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EXPERIENCE-DEPENDENT PLASTICITY OF VISUAL CORTICAL MICROCIRCUITS

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Abstract—The recent decade testified a tremendous increase in our knowledge on how cell-type-specific microcircuits process sensory information in the neocortex and on how such circuitry reacts to manipulations of the sensory environment. Experience-dependent plasticity has now been investigated with techniques endowed with cell resolution during both postnatal development and in adult animals. This review recapitulates the main recent findings in the field using mainly the primary visual cortex as a model system to highlight the more important questions and physiological principles (such as the role of non-competitive mechanisms, the role of inhibition in excitatory cell plasticity, the functional importance of spine and axonal plasticity on a microscale level). I will also discuss on which scientific problems the debate and controversies are more pronounced. New technologies that allow to perturbate cell-type-specific subcircuits will certainly shine new light in the years to come at least on some of the still open questions.

Key words: experience-dependent plasticity, microcircuits, layer specificity, cell-type specificity, visual system, barrel cortex.

Contents

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Abbreviations: A1, primary auditory cortex; BDNF, brain derived nerve factor; LTD, long-term depression; LTP, long-term potentiation; MD, monocular deprivation; NGF, nerve growth factor; NMDA, N-methyl-D-aspartate receptor; S1, primary somatosensory cortex; V1, primary visual cortex.

BASIC FACTS ABOUT EXPERIENCE-DEPENDENT CORTICAL PLASTICITY AND PURPOSE OF THIS REVIEW

The aim of this manuscript is to review the current status of knowledge on how the various cell types composing the microcircuits in mammalian sensory cortices react to changes of the sensory experience during development and when animals are adult. So, whenever possible, the analysis will be at the level of cell-type-specific microcircuits and will be focused on the synaptic mechanisms rather than on molecular mechanisms. This is because just few of the many studies dealing with the molecular mechanisms of experience-dependent plasticity did address the layer- or cell-type specificity of the effects of such molecular manipulations.

Experience-dependent plasticity is usually studied in two model primary sensory cortices in rodents, mostly due to the detailed knowledge of the functional anatomy and physiology of these two areas in rodents: the primary visual cortex (V1) and the whisker representation in the primary somatosensory cortex (barrel cortex, S1). In this review we will focus mostly on studies of the effects of a classical paradigm of experience-dependent plasticity: monocular deprivation (MD) effects in V1 circuits. This is because the effects of MD in V1 are phylogenetically conserved in all mammals tested so far (Berardi et al., 2003). However, when pertinent, works in both S1 and primary auditory cortex (A1) will be referred to with the purpose to illustrate the general value of the physiological principles revealed by studies on experience-dependent plasticity in V1.

Usually experience-dependent plasticity in cortical circuits is triggered by creating an imbalance of the level or of the quality of electrical activity between two (or more) different sets of inputs converging onto the same

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class of neurons. This is usually realized by studying the effects of depriving one sensory input pathway, for example by the classical paradigms of MD in V1, by whisker trimming in S1, or by exposing animals to restricted sound frequencies in A1. The plastic response observed when the manipulation is done in juvenile animals usually consists in a fairly rapid loss of responsiveness to the deprived input(s), followed by a slower increase of responsiveness to the spared input(s). Such neuronal plasticity in V1 is accompanied by behaviorally detectable consequences. In the visual system, a loss of spatial vision through the deprived eye (amblyopia) has been described in all species studied so far as a consequence of MD during the critical period (Berardi et al., 2000; Kiorpes, 2006). However, it is not clear whether all visual deficits of amblyopic animals can be attributable to ''simple'' loss of responsiveness of V1 neurons (El-Shamayleh et al., 2010). Other factors, such as degraded tuning of V1 neurons for spatio-temporal characteristics of visual stimuli (Kiorpes et al., 1998), or even malfunctions in higher visual association areas(El-Shamayleh et al., 2010), might be involved. With respect to this it should be emphasized that loss of vision has usually a more dramatic impact on V1 circuits compared to whisker deprivations in S1, at least when the shift of preference between the spared and deprived input responses is quantified in neurons receiving both inputs (Fox, 1992; Maffei et al., 1992). This might simply relate to the fact that for the visual system losing inputs from one eye is a more dramatic event compared to losing inputs from one whiskers because: (a) simply said, there are many whiskers and only two eyes; (b) whiskers are specialized hairs that continuously fall off and are replaced by new ones during animal's life.

Importantly, both visual and whisker deprivations have behavioral consequences in rodents: loss of spatial vision after MD (Prusky et al., 2000; Prusky and Douglas, 2003; Pizzorusso et al., 2006); altered exploratory strategies e.g. during the gap crossing tests after whisker deprivation – (Carvell and Simons, 1996; Celikel and Sakmann, 2007; Papaioannou et al., 2013).

An imbalance between different inputs sufficient to trigger plasticity can also be created by overstimulating one sensory path (e.g. after perceptual learning) and by reducing stimulation of the other channels (e.g. raising animals in environments where they are allowed to see only one orientation – ''stripe'' rearing – in the case of V1 (Blakemore and Cooper, 1970; Stryker et al., 1978; Sengpiel et al., 1999; Kreile et al., 2011), or by overexposing animals to certain sound frequencies to see the changes of the tonotopic map in A1 – e.g. (Chang and Merzenich, 2003; de Villers-Sidani et al., 2008)). Also in such cases, there is an expansion of the cortical representation of the overstimulated stimulus features that occurs at the expense of the representation of the remaining ones.

NOTES ON THE CONCEPT OF CRITICAL PERIOD

Most of the works on the circuitry basis of cortical sensory plasticity are done on developing animals, in line with the pioneering work of Hubel and Wiesel, that linked experience-dependent plasticity to postnatal development (Hubel and Wiesel, 1962; Wiesel and Hubel, 1965; Hubel et al., 1977). In all three cortices (A1, V1 and S1) it is possible to define the existence of ''critical periods'', that is, temporal windows of heightened plasticity, during which cortical circuits are particularly sensitive to manipulations of the sensory environment. There is no ''absolute'' critical period even in a given cortex, and the reason is due to the fact that the concept of critical period itself is intimately and causally related to the development of specific sets of connections. Indeed, in all sensory cortices there is a functional maturation of the main functional response properties of neurons during postnatal development, which is probably caused by the anatomo-functional maturation and fine-tuning of different sets of input connections. Hence, when we perturb the development of the cortex by manipulating certain attributes of the sensory environment (e.g. in the V1 we can manipulate separately the sets of orientation to which the animal is exposed by stripe rearing, or we can selectively manipulating binocularity by means of MD or strabismus), we get different critical periods because the sets of connections involved are probably developing within different time frames. For example, in the visual system, the development of retinotopic maps (Cang et al., 2005, 2008), the development of orientation selectivity (Godecke et al., 1997; Kreile et al., 2011; Kuhlman et al., 2011) and that of binocularity (Gordon and Stryker, 1996) occur in different time frames. Correspondingly, the temporal windows for manipulating the respective cortical maps are different. Similarly, in A1, the critical period for the establishment of the tonotopic map (de Villers-Sidani et al., 2007) precedes that for the sweep directional selectivity (Insanally et al., 2009).

Finally, the very same sensory manipulation affects different sets of connections when performed at different time points during postnatal development in relation to which connections were maturing within a certain time frame. Studies on the plastic response of S1 neurons in response to univibrissa rearing (a classical protocol where only one whisker is kept intact and all the remaining ones are trimmed) are particularly telling with this regard. Indeed, there is an early critical period for the effects of univibrissa rearing in layer 4 (the barrel itself), which correlates also with an anatomical expansion of the cortical representation of the spared input, as described by the pioneering study of Kevin Fox (Fox, 1992). Thus, this early critical period in layer 4 might be attributable to the refinement of thalamocortical innervation during the first postnatal week. Univibrissa rearing still elicits a plastic response in overlying layer 2/3 long after the first postnatal week (Glazewski and Fox, 1996). Of relevance, further occlusion experiments attributed this more persistent plasticity of supragranular layers to a continued capability of the layer 4-to-layer 2/3 connections to undergo plastic changes (Allen et al., 2003), after the initial formation of the thalamocortical map.

Thus, there is no ''absolute'' critical period, as the definition of critical period depends on the area, on the specific connections studied and, at least partially in

causal relation to this, on the specific functional response property under investigation. Similarly, there is no absolute ''closure'' of the critical period, as a certain degree of susceptibility to sensory manipulations persists into adulthood. This adult cortical plasticity can be considered as a lifelong ''tail'' of development, albeit it probably serves completely different functions with respect to the plasticity observed during postnatal development.

