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CHAPTER 12

The age of plasticity: developmental regulation of synaptic plasticity in neocortical microcircuits

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Abstract: Proper wiring of neural circuits during development depends on both molecular cues that guide connectivity and activity-dependent mechanisms that use patterned activation to adjust the strength and number of synaptic connections. In this chapter, we discuss some of the plasticity mechanisms underlying the experience-dependent rewiring of visual cortical microcircuits focusing on layer 4 of rat primary visual cortex. The microcircuit in layer 4 has the ability to regulate its excitability by shifting the balance between excitatory and inhibitory synaptic transmission in an experience-dependent manner. Early in postnatal development (shortly after eye opening), visual deprivation activates several forms of homeostatic plasticity that cooperate to adjust layer 4 excitability to compensate for reduced sensory drive. In contrast, during the classical sensitive period for rodent visual system plasticity, this homeostatic response is replaced by mechanisms that reduce the responsiveness of deprived cortex. We discuss this developmentally regulated switch in plasticity within layer 4 and how this might depend on the maturation of excitatory and inhibitory monosynaptic connections. Based on our published data, we propose inhibitory plasticity as an important player in circuit refinement that can contribute both to the compensatory forms of circuit plasticity in the early stages of development and to the pathological loss of function induced by visual deprivation during the critical period.

Keywords: critical period; synaptic plasticity; homeostatic; inhibitory interneurons; visual cortex

It is known that neocortical circuits in the rodent undergo a major period of maturation in the few weeks after birth. Circuit formation initially occurs under control of molecular cues (Tessier-Lavigne and Goodman, 1996; Charron and Tessier-Lavigne, 2005) which guide migration of the various neuronal types to the correct layers (Nadarajah et al., 2001, 2003), and also guide axons to form synaptic contacts with the correct targets (Goodman and Shatz, 1993; Bishop et al., 2000, 2003). During this phase a very large number of synapses are formed (Rakic et al., 1986), some of which are active very early in development (Rumpel et al., 1998). The initial patterns of connectivity that are set up through these molecular processes are not fully functional, but must be refined in a use-dependent manner. This process of refinement and maturation is activity-dependent and is thought to be shaped in large part by changes in synaptic strength and connectivity (Katz and Shatz, 1996; Catalano and Shatz, 1998; Inan and Crair, 2007). Many forms of

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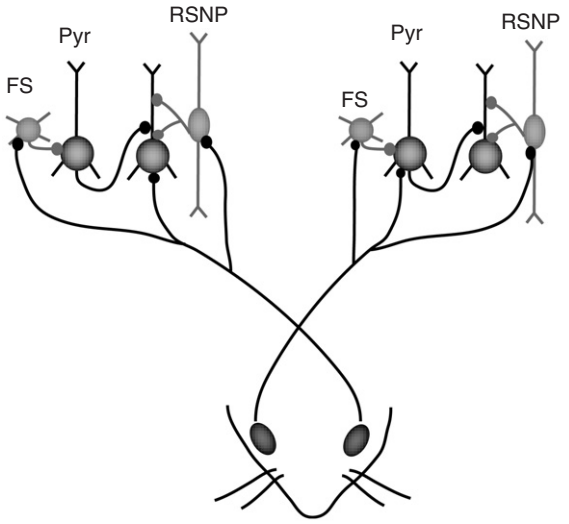

Fig. 1. Layer 4 in rat primary visual cortex. The sketch represents the neuron types and their synaptic connections in rat primary visual cortex. Pyr, star pyramidal neurons; FS, small GABAergic basket cells with multipolar morphology; RSNP, bipolar GABAergic neurons whose firing shows frequency adaptation in response to depolarizing current steps. The extent of the direct thalamic drive onto both types of inhibitory neurons is unknown; however, both are likely to receive feedforward input from thalamic afferents (Hajós et al., 1997; Sun et al., 2006).

plasticity are expressed at cortical synapses (Turrigiano et al., 1998; Maffei et al., 2004, 2006; Malenka and Bear, 2004), but we still know little about when and how these mechanisms are engaged during development or in response to particular forms of sensory experience. Here we will review the development and plasticity of synaptic transmission between excitatory and inhibitory cortical neurons, focusing on recent work from our lab on the microcircuitry in layer 4 of rat primary visual cortex (Fig. 1).

Plasticity and circuit excitability

One of the main principles of circuit wiring is captured by the phrase "cells that fire together wire together," meaning that synapses between excitatory neurons whose firing is correlated will become stronger and those between neurons whose firing is uncorrelated will become weaker (Brown et al., 1990). This principle leads to the maintenance of strong inputs and the loss of weak inputs. These correlation-based forms of synaptic plasticity are known as "Hebbian" after Donald Hebb, and include several forms of long-term potentiation (LTP) and depression (LTD). Besides being involved in circuit wiring and maturation, these long-lasting modifications of synaptic strength are thought to be a major substrate for learning and memory (Palm, 1982; Malenka and Bear, 2004).

