since many experiments have suggested a key role of activity-dependent competition in OD plasticity [1,20–22]. We show that a higher level of feedforward inhibition induces competition, which generates bistable synaptic pattern. The bistability provides synaptic weights with an ability to reflect sensory experience of MD, opening the critical period. However, a further higher level of feedforward inhibition makes the synaptic patterns too stable to alter according to sensory stimuli, closing the critical period. Our model may be beneficial for understanding the mechanism to regulate the start and end of the critical period, in a unified framework, through competitive dynamics of synapses.

2. Methods

We use a leaky integrate-and-fire (LIF) neuron to model a visual cortical cell [23]. The membrane potential V of the LIF neuron is described as $\tau_m(dV/dt)=g_{leak}(E_{leak}-V)+I$ with $\tau_m=20$ ms, $E_{leak}=-74$ mV, and $g_{leak}=1$ (the values of conductances are measured in units of the leak conductance for all cases) [24]. When the membrane potential arrives at a threshold value of -54 mV, the neuron fires and the membrane potential is reset to -60 mV following the absolutory refractory period of 1 ms. As shown in Fig. 1, the neuron receives 1000 excitatory and 200 inhibitory inputs. To model sensory inputs from two eyes to a visual cortical cell, the excitatory inputs are divided into two groups of equal size [25]. We consider that the excitatory inputs are of AMPA type, while the inhibitory inputs are of GABA type. The conductances for the excitatory and inhibitory inputs are described as $g_{exc}=\overline{g}_{exc}we^{-t/\tau_{exc}}$ and $g_{inh}=\overline{g}_{inh}(e/\tau_{inh})te^{-t/\tau_{inh}}$, respectively, where $\overline{g}_{exc}=0.015$, $\tau_{exc}=5$ ms, $\overline{g}_{inh}=0.005$, and $\tau_{inh}=10$ ms [25]. w denotes the synaptic weight for each excitatory input, which is modified by STDP (see below).

Each group of excitatory inputs are activated by the retinal activities for the corresponding eye (Fig. 1). Inhibitory inputs are activated through pathways originating from excitatory inputs, providing feedforward inhibition, which corresponds to the synaptic connection observed in animal visual cortex [26]. There is evidence that, for sufficiently noisy conditions, as in the in vivo state, the firing probability of a postsynaptic neuron is approximately proportional to the summation of the postsynaptic potentials (PSPs) occurring in the neuron [27,28]. Therefore, we consider that the activation timings of both excitatory and inhibitory inputs are described by non-stationary Poisson processes, the rate of which is determined by the PSPs [29]. With this assumption, the activation rates of the two groups of excitatory inputs ($r_1^{exc}(t)$ and $r_2^{exc}(t)$) and that of inhibitory inputs ($r^{inh}(t)$) are described by the following equations:

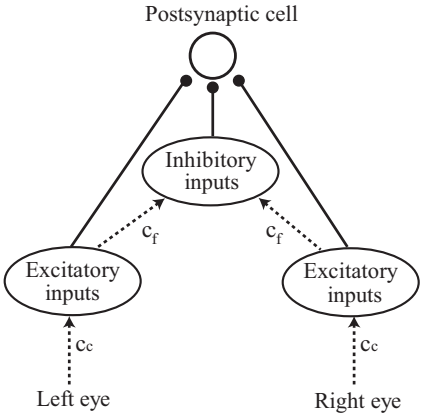

Fig. 1. The model neuron receives inputs from two groups of excitatory (AMPA) inputs and a group of inhibitory (GABA) inputs. Each group of excitatory inputs are driven by the afferent inputs from the corresponding eye. Inhibitory inputs are driven by the activities of excitatory inputs, providing feedforward inhibition. The parameters of c_c and c_f decide the levels of afferent inputs and feedforward inhibition, respectively.

$$r_I^{exc}(t)=c_c\sum_f \varepsilon(t-t_I^f)+r_0^{exc}\ (I=1,2), \tag{1}$$

$$r^{inh}(t)=\frac{c_f}{n_{exc}}\sum_i\sum_f \varepsilon(t-t_{exc,i}^f)+r_0^{inh}. \tag{2}$$

