Chapter 14

Environmental Influences on Visual Cortex Development and Plasticity

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1. Introduction

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, underlying the adaptive development and remodeling of neuronal circuitry. The primary visual cortex (V1) 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. They 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 the ocular dominance (OD) 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 [1]. Anatomically, the imbalance of activity between the two eyes results in the shrinkage of deprived eye ocular dominance columns, regions in V1 layer IV which receive thalamic inputs driven by the closed eye, and in the expansion of open eye ocular dominance columns [2-5], accompanied by a rapid remodeling of cortical horizontal connections [6]. Behaviorally, long-term MD is associated with a poor development of visual acuity (VA) and contrast sensitivity for the deprived eye and a loss of binocular vision. Strikingly, the same manipulation of visual experience appeared to be totally ineffective in the adult [4], leading to the characterization of a classic example or critical period, a time-window early in life in which the brain displays enhanced neural plasticity in response to experience [7-12].

In parallel to this seminal work based on a sensory deprivation approach, fundamental contributions to our knowledge of the effects of experience on the brain have been provided by the environmental enrichment (EE) paradigm, first introduced by the group of Rosenzweig and colleagues, in California. Originally defined as "a combination of complex

inanimate and social stimulation" [13], EE consists in wide and attractive cages where the animals are reared in large social groups and in presence of a variety of objects (e.g. toys, tunnels, nesting material, stairs) that are frequently changed by the experimenter to stimulate explorative behavior, curiosity and attentional processes. A further, essential component of EE is the opportunity for the animals to attain sustained levels of voluntary physical exercise on one or more running wheels. EE definition is based on the comparison with alternative rearing conditions, such as the standard condition (SC), 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, or the so-called impoverished condition (IC), in which even social interactions are impossible because the animals are reared alone in individual cages, otherwise identical to those used for SC. With respect to their standard-reared or impoverished companions, enriched animals have the opportunity for enhanced social interaction, multi-sensorial stimulation and increased levels of physical activity, with the additional advantage that they are totally free to choose when and how much to experience the environmental richness, without the contingencies and risks typically associated with living in the wild [14].

In over fifty years of research in the field, a great number of studies have documented the positive impact of EE on the morphology, chemistry and physiology of the brain [14-17]. Initial experiments by Rosenzweig et al. [18] showed that after 30 days of exposition to an enriched living condition the cortex of enriched rats increased robustly in thickness and weight compared with that of standard reared animals. These changes occurred in the entire dorsal cortex, including frontal, parietal and occipital cortex. Since then, many studies have reported various anatomical changes associated with enriched living conditions, including nearly all structural components analyzed, such as increased dendritic arborization and length of dendritic spines [19-21], augmented synaptic size and number [22, 23] and increased postsynaptic thickening [24] and gliogenesis [25].

More recently, EE studies have regained special interest with the fall of the dogma regarding the postulated incapability of adult brain to generate new neurons. Although, in mammals, the majority of neurons are generated by the time of birth, some brain structures, with the paradigmatic examples of the granule cells of olfactory bulb and hippocampal dentate gyrus, maintain this potentiality for neurogenesis even after sexual maturity [26, 27], a property that has been demonstrated not only in rodents but also in monkeys [28] and, remarkably, in humans [29]. Numerous studies have shown that exposure to an enriched environment produces a significant increase in hippocampal neurogenesis [30]. A similar effect is induced by enhanced levels of physical exercise through running [31, 32], but the two conditions appear to act with distinct mechanisms: while voluntary exercise alone in a standard cage increases neurogenesis with an increment in both proliferation and survival of new-generated neurons, exposure to an enriched environment is only able to increase the number of surviving newborn cells, leaving the proportion of newly born cells unaffected. It has been suggested that to induce a shortening of the cell cycle or to elicit additional quiescent cells to enter the cell cycle (both effects resulting in increased amount of cell proliferation and neurogenesis) one specific type of very focused activity is needed, such as

running. Running levels are probably not increased in the enriched condition to the same levels occurring with standard cage running. Interestingly, running increases brain uptake of the insuline-like growth factor I (IGF-I) [33], and IGF-I has been shown to accelerate cell cycle in the embryonic cerebral cortex [34]. If present at the level of adult brain neurogenesis, this effect could explain the strong influence elicited by sustained levels of voluntary running on hippocampal cell proliferation. The ability of EE to interact with the programs of nerve cell renewal extends beyond the influence on neurogenesis, including the capability to reduce apoptotic cell death in the hippocampus under both natural conditions and following excitotoxic insults [35]. These results challenge the traditional view that the anatomical structure of the brain is immutable under non-pathological conditions, revealing an unexpected plasticity induced by environmental stimulation at the structural level.