It has been suggested that LTP and LTD might be destabilizing for the neural circuit because increased synaptic strength between two excitatory neurons will increase the correlation between them, which will further strengthen the connection in a positive feedback cycle. On the other hand, if LTD is induced, the correlation between two neurons will be reduced and drive a further reduction in synaptic strength, potentially leading to loss of synaptic contacts. In the absence of mechanisms designed to stabilize network excitability, LTP can thus initiate a positive feedback loop that will lead to excessive excitability (Abbott and Nelson, 2000; Turrigiano and Nelson, 2000). Under these conditions, neurons are bound to respond strongly even to spontaneous background activity and will become unable to discriminate meaningful differences in the structure of incoming signals. Despite the need for Hebbian synaptic modification for learning, memory, and circuit wiring, it is very important that the network "gain" (the relationship between input and output magnitude) is maintained. Homeostatic forms of plasticity have been proposed to contribute to neural circuit stability and function by endowing neurons with the ability to readjust their excitability globally in response to changes in network activity (Turrigiano, 1999). Homeostatic changes are thought to preserve the relative differences in strength between excitatory synaptic inputs previously induced by Hebbian plasticity, but allow neurons to bring their excitability back into an optimal working range, thus maintaining their ability to discriminate fine differences in the structure of incoming signals (Turrigiano and Nelson, 2004). Synaptic scaling is one of these forms of plasticity. It globally scales up or down the strength of excitatory synapses onto one neuron by the same multiplicative factor depending on the level of

network activity (Turrigiano et al., 1998; Watt et al., 2000). It has been shown to act by regulating the number of glutamatergic receptors on the post-synaptic terminals while not affecting the probability of neurotransmitter release (Turrigiano et al., 1998; Wierenga et al., 2005). Neurons have also been shown to adjust their excitability by modulating their voltage-dependent conductance (Desai et al., 1999; Golowasch et al., 1999; Desai, 2003).

All of these forms of plasticity have been shown to occur at excitatory synapses; however, neuronal circuits also contain inhibitory interneurons with a variety of morphologies and firing properties (Kawaguchi and Kubota, 1997). Evidence is now accumulating for their role in circuit development (Hollrigel et al., 1998; Cohen et al., 2001) and for inhibitory synapses being plastic (Komatsu and Iwakiri, 1993; Holmgren and Zilberter, 2001; Maffei et al., 2006), properties that would make them important contributors to circuit refinement and function. The combination of changes in synaptic strength and excitability for both excitatory and inhibitory neurons would endow neural networks with a wide variety of strategies for information storage and experience-dependent rewiring.

Plasticity in the visual system

Visual cortex is one of the best-studied models for activity-dependent circuit wiring and experience-dependent plasticity. Most mammals are born with their eyes closed, and therefore the initial activity-dependent wiring events are driven by spontaneous retinal activity (Del Rio and Feller, 2006). After eye opening, however, patterned visual input is thought to be the main drive leading to maturation of the visual cortical circuit (Tagawa et al., 2005; Smith and Trachtenberg, 2007). Impairment of visual experience for long periods of time can retard the maturation of visual cortical circuitry and lead to irreversible loss of function (Blasdel and Pettigrew, 1978). However, the forms of plasticity that contribute to these changes are not fully understood. Both Hebbian and homeostatic forms of plasticity have been implicated in the changes induced by altered visual experience during development (Rittenhouse et al., 1999; Desai et al., 2002). Most of what is known about the effect of experience in visual cortex comes from experiments measuring neuronal firing in response to visual stimulation in anesthetized animals which were deprived of visual input by monocular deprivation (MD) during a developmental period known as the "critical period" for visual cortical plasticity. The critical period is a time when neurons in binocular cortex show a shift in ocular dominance toward the open eye in response to deprivation of the other eye (Hubel and Wiesel, 1970). The shift is thought to occur because the neurons activated by the deprived eye respond to visual flashes with lower firing rates than those driven by the open eye (Mioche and Singer, 1989; Frenkel and Bear, 2004). The interpretation proposed to explain this loss of visual responsiveness is that monosynaptic LTD had been induced at thalamocortical and intracortical excitatory synapses onto neurons activated by the deprived eye (Rittenhouse et al., 1999; Crozier et al., 2007). Such reduction of synaptic strength would result in lower firing rates and decreased visual responsiveness (Mioche and Singer 1989; Frenkel and Bear 2004).

The critical period has traditionally been considered to be the moment in cortical development when synapses are most plastic and are most strongly modified by experience (Hubel and Wiesel, 1970). Recently published data has provided new evidence for the ability of visual cortical synapses to be very plastic also during what is often referred to as the "pre-critical" period, which starts right at eye opening (in the rat at p14) (Maffei et al., 2004; Feller and Scanziani, 2005; Smith and Trachtenberg, 2007). The experience-dependent rewiring during these stages involve quite different sets of synaptic modifications and raise a new series of questions about developmental regulation of multiple forms of synaptic plasticity and their role in cortical function (Maffei et al., 2004, 2006).