Here, $\varepsilon(t)$ is a function describing the temporal change in PSPs, and $\varepsilon(t)=(t/\tau_e^2)e^{-t/\tau_e}$ with $\tau_e=20$ ms for $t\geq 0$ and $\varepsilon(t)=0$ otherwise. In Eq. (1), t_I^f is the arrival timing of the fth spike to the Ith group of excitatory inputs from retinal ganglion cells, and t_I^f is determined using Poisson spikes with a frequency of $r_{inp}=5$ Hz. The spike arrival timings for the two groups of excitatory inputs are independent, and therefore, the activation of the different groups are uncorrelated to each other. The parameter c_c is to determine the strength of afferent inputs from retinal ganglion cells, and c_c is set to be 0.5 unless otherwise stated. $r_0^{exc}=7.5$ Hz is a component of the activation frequency that corresponds to spontaneous activity. In Eq. (2), $t_{exc,i}^f$ is the fth activation timing of the ith excitatory synapse. Therefore, c_f is a parameter to decide a level of feedforward inhibition, which corresponds to the maturation of GABA inhibition, especially of the developing GABAergic innervation during critical period [30]. n_{exc} $(=500)$ is the number of excitatory inputs within each group, and r_0^{inh} is the frequency corresponding to spontaneous activity for the inhibitory inputs.

It has been suggested that homeostatic regulation may be involved in preserving the overall input activities that drive visual cortical neurons in early development [31]. Therefore, to maintain the activation rate of presynaptic inputs independent of the strength of feedforward connections c_f, the spontaneous activation rate of inhibitory inputs was modified such that $r_0^{inh}=10(1-c_f)$. With this equation, the mean activation rate of inhibitory inputs is kept at 10 Hz.

STDP was assumed to act on all the weights of excitatory inputs. The change in the synaptic weight by STDP, Δw, is described as a function of the interspike interval (ISI), $\Delta t=t_{post}-t_{pre}$, between the pre and postsynaptic activities as follows [24]:

$$\Delta w(\Delta t)=\begin{cases} A_+\exp(-\Delta t/\tau_+) & (\Delta t>0)\\ -A_-\exp(\Delta t/\tau_-) & (\Delta t<0)\\ 0 & (\Delta t=0)\end{cases} \tag{3}$$

In this equation, $A_+ = 0.003$ and $A_- = 0.003/0.99$ are the magnitude of LTP and LTD, respectively, and $\tau_+ = \tau_- = 20$ ms are the width of the temporal window for STDP. The magnitude of LTD is slightly larger than that of LTP, which is necessary to stabilize the postsynaptic activity [25]. We assumed that the effects of STDP caused by all the spike pairs are summed linearly. The magnitude of each weight is limited by the upper and lower bounds (1 and 0, respectively).

3. Results

In order to examine the GABA-dependent mechanism for OD plasticity, we investigated synaptic modification dynamics of a visual cortical cell (Fig. 1) in response to MD. The effect of MD was simulated by temporarily decreasing the value of c_c, the strength of afferent activities conveyed from the retina, for the input group corresponding to the deprived eye. To clearly examine the change in the synaptic pattern dependent on which eye is deprived, we used two times of deprivation for different eyes. This is reminiscent of the experiment using MD for one eye, which is followed by reverse suture of the other eye [32]. As shown in Fig. 2(A), the excitatory inputs of both groups were initially activated with the same strength of afferent activities ($c_c = 0.5$). During the first period of MD (100,000 s $< t <$ 200,000 s), the afferent activity for one group (denoted by black line) was deprived by decreasing the value of c_c to 0. The afferent activity for this group was restored after the end of the first MD. For the second period of MD (300,000 s $< t <$ 400,000 s), the afferent activity for the opposite group (denoted by red line) was removed. The afferent activity for the two groups was maintained after the termination of the second MD.

In Fig. 2 (B) (left column), the time courses of average weights for the two input groups were plotted when the feedforward inhibition is absent ($c_f = 0$; Fig. 2 (B1)), at an intermediate level