One striking peculiarity of EE is its ability to improve learning and memory functions, and with a specific reduction of the cognitive decline associated with aging [36, 37]. This last effect is related to a robust facilitation of hippocampal LTP, a widely accepted synaptic plasticity model of learning and memory [38] and linked with general signs of "cellular health" in the hippocampus, such as increased levels of synaptophysin [39, 40], a glycoprotein found in membranes of neurotransmitter-containing presynaptic vesicles, a reduced load of lipofuscin deposits [41], which are good indicators of chronic oxidative stress [42], and the pronounced induction of hippocampal neurogenesis [41]. EE positively affects also emotional and stress reactivity, both in normal animals and in strains of mice considered pathologically anxious [43]. Interestingly, the effects of EE are not restricted to the cerebral cortex, as demonstrated by a recent work in which this paradigm has been used to investigate the effects of lifestyle change on metabolic parameters [44]. Enriched mice showed decreased leptin, reduced adipose mass, and increased food intake compared to standard-reared animals, demonstrating that the leptin-hypothalamic axis can be enhanced by environmental stimulation.

At the molecular level, studies based on gene chip analysis have revealed that a large number of genes related to neuronal structure, synaptic transmission and plasticity, neuronal excitability and neuroprotection change their expression levels in response to EE [45]. One group of molecules particularly sensitive to experience are neurotrophins, a family of secreted factors critically involved in structural and functional plasticity during development and in adulthood [46].

An important line of research deals with the potential therapeutic effects of EE: indeed, it has been shown that enriching the housing environment delays the progression of, and facilitates recovery from, various nervous system dysfunctions, including neurodevelopmental disorders, neurodegenerative diseases, different types of brain injury and psychiatric disorders [47-54]. These studies have profound consequences for humans. The development of intervention protocols aimed at maintaining a healthy and active lifestyle has been effectively encouraged by the results of basic research on EE. For example, strong correlative and epidemiological evidence shows that living habits, including occupation, leisure activities and physical exercise, have a direct effect on the risk of cognitive decline, with an increasing number of results indicating that a higher level and

variety of mental and physical activity is associated with lower cognitive decline and reduced risk for dementia (for a review, [55]).

2. Environmental enrichment and visual system development

2.1. Acceleration of visual system development by EE

Most studies addressing the effects elicited by EE focused on the adult brain, leaving almost unexplored the question whether an enhanced environmental stimulation can also affect processes governing the development of the brain architecture. In Neuroscience and developmental Psychobiology, this is a fundamental issue dealing with the classic debate about the role of Nature and Nurture, or, in more biological terms, Genes and Environment, in the construction of brain structure and its functional output, the behavior.

The scarce interest attracted by early EE studies can be possibly attributed to the fact that pre-weaning enrichment is characterized by very little amounts of voluntary physical exercise, as the pups are too inert to engage in sustained motor activities. Since increased levels of physical activity are thought to be an essential component of the enrichment protocol [16], this can explain why the possibility to evoke neural and behavioral changes through pre-weaning enrichment have been considered quite limited. For instance, differently from adult animals, hippocampal neurogenesis was not found to be promoted by an intensive preweaning EE protocol consisting of increasing complex combinations of tactile, olfactory, visual, acoustic and vestibular stimuli to which pups were exposed from post-natal day 7 (P7) until P21 [56]. However, since early EE provides increased levels of polysensory stimulation occurring during a period of high anatomical and functional rearrangement of the cerebral cortex, it might be expected to elicit brain changes through experience-dependent plasticity processes.