Experience-dependent plasticity in the absence of competition

The majority of studies on visual cortical plasticity were designed to investigate the development of

ocular dominance columns and their plasticity in binocular cortex, where inputs from the two eyes compete with each other during development (Hubel and Wiesel, 1970; Rittenhouse et al., 1999; Smith and Trachtenberg, 2007). Circuit refinement in binocular cortex likely involves both competitive and non-competitive synaptic plasticity mechanisms, but it is difficult to tease apart their relative contribution. The effects of experience on microcircuits in monocular cortex of rodents, where competitive mechanisms are less pronounced, have recently been undertaken by us (Maffei et al., 2004, 2006). Our analysis is focused on the effect of development and sensory deprivation at excitatory and inhibitory synapses in the monocular region of rat visual cortex. Rat primary visual cortex is composed of a small binocular visual area and a much larger monocular portion driven only by the contralateral eye. MD affects only the circuit contralateral to the closed eye, leaving the other hemisphere unaffected. This is the ideal preparation to directly compare deprived and control hemispheres within the same animal, and to probe the contribution of non-competitive plasticity mechanisms in circuit refinement.

One of our major findings was that sensory deprivation induces dramatic microcircuit rewiring in monocular cortex, leading to pronounced changes in network excitability. This is achieved by readjusting the balance of excitation and inhibition in the deprived microcircuit through both Hebbian and homeostatic forms of plasticity. The effects of visual experience on the cortical circuit are very complex and developmentally regulated: different forms of plasticity were induced depending on the age of the animal at the time of deprivation (Maffei et al., 2004, 2006). Below, we discuss in turn the changes induced by visual deprivation during the pre-critical period (between eye opening and postnatal day 18) and during the critical period (after about postnatal day 19).

Pre-critical period plasticity within layer 4

To study the effect of experience-dependent plasticity during the pre-critical period, we sutured one eye (MD) between p14 (just before eye opening) and p17 (before the opening of the classical critical period), and obtained patch clamp recordings from coronal slices containing monocular cortex (data are summarized in Figs. 2 and 3).

To determine the specific synapses involved in regulating the balance between excitation and inhibition, we performed paired recordings between visually identified neurons. Four neurons were recorded simultaneously and the presence of synaptic connections between them was assessed by firing putative presynaptic neurons with precisely timed depolarizing steps in current clamp and recording the putative postsynaptic neurons in voltage clamp. Quadruple patch clamp allows us to test 12 putative connections at a time, increasing the probability of finding connected pairs. Connection probability was calculated measuring the ratio of found versus tested pairs (Figs. 2 and 3; CP). In addition, we measured the probability that two neurons were reciprocally connected by measuring the ration of reciprocally connected pairs versus the total number of pairs we found for any specific connection tested (Figs. 2 and 3; RCP).

MD induced a doubling in amplitude and connection probability for monosynaptic connections between star pyramidal neurons (Fig. 2b; p17, EPSC; layer 4 pyramidal neurons in V1 are named star pyramids because of their lack of complex arborization of their apical dendrite). Detailed analysis of synaptic responses showed no significant changes in the coefficient of variation (Fig. 2c; p17, CV) and failure rates (Fig. 2c; p17, % failure), parameters that have been shown to correlate with changes in release probability at the presynaptic terminal, suggesting that MD induces increased EPSC amplitude mostly through changes at the postsynaptic terminals. A small, but significant change was also observed in the steady-state short-term depression of EPSC amplitude in response to trains of presynaptic spikes at 20 Hz, suggesting a small presynaptic change that would not be enough to explain the large change in EPSC amplitude (Maffei et al., 2004; Fig. 2c; p17, SS STD). The data are consistent with previous published results showing that MD induces synaptic scaling of miniature EPSC (mEPSC) in