Another common characteristic of cortical plasticity is that cortical circuits remain functionally immature when animals are deprived of structured (better said, patterned) sensory activity. This is particularly detrimental for the functional development of cortical circuits. The main functional sensory maps seem to appear also in absence of patterned visual activity: for example, orientation selectivity maps in carnivores emerge clearly also in dark reared, developing animals (Crair et al., 1998), and embryonic ocular dominance columns form even in enucleated ferrets (Crowley and Katz, 2000). These data exclude the role of visually driven activity in the basic structure of sensory maps in V1, but do not exclude the role of the patterned, spontaneous activity present intrinsically within the cortex (Chiu and Weliky, 2001) or coming from the deafferented thalamus in the case of enucleated animals (Weliky and Katz, 1999). On the other side, after eye opening, exposure to a patterned visual activity seems important to promote and maintain the functional maturation of the main response properties of V1 neurons (Crair et al., 1998). Visual responses in dark reared animal remain sluggish (Pizzorusso et al., 1997) and often scarcely tuned for stimulus orientation and angular size ((Freeman et al., 1981; Benevento et al., 1992; Fagiolini et al., 1994; Gianfranceschi et al., 2003) but see (Rochefort et al., 2011)). In addition, visual acuity –whose increase is a signature of the functional development of V1-remains low and does not attain adult levels as a consequence of dark rearing in both rats (Pizzorusso et al., 2006) and mice (Gianfranceschi et al., 2003). So, dark rearing delays the functional maturation of V1. Similarly, exposure to tonotopically non-structured acoustic stimulation (white noise, containing all frequencies) retards auditory cortical development in rats (Chang and Merzenich, 2003). Such an effect can also be spatially confined: for example, band-limited noise exposure during early development prevents the maturation of the noise engaged A1 sector in rats (de Villers-Sidani et al., 2008).

How does sensory activity impact on (and eventually strengthen) the initially hardwired cortical connectivity – that determines the basic tuning of V1 neurons so to promote maintenance and maturation of such tuning properties? By combining functional two-photon imaging with *in vitro* assessment of synaptic connectivity, the group of Mrsic-Flögel found that in V1 the basic tuning properties are already present before eye opening (Ko et al., 2013) and that exposure to patterned vision selectively strengthened horizontal connections between similarly tuned cortical neurons.

This process of postnatal functional maturation – whose signature in V1 is the increase of visual acuity– is paralleled by a decline to sensitivity to MD effects in all mammals tested so far (Berardi et al., 2000). In line with a role of visually driven activity to ''close'' the critical period, it has been shown that dark rearing also prolongs the critical period in cats (Mower, 1991), rats (Pizzorusso et al., 2006) and mice (Gianfranceschi et al., 2003), meaning that V1 neurons remain susceptible to MD effects despite animals being somatically adult. A note of caution should then be put on this notion of ''critical period prolongation'' as a consequence of dark rearing. Indeed, a legitimate concern is that to state this one should proof that the mechanisms and the plastic modifications induced by MD after dark rearing are the same as those caused by MD in juvenile, light-reared animals. Indeed, the possibility cannot be excluded that MD might cause qualitatively and quantitatively different effects on the abnormal V1 circuitry that results from dark rearing. For example, visual deprivation perturbs key aspects of retinal functional development (Tian and Copenhagen, 2001), such as the segregation of retinal ganglion cells in ON and OFF subtypes (Tian and Copenhagen, 2003), not to mention the effect on retino-geniculate synapses (Hooks and Chen, 2006, 2008).

PHYSIOLOGY OF CORTICAL MICROCIRCUITS *IN VIVO*

The mammalian neocortex is composed by morphologically and molecularly distinct types of excitatory and inhibitory cells, whose input and output connectivity is both layer- and cell-type specific. Once again, Hubel and Wiesel's view that specific sets of connections onto a given cell type are essential determinants of its receptive field properties remains inspiring and guides modern neurobiological research in the field of cortical microcircuits. Such layer- and cell-type-specific connectivity of cortical neurons is thought to be reflected in the different functional response properties of the excitatory cortical neurons located in the various laminae in both V1 (Martinez et al., 2002, 2005; Medini, 2011a), S1 (de Kock et al., 2007; de Kock and Sakmann, 2009) and A1 (Sakata and Harris, 2009). In general, suprathreshold responsiveness is highest in layer 5 pyramids, the main source of subcortical output in cortical circuits, and is lowest in the ''integrative'' layer 2/3, which sends inputs to layer 5 (Burkhalter, 1989). In some cases, functional response properties are similar at the level of synaptic inputs between pyramids of different layers, but become different at the level of spike outputs – e.g. when comparing layer 4 and layer 2/3 pyramids (Medini, 2011a), indicating that layer-specific differences in spike responses might be generated by differences in the action potential generating mechanism. Importantly, the sparse responsiveness of layer 2/3 pyramids, which diffusely innervate layer 5 (Burkhalter, 1989), raises doubts on the idea that layer 2/3 pyramids represent the dominant source of functional inputs to layer 5 output pyramids, raising the possibility that the latter might receive direct thalamic inputs. This possibility was indeed suggested by a limited number of previous

recordings in V1 (Martin and Whitteridge, 1984) and by more recent anatomical and electrophysiological work in S1 (Constantinople and Bruno, 2013). Layer 5 contains two morphologically distinct cell types in all sensory cortices, based on the presence or absence of a tufted apical dendrite (layer 5 thick-tufted and slender-tufted pyramids), which also project to different subcortical anatomical targets as originally found by (Kasper et al., 1994) – reviewed in (Molnar and Cheung, 2006). Interestingly, data in S1 indicate that the two types of layer 5 pyramids have different sensory responsiveness (de Kock et al., 2007; de Kock and Sakmann, 2009) and that slender pyramids preferentially encode whisker movements in S1 of awake, whisking animals (de Kock and Sakmann, 2009). Also, recent data in V1 indicate that layer 5 contains the two neuronal populations that display the highest and lowest binocularity along the entire cortical column (thick- and slender-pyramids, respectively) (Medini, 2011b). Similarly, there are data indicating the coexistence of highly orientation selective (Martinez et al., 2002) and very scarcely orientation selective pyramids in layer 5 of V1, the latter being cortico-pontine pyramids (Klein et al., 1986). Taken together, these data indicate that sensory representation is highly layer- and cell-type specific along the vertical cortical circuits formed by excitatory pyramids, and that such differences – at least in some cases – might originate from the conversion of synaptic to spike responses.

Of relevance, sensory responsiveness is often found to be different in inhibitory interneurons compared to neighboring pyramids. In the majority of studies the major class of inhibitory cells, the soma-targeting, fast-spiking parvalbumin interneurons, have been found to have broader orientation selectivity compared to pyramids in V1 (Sohya et al., 2007; Kerlin et al., 2010; Kuhlman et al., 2011) – albeit some are orientation selective (Runyan et al., 2010), probably in relation with their different dendritic geometry (Runyan and Sur, 2013). Parvalbumin-positive interneurons are also found to be more binocularly driven compared to neighboring pyramids in mouse V1 (Yazaki-Sugiyama et al., 2009; Kameyama et al., 2010). In S1, putative fast spiking interneurons also showed broader selectivity for the direction of whisker movement (Swadlow, 1989). In A1, despite previous work reported scarce frequency tuning of putative inhibitory neurons in A1 (Atencio and Schreiner, 2008), a recent study used an optogenetic tag to selectively record from parvalbumin-positive interneurons and reported similar frequency tuning for parvalbumin-positive cells and pyramidal neurons (Moore and Wehr, 2013) – but see (Li et al., 2014b). Interestingly, the prototype class of dendritic-targeting interneurons, the somatostatin-positive interneurons, have functional response properties and electrophysiological characteristics (e.g. a regular spiking phenotype) that are more similar to those of pyramidal neurons compared to parvalbumin-positive cells in both V1 (Ma et al., 2010) and A1 (Li et al., 2014b). Noticeably, a striking difference of sensory responsiveness of somatostatin-positive interneurons compared to all neighboring cell types has been found in S1: deflection of the principal whisker determines depolarizations in both excitatory pyramids and in parvalbumin-positive interneurons, but reliably evokes hyperpolarizations in somatostatin-positive cells (Gentet et al., 2012). This indicates that when the tactile input arrives, the inhibitory gate provided by somatostatin-positive interneurons on the dendrites of excitatory cells – which is functionally relevant *in vivo* (Murayama et al., 2009) – is removed, possibly allowing more efficient processing of sensory information. Recent works in V1 tried to dissect a differential role of the two interneuron types in modulating orientation selectivity, a fundamental visual receptive field properties of cortical origin. Parvalbumin-positive cells were found to modulate the responsiveness of pyramidal neurons without affecting the orientation tuning (Atallah et al., 2012), whereas somatostatin-positive neurons have principally a subtractive effect that modifies the orientation tuning ((Wilson et al., 2012) – but see (Lee et al., 2012)). Taken together, these data indicate that sensory input representation is cell-type specific in the different inhibitory cell types of cortical microcircuits and that this differentially impacts the spike output of the projection, excitatory pyramidal cells.