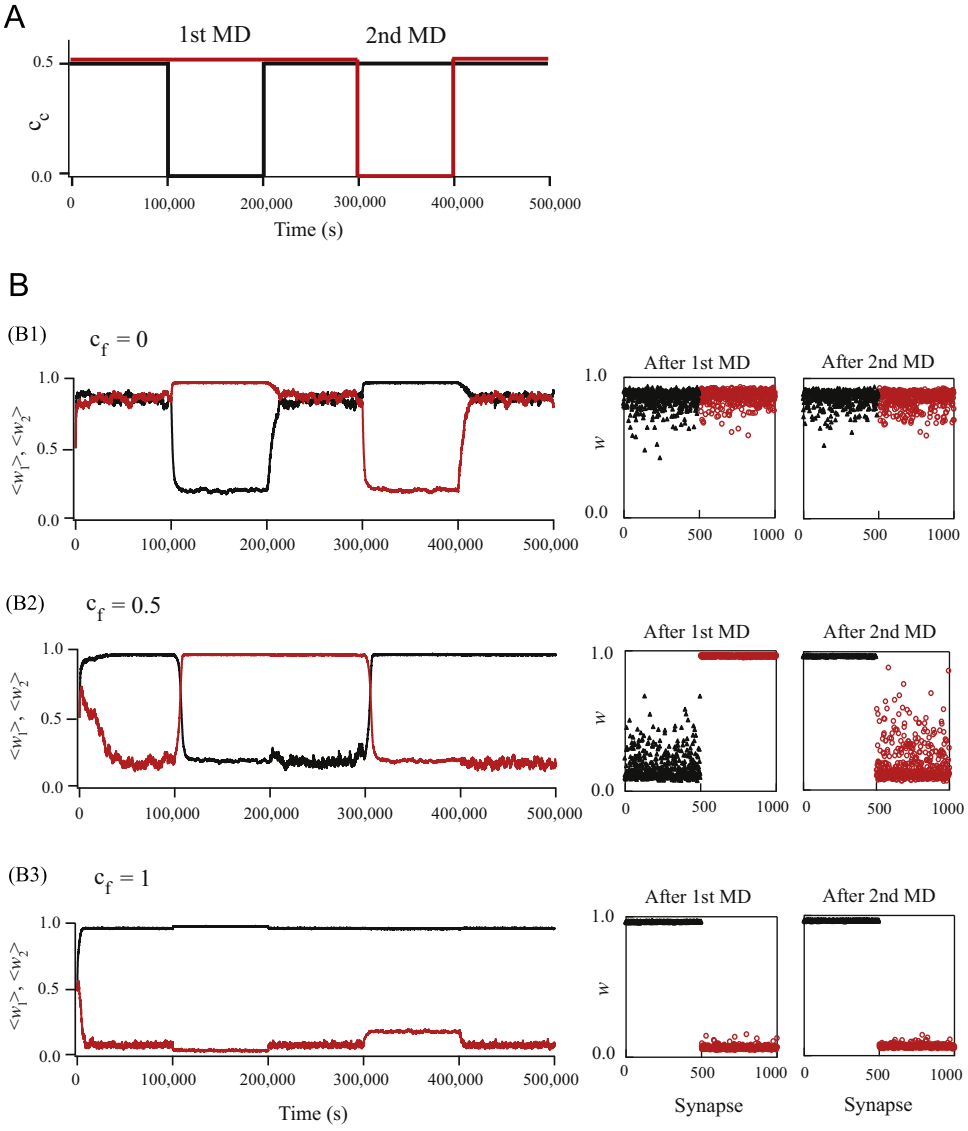

Fig. 2. The predicted effects of feedforward inhibition on the synaptic dynamics in response to MD. (A) The time courses of the strength of afferent activities c_c for the two groups of excitatory inputs are shown by the black and red lines. During each period of MD, the value of c_c for the input group corresponding to the deprived eye is decreased to 0. The first and second MD are applied to the input groups denoted by the black and red lines, respectively. (B) Left column: the temporal changes in the average weights are shown for the two input groups. Center and right columns: the weight distributions of both the groups (500 inputs for each group) are shown by the black and red symbols, for the cases after the first MD (center; $t = 250{,}000$ s) and the second MD (right; $t = 450{,}000$ s). The strength of feedforward inhibition c_f is 0 (B1), 0.5 (B2), or 1 (B3). The line colors in (B) correspond to those in (A). The between-group competition does not arise in (B1), while the competition segregates the two groups into dominant and recessive ones in (B2) and (B3). The switching in the dominant group by MD can and cannot occur in (B2) and (B3), respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(c_f=0.5; Fig. 2 (B2)), or strong (c_f=1; Fig. 2 (B3)). Without feedforward inhibition (Fig. 2 (B1)), the synaptic weight for the group deprived of afferent inputs was significantly weakened during each period of MD, as in many experiments of OD plasticity (e.g., [1]). However, after the end of MD, the two groups of inputs rapidly converged to nearly the same average strength. In addition, the weight distributions of both groups were almost identical after the two periods of MD (Fig. 2 (B1), center and right), so that the synaptic pattern could not reflect which group had received deprivation in the past period of MD. In contrast, with a moderate level of feedforward inhibition (Fig. 2 (B2)), the two input groups were segregated into strong and weak ones, even in the absence of MD, suggesting an existence of competitive interaction between the different groups [24,25]. In this case, the dominant group was switched during each period of MD such that the non-deprived group becomes dominant, and furthermore, the results of switching was maintained even after the termination of MD. Therefore, the weight distributions of the two input groups reflected which group had received deprivation in a recent period of MD (Fig. 2 (B2), center and right).