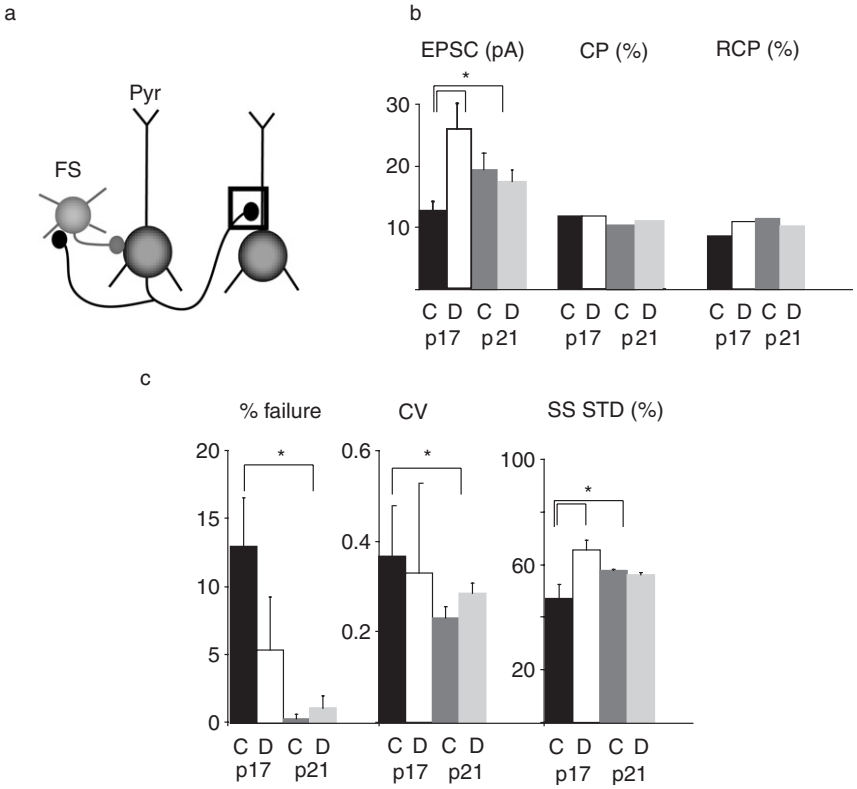

Fig. 2. Development and plasticity of star pyramidal connections (diagrammed in a). The box indicates the synapse examined in the rest of the plots. (b) Effect of development and experience-dependent plasticity on amplitude (EPSC), connection probability (CP), and recurrent connectivity (RCP) for monosynaptic connections between star pyramidal neurons in control (C) and deprived (D) conditions at p17 (black bar for control: C; white bar for deprived: D) and at p21 (dark gray bar for control: C; light gray bar for deprived: D). (c) Bar plot showing effects of development and monocular deprivation on failure rates (% failure), coefficient of variation (CV), and steady-state short-term depression (SS STD) of EPSC from connected pairs of star pyramids [p17 (black bars for control: C; white bars for deprived: D); p21 (dark gray bars for control: C; light gray bars for deprived: D)]. Data are presented as average and standard error. The asterisks mark significant changes.

star pyramids from layer 4 during the pre-critical period (Desai et al., 2002).

Changes in inhibitory synaptic transmission onto star pyramids also contributed to the shift in the excitation/inhibition balance (Fig. 3; p17). Two separate populations of inhibitory neurons provide most inhibitory drive in layer 4 and they both were affected by MD. One of them is composed of regular-spiking non-pyramidal neurons (RSNP; see Fig. 1) which show regular firing pattern in response to depolarizing current steps and have bipolar morphology. The global effect of MD on these inhibitory synapses was to maintain the overall level of inhibition by reducing their connection probability onto star pyramids to half of control and increasing the strength of inhibitory postsynaptic currents without changes in failure rates and coefficient of variation (CV) (Maffei et al., 2004). A very different set of changes was observed when we measured strength and synaptic properties for fast-spiking (FS) inhibitory interneurons (Fig. 3a–c; p17). These interneurons have multipolar basket-like morphology and show fast non-adapting firing in response to depolarizing current steps. The strength of their IPSC onto star pyramids was significantly reduced by MD with no changes in connection probability (Fig. 3b; p17, IPSC, CP). CV and failure rates were significantly

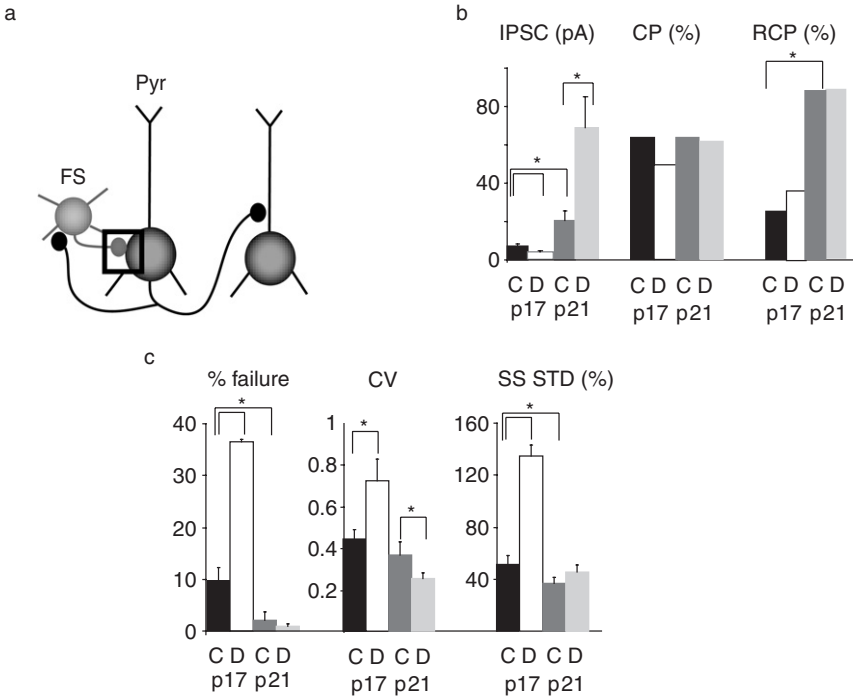

Fig. 3. Development and plasticity of inhibitory synapses between fast-spiking (FS) and star pyramidal neurons (diagrammed in a). (b) Data summarizing developmental and experience-dependent changes for amplitude (IPSC), connection probability (CP), and recurrent connectivity (RCP) for FS to star pyramidal neurons connections in control (C, black bars) and deprived (D, white bars) conditions at p17 and p21 (dark gray bar for control: C; light gray bar for deprived: D). (c) Bar plot showing changes in failure rates (% failure), coefficient of variation (CV), and steady-state short-term depression (SS STD) for IPSC measured from FS to star pyramids connected pairs [p17 (black bars for control: C; white bars for deprived: D); p21 (dark gray bars for control: C; light gray bars for deprived: D)]. Data are presented as average and standard error. The asterisks mark significant changes.