LAYER- AND CELL-TYPE-SPECIFIC PLASTICITY IN COLUMNAR, EXCITATORY CIRCUITS

Until recent times, not so much attention has been devoted to understand whether experience-dependent plasticity is layer- and cell-type specific in cortical circuits. As we will see in the next sections, this is probably due to the fact that most of the efforts were focused on understanding the general physiological principles underlying cortical map plasticity (e.g. role of input potentiation and depression, hebbian vs. homeostatic components of plasticity, role of structural changes in functional plasticity), rather than how the cortical circuitry was changed at the level of its distinct cellular components. However, the very same biophysical mechanisms and the differential connectivity that render sensory responsiveness different in the various cortical cell types could also account for different coincidence detection capabilities of the various cell types that may in turn result in differential experience-dependent plasticity.

After the initial observations of Hubel and Wiesel on plasticity of ocular dominance maps traced by transneuronal labeling of the thalamocortical radiation in V1 for example in monkeys (Hubel et al., 1977), single axon reconstructions showed that shrinkage of deprived axons occurs earlier and extension of open eye terminals occurs later (Friedlander et al., 1991; Antonini and Stryker, 1996) However, reconstructions of single thalamocortical axons showed that morphological plasticity is rapid in cat V1 and accompany functional plasticity within few days (Antonini and Stryker, 1993b). Similar results have more recently been obtained in mice (Coleman et al., 2010). These works were done after a brief period (3–4 days) of MD at the peak of the critical period of the two species.

Trachtenberg and Stryker however found that an even shorter period of MD (24 h) in kittens is enough to reduce responsiveness to the deprived eye in the extragranular

layers, whereas normal binocularity in layer IV was preserved (Trachtenberg et al., 2000). These data indicated that in cats thalamocortical rearrangements in layer 4 are instructed by earlier changes in the overlying supragranular layers. Conversely, layer 4 is affected since the very beginning after MD in rodents. Indeed, a brief MD (2 days) changes the ocular dominance of the synaptic responses of V1 in a similar way in layer 4 pyramids and in layer 2/3 pyramids (Medini, 2011b). In line with this report, a pharmacological technique designed to isolate thalamic inputs in V1 also showed that the ocular dominance shift is already expressed at the level of thalamocortical synaptic transmission after a brief MD episode (Khibnik et al., 2010). In interpreting these results, one should take into account the different functional anatomy of the thalamocortical radiation that forms ocular dominance columns in cats but not in rodents (Antonini et al., 1999). In other words, the two inputs remain segregated in the first thalamocortical synapse in layer 4 in cats whereas they are already intermingled in rodents.

At the light of anatomical observation that layer 5 is prominently innervated by layer 2/3 pyramids (Burkhalter, 1989), one would guess that the main output cortical layer 5 should be similarly affected compared to layer 2/3. An *in vivo* whole-cell study followed by morphological identification and reconstructions of dendritic morphologies showed that, whereas ocular dominance plasticity is strongly expressed in layer 4 and layer 2/3 pyramidal cells, layer 5 pyramids are only marginally (in the case of thick-tufted neurons) or not affected (in the case of slender-tufted cells), both at the level of synaptic input and spike output responses (Medini, 2011b) – see Fig. 1. These data raise a series of questions: (a) how can layer 2/3 drive responsiveness of layer 5, at least in MD animals? Indeed, since there is a dramatic loss of responsiveness to the deprived eye in terms of *spike outputs* in layer 2/3 pyramids, how come that the loss of responsiveness is so scarce (albeit significant) in terms of *synaptic inputs* in layer 5 thick-pyramids? We have already mentioned anatomic and functional data showing a prominent, direct thalamic innervation of layer 5 pyramidal neurons. More importantly, it has been shown that mechanical or functional ablation of layer 2/3 scarcely affect sensory responsiveness in infragranular layers in both V1 (Schwark et al., 1986) and S1 (Huang et al., 1998) and also experience-dependent plasticity in S1 (Huang et al., 1998); (b) the very same data set indicates that the initial degree of binocularity does not dictate the entity of the ocular dominance shift experienced by a given class of neurons. Indeed, layer 5 thick pyramids, that are much more binocular compared to layer 2/3 cells at the level of single cells, undergo a much smaller ocular dominance shift. Other factors, such as the determinants of the coincidence detection properties (e.g. complement of ion channels dictating the intrinsic excitability, or the level of inhibition) might cause such cell-type-specific differences in the outcome of experience-dependent plasticity; (c) which mechanisms render layer 5 pyramids partially refractory to MD? One possibility might be the different complement of ion channels in layer 2/3 vs. layer 5 pyramids: for example HCN channels – that reduce the temporal integration window of pyramidal neurons (Magee, 1999; Williams and Stuart, 2000) – are more expressed in layer 5 pyramids compared to layer 2/3 pyramids (Lorincz et al., 2002). Also, the different level of inhibition (Adesnik and Scanziani, 2010) or the more depolarized resting membrane potential values of layer 5 cells in the two layers (Medini, 2011b) might be responsible for this. Indeed, a more depolarized membrane potential might render dissimilar synaptic inputs almost equally able to drive the neuron to threshold. One way to resolve this might be to isolate synaptic currents instead of synaptic potentials in the near future. Finally, the scarce ocular dominance shift of layer 5 thick-pyramids was at least in part attributable to a limited depression of synaptic responses to deprived eye stimulation, coupled with a nearly significant loss of responsiveness to stimulation of the open eye. These data indicate a generalized loss of visual responsiveness in layer 5 pyramids after visual deprivation. Interestingly, this is in line with recent data from slice work indicating that MD reduces intrinsic excitability (input resistance) selectively in 5TPs (Nataraj et al., 2010), as opposed to 2/3Ps (Maffei and

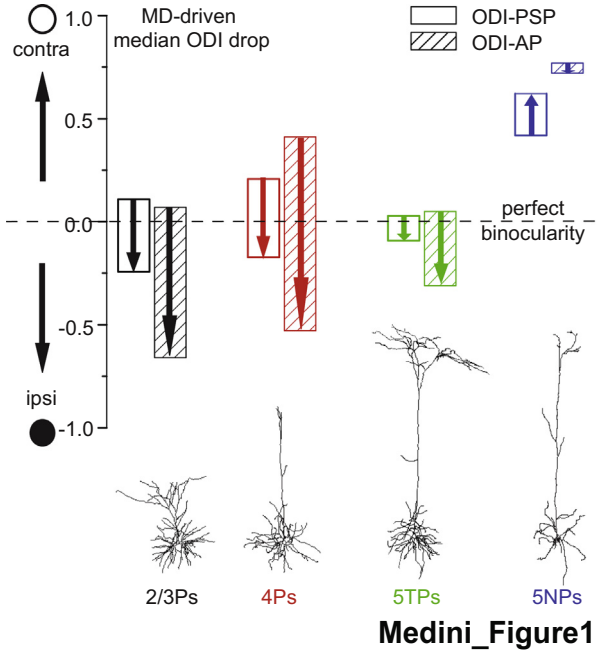

Fig. 1. Layer- and cell-type specific effects of MD on different types of pyramidal neurons in rat V1 during the critical period (P20-P30). The ocular dominance index (ODI) quantifies MD effects on the ocular dominance of neurons: it varies from 1 to −1 for cells solely driven by the contralateral or ipsilateral eye, respectively, with neurons with ODI = 0 being equally dominated by the responses of the two eyes. MD reduces the ODI of neurons from the usual contralateral dominance (ODI > 0) observed in controls to the ipsilateral dominance (ODI < 0), when the normally stronger contralateral eye is closed. MD effect is represented as the drop of the median ocular dominance index for synaptic and spike responses (postsynaptic potentials –PSP- and action potential –AP) in the different cell classes (L2/3P: layer 2/3 pyramids; L4Ps: layer 4 pyramids; L5TPs: layer 5 thick tufted pyramids; L5NPs: layer 5 non-tufted pyramids). Note that: (a) MD effects are more pronounced for APs compared to PSPs; (b) the smaller ocular preference shift of 5TPs – compared to overlying pyramids – despite their higher binocularity of origin; (c) the refractoriness of 5NPs in face of MD.

Turrigiano, 2008) and 4Ps (Maffei et al., 2006). However, it is hard to say whether such response is general in sensory cortices, as complete whisker trimming *increases* intrinsic excitability in layer 5 of S1 due to a decreased expression of HCN channels (Breton and Stuart, 2009).

Cell-type-specific differences between the two main types of layer 5 pyramids have been found also in S1: after whisker deprivation thick-tufted, intrinsically bursting cells showed only potentiation of responses to the spared whisker, but not depression of responses to the deprived whisker, whereas the reverse was true for slender-tufted, regular spiking layer 5 pyramids (Jacob et al., 2012). Interestingly, in this case, similar trends (toward potentiation or depression) were found in the corresponding sets of synapses coming into these cells from layer 2/3, thus in line with the idea that layer 2/3 is indeed driving layer 5 in whisker-deprived animals.

Interestingly, plasticity of the same sign for a given synaptic pathway (e.g. loss of responses to the deprived eye in V1) can be mediated by different molecular mechanisms in different layers. For example, loss of responsiveness to the deprived eye is mediated by retrieval of AMPA receptors from the neuronal membrane in layer 4 (Heynen et al., 2003; Yoon et al., 2009), whereas it is dependent on endocannabinoid-mediated LTD in layer 2/3 (Liu et al., 2008). Similarly, in S1, experience-dependent loss of responsiveness to deprived whiskers depends on GluR1 subunits in layers 4 and 2/3, but not in layer 5 (Wright et al., 2008). These works indicate that different molecular mechanisms might act in series in different synapses, thus possibly amplifying the synaptic changes at subsequent steps of intracortical processing.

