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Competition, inhibition, and critical periods of cortical plasticity

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Abstract

It is well established that the developmental maturation of cortical inhibition just after eye opening is necessary for the opening of a critical period of experience-dependent ocular dominance plasticity. How inhibition accomplishes this, however, is not clear. Here I outline new hypotheses on the roles of somatic and dendritic inhibition in the opening and closure of critical periods, and their roles in the competitive processes therein.

Introduction

A great deal has been written about the interaction between excitatory and inhibitory neurons during so-called critical periods [1–7], which occur in early postnatal life when cortical circuitry begins receiving indirect input from the sensory epithelium. During critical periods, our interactions with the environment change the anatomy and physiology of our cortex, presumably improving our ability to survive in that environment. I use this opportunity to outline new hypotheses on how inhibition establishes the conditions necessary for competitive plasticity during these critical periods of cortical development.

Much of our understanding of how inhibition shapes critical period plasticity comes from studies of ocular dominance plasticity. In mammals with forward facing eyes, and particularly primates and carnivores, the overlapping regions of visual space viewed from each of the two eyes defines a binocular zone. Because the two eyes view this region from slightly different angles, the spatial offset between the retinal images is used by cortical neurons to compute information about the depth of objects in space – stereopsis. In carnivores and primates the binocular zone spans, roughly, the central 120–130 degrees of visual space. In mice, whose eyes are more laterally positioned, this overlap is far more limited, spanning only about the central 30–40 degrees of visual space. Notably, the degree of binocular integration in cortex is determined by the quality of vision to each eye. Ocular dominance plasticity is this use-dependent competition between the two eyes to drive cortical responses.

This form of experience-dependent plasticity is not solely an abstraction for understanding brain function. More than a century of clinical studies have concluded that children who

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develop discordant vision or a cataract in one eye during a critical period suffer from a permanent degradation of vision through that eye because the penalizes and eliminates input from the ‘lazy’ eye and rewards and expands inputs from the ‘good’ eye [8].

Main text of review

1. Opening critical periods: getting the ipsilateral eye into the ring

Inhibition is needed to “open” critical periods of cortical plasticity [9,10]. Somatic inhibition, orchestrated by densely connected fast-spiking, parvalbumin-expressing basket cells [11], often referred to as PV cells, has been most thoroughly vetted [3]. However, recent results suggest that there is nothing special about somatic inhibition per-se because transplantation of embryonic nascent interneurons that differentiate into somatostatin-expressing interneurons also re-activates ocular dominance plasticity [12,13]. That a threshold of inhibition is necessary for critical period plasticity is clear; what this inhibition is doing is not. I propose that inhibition does something very simple: guided by visual experience, the maturation of inhibition establishes a substrate for competitive ocular plasticity by strengthening cortical responses to the ipsilateral eye.

In both cats and mice, the contralateral eye almost completely dominates cortical responses just after eye opening [14,15]. At this juncture, the contralateral eye has only a very weak competitor, and thus competitive plasticity cannot occur. With subsequent visual experience, cortical responses slowly strengthen to the ipsilateral eye, achieving adult strength at the onset of the critical period for ocular dominance plasticity [14,15]. In contrast, vision does *not* appear necessary for maturation of cortical responses to the contralateral eye. Thus, vision may to be acting selectively to mature ipsilateral eye responses. This distinct impact of vision on ipsilateral eye responses is evident not only in cats and mice, but also primates [14–18]. These studies reveal that the opening of the critical period is a conserved process that begins when the ipsilateral eye strengthens.

This hypothesis is derived from intrinsic imaging experiments, and is distinct from the predominant model where the visual cortex of immature mammals is roughly equally innervated by overlapping thalamic inputs from the two eyes that ultimately segregate into ocular dominance columns through Hebbian-like mechanisms [19–21]. The most parsimonious reconciliation of the anatomy with the weak response to the ipsilateral eye is that thalamic axons from both eyes grow into the cortex very early in life, but the formation of synapses by ipsilateral eye inputs requires visual experience.