Importantly, when the level of feedforward inhibition is further increased (c_f=1; Fig. 2 (B3)), the dominant group was not switched by MD even though the competition segregates the input groups, implying a higher stability of the synaptic pattern. Therefore, the synaptic weights could not represent earlier input experience by MD. In fact, for each input group, the weight distributions following the two periods of MD were nearly the same (Fig. 2(B3), center and right). These results indicate that an adequate level of feedforward inhibition would be required for the synapses to reflect the experience of earlier inputs, and a too low or high level of feedforward inhibition may suppress the ability of synapses to memorize the information about sensory experience. Therefore, our model expects that an increase in the feedforward inhibition from a low level will first initiate and then terminate the experience-dependent plasticity, as shown in recent experiments of OD plasticity [7,10].

We also performed simulations similar to Fig. 2, except that the level of activity reduction by MD was modifiable (Fig. 3). As shown in Fig. 3(A), the magnitude of afferent activity, c_c, for the deprived group was decreased by the amount of Δc_c, during each period of MD. Thus, Δc_c is a parameter to regulate the strength of input deprivation by MD. Fig. 3 (B) shows a result of bifurcation analysis by using c_f and Δc_c as two bifurcation parameters. When the feedforward inhibition is smaller than a threshold value ($\sim$0.35), the between-group competition does not arise, as in Fig. 2 (B1), regardless of the value of Δc_c. For an intermediate level of feedforward inhibition ($0.35 < c_f < 0.7$), the competition between the groups emerges, although the consequence of MD depends on the value of Δc_c: a stronger level of deprivation (larger Δc_c) causes the switching in the dominant group during a MD period as in Fig. 2(B2), whereas a weaker level of deprivation (smaller Δc_c) does not cause the switching, as in Fig. 2(B3). For further higher level of feedforward inhibition ($c_f > 0.7$), the competition takes place but the switching in the dominant group does not occur for all Δc_c. In Fig. 3(C), we showed the examples of synaptic weight dynamics using three different levels of activity reduction (Δc_c=0.2 (C1), 0.3 (C2), or 0.4 (C3)) for an intermediate value of c_f (c_f=0.6). A weaker level of input deprivation does not significantly affect the weight dynamics and cannot cause the switching in the dominant group (Fig. 3(C1)). In contrast, stronger input deprivation induces the switching between the groups, and therefore, the weight distribution following MD can reflect the sensory experience (Fig. 3(C2) and (C3)). Additionally, the timing at which the switching occurs during MD is earlier for Fig. 3(C3) than for Fig. 3(C2) (see vertical dashed lines in the two figures). This finding suggests that the synaptic change in response to MD is accelerated by increasing the strength of input modification. The results here clearly suggest that an moderate level of feedforward inhibition, combined with a stronger level of input deprivation during a MD period, is required to embed the sensory experience of MD into the synaptic weights.

To examine a mechanism for preventing the switch in the dominant group for a high level of feedforward inhibition, we investigated the firing statistics of the neuron with two different levels of feedforward inhibition (c_f=0.4 in Fig. 4(A); c_f=1 in Fig. 4 (B)). Both of c_f values are selected to be large enough to elicit the between-group competition. Just like the previous simulations (Fig. 2(B2) and (B3)), after the input groups were separated into dominant and recessive groups, the afferent input for the dominant group was deprived, by decreasing c_c to 0, to simulate the effect of MD. Then, we calculated the correlation function between the activity of each input group and that of postsynaptic cell during the first 2000 s of the MD period, to examine the transient dynamics in response to MD. The correlation function is defined as

$$C(\Delta t) = \langle S_{pre}(t) S_{post}(t+\Delta t) \rangle, \tag{4}$$

where $S_{pre}(t) = \sum_i \sum_f \delta(t - t^f_{exc,i})$ and $S_{post}(t) = \sum_f \delta(t - t^f_{post})$ denote the spike trains for a group of excitatory inputs and the postsynaptic cell, respectively. $\langle x(t) \rangle$ means the temporal average of $x(t)$.