Some years ago, we started in Pisa a series of studies in which we focused on visual system maturation in environmentally enriched rodents as a paradigmatic model to probe the impact of experience-dependent stimulation on central nervous system development. This approach has proved quite fruitful, allowing us to open a window on the dynamic building of the brain according to different levels of environmental stimulation.

One sensitive parameter which allows researchers to faithfully follow visual system maturation is the progressive increase of visual acuity that occurs during the first postnatal weeks (in rodents), months (in monkeys) or years (in humans). The time course of this process, which results in the ability to perceive fine spatial details in the visual world, turned out to be highly susceptible to the influence exerted by EE, with a one- (in the mouse) or two- (in the rat) week acceleration displayed by both mice and rats exposed to EE since birth [57, 58]. In the timescale of human visual development this is a strong effect, if one considers that is corresponds to an acceleration of about two years in the five-year period normally required for a child to reach adult-like visual acuity values. At the synaptic plasticity level, EE induces a faster closure of the time-window during which it is possible, early in development, to induce LTP in visual cortical slices through theta-frequency

stimulation from the white-matter [57]. Moreover, the functional effects of EE are preceded by a very early increase in the visual cortex of the expression of brain-derived neurotrophic factor (BDNF), a neurotrophin strongly involved in the maturation of brain circuitries. BDNF increase at P7 is accompanied by an enhanced expression of the GABA biosynthetic enzymes, GAD65 and 67, detectable both at P7 and P15. These findings led us to compare our results (see [14]) with those previously found in BDNF overexpressing mice. In these animals, BDNF expression in the visual cortex is higher than in wt mice starting from very early postnatal ages and this correlates with a precocious development of intracortical GABAergic inhibition, as shown by the faster developmental increase in inhibitory postsynaptic currents and GABA biosynthetic enzyme GAD65 in the perisomatic region of pyramidal cells [59]. This early development of GABAergic inhibition is accompanied by an accelerated maturation of visual acuity, likely due to the refinement of visual receptive fields under the direct control of inhibitory interneurons. Thus, EE effects on BDNF and GABA biosynthetic enzymes provide an explanation for EE action on visual cortical development and confirm the role of neurotrophins and of the intracortical GABAergic inhibition as determinants of visual functional development.

Application of EE paradigms allowed us also to demonstrate a key role in visual development of another molecule, insuline-like growth factor-I (IGF-I). IGF-I expression is increased at P18 in the visual cortex of rats raised in EE compared to standard-reared animals, and exogenous IGF-I supply mimics, whereas blocking IGF-I action prevents, the EE effects on visual acuity maturation [60]. It is possible that BDNF and IGF-I signaling may eventually converge on the same pathways, as suggested by results showing that the CREB/CRE-mediated gene expression, which is regulated by both molecules [61, 62], is developmentally accelerated in the visual cortex of enriched animals, while chronic injections of control animals with rolipram, a pharmacological treatment increasing the phosphorylation of CREB, partially mimic the EE outcome on visual acuity maturation [57]. Another biochemical pathway shared by BDNF and IGF-I might be regulation of the inhibitory GABAergic system, since cortical interneurons respond to IGF-I infusion increasing GAD65 expression in their synaptic terminals [60].

The precociousness of EE effects on BDNF and GAD65/67 challenges the intuitive view by which the development of a particular sensory system should be strictly dependent on experience of the same sensory modality. Indeed, the increase in BDNF and GAD enzymes does not require vision at all, if one considers that it is clearly evident before eye opening and even before photoreceptor formation. This is confirmed by results obtained in enriched rats raised in darkness during development [63]. It is well known that rearing mammals in total darkness affects the maturation of visual cortical circuits, prolonging the duration of the critical period and impairing the process of visual acuity maturation until normal visual experience is re-established [64, 65]. We found that both effects of dark rearing were completely counteracted by EE [63]. Once again, the effect is very similar to that found in BDNF over-expressing mice, where a full rescue of the typical dark-rearing phenotype has been reported [66].