increased, suggesting a decrease in presynaptic release probability as the main mechanism for the reduction in IPSC amplitude (Fig. 3c; p17, CV, % failure). One striking effect of MD at these synapses was a switch in short-term plasticity: they showed depression in response to trains of presynaptic spikes at 20 Hz in the control hemisphere, but became strongly facilitating in response to the same trains of stimulation in the deprived hemisphere so that the steady-state IPSC amplitude in the train was not significantly different between control and deprived conditions (Maffei et al., 2004; Fig. 3c; p17, SS STD). One possible functional consequence of these changes is that, while at low levels of network excitability weak inhibition would boost the excitability of the layer 4 microcircuit, when network excitability becomes too high a facilitating FS to star pyramid IPSC will recruit additional inhibition and prevent runaway excitation from completely destabilizing it. The global effect of the deprivation on the layer 4 circuit at this developmental stage was to increase the excitability of the local microcircuit. This occurred through a shift in the balance between excitatory and inhibitory inputs onto star pyramids to favor excitation, therefore increasing spontaneous firing rates (Maffei et al., 2004; Fig. 4; left panel).

The complex set of changes we observed in layer 4 microcircuit appears to be a compensatory (or homeostatic) response. It contributes to maintaining network function in the face of reduced sensory drive and is mediated by the induction of specific forms of plasticity at different synapse depending on the role each of them plays within the microcircuit. In our experimental condition,

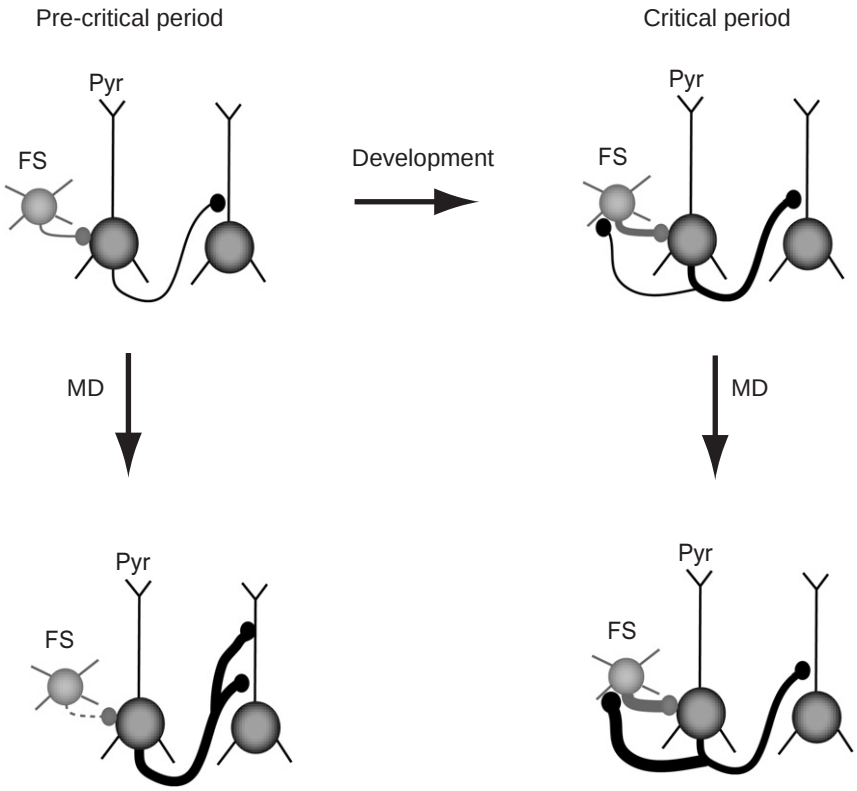

Fig. 4. Summary showing the significant changes induced by development and experience-dependent plasticity at excitatory and inhibitory synapses composing the cortical microcircuit in layer 4 of rat primary visual cortex.

neurons from the deprived hemisphere have never been primed by visual stimulation because MD began before eye opening. Homeostatic plasticity might allow the layer 4 microcircuit to remain in a functional, "receptive" state while waiting to be activated by sensory input.