The comparison between Figs. 4(A) and 4(B) clearly indicate that the increase in c_f values, from 0.4 to 1, can qualitatively modify the shape of the correlation function for the group that has been recessive before the MD period. For c_f=0.4, the correlation function for the initially recessive group is approximately symmetric with respect to Δt=0 (Fig. 4(A), red), whereas, for c_f=1, the value of correlation function is considerably smaller for $\Delta t > 0$ than for $\Delta t < 0$ (Fig. 4(B), red). This is because, at larger c_f, stronger feedforward inhibition elicits hyperpolarizing currents in the postsynaptic neuron just following excitatory inputs, which can significantly decrease the probability of action potentials for $\Delta t > 0$.

We have also calculated the synaptic drift (i.e., the temporally averaged value of the rate of synaptic weight changes) [27,29] for each group of excitatory inputs. The synaptic drift was obtained by the convolution between the correlation function, for the pre- and postsynaptic activities, and the STDP learning curve, $\int_{-\infty}^{\infty} C(s) \Delta w(s) ds$, which was added with the net synaptic changes due to the presence of upper and lower boundaries of synaptic weights. As shown in Fig. 4 (C), the increase in c_f was shown to produce a switching in the sign of the synaptic drift for the two groups. For the value of c_f smaller than a threshold ($\sim$0.5), the synaptic drift for the initially recessive group is positive (i.e., the average weight increases), whereas the synaptic drift for the initially dominant group is negative (i.e., the average weight decreases). Therefore, the switching in the dominant group occurs by MD, as in the case of Fig. 2(B2). In contrast, for c_f values larger than the threshold, the synaptic drift for the initially dominant and recessive groups are positive and negative, respectively; therefore, the switching in the dominant group cannot occur, as in Fig. 2(B3). The change in the synaptic drift dependent on c_f may be partly explained by the corresponding change in the correlation function shown in Figs. 4 (A) and 4(B). As mentioned above, larger c_f significantly decreases the value of correlation function, between the activity of the initially recessive group and that of the postsynaptic cell, for $\Delta t > 0$ more than $\Delta t < 0$ (Fig. 4(B), red line). This change will act to reduce the overall effects of the pre-post timing LTP than those of the post-pre timing LTD in STDP, leading to a negative shift of the synaptic drift for this input group. The argument here suggests that the change in the synaptic dynamics in response to MD would be attributable to the modulation of the temporal correlation