Why is there an interest in experience-dependent plasticity of layer 5 pyramidal neurons? Because these are the main output cells of the cerebral cortex. However, layer 2/3 pyramids also send their axons to other cortical areas, albeit not to subcortical targets (as layer 5 cells do). One future challenge of the neurobiology of the cortex is certainly to gain a better understanding of the differential role of layer 5 and layer 2/3 pyramids in inter area communication and in driving behavior. An important step forward in improving our understanding of the physiology of layer 5 *in vivo* will be to improve the depth penetration of multiphoton microscopy there (Mittmann et al., 2011). These advances will be particularly important to address the issue of the functional significance of layer- and cell-type-specific plastic responses *in vivo* at the more integrative, behavioral level.

HEBBIAN VS. HOMEOSTATIC PLASTICITY: ROLE OF INPUT COMPETITION IN CORTICAL MAP PLASTICITY

The initial Hubel and Wiesel's result that loss of responsiveness to the deprived eye in V1 is more pronounced when only one eye is closed (compared to binocular deprivation), raised the idea that ocular dominance plasticity is the outcome of a process of activity-dependent competition between (possibly thalamo-cortical) terminals driven by the two eyes and innervating the same set of postsynaptic cortical neurons (Wiesel and Hubel, 1965). Similarly, in S1, depression of responsiveness to trimmed whiskers is greater if a single vibrissa has been deprived than if all vibrissae have been deprived (Glazewski et al., 1998). Such results are in line with experience-dependent plasticity being the outcome of a process of hebbian competition where ''cells that fire together wire together''. Many molecular evidences indicated that indeed V1 neurons act as coincident detectors. First, blockade of molecular coincident detectors such as N-methyl-D-aspartate receptor (NMDA) (Kleinschmidt et al., 1987) – in a way that did not significantly interfere with responsiveness – also prevents the outcome of MD (Roberts et al., 1998). Second, pioneering work by the group of (Maffei et al., 1992) indicated the molecular identity of the ''rewarding factors'' for which nerve terminals might compete for: neurotrophins such as nerve growth factor (NGF) or brain derived nerve factor (BDNF). Indeed, in case presynaptic terminals would compete in an activity-dependent way for access to limited amount of neurotrophins, administering them in large excess during the MD period would eliminate competition, in turn allowing also presynaptic terminals driven by the closed eye to remain connected to V1 neurons. Indeed, local infusions of large excesses of BDNF or NGF in V1 completely counteract the ocular dominance shift induced by MD (Lodovichi et al., 2000). It must be said however, that the neurotrophic hypothesis of ocular dominance plasticity has been recently revised at the light of data showing that blockade of the TrkB receptor – which binds BDNF – with a new chemical-genetic approach, does not interfere with MD effects in V1 (Kaneko et al., 2008a). Conversely, recovery of deprived eye responses after restoration of binocular vision was dependent on the integrity of the BDNF-TrkB signaling.

There are now clear indications that not all components of the plastic response to MD in V1 are driven by competitive processes (see also Fig. 2). First, in the original work where Hubel and Wiesel themselves compared the effects of monocular and binocular eye closures on V1 responsiveness, they showed that complete deprivation of patterned vision during postnatal development degrades responsiveness in V1, as the number of visually unresponsive units was abnormally high in binocularly deprived kittens compared with normal ones (Wiesel and Hubel, 1965). In that study, another third of cells were poorly or abnormally responsive, with broader than normal orientation tuning. Similar detrimental effects have been found in kittens experiencing just a few days of dark rearing during the critical period (Freeman et al., 1981).

Other works indicated that depression of deprived eye responses and potentiation of open eye processes are two temporally and mechanistically distinct processes (see Fig. 2). Indeed, evoked potentials (Frenkel and Bear, 2004), chronic single-unit recordings (Mioche and Singer, 1989), two-photon calcium imaging (Mrsic-Flogel et al., 2007) and *in vivo* whole-cell recordings (Medini, 2011b) indicated that loss of responses to the closed eye occurred earlier than potentiation of open eye responses. More importantly, it is possible to selectively

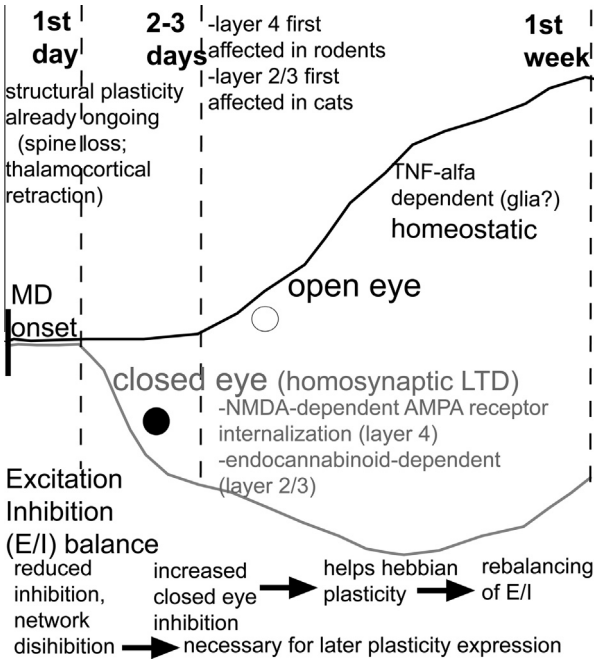

Fig. 2. Summary of the mechanistic events occurring during juvenile ocular dominance plasticity. A network disinhibition -attributable to a selective reduction of activity in parvalbumin, fast spiking inhibitory cells(Aton et al., 2013; Kuhlman et al., 2013), together with early spine plasticity (Yu et al., 2011), have been observed immediately after the first 24 h of MD. Importantly, such early network disinhibition is necessary for later ocular dominance plasticity (Kuhlman et al., 2013). Loss of response to the deprived eye is already at quasi-saturating levels after 2–3 days of MD, whereas potentiation of open eye responses is observed later – e.g. (Frenkel and Bear, 2004; Medini, 2011b). Depression is expressed in layer 4 at the level of thalamo-cortical inputs in rodents (Coleman et al., 2010; Khibnik et al., 2010; Medini, 2011b), where the inputs from the two eyes converge primarily in layer 4. Such depression is attributable to a process of homosynaptic LTD (Rittenhouse et al., 1999; Frenkel and Bear, 2004) whose molecular mechanisms are layer-specific (NMDA-dependent internalization of AMPA receptors in layer 4 (Heynen et al., 2003; Yoon et al., 2009), endocannabinoid-dependent in layer 2/3 (Liu et al., 2008)). Note that in cats, where convergence of synaptic inputs from the two eyes occurs primarily in layer 2/3, plasticity in upper, supragranular layers precedes thalamo-cortical plasticity (Trachtenberg et al., 2000). In this early time windows (2–3 days), inhibitory cells remain normally (Gandhi et al., 2008; Kameyama et al., 2010) or even more responsive (Yazaki-Sugiyama et al., 2009) to the closed eye, whereas excitatory plasticity have already lost responsiveness. Interestingly, modeling shows that this delayed plasticity of inhibitory interneurons could facilitate later hebbian loss of responsiveness (Gandhi et al., 2008). Open eye potentiation is a later phenomenon – e.g. (Mioche and Singer, 1989; Frenkel and Bear, 2004; Medini, 2011b) that could have a homeostatic functional significance as it maintains the global network activity levels to quasi-normal levels (Mrsic-Flogel et al., 2007). Consistently with this idea, postnatal open eye potentiation is mediated by molecular factors of largely glial origin such as TNFalfa, that also mediates homeostatic synaptic scaling in response to visual deprivation (Kaneko et al., 2008b). Estimates of synaptic conductances *in vivo* indicate that at this stage the ratio between synaptic inhibition and excitation evoked by the deprived eye attains normal levels (Iurilli et al., 2013; Ma et al., 2013), indicating a rebalancing of the excitation/inhibition ratio when the plastic process is over.

interfere with loss of responsiveness to the deprived eye or with potentiation of the open eye responses by interfering with different molecular mechanisms. Indeed, blockade of AMPA receptor internalization blocks depression of closed eye responses but does not interfere with potentiation of open eye responses (Yoon et al., 2009), whereas TNFalfa blockade selectively interferes with potentiation of open eye responses (Kaneko et al., 2008b).

In line with the view that the two synaptic paths – the one driven by the deprived eye and the one driven by the open eye – undergo independent plastic processes is a series of work indicating that loss of responsiveness through the deprived eye occurs through a process of *homosynaptic* depression. Indeed, Rittenhouse et al. showed that in V1 monocular lid suture causes a significantly greater depression of deprived-eye responses compared to complete silencing of retinal activity with intravitreal tetrodotoxin (Rittenhouse et al., 1999). This indicated that the residual activity coming from retina after eyelid suture is actually driving a process of active homosynaptic synaptic depression, in line with the idea that LTD requires neuronal activity to occur. Interestingly, monocular silencing leaves intact and even strengthens potentiation of open eye responses in mice V1 (Frenkel and Bear, 2004), indicating that the two processes are actually mechanistically independent.

