CHAPTER 1

Environmental enrichment and brain development

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Introduction: critical periods and experience-dependent plasticity in brain circuits

The term "plasticity" refers to the ability of the nervous system to reorganize its connections functionally and structurally in response to changes in environmental experience. This property underlies the adaptive development and remodeling of neuronal circuitry that makes brain development, behavioral flexibility, and long-term memory possible.

Plasticity is particularly high during developmental time windows called critical periods (CPs), when experience is crucial in promoting and regulating neural maturation and, consequently, the behavioral traits of the newborn, in every vertebrate species tested so far, from birds to rodents to primates (Berardi et al., 2000). Essentially, a CP is a phase of exceptionally high sensitivity to experience displayed by developing neural circuits. During CPs, experience exerts a key role in building the precise assembly of connections that endows each individual with his/her unique characteristics. Different species show different CPs for the same function, in good accordance with a different time course of development and life span. On the other hand, distinct functions show different CPs in the same species, correlating with different time courses of development in different brain areas.

Essential information on developmental brain plasticity and CPs has been provided by studies focusing on the primary visual cortex (V1), which has been for decades the election model for studying experience-dependent plasticity in the brain. The pioneering experiments performed by Hubel and Wiesel showed how dramatically can early sensory deprivation affect the anatomy and physiology of the visual cortex (Figure 1.1). Many neurons in the visual cortex are binocular, that is, receive input from both eyes, and exhibit different degrees of dominance from either eye, a property called ocular dominance. Hubel and

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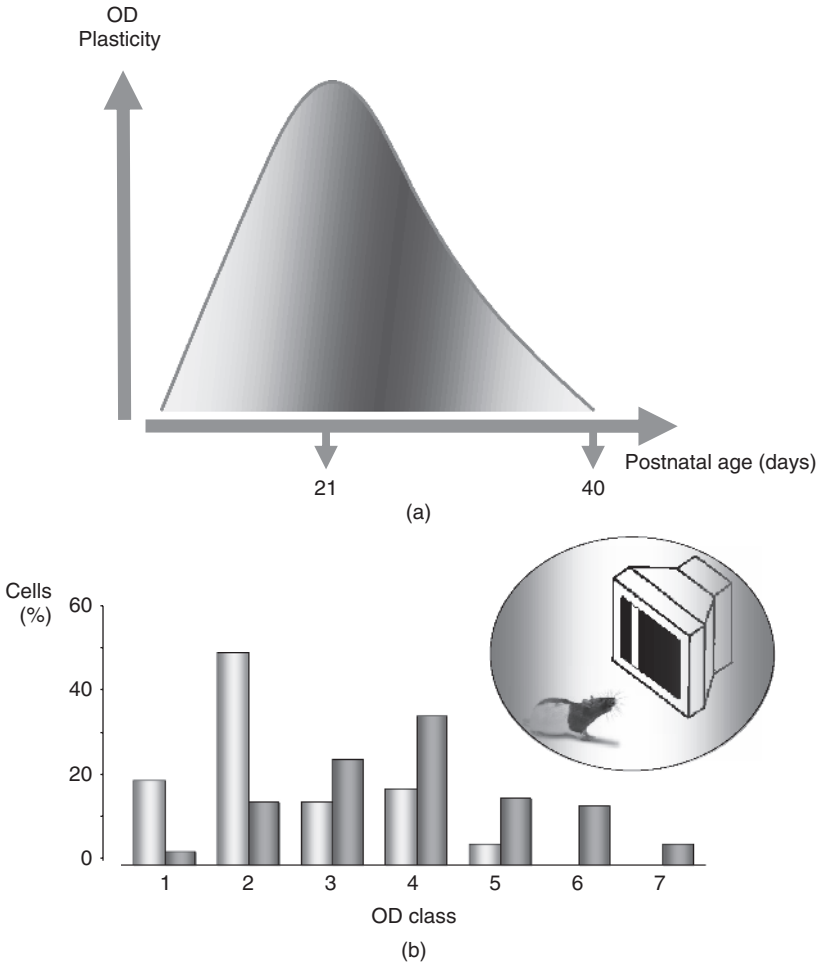


Figure 1.1 Critical period (CP) for ocular dominance plasticity in the rat visual cortex. (a) Schematic representation of the time course of CP for ocular dominance plasticity in the rat, which peaks around postnatal day (P) 21 and is definitively closed by the age of P45. (b) Single unit recordings from the primary visual cortex allow classification of neurons with respect to their ocular preferences: in a typical recording from a nondeprived animal (light cyan columns), cells in class 1 are activated exclusively by the contralateral eye, cells in class 7 are activated exclusively by the ipsilateral eye, neurons in classes 2–3 and 5–6 are activated to varying degrees by both eyes, and neurons in class 4 respond equally to both eyes. Following closure of the contralateral eye from 1 week during the CP, cells become much more responsive toward the ipsilateral open eye, at the expense of the deprived eye (dark cyan columns). (See insert for color representation of this figure.)

Wiesel reported that, early in development, reducing the visual input to one eye by means of lid suture, a treatment classically referred to as monocular deprivation (MD), disrupts ocular dominance of V1 cells, with a loss of neurons driven by the deprived eye and a strong increment in the number of cells driven by the open eye, and reduces the number of binocular neurons (Wiesel

and Hubel, 1963). The imbalance of activity between the two eyes results in remarkable anatomical changes in V1, with a shrinkage of the deprived eye ocular dominance columns, those layer IV regions that receive thalamic inputs driven by the closed eye, and in the expansion of the open eye's columns (Hubel et al., 1977; Shatz and Stryker, 1978; LeVay et al., 1980; Antonini and Stryker, 1993), accompanied by a remodeling of cortical horizontal connections (Trachtenberg and Stryker, 2001). At the behavioral level, if the condition of MD is protracted for a long period during development, it eventually leads to lower than normal visual acuity and contrast sensitivity values for the deprived eye (amblyopia), together with a deterioration of binocular vision. Strikingly, the same manipulation of visual experience appeared to be ineffective in the adult (LeVay et al., 1980), leading to the characterization of the first and most widely studied example of CP (Berardi et al., 2000; Berardi et al., 2003; Knudsen, 2004; Hensch, 2005a, 2005b; Levelt and Hubener, 2012).

Another well-studied CP is that regulating age-dependent changes in fear memory acquisition, which in rodents emerges at the end of the second postnatal week of life (Akers et al., 2012). Interestingly, the potential for fear extinction does also follow a CP, displaying a permanent fear erasure in preadolescent mice but leading to incomplete erasure and thus persisting or returning fear responses in juveniles about 10 days older.