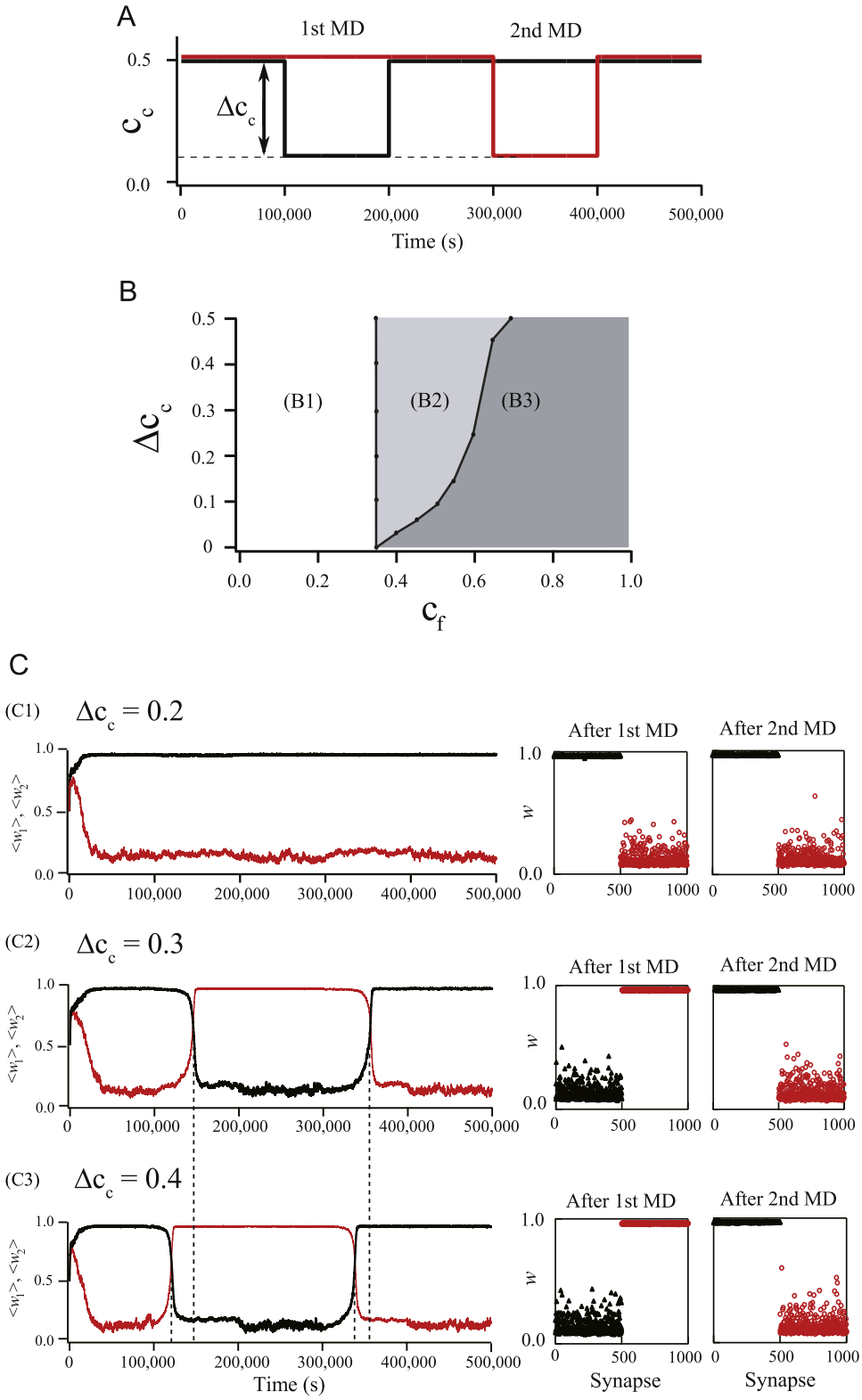

Fig. 3. Bifurcation analysis of the synaptic dynamics in response to MD. (A) The time courses of the strength of afferent activities c_c for the two groups of excitatory inputs. During each MD period, the value of c_c is decreased for the deprived group by an amount of Δc_c, which represents the level of input deprivation. (B) The synaptic dynamics are examined for various values of Δc_c and c_f in response to MD. In the region represented as (B1), the competition between the groups does not occur (as in Fig. 2(B1)). In the region denoted as (B2), the competition occurs and the dominant group can be switched by MD (as in Fig. 2(B2)). In the region denoted as (B3), the competition takes place but the dominant group cannot be switched by MD (as in Fig. 2(B3)). (C) Examples of synaptic weight dynamics in response to MD for three cases of Δc_c (Δc_c=0.2 (C1), 0.3 (C2), or 0.4 (C3)) when c_f=0.6. Left column: the time courses of the average weights are shown for the two input groups. The vertical dashed lines in (C2) and (C3) show the timing at which the switching in the dominant group occurs during each MD period. Center and right columns: the weight distributions of both groups are represented by the black and red symbols, for the cases after the first MD (center; t=250,000 s) and the second MD (right; t=450,000 s). The line colors in (C) correspond to those in (A). The sensory experience of MD can be reflected into the weight distributions in (C2) and (C3), but not in (C1).