A major unresolved question emergent from my hypothesis is how does a functionally weak ipsilateral eye input gain enough strength to compete if the contralateral eye already dominates the cortex? For the ipsilateral eye to strengthen through a process akin to spike timing-dependent synaptic potentiation, evoked ipsilateral eye cortical responses would need to be temporally correlated with evoked contralateral eye cortical responses. Michael Crair and colleagues identified this problem [14], and they offered the idea that perhaps “…the ipsilateral eye may just go along for the ride” during the formation of functional responses common to the two eyes, like orientation and binocularity. In support of this view, binocular vision provides temporal correlation. However, there are good reasons to believe that

something other than spike timing-dependent plasticity (STDP) is at work at strengthening ipsilateral eye responses [22]. First, STDP appears to *depress*, rather than strengthen connections between layer 4 neurons between the time of eye opening and the onset of the critical period [23]. Second, evoked firing rates of pyramidal neurons are adult-like during the pre-critical period [24]; in BCM and homeostatic models of plasticity [25,26], this high firing rate would make it difficult to strengthen addition inputs onto these neurons. How then, might the ipsilateral eye gain cortical synaptic strength through these mechanisms?

Earlier it was noted that the abundance of evidence supports a role for inhibition in opening the critical period. Visual experience strongly impacts the development of PV cell firing rates, but not excitatory neurons [24], and PV cells receive strong, direct input from thalamo-cortical axons [27]. One possible scenario is that, since contralateral eye inputs are dominant during the pre-critical period, the maturation of inhibition by vision has an initially greater impact on decreasing contralateral eye evoked firing rates [28]. This drop in excitatory firing rates would lower the LTP threshold in BCM and homeostatic models, enabling the relatively weaker ipsilateral eye inputs to strengthen where correlated with contralateral eye responses. An alternative model is that inhibition is acting to suppress spontaneous activity, thereby enhancing the influence of visually evoked activity in shaping cortical circuitry [29–31], perhaps by enhancing the coincidence of binocular inputs [32]. Lastly, it is quite possible that inhibition is directly influencing dendritic integration of subthreshold inputs from the two eyes.

The hypothesis that ocular dominance plasticity emerges only when the ipsilateral eye matures is testable. Administration of the use-dependent GABA positive allosteric modulator diazepam accelerates the opening of the critical period [33]. Diazepam should also act to accelerate the maturation of ipsilateral eye cortical responses preferentially, thereby pharmacologically bypassing the normal first step of inhibitory maturation by vision. Similarly, over-expression of brain-derived neurotrophic factor, another route to a precocious critical period [34,35], would also be expected to uncouple maturation of cortical responses to the ipsilateral eye from visual experience.

2. Competitive plasticity: the opening bell

Once the two eyes are able to strongly drive cortical responses and the critical period has opened, penalizing one eye's ability to drive cortical responses results in ocular dominance plasticity. The loss of cortical responsiveness to the deprived eye appears to require a very rapid decrease in cortical inhibition [36]. That is, once established, cortical inhibition appears to hinder competitive plasticity of excitatory inputs [37].

How would a rapid disinhibition of pyramidal neurons promote ocular dominance plasticity? The most immediate effect of monocular deprivation is a drop in the firing rates of binocular cortical neurons [36]. This occurs simply because these neurons are accustomed to being driven by coincident input from the two eyes but are now only being driven by the inputs from one eye. This drop in activity is actually a problem. With amplyopia, the cortex loses inputs from the penalized eye. Yet in models of plasticity based on firing rates to target neurons [25,26,38], a drop in the activity of the target cell would attenuate decreased responsiveness to the closed eye or even *strengthen* remaining inputs to return firing rates

back to normal levels. The solution to this problem is to restore the firing rates of cortical pyramidal neurons to normal levels – levels they experience during normal binocular vision [36].

The most immediate change in cortical responsiveness after monocular deprivation is a binocular disinhibition of pyramidal neurons resulting from a rapid loss of excitatory input to PV cells. When this occurs, vision no longer drives strong inhibitory responses, and the evoked firing rates of excitatory neurons increase back to normal levels, despite continued monocular deprivation [36,39]. Two goals are achieved by the restoration of evoked firing rates. First, there is an amplification of the discordant vision between the two eyes, enhancing competition. Second, the resurgence of evoked firing rates decreases the threshold for synaptic depression, promoting the loss of weakly driven deprived eye inputs. Note that in this model, it is a loss of feed-forward excitation, rather than the recruitment of feedback neuromodulation [40,41], as occurs in adulthood, that underlies disinhibition.

PV cell-mediated somatic disinhibition is not likely to be instructive in ocular dominance plasticity. Instead, the outcome of competitive plasticity must be decided in the dendrites of pyramidal neurons.