In humans, CPs have been documented for several brain modalities (Figure 1.2). Examples of CPs in the sensory domain are those for the maturation of visual acuity and stereopsis, the acquisition of language-specific abilities in phonemic perception, and the acquisition of gustatory and olfactory preferences (Lewis and Maurer, 2005; Werker and Tees, 2005; Ventura and Worobey, 2013). A particularly relevant case of olfactory learning regulated by a CP is that underlying maternal attachment, clearly present in newborn babies and well described at the neurobiological level in rodents (see also the chapter by Sullivan and colleagues in this book [Chapter 6]). CPs in humans have been also found for second language acquisition, both speech and sign language, or for proficient performance in musical instrument playing (Bengtsson et al., 2005; Kuhl, 2010).

As in the case of MD, the importance of a proper experience during the CP is made particularly clear by the detrimental effects caused by its absence or deterioration, like in the classic example of the negative effects in the social/affective domain produced by rearing under conditions in which the mother is absent or early removed and sufficient maternal care levels are not available (Sullivan et al., 2006). Developmental plasticity, indeed, is by itself neither good nor bad, it simply takes its course, allowing the system to proceed toward an adaptive developmental trajectory when the stimuli are adequate and available, or instead resulting in severe and even permanent deficits under harsh environmental conditions. Thus, while the existence of a mechanism by which high levels of plasticity during the CP are followed by an abrupt reduction of circuit modifiability after its closure is likely to provide adaptive advantages

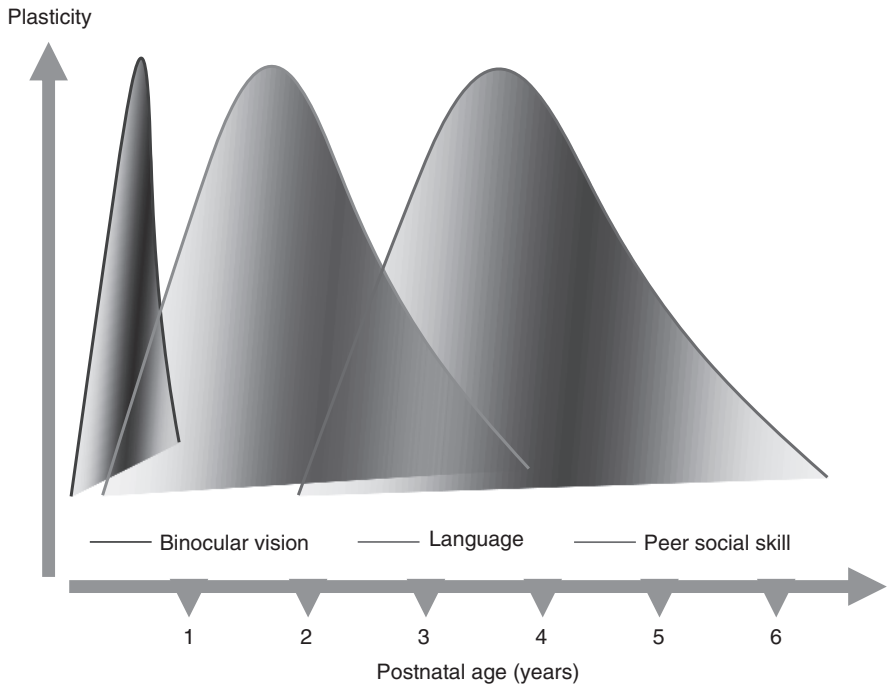


Figure 1.2 Critical periods across brain functions in humans. The picture represents a schematic of the critical period time course for acquisition of binocular vision, language learning, and adequate peer social skills in children. Different functions display different time courses, both in terms of total duration of the heightened sensitivity window and concerning the age of onset and closure of the potential for plasticity. In the three curves, levels of plasticity have been normalized to the peak. (See insert for color representation of this figure.)

in terms of the possibility to fix the acquired neural assemblies without the need of continuous maintenance, it may also expose the nervous system to severe dysfunctions when development is perturbed.

Importantly, the potential for recovery after reestablishment of proper environmental conditions can also be regulated by CPs, with studies in postinstitutionalized children demonstrating that the most severe and persisting effects of raising children in impoverished environments lacking sufficient social stimuli are more likely to be documented when adoption occurs beyond 4–6 months of age (for a comprehensive survey of the literature on the effects of institutional deprivation, see the chapter by Doom and Gunar in this book [Chapter 9]).

Not surprisingly, much effort in Neuroscience research is currently devoted to understanding the molecular mechanisms underlying the closure or the sudden reduction of plasticity at the end of the CPs. Among the most promising candidates are factors exerting a key role as plasticity brakes, such as critical components of the extracellular matrix, that is, the chondroitin sulphate proteoglycans that surround neuronal cell bodies in structures called perineuronal nets, myelin-related Nogo receptors, proteins belonging to the

newly discovered class called Lynx family, epigenetic regulators of the functional state of chromatin such as histone deacetylase inhibitors, and the maturation of intracortical GABAergic interneurons (Bavelier et al., 2010; Nabel and Morishita, 2013).

Optimization of environmental stimulation: environmental enrichment

In parallel to the Hubel and Wiesel seminal work based on a sensory deprivation approach, fundamental contributions to the knowledge of how experience affects brain development have been provided by the group of Rosenzweig and colleagues, using the so-called environmental enrichment (EE) paradigm. Originally defined as "a combination of complex inanimate and social stimulation" (Rosenzweig et al., 1978), EE is performed in wide cages where the animals are reared in large social groups and in the presence of a variety of objects, like tunnels, nesting material, stairs, and plastic recoveries, that are changed by the experimenter at least once a week in order to stimulate the explorative behavior, curiosity, and attentional processes of the animals. An essential component of EE is voluntary physical exercise, the opportunity to attain high levels of motor activity on dedicated devices, such as running wheels. The EE definition and description is based on the comparison with alternative rearing conditions, such as the standard condition, in which the animals are reared in small social groups and in very simple cages where no particular objects other than nesting material, food, and water are present, and the very simple impoverished condition, in which social interactions are impossible because the animals are reared alone in individual cages. Compared with these more simplified environments, EE gives the animals the opportunity for structured social interaction, multisensory stimulation, and increased levels of physical activity.

Since its original introduction in the early 1960s, extensive work has been done investigating the impact of EE on the morphology, chemistry, and physiology of the brain, for the vast majority focusing on adult subjects (Rosenzweig and Bennett, 1996; van Praag et al., 2000; Diamond, 2001; Sale et al., 2009). The beneficial results associated with EE are as various as the fantasy of the researchers in documenting them: enriched animals display a marked improvement in complex cognitive functions and reduced stress reactivity, are characterized by increased levels of hippocampal long-term potentiation (LTP) and have robust increments in cortical thickness and weight, together with modifications of neuronal morphology in terms of increased dendritic arborization, number of dendritic spines, synaptic density, and postsynaptic thickening, occurring in several brain regions (Baroncelli et al., 2010).