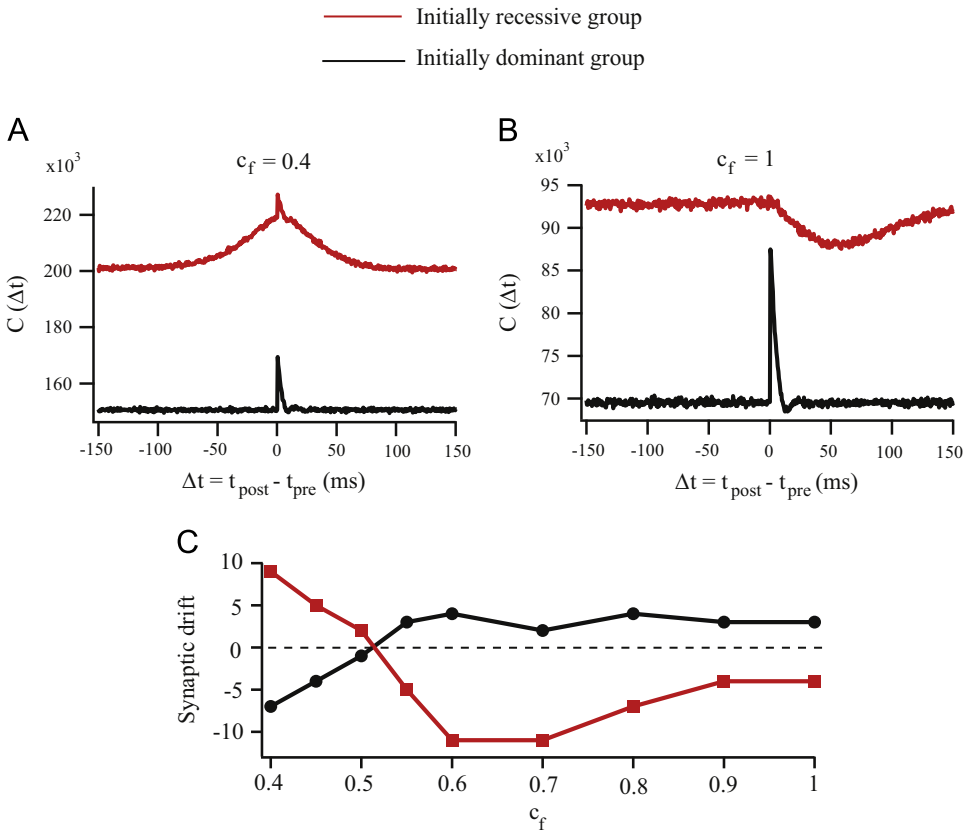

Fig. 4. (A and B) The correlation functions between the activity of each input group and the postsynaptic activity during the first 2000 s of the MD period. The black and red lines correspond to the input groups that are dominant and recessive, respectively, before the MD period. The inputs for the initially dominant group (black line) are deprived of afferent activities, by decreasing c_c to 0, during MD. The strength of feedforward inhibition is c_f=0.4 (A) and 1 (B). (C) The synaptic drift (i.e., the temporally averaged value of the rate of synaptic weight changes) for the initially dominant (black) and recessive (red) groups are plotted as function of c_f. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

between the pre- and postsynaptic activities through feedforward inhibition.

4. Discussion

In this study, we investigated a mechanism to both start and end the critical period of OD plasticity through feedforward GABA inhibition. We simulated a neuron model receiving correlated activities from two groups of inputs, and examined how the synaptic modification dynamics, in response to MD, can be regulated by feedforward inhibition. Based on the simulations, we propose a mechanism for the opening and closure of visual plasticity, as shown in Fig. 5. In the precritical period (Fig. 5(A)), due to a low level of feedforward inhibition, there does not exist competition between the inputs originating from different eyes. Thus, the two groups of inputs converge to the same weight distribution in the absence of MD, as in Fig. 2(B1), meaning that the synaptic pattern is monostable. In this case, the synaptic weights do not have an ability to reflect the sensory experience of MD. On the other hand, when the level of feedforward inhibition becomes greater than a threshold (Fig. 5(B)), the competitive interaction between the inputs from two eyes segregates them into dominant and recessive ones. In this case, the synaptic weight dynamics are bistable, because the synaptic patterns where one group is dominant and the other group is dominant are both stable, as depicted in Fig. 5(B1) and (B2). During the critical period, at which the feedforward inhibition is at a moderate level, which group becomes dominant depends on which group has recently received deprivation as in Fig. 2(B2).