The impact of EE on visual system development turned out not to be restricted to the cerebral cortex, but was clearly present also at the level of the retina, a peripheral part of the central nervous system traditionally considered little or not plastic at all in response to changes of sensory inputs. This classic concept has been mostly based on results showing that retinal acuity, i.e. the spatial discrimination limit of the retinal output, determined with electroretinogram, is unresponsive to visual deprivation in cats, rats and humans [64, 67, 68]. However, when probed with EE, retinal development resulted to be robustly accelerated, both when taking into account retinal acuity development [58] and when analyzing the process of retinal ganglion cell dendrite segregation into ON and OFF sublaminae [69]. The molecular alphabet underlying these changes appears to be the same followed by the visual cortex: levels of retinal IGF-I and BDNF are precociously increased in the retinal ganglion cell layer of developing rats raised under enriched conditions, and separately blocking IGF-I or BDNF action prevents EE effects [58, 69]. Interestingly, the possibility to evoke retinal plasticity is not a prerogative of an enhanced environmental stimulation, as both the anatomical and physiological maturation of retinal circuits is also altered by a complete lack of visual experience in mice [70, 71].

2.2. Maternal enrichment effects

The precociousness of the effects elicited by EE on brain development led us to hypothesize that they might be mediated by maternal behavior differences between enriched and non-enriched dams. What else, indeed, might cause a P7 increase of BDNF in pups spending the whole time in the nest, with no exploration of the enriched surroundings and no visual experience of it? Experience acquired between birth and weaning is essential in promoting and regulating neural development and behavioral traits of the newborn in both rodents and primates [72]. During this critical period of high developmental plasticity, maternal influence can be considered one of the most important sources of sensory experience for the developing subject [73-75], regulating physical growth and promoting the neural maturation of brain structures [72, 76, 77]. Our hypothesis of a critical involvement of maternal behavior in early EE effects has found experimental support in a detailed quantitative study of maternal care in different environmental conditions, which showed that enriched pups receive higher levels of maternal stimulation compared to standard-reared animals [78]. More specifically, enriched rats experience a continuous physical contact due to the presence of adult females in the nest and are also provided with increased levels of licking and grooming, a fundamental source of tactile stimulation. Thus, living in an EE setting provides the animals with an additional source of stimulation other than the social, cognitive and motor components: maternal touch. More recently [79], we were able to reproduce the EE-dependent acceleration of visual development by providing standard-reared rat pups, during their first ten postnatal days of life, with a tactile stimulation (massage) mimicking maternal behavior, a procedure previously shown to compensate for the deleterious effects of long-lasting maternal deprivation (Figure 1) [80-82]. In addition to

an accelerated maturation of visual acuity, stimulated pups exhibited increased IGF-I levels at P18, and blocking the IGF-I action prevented its effects on visual system development [79].