Even if EE may appear as a way of rearing the animals in a semi-naturalistic setting more similar to the wild life, the beneficial effects observed in enriched

animals cannot be simply interpreted as a functional restoration to a more physiological condition from deficits caused by living in the typical deprived setting imposed on laboratory animals. Indeed, the most commonly used strains of rats and mice are highly inbred animals, maintained for hundreds of generations in artificial enclosures, thus subjected to a strong genetic drift responsible for main differences in their gene pool with respect to the natural populations (see Sale et al., 2014). Thus, which kind of environmental stimuli can be considered physiological or "naturalistic" is not immediately clear for these strains. Moreover, differently from the condition characterized by multiple contingencies and risks associated with living in the wild, enriched animals are totally free to choose when and how much to explore the surroundings and thus to experience the enriched stimuli, living in a danger-free environment much more similar, in human terms, to a well-equipped playroom than a jungle.

Environmental enrichment and visual system development

Despite the interest raised by the possibility to induce beneficial effects on brain and behavior by means of environmental manipulations, most studies addressing the impact of EE remained focused on adults, leaving almost unexplored the question of whether an enhanced environmental stimulation can also affect brain development, modulating the processes that govern maturation of neural circuits in the central nervous system. This fundamental issue is at the core of the classic debate about the role of nature and nurture, or, in more biological terms, genes and environment, in the construction of brain architecture and its functional output, the behavior. While the widely accepted consensus is that genes and environment work in concert in shaping neural circuits and behavior, the contribution of specific genetic programs to brain development has been characterized much earlier in the debate, with studies concerning the impact of environment remaining for a long time at a merely descriptive level of analysis.

Since early EE provides increased sensory stimulation during CPs, when anatomical and functional rearrangements of the cerebral cortex proceed at their maximum level, it might be expected that procedures aimed at increasing the intensity and optimizing the quality of experience might elicit robust brain changes through experience-dependent plasticity processes. Accordingly, preweaning EE has been sporadically shown to result in more complex dendritic branching in cortical pyramidal cells, particularly in the parieto-occipital cortex (Venable et al., 1989), to promote an earlier neuronal cytodifferentiation in the rat motor cortex, correlating with better performance in a number of motor adaptive responses (Pascual and Figueroa, 1996), and to significantly increase ippocampal and cortical expression levels of the neural cell adhesion molecule (NCAM), synaptophysin, and brain-derived neurotrophic factor (BDNF) (Koo et al., 2003).

What remained almost unknown for long time was the actual extent of the impact of the environment on brain development at the very functional level, such as in terms of maturation of fine neuronal properties. With the aim to fill this gap, some years ago our group started a series of studies focusing on visual system maturation in environmentally enriched rodents. In this new approach, the rigorous and highly quantitative methodology typical of visual system research has been combined with the theoretical framework of the EE paradigm, resulting in quite a powerful new tool that allowed us to open a window on the dynamic building of the brain according to different levels of environmental stimulation (Sale et al., 2009) (Figure 1.3).

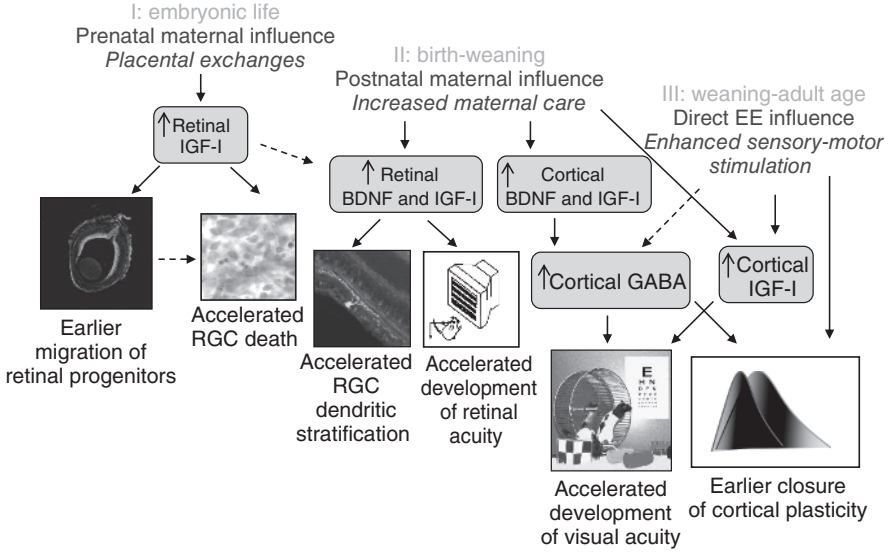


Figure 1.3 Environmental enrichment and visual system development acceleration: a three phases model. The figure depicts an interpretative framework of the data regarding EE effects on the developing visual system. Three consecutive temporal phases are differently controlled by the richness of the environment: (I) a prenatal phase in which the mother mediates the influence of the environment through placental exchanges with the fetus, leading to an accelerated anatomical retinal development that is mostly due to increased levels of IGF-1; (II) an early postnatal phase in which enhanced maternal care received by EE pups stimulates the expression of experience-dependent factors in the visual system, resulting in an early increase of BDNF and IGF-1 in the retina and the visual cortex; this guides the accelerated maturation of retinal ganglion cells (RGCs) observed in EE pups and, through an increased GABAergic inhibitory transmission, triggers a faster visual cortex development; and (III) a third and final phase in which the autonomous interaction of the developing pup with the enriched environment further increases cortical IGF-1, which promotes the maturation of the GABAergic system, also leading to an acceleration in visual acuity maturation. Continuous lines represent well-documented interactions between boxes; dashed lines indicate likely interactions in the context of visual cortex development requiring further experimental characterization. (See insert for color representation of this figure.)

A first result was the demonstration of a marked acceleration in the visual system development in mice and rats exposed to EE since birth (Cancedda et al., 2004; Landi et al., 2007b). This effect was particularly evident for the maturation of visual acuity, a highly sensitive parameter of visual development. Moreover, early exposure to EE was also able to induce an earlier closure of the time window during which it is possible, during the first postnatal weeks of life, to induce LTP in visual cortical slices through theta-frequency stimulation from the white matter (Cancedda et al., 2004). Looking for possible molecular mediators underlying the EE-induced acceleration of visual system development, the neurotrophin BDNF and its action as regulator of the maturation of the GABAergic system emerged as key factors. Indeed, BDNF increased at the end of the first postnatal week of life in the visual cortex of enriched pups, and this increase was paralleled by an enhanced expression of the two GABA biosynthetic enzymes, GAD65 and 67.