An alternative interpretation proposed to explain the effects of deprivation, which begun before eye opening, is that visual deprivation prevents the maturation of both excitatory and inhibitory circuits in the deprived hemisphere, maintaining it in an underdeveloped state (Blasdel and Pettigrew, 1978; Bartoletti et al., 2004). We will discuss this hypothesis in the next paragraphs where new evidence for developmental changes in layer 4 microcircuit will be presented together with experience-dependent changes. What remains clear is that contrary to what has traditionally been thought, the pre-critical period is a very plastic phase of development when the basis for proper circuit wiring and plasticity are being set. Furthermore, experience dramatically affects circuit wiring and plasticity even in the absence of competition between inputs from the two eyes, suggesting that some of the early events of sensory-dependent rewiring might be needed to adjust the balance between excitation and inhibition of the deprived neurons so that the events triggered by competition may take place.

Developmental changes in synaptic properties within cortical layer 4

Most of the published data on experience-dependent visual system plasticity has found a loss of visual responsiveness in vivo in neurons activated by the deprived eye. This is in apparent contrast with our

data on early deprivation in layer 4, where MD increases excitability and thus would be expected to increase visual responsiveness. This discrepancy is likely because most visual deprivation studies have been conducted later in life, during the classical critical period for ocular dominance plasticity, whereas our experiments were performed during the pre-critical period (Mioche and Singer, 1989; Frenkel and Bear, 2004; Maffei et al., 2004). If there are developmentally regulated changes in connectivity, synaptic strength, and synaptic plasticity within the microcircuit in layer 4, then visual deprivation may have very different effects depending on when it is performed during development. The classically defined critical period is the time during development in which a shift in ocular dominance is observed in binocular cortex in many mammals in response to monocular alteration of visual inputs. In the rat, it begins around p18 and ends around p45 (Fagiolini et al., 1994). There are just a few days between eye opening and the beginning of the critical period, but such short period of visual experience during a very plastic moment in visual cortical development might produce maturational changes in the cortical microcircuit, which might then induce a different pattern of rewiring in response to MD.

To examine developmental changes in layer 4 microcircuitry between the pre-critical and critical period, we compared strength and connectivity of excitatory and inhibitory synapses in layer 4 taken in control rats at p17 (end of pre-critical period) and at p21 (beginning of critical period). These few days were sufficient to dramatically alter synaptic strength and connectivity in this cortical layer. Monosynaptic connection between star pyramids more than doubled in amplitude (Fig. 2b; EPSC, p21: 251% of p17; $p<0.05$) and their CV (Fig. 2c; CV, p21: 64% of p17; $p<0.006$) and failure rates decreased significantly (Fig. 2c; % failures, p21: $2.00\pm1.73\%$, p17: $9.72\pm2.45\%$; $p<0.006$), while their connection probability and the probability of finding recurrent connections remained unchanged (Fig. 2b; CP and RCP; p21: 79 out of 739, 10.7%; p17: 25 out of 236, 10.6%). Excitatory synapses therefore became stronger and more reliable as presynaptic release probability increases (Maffei et al., 2004, 2006; Fig. 2; p17, p21).

What are the mechanisms underlying these developmental changes in synaptic strength? The increased strength of EPSCs seems to recapitulate the effect of MD before eye opening. However, the mechanisms through which the increase in EPSC amplitude is achieved during normal development and in response to visual deprivation are fundamentally different: the developmental change appears to be driven by presynaptic changes (such as increased release probability), while MD induces postsynaptic changes that closely resemble synaptic scaling (Turrigiano et al., 1998; Desai et al., 2002). LTP of some excitatory synapses in neocortex has been shown to depend on presynaptic mechanisms (Hardingham et al., 2007), suggesting that this developmental strengthening could be due to a presynaptic form of LTP. Furthermore, the increase in connection probability between pyramidal neurons after MD might be due to an activity-dependent increase in formation of new connections or the prevention of visually driven pruning that might normally occur between p14 and p17. Since connection probability does not get reduced developmentally between p17 and p21 (Fig. 2b; CP and RCP, p17, p21), the pruning idea seems less likely, although further experiments are needed to measure connection probability at these synapses before eye opening in order to confirm this hypothesis.

In addition to developmental changes at excitatory synapses, dramatic changes in connectivity and synaptic strength were observed also at inhibitory synapses between FS neurons and star pyramids between p17 and p21 (Fig. 3a–c; p17, p21). There was a threefold increase in IPSC amplitude (Fig. 3b; IPSC, p21: 282.1% of p17, $p<0.01$) without any significant changes in CV, failure rates, or steady-state depression (Fig. 3c; $p<0.32$, $p<0.76$, $p<0.15$; Fig. 2; p17, p21). One of the most striking changes in the inhibitory feedback loop between FS neurons and star pyramids during these few days of development is a fourfold higher chance of finding recurrent connections from star pyramids back onto FS neurons (Fig. 3b; RCP). At p17, these connections would occur for only 28.5% of the FS to star pyramid pairs, whereas at p21 they were found in 82.3% of the pairs found (Fig. 3b; RCP, p17, p21; $p<0.01$ χ^2),

while their strength was not changed (p21: 19.9±8.3 pA; p17: 15.4±4.8 pA; $p=0.48$). FS neurons have been shown to receive direct thalamic drive. Our developmental data on connection probability also show that by the beginning of the critical period this population of inhibitory interneurons receives a strong recurrent excitatory drive within layer 4 (Fig. 4). The increase in amplitude and connectivity of the inhibitory feedback loop between FS neurons and star pyramids is consistent with recent data suggesting that visual stimulation triggers the maturation of GABAergic synapses (Fagiolini and Hensch, 2000). The authors in fact suggest that the maturation of the inhibitory circuit determines the closure of the critical period for visual cortical plasticity; moreover, they indicate the synapse between FS and star pyramidal neurons as the one involved in determining the duration of this plastic period (Katagiri et al., 2007).