Finally, another series of behavioral observations in cats also suggested that also the process of recovery from MD is *not* fully accountable for by competitive mechanisms. Indeed, a purely competitive mechanism would foresee that recovery of vision though the closed eye should be facilitated more by closure of the other, previously closed eye (reverse-suture) rather than by binocular vision. Experimental data showed instead that behavioral recovery of spatial vision is quicker if the animal is let in intact binocular vision compared to both reverse suture (Mitchell et al., 2001; Kind et al., 2002), indicating that it is the *absolute* amount of *correlated* activity arriving to visual cortical neurons that matters in setting the threshold for facilitating recovery of the strength of the synapses driven by the previously deprived eye. It is indeed possible that not only the absolute amount of activity matters, but also the relative timing (i.e. the degree of temporal correlation) between the two eyes that matters. Indeed, the more powerful activity coming from the open eye could facilitate, if correlated in time, synaptic strengthening of the previously deprived eye via some kind of heterosynaptic facilitation, that at least in rodents requires the integrity of the TrkB signaling (Kaneko et al., 2008a).

To test directly whether loss of synaptic inputs from the deprived eye can occur in absence of competing inputs, we tested with *in vivo* whole-cell recordings for loss of responsiveness in the main thalamorecipient layer 4 in the *monocular* segment of V1, where competing thalamic afferents cannot arrive. Importantly, the effects of MD in mV1 remained controversial. Evoked potential intracortical recordings (Smith et al., 2009), flavoprotein intrinsic imaging (Tohmi et al., 2006), and functional anatomy with c-fos staining (Pham et al., 2004) revealed that MD is ineffective in monocular V1. Conversely, intrinsic signal imaging (Kaneko et al., 2008b; Faguet et al., 2009), epidural evoked potentials (Heynen et al., 2003), and extracellular spike recordings (Spolidoro et al.,

2011) reported a significant depression of responsiveness upon critical period MD in mouse monocular V1. In some of these reports (Kaneko et al., 2008b; Spolidoro et al., 2011), the loss of responsiveness in monocular V1 was only temporarily observed upon brief MD and not after prolonged MD (but see (Faguet et al., 2009)). Another important work using two-photon calcium imaging *in vivo* reported instead a potentiation of responsiveness (Mrsic-Flogel et al., 2007) after 5–6 days of MD. This latter work did not show how responses changed in monocular V1 after brief MD (2 days), so a transient reduction of responsiveness could have also been present in Mrsic-Flogel experiments. Our results indicated that a prolonged period of MD during the critical period (P20-P30 in rats) causes the same amount of depression of synaptic responses in monocular and binocular V1 (Iurilli et al., 2011). Also, the same amount of depression occurred after binocular deprivation in binocular V1. Such depression in layer 4 of monocular V1 was not observed upon retinal silencing with intravitreal TTX, and was attributable to pure depression of thalamocortical inputs to layer 4.

Taken together, all these evidences require us to reconsider the role of competition in triggering the behaviorally relevant loss of responsiveness to the deprived eye that follows MD.

The effects of MD in monocular V1 are interesting because in such conditions one expects to document some signs of the so-called homeostatic plasticity (see Fig. 2). Homeostatic plasticity has been observed initially by the group of Gina Turrigiano. After network silencing with TTX cultured neurons react by increasing the amplitude of miniature excitatory currents, a phenomenon that is attributable to increased postsynaptic sensitivity to glutamate (Turrigiano et al., 1998). Homeostatic plasticity has the role of restoring quasi-normal level of spiking activity in the network upon input changes. Such homeostatic potentiation of excitatory mini currents has been observed also after MD in V1 (Desai et al., 2002). Importantly, a two-photon calcium imaging has shown increased responsiveness of layer 2/3 neurons in monocular V1 after MD (Mrsic-Flogel et al., 2007) – an observation we confirmed at the level of synaptic inputs (Iurilli and Medini, unpublished data). As we observed a loss of visual responses in layer 4 instead, these latter observations suggest that homeostatic changes can be also layer- and cell type-specific. In line with this possibility, recent slice works indicated that MD during the critical period causes layer-specific changes in the excitability of pyramidal neurons in monocular V1, being excitability increased in supragranular layers (Maffei and Turrigiano, 2008) but decreased in infragranular layers (Nataraj et al., 2010).

Moreover, the observation that layer 5 slender pyramids, that in binocular V1 are almost monocularly driven, do not potentiate their response to the open eye after MD (Medini, 2011b) is also in line with the idea that homeostatic changes are highly layer- and cell-type specific. Of relevance, their precise impact on how the functionality of visual cortical circuits changes *in vivo* after manipulations of the visual environment remains rather obscure.

An interesting question is *when* homeostatic changes occur in response to MD in V1. The *late* eye potentiation driven by MD in binocular V1 might have a homeostatic significance, because removing inputs from one eye reduces the net level of firing in the cortical network. Interestingly, TNFalfa, which mediates synaptic homeostatic scaling in cultures, (Stellwagen and Malenka, 2006), is also essential for potentiation of open eye responses in V1 (Kaneko et al., 2008b).

However, recent work showed that homeostatic plastic changes of the cortical network occur pretty quickly, beginning as soon as the deprivation begins (Fig. 2). This quick response dynamics makes sense at the light of the functional significance of such plastic response. Indeed, a recent work (Kuhlman et al., 2013) indicated that within the first 24 h after MD onset there is a disinhibition of the cortical excitatory network that is mediated by a reduction of firing of parvalbumin-positive inhibitory cells. Importantly, such initial homeostatic response is essential for later ocular dominance plasticity, as pharmacogenetic increase of inhibition in this initial time window prevents full expression of the subsequent plasticity. Recent extracellular chronic recordings in cat V1 followed by spike sorting of putative inhibitory and excitatory neurons (Aton et al., 2013) also showed a selective reduction of the firing responses and of the firing rates of fast-spiking interneurons to open eye stimulation immediately after MD (first 24 h), suggesting that such a quick disinhibitory response of the network immediately after MD is conserved across species. Interestingly, such an early disinhibitory responses seems a general response in other primary sensory cortices because it has been recently documented also in S1 after whisker deprivation (Li et al., 2014a), and also in that case it has been associated with a reduced sensory-driven inhibition.

Thus, the picture that begins to emerge is that the two types of plastic response (hebbian and homeostatic) occur in the cortical network in a precise temporal sequence, where one plastic event possibly ‘‘sets the stage’’ for the next one (e.g. a hebbian phase) – see Fig. 2.

INHIBITORY CIRCUITS PLASTICITY: ROLES IN MODIFYING EXCITATORY CELL RESPONSIVENESS AFTER EXPERIENCE-DEPENDENT PLASTICITY

Synaptic inhibition in the cerebral cortex is a crucial determinant of experience-dependent plasticity. Current data are in line with the idea that a first minimal level of synaptic inhibition must be reached to initiate the critical period. Indeed, mice lacking the isoform of the GABA synthesizing enzyme GAD65 present in the synaptic terminals are never sensitive to MD, unless the use-dependent agonist diazepam is administered (Hensch et al., 1998). Enhancement of inhibition by diazepam opens a normal critical period for ocular dominance plasticity at any age in such mice. Surprisingly, a single diazepam injection is able to open the critical period also in wild-type mice at P15, earlier than normal (Fagiolini and Hensch, 2000).

After the critical period opening, maturation of synaptic inhibition continues in an activity- and BDNF-dependent way. There is a positive loop between sensory-driven activity and BDNF synthesis and release (Thoenen, 1995). Importantly, mice that overexpress BDNF display an accelerated maturation of inhibition and an accelerated critical period closure (Huang et al., 1999). In line with the idea that an increase of synaptic inhibition in the adult limits experience-dependent plasticity in the adult are also experiments showing that reducing inhibition in adults – either pharmacologically (Maya Vetencourt et al., 2008; Harauzov et al., 2010) or through exposure to environmental enrichment (Sale et al., 2007, Greifzu et al., 2014) – reinstates ocular dominance plasticity in adult V1. In the interpretation of these results, one should take into account that in both situations the pattern of electrical activity of neurons might have changed as a consequence of these manipulations and hence other factors might have caused this effect (e.g. activity-dependent secretion of growth factors). Reducing inhibition in adulthood could be a sort of ''common final pathway'' reinstating a permissive state for plasticity, with several environmental and molecular manipulations leading to such a favorable condition for plasticity reinstatement.