The impact of EE on visual system development appeared to be very similar to what was previously established for an artificial BDNF overexpression obtained by genetic engineering (see Sale et al., 2009 for review), which was shown to drive an earlier development of intracortical GABAergic inhibition, followed by faster visual acuity maturation, likely due to the refinement of visual receptive fields under the direct control of inhibitory interneurons (Huang et al., 1999). In both enriched and BDNF overexpressing mice, the acceleration of visual system development elicited by BDNF and the intracortical GABAergic system do not require vision at all, considering that it is evident before eye opening and even before photoreceptor formation. This striking conclusion was also confirmed by results obtained in enriched rats raised in darkness during development (Bartoletti et al., 2004), a procedure that usually prolongs the duration of the CP and impairs visual acuity maturation (Timney et al., 1978; Fagiolini et al., 1994). Indeed, the detrimental effects of dark rearing were completely counteracted by either EE (Bartoletti et al., 2004) or BDNF overexpression (Gianfranceschi et al., 2003). This strongly demonstrates that the maturation of a sensory system can be forced to proceed even in the absence of specific sensory experience impinging on it, provided that adequate levels of some critical molecular factors are available to the developing neural circuits.

A second major finding was the demonstration of a key role in visual development exerted by the insulin-like growth factor-1 (IGF-1), a molecule that promotes the survival and proliferation of neural cells, thus exerting a wide variety of actions both during development and in adulthood (O'Kusky and Ye, 2012). IGF-1 expression is increased during the second postnatal week in the visual cortex of rats raised in EE compared to standard-reared animals, and exogenous IGF-1 supply mimics, whereas its blocking prevents, EE effects on visual acuity maturation (Ciucci et al., 2007). Interestingly, IGF-1 eventually converges on the same biochemical pathway as BDNF, that is, the inhibitory GABAergic system, leading to an increased GAD65 expression in V1 (Ciucci et al., 2007). The essential role of IGF-1 as a key mediator of the EE control on

experience-dependent development has been recently reinforced by Wang and colleagues (Wang et al., 2013). They found that a mismatch between two visual developmental processes, ocular dominance development and binocular matching of orientation selectivity development, can be caused by overexpression of BDNF, which acts on ocular dominance development and cortical plasticity decline but is unable to drive binocular matching of orientation selectivity, with negative results for the quality of binocular vision; EE exposure and IGF-1 are able to correct this mismatch, ensuring an harmonic development of all properties of visual cortical neurons.

While the classic sensory deprivation approach based on dark rearing or eye-lid suture led to postulate that the prime site for experience-dependent plasticity is the cerebral cortex, the impact of EE on visual system development turned out not to be restricted to the visual cortex. The retina, a peripheral part of the central nervous system traditionally considered little plastic in response to changes of sensory inputs (Baro et al., 1990; Fagiolini et al., 1994; Fine et al., 2003), indeed appeared much responsive to EE: retinal acuity, which is the spatial discrimination limit of the retinal output, was accelerated in enriched rats to the same extent as the visual cortex (Landi et al., 2007b), an effect accompanied, at the morphological level, by an earlier segregation of retinal ganglion cell dendrites into ON and OFF sublaminae (Landi et al., 2007a). The similarity of the response displayed by the visual cortex extended to the molecular level of analysis, with increased retinal IGF-1 and BDNF in the retinal ganglion cell layer of developing rats raised under enriched conditions (Landi et al., 2007a; Landi et al., 2007b).

Based on the convincing finding that the environment can be exploited as a driving force to increase the expression of neuronal protective factors, a recent work investigated the impact of EE on a mouse model of Retinitis Pigmentosa, a family of inherited disorders in which a mutation in a retinal-specific gene causes the primary degeneration of rods, followed by the secondary death of cones, leading to near blindness. The results show that early EE delays the loss of rod photoreceptors and the secondary death of cones, thus preventing vision for a much longer time than control animals maintained in conventional standard-rearing conditions (Barone et al., 2012).

Maternal touch

What might cause such very early changes in the developing brain of an enriched pup? Answering this question is not trivial, considering that the offspring mostly spend the whole time in the nest during the first days of postnatal life, with very few chances to explore the surroundings and receive an enhanced sensory stimulation. During the initial phase of postnatal development, maternal influence is certainly the most important source of sensory experience for the developing subject (Hofer, 1984; Ronca et al., 1993; Liu et al., 2000), directly regulating physical growth and promoting the neural maturation of brain structures

through highly adaptive behaviors such as licking, grooming, and feeding (Fleming et al., 1999; Meaney and Szyf, 2005; Champagne et al., 2008).

We postulated that maternal behavior could be the solution to the mystery of visual system acceleration in very young pups born in enriched conditions, with the possibility of maternal behavior differences between enriched and nonenriched dams. Our theory stood up to the facts quite well. Enriched pups were demonstrated to receive higher levels of maternal stimulation compared to standard-reared animals (Sale et al., 2004), experiencing an almost continuous physical contact provided by the mother or other adult females, and receiving increased levels of licking during the first 10 days of life. Moreover, when we willingly replaced enriched mothers mimicking maternal behavior with an artificial tactile stimulation (massage), we were able to reproduce the EE-dependent acceleration of visual development, an effect mediated by increased IGF-1 levels in the primary visual cortex (Guzzetta et al., 2009).

Mimicking early enrichment with maternal stimulation offered a fascinating chance for clinical application. In parallel to the effects obtained in massaged rats, together with Prof. Cioni's group at the Stella Maris Hospital (Calambrone, Pisa), we reported that enriching the environment in terms of body massage ("massage therapy") accelerates brain development in healthy preterm infants (gestational age between 30 and 33 weeks) (see the chapter by Guzzetta and Cioni in this book [Chapter 10]). Massaged infants displayed increased levels of plasma IGF-1 and exhibited a faster developmental reduction in the latency of flash visual evoked potentials and an increase in behavioral visual acuity, which persisted above 2 months past the end of the treatment (Guzzetta et al., 2009, 2011).

Despite this first attempt to investigate the effects elicited by enriched living conditions in children, very little is known on the impact of early EE in humans. Previous studies showed that early educational and health enrichment at ages 3–5 years is associated with long-term increases in psychophysiological orienting and arousal at age 11 (Raine et al., 2001), and that early nutritional, educational, and motor enrichment is prophylactic for antisocial and criminal behavior at age 17–23 years (Raine et al., 2003). In our opinion, this is a research field that deserves much more attention, bearing a great potential for translation of the results obtained in well-designed experiments to educational programs and national health services.