3. The emergence of ocular dominance shifts: scoring points in cortex

Subthreshold, dendritic inhibition, driven by somatostatin-expressing interneurons [42,43] is more likely to shift the outcome of competitive synaptic plasticity than somatic inhibition. Two really clever and informative studies identifying subthreshold somatic integration as key to competitive ocular dominance plasticity came from Rafi Malach [44] and Laurence Mioche [45]. More recent experiments provide definitive evidence that synaptic plasticity in vivo is readily achieved in the absence of back-propagating action potentials [46], which are essential in models of experience-dependent plasticity invoking STDP.

The majority of excitatory inputs to pyramidal neurons are made onto dendritic spines, the postsynaptic structures protruding at thousands of sites along the apical and basal dendrites of pyramidal neurons [47]. Dendritic spines are known to rapidly grow or retract in response to changes in sensory input to cortex [48–50]. Somatostatin-expressing interneurons innervate the dendrites of pyramidal cells, and influence local dendritic integration of synaptic currents [51,52]. This local inhibition likely exerts a potent influence on the outcome of synaptic competition.

A growing body of work is pointing at SOM cells as the ultimate target of neuromodulation in adult cortex. SOM cells are inhibited by VIP cells [53,54], which in turn receive strong input from basal forebrain cholinergic projections and likely noradrenergic projections from locus coeruleus as well [55]. Furthermore, there is strong evidence that feedback excitation from cingulate cortex preferentially targets inhibitory neurons in primary visual cortex [56]. Thus, in the adult cortex, feedback projections act to inhibit SOM cells, thereby reducing inhibition in dendrites. Unpublished observations from my own laboratory indicate that these connections either do not yet exist or are quite weak during the critical period, suggesting that, again, feed-forward excitation dominates plasticity at this stage of development.

The interaction between SOM cells and neuromodulation, and the maturation of this circuitry, is intriguing in this context because it is well established that ocular dominance plasticity requires neuromodulation [57,58]. How subthreshold dendritic integration impacts the outcome of ocular synaptic competition, and what role neuromodulation plays in this during the critical period, are questions ripe for attention.

4. Closure of the critical period: the final bell

Strong somatic inhibition impairs ocular dominance plasticity. I propose that the closure of the critical period occurs when feed-forward excitatory inputs to PV cells (and possibly SOM cells) are effectively cemented in place, perhaps by the maturation of perineural networks of extracellular matrix glycoproteins [2,59,60]. Indeed, in mice that lack fully formed perineural nets, the critical period does not close [61]. Many studies have “reopened” or vastly extended critical periods of plasticity [12,13,57,59,62,63]. It is likely that all of these studies are accomplishing the same thing: re-establishing the anatomical plasticity of excitatory input to PV cells, as occurs in the juvenile cortex. By doing so, closing one eye once again causes the rapid loss of these inputs, thereby decreasing PV cell activity, disinhibiting pyramidal cells, restoring binocular-like firing rates in the face of unilateral vision, and permitting the competitive loss of deprived eye inputs.

This view is readily tested by mapping excitatory input to PV cells before and after monocular deprivation using glutamate uncaging via laser stimulation [36].

Conclusions

a. Opening the critical period: Visual experience drives the maturation of PV cell-mediated, and possibly SOM-mediated cortical inhibition. This, in turn, facilitates the strengthening of weak ipsilateral eye inputs onto neurons already dominated by the contralateral eye, thereby establishing a substrate for competitive ocular dominance plasticity.

b. Competition: PV cell circuitry is sensitive to visual experience during the critical period. Closing an eye results in a rapid elimination of excitatory input to PV cells. This drops the firing rate of PV cells. The net result is a drop in somatic inhibition of local pyramidal neurons, which now fire more action potentials. Monocular vision becomes as strong a driving force as binocular vision was prior to deprivation, reducing the threshold for synapse weakening/elimination and promoting the elimination of deprived eye inputs. SOM cell activity, strongly driven by feed-forward excitation at this stage of development, also drops, amplifying subthreshold differences in each eye’s inputs to dendrites.

c. Closure: In adults, PV cells no longer lose excitatory inputs following monocular deprivation. Disinhibition does not occur after monocular deprivation. Thus, monocular vision is only half as effective at driving cortical responses as binocular vision. Because firing rates of cortical neurons remain low the threshold for synaptic weakening increases and deprived eye inputs are not eliminated. Neuromodulatory feedback inputs to VIP cells mature, and now become the dominant driver of cortical disinhibition and excitatory plasticity.

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Highlights

- Experience-dependent maturation of inhibition strengthens ipsilateral eye inputs
- Once established, inhibition is detrimental to competitive plasticity
- Disinhibition promotes synaptic depression and ocular dominance plasticity
- Feed-forward input to fast-spiking interneurons gates critical period plasticity