Further work identified that GABAergic synapses containing the alfa1 receptor subtype are those that are crucial for critical period opening. Indeed, using mice with mutation in alfa subunits that render the GABA receptor insensitive to diazepam, Fagiolini et al. (2004) identified that mutant alfa2 and alfa3 subunits, but not alfa1 subunits, could still produce a precocious critical period opening upon early diazepam injections(Fagiolini et al., 2004). Since such receptors are particularly enriched at perisomatic synapses formed by parvalbumin-positive, fast spiking interneurons around the somata of target neurons, this work identified these inhibitory cells (that represent about 50% of cortical interneurons (Gonchar and Burkhalter, 1997)) as a critical cellular determinant of experience-dependent plasticity. Taken together, these evidences indicate that a certain level of inhibition (neither too low nor too high) is crucial for ocular dominance plasticity. The precise mechanisms underlying this permissive action of inhibition on experience-dependent plasticity *in vivo* remain elusive. The hypothesis that either too much or too low inhibition can impair the capability of excitatory pyramidal cells to act as coincidence detector should be carefully tested in the near future, at the light of the observation that GABAergic inhibition can profoundly alter the synaptic integration properties of neurons (Pouille and Scanziani, 2001).

It is interesting to observe that lowering of inhibitory transmission occurs also in other circumstances know to trigger cortical circuit rearrangements. Indeed, after a focal cortical lesion, plastic changes that possibly underlie functional recovery occur in the perilesional area (Murphy and Corbett, 2009). For example, in the surroundings of a visual cortical lesion, the surviving neurons display a receptive field enlargement (Eysel and Schweigart, 1999; Zepeda et al., 2004), similar to what has been observed in the limb representation of S1 (Murphy and Corbett, 2009). In the perilesional area phasic, synaptic inhibition has been shown to be reduced (Mittmann et al., 1994; Wang, 2003) – albeit tonic, extra synaptic inhibition is increased (Clarkson et al., 2010): noticeably, the two things might together render the synaptic impact of sensory-driven inhibition smaller than normal. The precise role played by such a lowering of phasic, synaptic inhibition in receptive field plasticity remains obscure, but what is known is that once again this postlesional lowering of inhibition is accompanied by a facilitation of synaptic plasticity (such as LTP) in the lesion surroundings (Mittmann and Eysel, 2001). Interestingly, there are reports suggesting a reduction of inhibition also within the cortical representation of a retinal scotoma (Massie et al., 2003; Keck et al., 2011). A focal retinal scotoma leaves a ''blind spot'' in the V1, where neurons are not visually responsive at the beginning after the lesion. However, after some weeks neurons inside the blind spot in V1 begin responding to stimulation of visual field positions neighboring the blind spot – a phenomenon documented in both cats (Gilbert and Wiesel, 1992) and mice (Keck et al., 2008). Since RF expansion occurs inside the cortical representation of a scotoma, as well at the border of a focal stroke, and since in both cases there are indications of a reduced level of inhibition in the areas where compensatory plasticity occurs, the existence of a causal link between reduced functioning of inhibitory circuits and excitatory circuit RF plasticity (i.e. RF expansion) should be explored in the near future.

The second type of question concerning the role of inhibition in experience-dependent plasticity is whether changes of inhibitory circuits could be responsible for the *expression* of plasticity in excitatory pyramidal cells. In other words, several investigations tried to understand whether inhibitory neurons contribute to the changes of responsiveness of excitatory cells, possibly by undergoing plastic changes that are equal but opposite in sign. So, this question of whether inhibition has also some kind of ''instructive'' role in experience-dependent plasticity of the excitatory network is strictly linked to the question of whether inhibitory cells undergo a differential plastic response compared to excitatory cells. Simply formulated, the loss of sensory responses normally observed after sensory deprivations might be due to reduced excitatory drive (for example from the thalamus), but also to increased or at least unaltered inhibition compared to controls. Experimental works have tried to address this important point in three ways (see Fig. 2).

(1) First, do inhibitory interneurons remain selectively connected to the deprived input after the sensory deprivation has started? In other words, do they continue to spike normally or even supra-normally to deprived eye stimulation upon MD? Several recent works have tried to address this issue. In one work Gandhi et al. (2008) used knock in mice in which GFP expression was under the control of the GABA synthesizing enzyme (GAD67) promoter to study the response of GFP-labeled interneurons to MD (Gandhi et al., 2008). They found that after

5–6 days of MD both excitatory and inhibitory cells shifted their ocular dominance in favor of the open eye and lost responsiveness to the closed one. Surprisingly, a briefer MD period (2 days) resulted in a detectable ocular dominance shift in excitatory cells, but not in inhibitory interneurons. In a second work, Kameyama et al. (2010) repeated this experiment in mice in which a GFP variant was under the control of the vescicular GABA transporter VGAT (Kameyama et al., 2010). They found that a brief MD episode similarly shifted the ocular dominance of excitatory and inhibitory cells toward the open eye. However, the ocular dominance shift of inhibitory cells was mostly attributable to potentiation of open eye responses, whereas the response to the deprived eye remained normal. Finally, sharp microelectrode recordings in mouse V1 found that fast-spiking, putative parvalbumin-positive interneurons shifted their ocular dominance in favor of the open eye in a similar way to excitatory cells after prolonged MD (Yazaki-Sugiyama et al., 2009). Conversely, a brief MD episode caused a normal shift of ocular dominance shift in excitatory neurons but a paradoxical shift of the responses of inhibitory cells toward the open eye. In rats, data are available only for prolonged MD times: a c-fos study showed that parvalbumin-positive cells remain selectively connected to the deprived eye (Mainardi et al., 2009). Conversely, putative inhibitory interneurons isolated with spike sorting from extracellular recordings undergo a similar preference shift of ocular dominance compared to excitatory cells after a prolonged MD (10 days) (Iurilli et al., 2013). The difference between these two studies in rats might be due to the much longer deprivation time used in the c-fos study (several weeks), but also to the different technical approaches used. Importantly, in all three studies in mice there was a differential response of inhibitory interneurons and excitatory cells to a brief MD episode, because the plastic response of inhibitory cells is slower. The differences among these works could be related to both the use of different promoter of the reporters for labeling interneurons in the two-photon studies and in the different techniques used (two-photon population calcium imaging vs. intracellular sharp recordings). In other words, there is no certainty that the populations of cells sampled in the three works were precisely overlapping.

(2) The second type of approach is to understand whether and how inhibitory synaptic input onto pyramidal cells changes after a sensory deprivation. Works in slices show that after a brief MD episode synaptic inhibition from fast-spiking cells to excitatory pyramids is potentiated within layer 4 in both the monocular (Maffei et al., 2006) and binocular (Maffei et al., 2010) portions of V1 a brief MD episode. However, this work might not necessarily predict the total amount of postsynaptic inhibition received *in vivo* because this also depends, for example, on the amount of presynaptic recruitment of inhibitory cells on one side, and on how other types of inhibitory cells (e.g. somatostatin-positive or 5HT3-positive) might be influenced by sensory deprivation, as well as from interlaminar inhibition. Two recent studies tried to quantify excitatory and inhibitory visually driven conductances *in vivo* in MD rodents. The first work (Ma et al., 2013) was done in voltage clamp in mice and reports that excitatory and inhibitory conductances measured upon deprived eye stimulation were similarly reduced after both brief and prolonged MD in mice. The second work (Iurilli et al., 2013), done in current clamp in rat V1, also showed a similar reduction of excitatory and inhibitory conductances after prolonged MD, but did not explore the effects of brief MD. Both works indicate that the loss of deprived eye inputs is not accompanied by an increased inhibition driven by that eye.

(3) The third experimental approach to the question of whether inhibition plays a causal role in shaping the response of excitatory cells consisted of various attempts to reduce inhibitory transmission and seeing whether this manipulation caused a selective increase of deprived input responses (unmasking of deprived inputs). Microiontophoresis of GABA antagonists showed that in cat V1 only 30% of cortical neurons changes their ocular dominance after MD (Sillito et al., 1981). Based on the data in mouse V1 showing that inhibitory interneurons remain preferentially connected to the deprived eye after a brief MD (Gandhi et al., 2008), one would expect that GABA blockade might cause a selective unmasking of responses to the deprived eye. Intracellular blockade of GABAergic transmission in a sharp microelectrode study revealed indeed that the ocular dominance of neurons dominated by the closed eye shifted in favor to the open eye, but also the inverse effect was reported (cells dominated by the open eye became dominated by the closed eye), so that in the end the ocular dominance distribution of the *population* remained unaltered after such manipulation (Yazaki-Sugiyama et al., 2009). Overall, the interpretation of the results of GABA blockade experiments is always rendered difficult by the fact that this manipulation is changing the excitability of cortical neurons (e.g. increasing the input resistance), and hence modifying the responses to both eye stimulation.

So, the role of inhibitory plasticity in shaping sensory responsiveness of excitatory cells after sensory deprivation remains not completely understood. However, analysis of the most recent literature in mice indicates that after a brief MD there is an initial period of imbalance where visually driven inhibition through the deprived input is higher than normal. Interestingly, modeling results (Gandhi et al., 2008) also indicate that the initially preserved or even increased synaptic inhibition (at least in relative terms, compared to excitation) upon brief MD can accelerate the further loss of responsiveness by Hebbian mechanisms.