As previously noted (Sale et al., 2014), the remarkable ability of an early exposure to EE conditions to accelerate brain development should not be viewed as necessarily always beneficial. As a delicate equilibrium among an orchestra's elements, speeding up the circuit maturation in a system, or feeding an excessive stimulation upon it, might cause that system to either fail an exact temporal matching with the maturation of other developing circuits or to suffer from overstimulation detrimental effects. Again, the same treatment might result in excessively narrow CPs, possibly reducing the chance for a proper

interaction with the environment (Wang et al., 2013). Fortunately, it appears that the EE protocols employed in current laboratory practice not only do not force the animals in terms of the amount of received stimulation but in very young individuals are mostly mediated by maternal behavior, an absolutely natural source of experience that is very unlikely to be associated with stressful conditions.

Prenatal effects

Having focused on maternal influence as a key mediator of early EE effects on brain development, we went back to retinal development to also show that a substantial fraction of the acceleration previously reported in this structure as a result of early EE exposure was actually due to prenatal maternal effects. Enriching female rats for the entire length of gestation resulted in faster dynamics of neural progenitor migration and spontaneous apoptosis in the retinal ganglion cell layer, an effect mediated also in this case by IGF-1 (Sale et al., 2007a). To explain how changes in the environment experienced by the mother are finally translated in variations of the developmental trajectories in the offspring, we put forward a model in which sustained physical exercise during pregnancy increases IGF-1 in the mother, promoting placental transfer of nutrients to the fetus; this in turn leads to increased amounts of IGF-1 autonomously produced by the fetus, resulting in an earlier development, detectable at the retinal level (Figure 1.4).

Apart from the visual domain, other systems appear to be influenced by prenatal enrichment. The hippocampus of rat pups born from physically trained mothers displays an increased expression of BDNF and proliferation of progenitor cells in the granule layer (Parnpiansil et al., 2003; Bick-Sander et al., 2006). The beneficial effects of prenatal enrichment are long-lasting, resulting in enhanced cognitive abilities at very early and older postnatal ages (Parnpiansil et al., 2003; Lee et al., 2006), providing enduring protection from neurodegeneration in old age through a reduction of beta-amyloid plaque burden (Herring et al., 2012) and leading to increased synaptic elaboration and complexity in the hippocampus. Moreover, maternal complex housing during pregnancy as a form of prenatal enrichment has been recently shown to alter brain organization and to offer neuroprotection against major consequences of perinatal brain injury (Gibb et al., 2014).

Strikingly, maternal exercise during pregnancy also exerts beneficial effects on human fetal development (Prather et al., 2012), with the recommendation made by the American College Congress of Obstetricians and Gynecologists in 2002 in which at least 30 minutes of moderate exercise during pregnancy on most days of the week is considered as a safe way to promote benefits for the mother, fetus, and future newborn (American College of Obstetricians and Gynecologists, 2002).

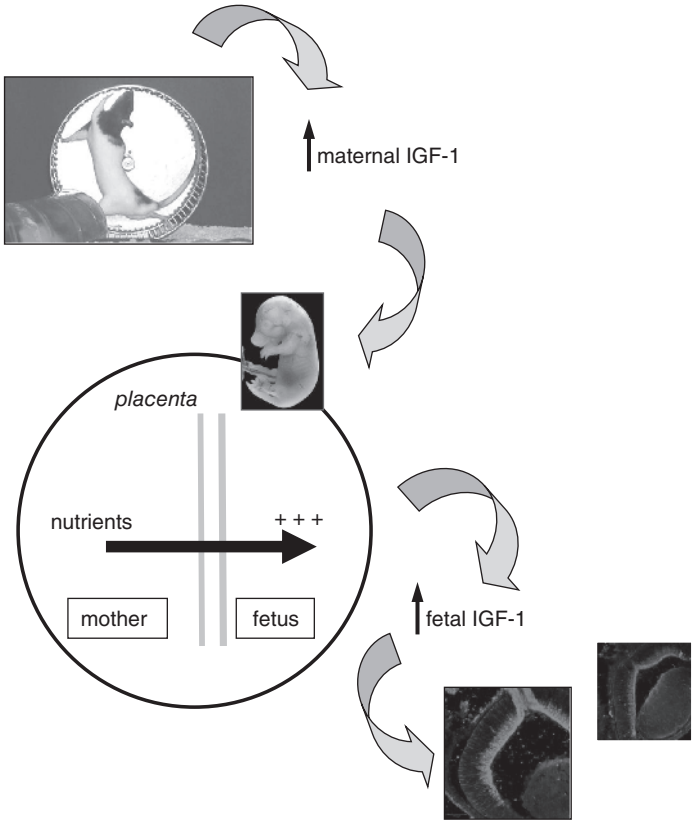


Figure 1.4 Prenatal enrichment modulates retinal development in the fetus. The figure shows a possible explicative model for the effects elicited by maternal enrichment during pregnancy on retinal development. Increased levels of physical exercise in gestating dams lead to higher amounts of circulating IGF-1 in the maternal blood stream, stimulating the supply of nutrients transferred to the fetus through the placental barrier. The enhancement in glucose and placental lactogens received by the fetus stimulates the autonomous production of IGF-1 in his tissues, with an increased expression detectable in the ganglion cell layer of the retina. IGF-1, in turn, stimulates the maturation of retinal circuitries. The photographs depict two examples of one enriched (left) and one nonenriched (right) retinal sections immunostained for double cortin, which labels migrating cells and is a good marker of the temporal and spatial distribution of neural progenitors during the early developmental stages of the rat retina. Reprinted from Sale et al., 2012. (See insert for color representation of this figure.)

Thus while for many years the best-documented maternal effects were those elicited by prenatal stress protocols, which has long been linked to growth retardation and structural malformations in the offspring (Mulder et al., 2002; Seckl, 2004; Graignic-Philippe et al., 2014), the results obtained with prenatal EE underscore the impact of positive changes in the quality and intensity of maternal stimulation during pregnancy as powerful modulators of several growth factors known to be critical for central nervous system development.

Beyond the visual system

An intrinsic strength of the EE paradigm is its remarkable ability to impact on the whole brain and not to specifically act on a single developing system. The beneficial effects of EE, indeed, are not exclusive of the visual system. The auditory cortex, for instance, displays major changes when EE is applied at juvenile developmental stages, with increased strength of auditory responses and improved sound sensitivity and tone frequency/directional selectivity (Engineer et al., 2004; Zhang et al., 2009). Moreover, exposure to enriched environments at very early postnatal ages has been associated with an early maturation of major components of the brain extracellular matrix, the chondroitin sulfate proteoglycans (CSPGs), in the striatum, leading to increased cognitive and motor abilities (Simonetti et al., 2009). As reported for the visual system, an accelerated maturation of GABAergic and glutamatergic synapses has been documented also in the hippocampus of enriched mice, together with a faster transition from excitatory to inhibitory GABA action (He et al., 2010).