As previously mentioned, one of the hypotheses proposed to explain the effects of MD initiated before eye opening is that visual cortical circuit is maintained in an immature state. In light of our data about cortical circuit rewiring during development and after MD, this hypothesis does not seem to be valid. In fact excitatory synapses increase in strength, recapitulating one of the changes driven by development at these synapses, but on top of this their recurrent connectivity is also increased. The increase in connectivity seems to be specifically dependent on decreased visual drive because connection probability does not change during development. Moreover, inhibitory synapses are modified quite differently by development and by visual deprivation, suggesting that the changes in the inhibitory circuit depend on the role that specific types of interneurons play in layer 4 microcircuit. The visual input sets in motion a very complex set of changes in synaptic strength and connectivity at excitatory and inhibitory synapses that are likely to contribute to the maturation of cortical microcircuits. Instead of freezing the cortical circuit in an immature state, the deprivation of sensory drive induces a unique set of experience-dependent changes that contribute to rewire the microcircuit in layer 4.

Critical period plasticity within cortical layer 4

Over the past 50 years, it was proposed that changes at the level of the cortical excitatory and inhibitory circuits might determine the complex set of events underlying experience-dependent plasticity (Hensch and Fagiolini, 2005). It was shown that visual deprivation during the critical period induces profound functional changes in the visual responsiveness of cortical neurons. The neurons activated by the deprived eye show reduced responsiveness to visually evoked potentials, loss of orientation selectivity, and loss of visual acuity (White et al., 2001; Prusky and Douglas, 2002; Frenkel and Bear, 2004). One of the models proposed to explain these dramatic effects is that visual deprivation induces homosynaptic LTD at excitatory cortical synapses (Rittenhouse et al., 1999), therefore depressing the ability of cortical neurons to respond to visual inputs. In addition, it was also shown that changes in cortical inhibition play an important role in regulating the beginning and duration of the window for plasticity in visual cortex (Fagiolini and Hensch, 2000), and that cortical infusion of GABA blockers restored visual responsiveness to the deprived neurons (Reiter and Stryker, 1988; Duffy et al., 1976; but see also Sillito et al., 1981). At the cellular level, it was shown that the beginning of the maturation of perisomatic inhibition was the permissive stage for the opening of the critical period for visual cortical plasticity and the complete maturation of these synapses is involved in determining the end of this plastic stage of plasticity (Huang et al., 1999; Chattopadhyaya et al., 2004). Our experimental paradigm allowed for a fine analysis of these hypotheses, thanks to the possibility of directly measuring strength, connectivity, and plasticity of both excitatory and inhibitory unitary synapses within layer 4.

If MD induced LTD at cortical excitatory synapses, we would expect that the amplitude of monosynaptic connections in connected pairs of star pyramids in the deprived hemisphere would be smaller than at pairs in the control hemisphere. We performed MD between p18 and p21 (the beginning of the critical period), and recorded monosynaptic currents in connected pairs of star pyramidal neurons in control and deprived

hemispheres (Maffei et al., 2006). To our surprise, the amplitude of unitary EPSCs within layer 4 remained unchanged (Fig. 2b; EPSC, p21). This is in contrast with the proposed idea that MD induces homosynaptic depression at excitatory synapses and suggests that changes at the level of inhibitory transmission might be involved in determining the decreased responsiveness of excitatory neurons to visual stimulation. Their short-term dynamics and ability to undergo LTD were also unaffected. However, the overall excitability of the layer 4 circuit was indeed reduced by MD, requiring further circuit analysis in order to understand how this might be explained (Maffei et al., 2006). We turned our attention to the inhibitory circuit whose connectivity and synapses were profoundly affected by development (Fig. 3a–c).

First, we measured possible changes at excitatory synapses between star pyramids and FS neurons. Their connectivity dramatically increased after eye opening, and possible changes in the excitatory drive onto this type of interneurons might have important repercussions on the overall excitability of the microcircuit in layer 4. Indeed their strength increased threefold following deprivation. There was also a significant increase in steady-state depression in response to presynaptic spiking at 20 Hz and no significant change in connection probability (Maffei et al., 2006). These data show that the neuronal type targeted by star pyramid synapses has an important part in determining the change in synaptic strength. When the target of synaptic contacts from star pyramids was an FS cell, excitatory synapses were potentiated following MD, whereas when the target was another star pyramid, there was no change in excitatory synaptic strength. These results illustrate the important point that synaptic changes within the cortical microcircuit are highly cell-type specific.