POSTNATAL AND ADULT CORTICAL PLASTICITY: DIFFERENCES IN MECHANISMS AND SIGNIFICANCE

The critical period is defined as a temporally defined time window during postnatal development when cortical circuits are particularly sensitive to manipulations of the sensory environment. Previous works defined the duration of the critical period for ocular dominance plasticity in monkeys (Horton and Hocking, 1997), kittens (Mower, 1991), ferrets (Issa et al., 1999), rats (Fagiolini et al., 1994) and mice (Gordon and Stryker, 1996). Initial extracellular recordings – where the ocular dominance was expressed as relative strength of single units between the two eyes – identified a clear critical period in anesthetized mice (Gordon and Stryker, 1996). However, absolute visually evoked potential measurements of the responses to independent stimulation of the two eyes showed that, whereas depression of deprived eye responses is only observed in juvenile animals, potentiation of open eye responses is observed also in adult mice – such potentiation being dependent on NMDA receptor function (Frenkel and Bear, 2004). Interestingly, somewhat similar results have been reported in S1, where whisker deprivation continues to be effective in layer 2/3 during adulthood (Glazewski et al., 2000). The main difference between adult and juvenile animals is that in adult animals only potentiation of spared whisker responses is observed, whereas deprived whisker depression occurs only in juvenile animals. These studies forced us to revise critically and to refine the concept of ''critical period plasticity'' (Hofer et al., 2006).

Experience-dependent plasticity observed in cortical circuits during adulthood is both qualitatively and quantitatively different from the juvenile cortical plasticity. The first consideration is that the capability of cortical circuits to suppress unused synaptic inputs seems restricted to the postnatal critical period. Indeed, only potentiation of open eye responses is observed after long-term MD in adult mice (Sawtell et al., 2003), whereas both depression of deprived eye inputs and potentiation of open eye responses occur in juvenile animals (Frenkel and Bear, 2004). Second, ocular dominance plasticity is quantitatively larger in younger animals and it takes more time for full expression (Sato and Stryker, 2008). Third, the duration and maybe even the existence at all- of a critical period depends on the parameters of the sensory stimulus under investigation and on the synaptic path, as exemplified by the fact that in S1 different layers have different critical periods in response to the very same manipulation of the sensory environment (univibrissa rearing) (Fox, 1992; Glazewski and Fox, 1996). Fourth, adult V1 plasticity relies on different molecular mechanisms. Indeed, genetic interferences with either TNF signaling or GluA1 impairs ocular dominance plasticity in juvenile animals, but none of these manipulations impaired open eye response potentiation in adult mice (Kaneko et al., 2008b, Ranson et al., 2012, 2013). Conversely, adult visual cortical plasticity depends on NMDA-receptor dependent mechanisms and on autophosphorylation of CaMKII (Ranson et al., 2012). So, in V1 adult potentiation of open eye responses depends on NMDA receptors (see also (Sawtell et al., 2003) but not on AMPA receptors. Fifth, the same type of plastic response (e.g. input potentiation) can depend on different molecular mechanisms as a function of the stimulus parameter. For example, another form of response potentiation observed in both juvenile and adult mice – the one observed after repeated exposures of an animal to a grating of a given orientation – depends at all ages on *both* AMPA and NMDA receptors (Frenkel et al., 2006).

In general, adult cortical plasticity seems to be favored by a decrease in the level of inhibitory neurotransmission. This is in line with all works summarized above indicating that maturation of synaptic inhibition in the cortex is an essential determinant of the closure of the critical period. Reducing inhibitory transmission in the adult cortex – either pharmacologically (Maya Vetencourt et al., 2008; Harauzov et al., 2010) or by exposing animals to an enriched environment (Sale et al., 2007, Greifzu et al., 2014) – reinstates sensitivity to MD in V1. Visual experience is considered to be an essential determinant to trigger a proper maturation of inhibitory transmission during postnatal development, as dark rearing animals during postnatal development is known to leave V1 in a functionally immature state and delay critical period closure (Gianfranceschi et al., 2003; Pizzorusso et al., 2006). Dark rearing also prevents functional maturation of inhibitory transmission (Morales et al., 2002; Gianfranceschi et al., 2003; Jiang et al., 2010a,b). Significantly, depriving animals of patterned vision through dark rearing has been shown to reopen a window for juvenile-like plasticity (e.g. accompanied by loss of responsiveness to the closed eye) in adult V1 (He et al., 2006, 2007; Duffy and Mitchell, 2013), and that this reinstatement of juvenile-like plasticity is accompanied by a reduced level of inhibitory transmission (Huang et al., 2010).

Several studies have attempted to re-open a window of opportunity for experience-dependent plasticity in adult animals. These works had the important role of defining the molecular determinants of the juvenile critical period, because one of the criteria for defining a molecule as a ''molecular determinant of the critical period'' is the possibility to reinstate ocular dominance plasticity upon molecular interference with this very same molecule in adult animals. For example, condensation of specific extracellular matrix components (chondroitin-sulfate proteoglycans) around parvalbumin-positive interneurons is a molecular determinant of the critical period, as their enzymatic degradation in adult V1 by chondroitinase robustly reinstates sensitivity to MD in rats (Pizzorusso et al., 2002) – but note the weaker effect in cats (Vorobyov et al., 2013). Similar results have been obtained by molecular interference with myelination (McGee et al., 2005), exposure to environmental enrichment (Sale et al., 2007), to antidepressants (Maya Vetencourt et al., 2008), enhancement of nicotinic cholinergic transmission (Morishita et al., 2010), or transplantation of precursors of inhibitory neuronal precursors (Southwell et al., 2010). Interestingly, the common final

mechanisms behind the reinstatement of experience-dependent plasticity in the adult neocortex might have been a reduction of inhibitory transmission in several of these works: this is for example the case of environmental enrichment (Sale et al., 2007), antidepressant treatment (Maya Vetencourt et al., 2008), might have been the case for transplantation of inhibitory precursors (as the connections formed by these transplanted inhibitory cells were weaker than normal, albeit more numerous (Southwell et al., 2010)). Interestingly, also chondroitinase treatment reduces inhibitory transmission in the V1 (Liu et al., 2013), and it might be interesting to understand the role of extracellular matrix digestion on the spiking of inhibitory cells *in vivo*.

These studies are very interesting as they provide essential information on how to reinstate experience-dependent plasticity on one side, and to design new strategies to promote recovery from lesions on the other side (because this latter process is also a form of experience-dependent plasticity). However, a word of caution is necessary in the interpretation of these results. One should indeed be careful in stating that these are ways to prolong or ''reactivate the critical period'', because one should first proof that this enhanced adult visual cortical plasticity has the same features of that observed in juvenile animals (e.g. loss of responsiveness to the deprived eye – as shown for example in He et al. (2006)).

This discussion on the functional significance of the critical period for ocular dominance plasticity is interesting at the light of a recent work showing a possible functional role of the ''juvenile'' critical period (Wang et al., 2010). This work showed that the orientation preference of the responses evoked by separate stimulation of the two eyes in binocular V1 neurons is mismatched at the beginning of the critical period. Matching of orientation preference between the two eyes is attained later by the end of the critical period. Such orientation match is also prevented by dark rearing and is not observed in MD animals, indicating that one of the functions of exposure to a normal, patterned visual experience during development, and hence one of the functions of the critical period itself, might be allowing such experience-dependent matching of orientation tuning between the two eyes. This opens questions on the possible functional significance of the reactivated forms of ocular dominance plasticity in adult animals present in the literature, because such matching phenomenon has already occurred in adult animals.

A possible functional significance of the residual sensory cortical plasticity might be for learning purposes. Indeed, when adult rats experience an association between visual stimuli and subsequent rewards, V1 neurons begins to respond and predict the timing of the reward, rather than simply responding to the physical attribute of the visual stimulus (Shuler and Bear, 2006). Such mechanisms require the integrity of cholinergic innervation to V1 (Chubykin et al., 2013). Also, repeated presentation of orientation or of a specific sequence of visual stimuli gives rise to a selective potentiation of the repeatedly presented configuration (Frenkel et al., 2006) or sequence (Gavornik and Bear, 2014) of visual stimuli. Of relevance, work in A1 showed that it is possible to obtain tonotopic map plasticity in adult rats by paring the presentation of a given tone with electrical stimulation of the nucleus basalis of Meynert, a major source of cholinergic fibers to the cortical mantle (Kilgard and Merzenich, 1998). Several important questions remained open. First, by which cellular mechanisms such cholinergic-mediated plasticity, that can be instrumental for learning the behavioral meaning of certain stimuli, occurs in the cortex? Second, by which type of interaction with the cortical circuits could cholinergic stimulation modify the receptive field of cortical neurons? Insights came from an *in vivo* whole-cell recording study in A1 in adult rats that displayed tonotopic RF plasticity in response to association between a certain tone presentation and cholinergic stimulation (Froemke et al., 2007). Pairing caused a reduction of the inhibitory response and an increase of the excitatory response specifically to the paired stimulus that was followed by a rebalancing of the two later in time. Once again, these data suggest that a temporary disinhibition of excitatory cortical circuitries could be necessary to trigger a plastic receptive field change.