A recent study suggests that exposure to EE is also able to modulate the programming of energy balance and food intake. Mice enriched from birth, but not mice exposed to EE when adult, show decreased levels of leptin, despite similar adipose mass and normal food intake. This effect is based on an enhanced leptin signaling and higher excitatory input on anorexigenic neurons in the arcuate nucleus of the hypothalamus found in young EE mice (Mainardi et al., 2010a; Mainardi et al., 2013).

The beneficial effects of EE are not limited to subtle functional changes evoked by the environment in the absence of pre-existing pathologies but extend to include the case of genetically programmed states of brain disability. One paradigmatic example is that of Down syndrome, the most common genetic cause of mental retardation caused by triplication of chromosome 21. People with Down syndrome have a severe cognitive impairment (Nadel, 2003; Pennington et al., 2003) and a number of attention and visual deficits (Brown et al., 2003; Clark and Wilson, 2003; John et al., 2004). The most widely studied animal model of Down syndrome is the Ts65Dn mouse, which carries triplication of a segment of Chr16 syntenic with human Chr21 (Gardiner et al., 2003; Seregaza et al., 2006). Ts65Dn mice recapitulate the main hallmarks of the Down syndrome phenotype, with severe defects in learning abilities and attention and visual functions (e.g., Holtzman et al., 1996; Escorihuela et al., 1998; Scott-McKean et al., 2010). An essential mechanism underlying these defects has been shown to be excessive brain inhibition, leading to a failure of long-term synaptic (LTP) plasticity in the hippocampus (Siarey et al., 1999; Kleschevnikov et al., 2004; Fernandez et al., 2007; Best et al., 2012). The central role of overinhibition in the Down syndrome pathogenesis is confirmed by the demonstration that administration of various classes of antagonists of GABA receptors reverses major cognitive disabilities and LTP deficits in Ts65Dn mice (Rissman and Mobley, 2011). Recently, we tested the EE potential for

therapeutic application in the Ts65Dn model of Down syndrome. Our findings show that EE promotes recovery from cognitive impairment and synaptic plasticity failure and induces a full rescue of visual acuity, ocular dominance, and visual neuronal response latencies in Ts65Dn mice compared to their littermates reared in standard conditions, an effect accompanied by normalization of GABA release in hippocampal and visual cortex synaptosomes (Begenisic et al., 2011). Interestingly, it has been reported that transgenic mice with overdosage of Dyrk1A, a key Down syndrome candidate gene, display recovery from their deficits in adult hippocampal neurogenesis after exposure to EE, an effect due to normalization of DYRK1A kinase overdosage (Pons-Espinal et al., 2013). The beneficial effects of EE are not limited to adulthood: indeed, we recently found that exposure to early EE in developing Ts65Dn mice is able to prevent most of their characteristic deficits in terms of declarative memory abilities, hippocampal synaptic plasticity, and visual system maturation (Begenisic et al., 2015).

Other well-established cases of mouse models of syndromes linked to gene mutation having their phenotype ameliorated following exposure to an enriched environment are heterozygous Mecp2 null mice, a model of Rett syndrome, and Fmr1-knockout mice, a model of Fragile X syndrome (Restivo et al., 2005; Lonetti et al., 2010).

Strikingly, there have been recent attempts to directly translate these successful results from the animal models to humans, specifically in the fields of autism and Down syndrome treatment. A randomized controlled trial enrolled 2- to 12-year-old children with autism and assigned them to either a control group or to a sensorimotor enrichment procedure mostly consisting of daily olfactory-tactile stimulation. The results, very encouraging, demonstrated a marked clinical improvement for the enrichment group in terms of the severity of autism as assessed with the Childood Autism Rating Scale, together with a clear improvement in cognition (Woo and Leon, 2013). Moreover, the same procedure of early multisensory massage intervention previously used in preterm babies has been shown to be very effective in also promoting visual acuity and stereopsis maturation in children with Down syndrome (Purpura et al., 2014), who are often at high risk for environmental impoverishment due to prolonged hospitalization and frequent deterioration in parent-infant bonding.

Is it possible to rejuvenate the brain? Impact of EE on adult visual system plasticity

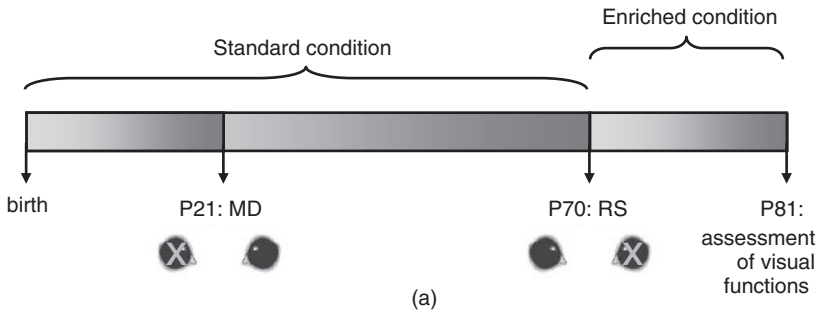
The study of visual system plasticity under environmental conditions of scaled complexities has provided significant advances not only in the field of brain development but also in our knowledge concerning the molecular processes underlying the closure of the CP and the ensuing dramatic decline in the potential for neuronal plasticity.

With the closure of the CP in the primary visual cortex, the possibility to induce functional and structural changes in this structure in response to a modulation of sensory experience abruptly wanes. This leads to permanent brakes to the cerebral potential for recovery from possible defective processes that may have occurred during development, preventing or robustly limiting functional rehabilitation. Certainly one of the most ambitious goals in basic and clinical neuroscience research is to develop suitable procedures able to overcome the major obstacles that reduce plasticity levels in the adult brain (Bavelier et al., 2010). Also in this case, the visual system emerges as one of the favorite testing grounds.

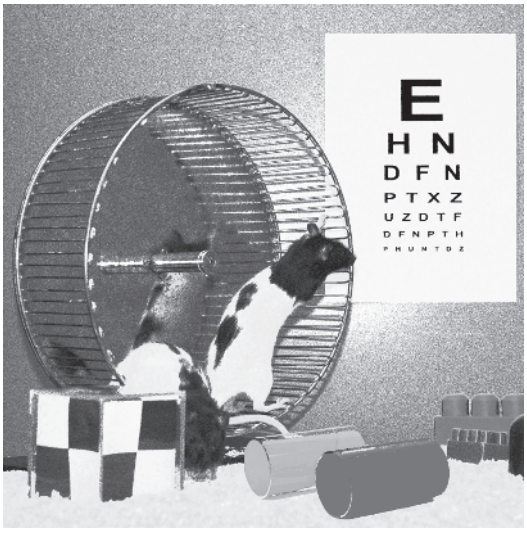
It has to be underlined that the decay of plasticity in the adult visual system may be not as absolute as previously thought, but it seems actually dependent on the specific neural processes under investigation. A striking example of use-dependent plasticity persisting for the entire life span has been described by Bear and colleagues (Frenkel et al., 2006), who showed that repeated exposure to grating stimuli of a single orientation results in a long-lasting increase of VEP amplitudes in response to the test stimulus. Another previously described example is the shift in orientation or spatial frequency selectivity displayed by cat primary visual cortical neurons after a period of adaptation consisting in the presentation of a stimulus at nonpreferred orientations or spatial frequencies (Ghisovan et al., 2008; Marshansky et al., 2011).