In addition, when measuring the amplitude of IPSC from FS to star pyramids, we found that they were also increased in amplitude by about threefold (Fig. 3b; IPSC, p21). There was a significant reduction in CV, but no changes in short-term plasticity, connection probability, or IPSC reversal potential (Fig. 3b, c; CV, SS STD, CP; Maffei et al., 2006). Non-stationary fluctuation analysis showed that increased IPSC amplitude depends upon a significant increase in number of open channels at the peak of the IPSC, suggesting that visual deprivation induced either an increase in quantal content or an increase in the number of postsynaptic GABA receptors, or both.

This dramatic increase in the strength of inhibitory feedback within layer 4 should make it much harder to propagate sensory input through the layer, and may be a major contributor to the loss of visual responsiveness of neurons activated by the deprived eye. We found that a form of LTP of GABAergic transmission (LTPi; Maffei et al., 2006) can be induced at this synapse, and that the expression characteristics of this LTPi and of the MD-induced change in inhibition were the same.

We tested the hypothesis that the increase in inhibition induced by MD is due to an experience-dependent induction of LTPi at FS to star pyramid synapses. In support of this idea, our experiments showed that further LTPi induction was occluded after MD. Further investigation on the properties of LTPi suggested that it is successfully induced only when presynaptic and postsynaptic firing are uncorrelated (Maffei et al., 2006). LTPi induction, therefore, has unique induction rules, and would be predicted to be activated by changes in sensory input that de-correlated FS and star pyramid activity.

This is a different form of inhibitory plasticity than that described in hippocampal preparations (Woodin et al., 2003) in which it depends on a de-correlation of FS and star pyramidal neuron firing, and it does not determine changes in chloride reversal potential (measured in perforated patch; Maffei et al., 2006), excluding the involvement of modulation of chloride pumps.

Experience-dependent rewiring is regulated by cortical development

Taken together, the above experiments on pre-critical and critical period plasticity suggest that there is a developmentally regulated switch in experience-dependent plasticity mechanisms within layer 4, which leads to very different

changes in the layer 4 microcircuit depending on when the activity deprivation is initiated. Early in development, the circuit in layer 4 is able to respond homeostatically to brief visual deprivation by increasing its excitability, suggesting that the gain of the circuit is increased in order to compensate for reduced visual drive. This ability to compensate is lost by the beginning of the critical period. Visual deprivation performed at this time in fact induces a strengthening of the inhibitory feedback loop between FS and star pyramids, thus reducing layer 4 excitability. The maturation of both excitatory and inhibitory transmission during the few days between eye opening and the beginning of the critical period may be instrumental in determining the forms of plasticity that are present within layer 4 and its ability to rewire itself in response to altered sensory experience.

It has been recently shown that between eye opening and the beginning of the critical period, $GABA_A$ receptors change their subunits composition and that around p21 the composition of the receptor reaches its mature configuration (Heinen et al., 2004). NMDA receptors are also undergoing a major subunit rearrangement between eye opening and the beginning of the critical period (Cao et al., 2000). Such shifts in NMDA and $GABA_A$ subunits composition might contribute to the developmental changes in inhibitory plasticity that we have observed following MD in layer 4. In addition, developmental changes in the wiring of the microcircuit in layer 4 likely contribute to differences in plasticity following visual deprivation, since they will affect how activity propagates through the network and thus may influence both correlation-based and homeostatic plasticity. For example, the increase in recurrent connectivity between FS and star pyramids affects dramatically the excitability of FS neurons which during the critical period receive two major sources of excitatory drive, from thalamic neurons as well as from star pyramids within layer 4.

This opens the possibility that the changes in the circuit triggered by eye opening will determine the switch between homeostatic and non-homeostatic rewiring of layer 4 circuit. In addition, the density of GABAergic synapses and their positioning onto star pyramidal neurons make LTPi a possible player in determining experience-dependent changes also in the presence of competition between the inputs from the two eyes. In fact there is evidence that GABAergic synapses are positioned near the site of thalamic input on star pyramids (Beaulieau et al., 1994). An interesting possibility is that such localized positioning could provide a precise increase in inhibition localized at synapses driven by the closed eye, therefore contributing to a depression of thalamocortical synaptic efficacy driven by the deprived eye.

Is homeostatic plasticity still induced during the critical period?

The experience-dependent changes we observed suggest that the layer 4 microcircuit loses the ability to respond homeostatically to a decrease in sensory drive. This is potentially a source of instability for a cortical circuit, which will not be able to achieve the optimal balance between excitation and inhibition required for sensory processing. Desai et al. (2002) showed that during the critical period, brief periods of visual deprivation by intraocular TTX injection could not induce synaptic scaling in layer 4, but could induce scaling of AMPA miniature EPSCs in layer 2/3 pyramidal neurons. These results suggest that the cortical microcircuit in layer 2/3 becomes the site of homeostatic plasticity during the critical period, endowing this microcircuit with the ability to produce compensatory responses when layer 4 is overwhelmed by inhibition. New experiments are needed to investigate whether visual deprivation during the critical period induces shifts in the balance between excitation and inhibition, thus affecting the excitability of layer 2/3 in a compensatory manner.

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