FUNCTIONAL AND STRUCTURAL PLASTICITY: UP TO WHICH DEGREE CAN THE TWO COMPONENTS BE TEMPORALLY AND MECHANISTICALLY SEPARATED?

The initial studies on the anatomical substrate of ocular dominance plasticity focused on structural changes of thalamocortical fibers. Subsequent single axon reconstructions in kitten V1 showed that the shrinkage of thalamocortical axons requires at least 3–4 days of MD (Antonini and Stryker, 1993a). However, such thalamocortical plasticity cannot explain the earliest plastic response in cat V1, because 1 and 2 days of MD are enough to cause a nearly saturating ocular dominance shift in layer 2/3, without a detectable ocular dominance shift in the thalamo-recipient layer 4 (Trachtenberg et al., 2000). Consistently, anatomical changes in layer 2/3 are much quicker upon changes of the visual environment: 2 days of strabismus are enough to cause a selective strengthening of horizontal connections that in layer 2/3 link ocular dominance columns representing the same eye (Trachtenberg and Stryker, 2001).

The scenario might be different in mice, where the inputs from the two eyes are highly intermingled already in the main thalamorecipient layer 4 and where there is no columnar architecture of V1 neurons according to ocular dominance (Antonini et al., 1999). In line with the idea that in rodents the initial effects of MD are in layer 4, there is evidence that anatomical shrinkage of thalamo-cortical fibers accompanies MD since the very beginning in layer 4 (Coleman et al., 2010).

The postsynaptic correlate of morphological plasticity is the plasticity of dendritic spines – the postsynaptic side of excitatory synapses. Di-olistic labeling of spines with the lipophilic dye DiI showed that brief MD causes a reduction of spine density on the dendritic arbours of layer 2/3 pyramidal cells and that such spine pruning is

dependent on extracellular matrix proteases such as tPA (Mataga et al., 2004). *In vivo* two-photon microscopy allows longitudinal monitoring of spine and dendritic anatomical dynamics *in vivo*. We talk about spine ''dynamics'' because dendritic spine heads move with respect to their parent dendrite (Fischer et al., 2000) and undergo a constant turnover *in vivo*, meaning that some of them continuously disappear and new ones are continuously formed. Pioneering work in S1 by the group of Karel Svoboda showed that dendritic spine turnover is sensitive to alterations of the sensory environment (Lendvai et al., 2000). Short MD, but also tPA infusion (Oray et al., 2004) and CSPG digestion (de Vivo et al., 2013) increases spine motility in V1 in layer 5 and layer 2/3 pyramidal neurons. Further work also showed that MD doubles the addition of dendritic spines into the apical tufts of layer 5 pyramidal cells (Hofer et al., 2009). This works highlights once again the presence of layer-specific changes in spines during ocular dominance plasticity, as brief MD causes loss of spines in the dendrites of layer 2/3 pyramids (Mataga et al., 2004), but addition of new spines in layer 5 pyramids.

Also axonal terminals display significant structural plasticity *in vivo* as documented by longitudinal two-photon imaging through cranial windows. Axonal boutons also disappear and new ones appear continuously. For example, ingrowth of horizontal connections (formed by excitatory cells) has been documented from the periphery of the cortical representation of a retinal scotoma to the cortical blind spot in mice (Darian-Smith and Gilbert, 1994; Keck et al., 2008), cats (Darian-Smith and Gilbert, 1994) and monkeys (Yamahachi et al., 2009). Interestingly, axonal boutons formed by inhibitory cells are significantly reduced inside the cortical representation of the scotoma (Keck et al., 2011), in line with findings of reduced inhibitory transmission within the cortical representation of the scotoma (Massie et al., 2003).

Other technically challenging studies monitored how inhibitory neurons respond over time to alterations of the sensory environment. Surprisingly, single inhibitory neurons (but not excitatory ones) undergo remodeling of entire dendritic branches over time in normal animals (Lee et al., 2006). MD during adulthood induced net retractions of the dendritic branches of inhibitory interneurons, which were accompanied by a reduction of inhibitory synapses selectively onto neighboring layer 5 pyramids (Chen et al., 2011). Another important piece of work was the recent finding that MD in adult mice causes a transient loss of Gephryn-labeled inhibitory synapses on spine heads of excitatory pyramids (van Versendaal et al., 2012). Such a putative reduction of inhibition might be a favoring factor for LTP of synapses driven by the open eye, in line with the observation that LTP in V1 is favored by a reduction of the inhibition (Kirkwood and Bear, 1994).

Two general comments on the functional relevance of this morphological (subcellular) plasticity should be made: first, that spine plasticity accompanies experience-dependent plasticity on a very quick time scale (even within few hours (Yu et al., 2011)). Second, electron microscopy showed that newly formed spines in excitatory cells (Trachtenberg et al., 2002) and also remodeled dendritic branches in inhibitory neurons host synaptic contacts (Chen et al., 2011), indicating that these morphological changes can reflect the changes observed functionally with electrophysiology or calcium imaging (Fig. 2).

ROLE OF GLIAL CELLS IN CORTICAL NEURONAL PLASTICITY

Cortical astrocytes respond to sensory stimuli in both S1 (Wang et al., 2006) and V1 (Schummers et al., 2008) with calcium oscillations, because they are endowed with metabotropic classes of both glutamatergic and GABAergic receptors that sense the spillover of such neurotransmitters from synapses in the extracellular space (reviewed in (Parpura et al., 2012)). Astrocytes have an extended plexus of cellular terminations that are intimately associated to synaptic clefts. Such astrocytic processes are thought to be part of a morpho-functional unit called ''the tripartite synapse'' (including the presynaptic neuron, the postsynaptic neurons and the astrocyte). Due to the capability of astrocytes to sense the ''integrated'' activity of the local network, and due to their capability to release plasticizing growth factors such TNFalfa, astrocytes are thought to be ideal candidates to mediate those plastic responses to the alteration of the total level of activity of the local network, namely homeostatic responses.

A possible role of glial cells in experience-dependent plasticity was suggested by provocative studies at the end of the 80s' showing that transplantation of immature astrocytes in the adult V1 reinstates plasticity in response to MD (Muller and Best, 1989) and that cytological maturation of astrocytes is delayed by dark rearing in those layers where dark rearing is known to retard plasticity (Muller, 1990).

Astrocytes can release growth factors important for homeostatic plasticity such as TNFalfa. Indeed, TNF alfa of astrocytic origin mediates synaptic scaling in astro-neuronal co-cultures (Stellwagen and Malenka, 2006). So, it is possible to postulate that the TNFalfa that mediates homeostatic potentiation of open eye responses in MD animals (Kaneko et al., 2008b) might be of astrocytic origin.

A second type of plasticity in which astrocytes might be involved is the one that follows strokes. Reactive astrocytosis after stroke is neuroprotective (Li et al., 2008). After stroke, astrocytes might play a role in the changes in the inhibitory transmission in the lesion periphery, where compensatory plasticity occurs. Indeed, reactive astrocytosis has been shown to selectively impair inhibitory neurotrasmission, due a reduced activity of the glutamine synthase enzyme in reactive astrocytes that in turn reduces the availability of the substrate for GABA synthesis in principal neurons (Ortinski et al., 2010). Such an effect could play a role in the reduction of phasic, synaptic inhibitory transmission that has been observed in the lesion surroundings (Mittmann et al., 1994). Conversely, tonic, extrasynaptic inhibition has been shown to increase

in the lesion surroundings, a phenomenon that plays a role in functional recovery (Clarkson et al., 2010). Interestingly, such an effect is also mediated by astrocytes, as it is due to the downregulation of specific isoforms of GABA re-uptake transporters in reactive astrocytes.

After all, the precise roles played by astrocytes in experience-dependent plasticity of cortical microcircuits has only begun to be addressed, but new discoveries in this field are expected, also because it is now becoming possible to molecularly or optogenetically interfere with the activity and with the release of glial-derived factors in the extracellular space (the so-called process of ''glio-exocytosis'' (Li et al., 2013)).

CONCLUDING REMARKS ON FUTURE DEVELOPMENTS

The biggest challenge in the future would be to exploit recently developed electrophysiological tools and design new optical approaches to study how *functional* connectivity between identified neuron types is modified by experience-dependent plasticity in the living brain. The combination of transynaptic tools with optogenetics and optical advances to explore synaptic connectivity *in vivo* will certainly qualitatively modify our understanding of how cortical microcircuits are modified during experience-dependent plasticity. Such innovative approaches will allow to identify *the order* in which synaptic connectivity of cortical circuits are modified by changes of the sensory experience (see Fig. 2). In turn, this will allow studying whether one given modification in one set of synapses *casually* modifies another set of synapses. Also, such an innovative, yet very challenging approach, will allow testing the differential role of specific molecular players in the series of synaptic modifications observed *in vivo*. The second big challenge will be then to understand whether modifications of identified, cell-type-specific connections differentially impact on the animal behavior.

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