Despite these examples of plasticity not restricted to a CP, the possibility to obtain functional recovery from alterations of visual experience starting at early postnatal ages is extremely limited. One paradigmatic example of a permanent loss of visual abilities that is still orphan of treatment is amblyopia (lazy eye), a severe condition with an estimated prevalence of 1–5% in the total world population (Holmes and Clarke, 2006). Amblyopia is caused by an early imbalance between the two eyes, typically caused by unequal refractive power in the two eyes (anisometropia), abnormal alignment of ocular axes (strabismus), or visual clouding (Mittelman, 2003). If not precociously recognized and reversed, these defects eventually lead amblyopic subjects to develop a dramatic degradation of visual acuity and contrast sensitivity in the affected eye, experiencing multiple perceptual deficits that include stereopsis defects (Holmes and Clarke, 2006; Kiorpes, 2006; Levi, 2006).

In rats and mice, amblyopia can be very efficiently induced by means of a long-term occlusion of vision through one eye, using an enduring MD procedure that starts early in development and is protracted until adulthood (Figure 1.5). Using this useful model of experimental amblyopia, we showed that exposure to an enriched environment setting is one of the most effective procedures to reverse visual deficits in adult rodents, challenging the CP dogma. Indeed we reported that adult amblyopic rats transferred to an EE enclosure for 3 weeks undergo a full recovery of visual acuity and binocularity, with beneficial



(a)



(b)

Figure 1.5 Exposure to enriched conditions promotes recovery of visual functions in adult amblyopic rats. (a) Experimental amblyopia is easily induced in juvenile rats by imposing an artificial closure of one eye through lid suture (monocular deprivation [MD]), started at the peak of the critical period (postnatal day 21) and maintained until the animals reach the adult age (around P70). Then, reverse suture (RS) is performed, consisting in the reopening of the long-term deprived eye and simultaneous closure of the fellow eye, in order to force the animals to use their lazy eye. After RS, the animals are divided in two groups, one left undisturbed under standard-rearing conditions, the other one being transferred to an enriched environment setting. (b) Rearing adult amblyopic rats in an enriched environment for 3 weeks leads to a complete recovery of visual functions, in terms of visual acuity, binocularity, and stereopsis. (See insert for color representation of this figure.)

effects detectable at both the electrophysiological and the behavioral level, and outlasting the end of the treatment for at least 10 days (Sale et al., 2007b). The recovery of plasticity in enriched rats is accompanied by a three-fold reduction in GABA release detected in the visual cortex contralateral to the previously deprived eye, without any significant change in the release of glutamate, and it

is totally prevented by intracortical infusion of the GABAergic agonist diazepam. These observations led to the now widely accepted notion that the compelling ability of EE to promote adult brain plasticity is tightly linked to its impact on the brain excitation/inhibition balance, with a marked decrease in GABAergic transmission (Baroncelli et al., 2011). The possibility to reinstate juvenile-like levels of plasticity in the adult brain by manipulating the excitation/inhibition balance has been subsequently confirmed in more artificial conditions, with the demonstration that a pharmacological reduction of inhibition levels obtained through intracortical infusion of either MPA (an inhibitor of GABA synthesis) or picrotoxin (a GABAA antagonist) or through systemic administration of fluoxetine reactivates plasticity in response to MD in adult rats (Maya Vetencourt et al., 2008; Harauzov et al., 2010).

One case of particularly relevant clinical interest in the amblyopia field is that of those patients who lose the more functional eye due to an accident or ocular illnesses, thus becoming severely visually impaired. We recently addressed the possibility to rescue visual acuity in long-term deprived adult rats exposed to EE immediately after silencing of retino-thalamic projections of the fellow (nonamblyopic) eye due to optic nerve dissection (Tognini et al., 2012). Exposure to EE induced a full recovery of visual acuity in monocular rats, leading to lower numbers of GAD67+ cells and increased BDNF in the visual cortex.

The positive results obtained in enriched amblyopic animals strongly encourage researchers to find possible ways of application to clinics of the promising and noninvasive approach of EE. An intermediate and reasonable step might be that of investigating the impact of various independent EE components (e.g., social, sensory, motor). The general aim here is to design possible therapeutic approaches based on the most promising and effective variables.

Following this idea, we separately assessed the effects of either enhanced physical exercise, increased levels of social interaction, or sustained visual stimulation for their potential in promoting recovery from amblyopia in adult rats (Baroncelli et al., 2012). Our results show a full recovery of ocular dominance and visual acuity in exercised animals and in rats exposed to a protocol of visual enrichment. To further characterize the contribution of visual stimuli, we reused a protocol of classic EE (social, cognitive, motor and sensory stimuli together), but we placed enriched amblyopic animals under complete dark-rearing conditions, showing that they failed to recover their visual functions; visual recovery was also impossible even under normal light conditions, when the long-term deprived eye was maintained closed to prevent visual pattern perception; thus, EE must be coupled with proper visual stimulation in order to exert its beneficial effects. In agreement with this result, binocular lid suture has been shown to be unable to stimulate visual recovery from a preceding amblyogenic period of MD in kittens (Duffy et al., 2014).

In contrast to motor and visual enrichment, enhancing social stimulation alone was not able to induce restoration of normal visual acuity and ocular

dominance. Recovery from amblyopia was faithfully associated with a reduction of GABAergic intracortical inhibition, as revealed by decreased GABA release in synaptosome analysis. Thus, potentiation of single environmental components is able to reproduce the effect of visual function recovery from amblyopia previously reported in classically enriched animals (Baroncelli et al., 2012), possibly encouraging the implementation of new environmental strategies devoted to promote stimulation of the amblyopic eye in adult patients as a way to increase their chance of visual functional improvements.

A second way toward future applications of EE strategies to clinics is to find paradigms of increased sensory and/or motor activity that, resembling part or the whole ensemble of the EE beneficial effects, appear more promising in terms of the ensuing results on brain and behavior. In the visual system model, increasing evidence shows that experimental procedures akin to EE, such as playing videogames or practicing visual perceptual learning (PL), are quite effective in promoting recovery from amblyopia in adulthood (Levi and Li, 2009; Astle et al., 2011; Li et al., 2011; Green and Bavelier, 2012), likely acting by either modulating levels of molecular brakes or by promoting the expression of endogenous permissive factors such as neuromodulators.