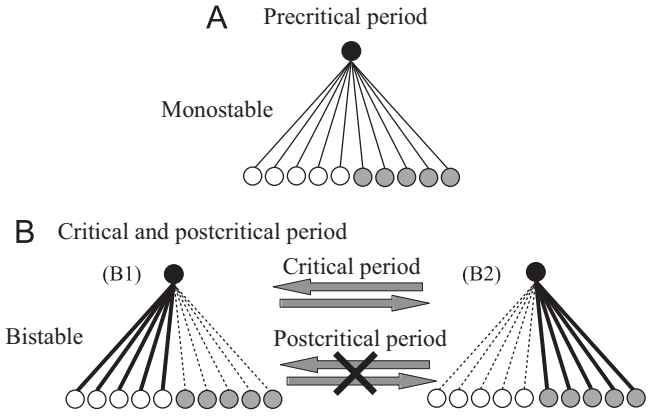

Fig. 5. Hypothesis of regulation of critical period plasticity by the competitive dynamics of synapses. The postsynaptic neuron (black circles) receives two groups of presynaptic inputs (white and gray circles), which are activated through the retinal cell activities of different eyes. (A) In the precritical period, due to a lack of competition between the inputs from two eyes, the two input groups have nearly the same average strength. Since the weight pattern is monostable, the sensory experience by MD cannot be embedded into the synaptic efficacies. (B) In the critical and postcritical period, stronger feedforward inhibition elicits competition between the inputs from two eyes, producing bistable synaptic patterns in (B1) and (B2). During the critical period, the switching between the two synaptic patterns occurs in response to MD, inducing experience-dependent OD plasticity. However, after the critical period, the switching cannot occur because of a too strong stability of each synaptic pattern, preventing OD plasticity.

Thus, the information about past sensory experience can be embedded into the synaptic efficacies, inducing OD plasticity. However, in the postcritical period, at which the feedforward

inhibition is very strong, each of the synaptic patterns becomes too stable to change by MD, as in Fig. 2(B3). Therefore, although the synaptic dynamics are bistable, the modulation of input stimuli by MD cannot control which group becomes dominant. Therefore, the ability of synapses to reflect earlier sensory experience disappears, closing the critical period of OD plasticity.

It should be noted that our model does not indicate that the absolute level of inhibition is the determinant of critical period plasticity. In our model, the ratio of the feedforward to total inhibitory currents, which is determined by c_f, plays a role in regulating OD plasticity. Thus, we consider that the change in the relative contribution of the feedforward pathway of inhibition, rather than the total inhibitory activities, may be important to control plasticity. This idea appears to be consistent with the fact that not all GABA circuits are involved in visual plasticity [7,23]. An experiment using a knockin mutation to α subunits suggest that the GABA circuits associated with α1-containing $GABA_A$ receptors can selectively induce OD plasticity [6]. In addition, given that many $GABA_A$ receptors including the α1 subunits are located at somatic synapses, which receive connections from parvalbumin (PV)-positive neurons [7,33], the localized GABA circuits mediated by PV interneurons could play a key role in OD plasticity. Since the PV cells are highly associated with the feedforward inhibition in the thalamocortical and intracortical circuits [34], it is conceivable that the contribution of feedforward inhibition is particularly important to regulate visual plasticity, as in our model.

Many studies suggested a role of activity-dependent competition in OD plasticity [1,20–22], as mentioned above. An important evidence for the involvement of competitive mechanism is that when the visions are deprived from both eyes at the same time (i.e., binocular deprivation (BD)), the OD histogram is nearly the same as that seen in normally reared animals and the cortical cell responses are also quite normal [1,22]. This implies that the effects of MD, which produce a bias in OD toward non-deprived eye, are not simply explained by a disuse of the deprived eye, but are attributable to the competitive interaction between the unbalanced inputs from two eyes. Our hypothesis may give an explanation for the requirement of competitive mechanism: the activity-dependent competition is necessary to produce bistable synaptic dynamics, as shown in Fig. 5(B). In addition, our model seems to be consistent with the fact that the cortical circuit is basically normal after BD, because fractions of the neurons having preferences for one and the other eyes (as in Fig. 5(B1) and (B2)) do not alter in the lack of unbalance between the inputs from two eyes. Furthermore, our hypothesis gives the following experimental prediction: when the strength of the deprivation of visual inputs by MD is controllable (for example, by using semi-transparent contact lens), the timing of the onset of critical period basically does not depend on the strength of input deprivation, whereas the timing of the closure of critical period strongly depends on it, as shown in Fig. 3(B). This is because the onset of the critical period depends on whether the bistable synaptic pattern exists, whereas its closure relies on the increased stability of synaptic patterns which counteracts the action of MD. The viewpoint of synaptic dynamics, including bistability, would be important to understand the mechanism of critical period and design future experiments.

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