PL is currently considered one of the most promising active strategies for treating amblyopia in adulthood (see Levi, 2012; Bonaccorsi et al., 2014). PL consists in the improvement in performance on a variety of simple sensory tasks, following practice and, in the visual system, involves identifying small differences in simple visual attributes, such as position, orientation, texture, or shape. Despite its suitability for inducing vision recovery in human subjects, the cellular and molecular mechanisms underlying PL effects are still scarcely known. Recently, we set up a new model of visual PL in rodents that led us to the possibility to test the impact of this procedure on visual cortical plasticity at the cellular and molecular level, a kind of analysis normally prevented when working on human subjects (Sale et al., 2011). To elicit visual PL, we first trained a group of adult animals to practice in a forced-choice visual discrimination task that requires them to distinguish between two vertical gratings differing only for their spatial frequency; then, we made the two stimuli progressively more similar to each other, until the animal performance reached a steady plateau (Figure 1.6(a)). This task requires activation of V1 circuitries, as indicated by the strong selectivity of PL for the orientation of gratings employed during training (Sale et al., 2011) (Figure 1.6(b)). Control animals only learned the association task, that is, they were only required to discriminate between a grating and a homogeneous gray panel, matching the overall swim time and number of training days in the water maze with those of PL rats (Figure 1.6(a)). Within 1 hour from the last discrimination trial, LTP from layer II-III of V1 slices appeared occluded in PL animals compared to controls, both when testing its inducibility in vertical connections (stimulating electrode placed in layer IV) and when

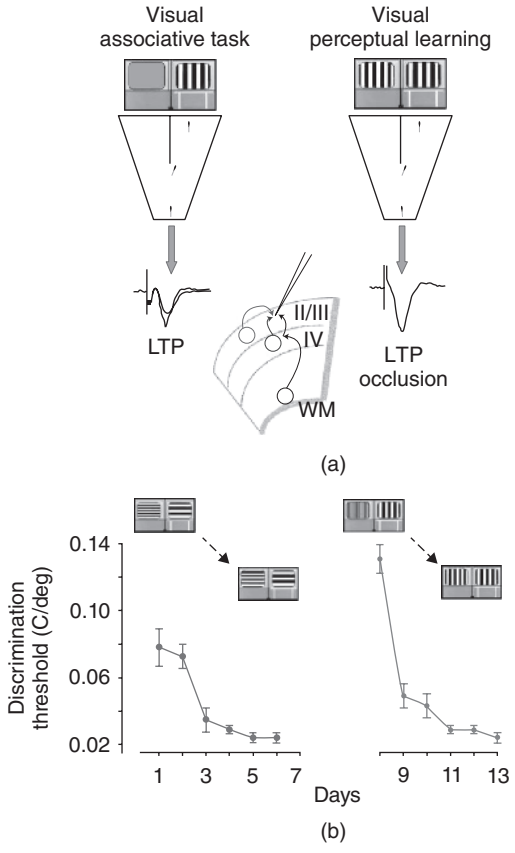


Figure 1.6 Visual perceptual learning induces long-term potentiation in the primary visual cortex. (a) A modified version of the visual water box task (Prusky et al., 2000; Cancedda et al., 2004) was used to induce visual perceptual learning in a group of adult rats that were first trained to distinguish a low 0.117 cycles per degree (c/deg) spatial frequency (SF) grating (reference grating) from a 0.712 c/deg SF grating (test grating) (right panel) and then learned to distinguish the two gratings when they became more and more similar to each other. A group of control animals was trained to distinguish the reference grating from a homogeneous gray (left panel). After training, LTP from layer II–III of V1 slices was occluded in PL animals compared to controls, at the level of both vertical (blue arrow) and horizontal (red arrow) connections. Sample traces from PL and control slices 5 minutes before (thin line) and 25 minutes after (thick line) induction of LTP are shown. (b) Visual perceptual learning is specific for stimulus orientation. The graphs show daily discrimination threshold values obtained in PL animals trained in discriminating first horizontal gratings and then tested with vertical. After the orientation change, the animals displayed a marked impairment in their discrimination abilities. Reprinted from Sale et al., 2012. (See insert for color representation of this figure.)

stimulating at the level of horizontal connections (stimulating electrode placed in layer II/III) (Figure 1.6(a)). Moreover, a significant shift toward increased amplitude of fEPSPs was found in the input/output curves of trained animals compared to controls (Sale et al., 2011). Thus, the data fulfill two of the most

commonly accepted criteria used to relate LTP with learning, that is, occlusion and mimicry, demonstrating that the improvements displayed by PL rats in discriminating visual gratings of progressively closer spatial frequencies can be explained in terms of long-term increments of synaptic efficacy in V1, the same cortical area at work during perception. This is consistent with the critical role of LTP in mediating learning processes previously reported in other brain areas such as the amygdala, the hippocampus, and the motor cortex (Rogan et al., 1997; Rioult-Pedotti et al., 2000; Whitlock et al., 2006). An impact on V1 LTP appears to be a common prerogative of visual PL and EE. Indeed, enriched rats also show an enhancement of thalamocortical LTP triggered by theta-burst stimulation (TBS) of the dorsal lateral geniculate nucleus of the thalamus (Mainardi et al., 2010b), leading to an enhancement in VEP responses to visual stimulation across a wide range of contrasts.

Since potentiation of synaptic transmission might help the recovery process of visual responses for the long-term deprived eye, practice with visual PL through the amblyopic eye is expected to favor a functional rescue in amblyopic animals. In agreement with this hypothesis, a marked recovery of visual functions was evident in amblyopic rats subjected to visual PL, while no recovery occurred in two control groups in which the treatment did not induce LTP in V1, that is, in rats that only learned the associative visual task and in animals that were trained only until the first step of the discrimination procedure between the test and the reference grating, without proceeding further with a progression of finer discrimination trials (Baroncelli et al., 2012). Recovery of visual abilities in PL animals was accompanied by a robust decrease of the inhibition-excitation balance.

Concluding remarks

The data reviewed in this chapter demonstrate that exposure to EE conditions is a powerful tool to modulate the development of the central nervous system and to boost plasticity in the adult brain. The secret of the EE approach resides in its ability to impact, under physiological developmental conditions, on molecules critically involved in brain maturation and plasticity, such as growth and neurotrophic factors or GABA-ergic inhibition levels, or to successfully implement, in the presence of concurrent developmental pathologies, a kind of endogenous pharmacotherapy (Sale et al., 2014), that is, the stimulation of the spontaneous reparative potential held by the brain even without the concomitant administration of external artificial substances. Finding suitable strategies for translating EE in human terms in order to apply its framework to the treatment of several neurodevelopmental disorders and adult neurological diseases emerges as an urgent need for clinical practice and a major challenge for future neuroscience research.

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