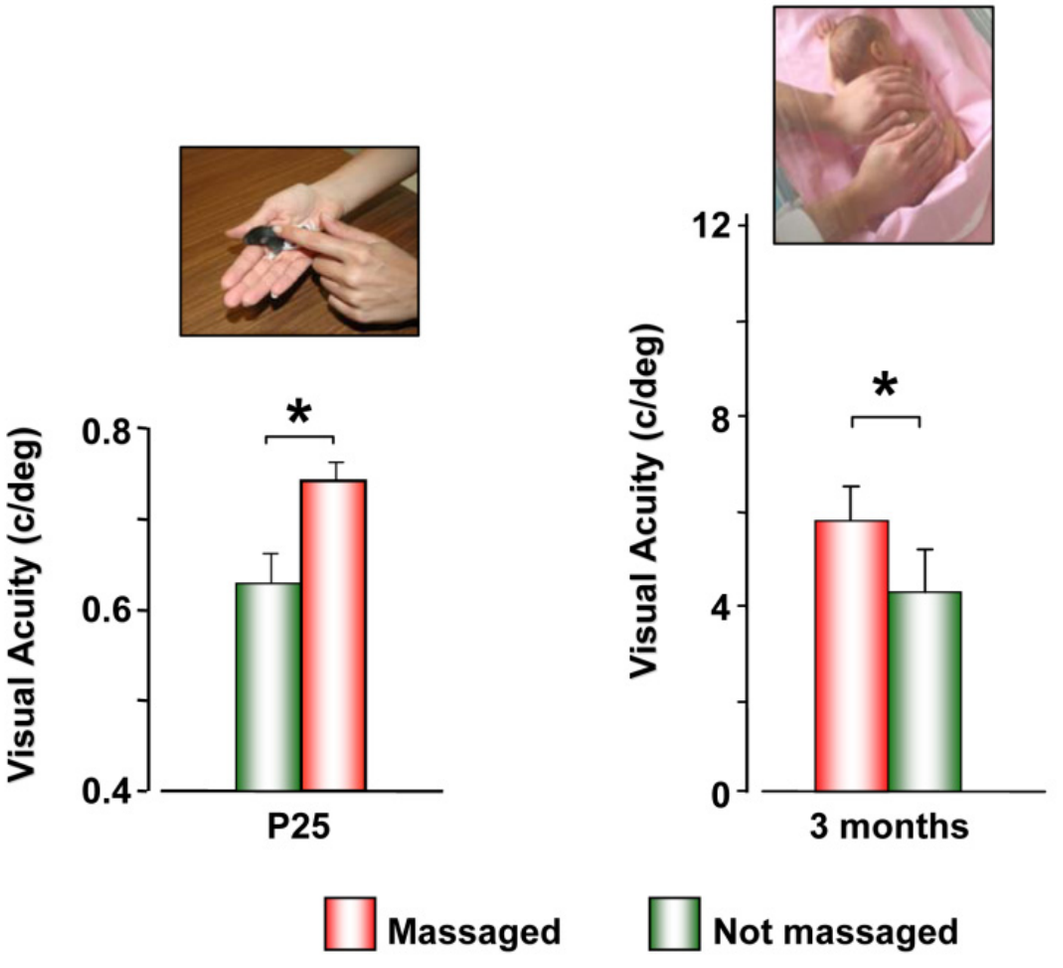

Figure 1. Massage therapy promotes visual acuity maturation in pre-term infants and rat pups. In rat pups, massage was performed during the first twelve postnatal days, three times per day. Stimulated rats exhibited higher visual acuity values compared to non-stimulated controls at postnatal day (P) 25. In pre-term babies, massage therapy started on day 10 after birth and continued for a total of ten days. During tactile stimulation, the infants were placed prone and given moderate pressure stroking with the flats of the fingers of both hands. In addition, passive flexion/extension movements of the limbs were applied in sequence. Visual acuity in massaged infants was significantly higher than in controls at 3 months. Asterisks indicate statistical significance. Data replotted from Guzzetta et al. [79].

Since the essence of EE embodies the concept of "optimization" of sensory-motor stimulation rather than its "alteration or reduction", this paradigm is an ideal candidate for application to humans. In parallel to the effects obtained in massaged rats, Guzzetta et al. [79] reported that enriching the environment in terms of body massage ('massage therapy') accelerates brain development in healthy pre-term infants (gestational age between 30 and 33 weeks). Massaged infants exhibited a faster developmental reduction in the latency of flash visual evoked potentials (VEPs) and an increase in behavioral visual acuity, which persisted above two

months after the end of the treatment. Moreover, a faster EEG maturation was evident in massaged babies, as shown by the more rapid shortening of the interbust intervals, a reliable index of the developmental stage of the brain electrical activity. Interestingly, massaged babies did not exhibit the change in EEG spectral power found in the comparison group [83], confirming that massage intervention affects the maturation of brain electrical activity and suggesting that if may favor a process more similar to that observed in utero in term infants. In good agreement with results obtained in the animal model, massaged infants displayed increased levels of plasma IGF-1 [79]. The results of these studies, which are one of the first attempts to rigorously investigate the effects of early EE on human brain, emphasize the role of mother Nurture as a driving force for brain development in humans.

Maternal influence on the offspring development not only takes the form of maternal care given to pups during the first postnatal weeks, but it also includes the complex supply of nutrients, hormones and respiratory gases provided by the mother to the fetus during pregnancy, through placental exchanges [84]. The extent to which different environmental conditions experienced by the mother during pregnancy affect fetal development is still debated. For many years, the best documented effects were only those elicited by prenatal stress protocols, which have a well established role in growth retardation and structural malformations of the offspring [85, 86]. We found that the ability of EE to modulate growth factors critical for central nervous system development is present also during prenatal life (Figure 2).

Indeed, enriching female rats for the entire length of gestation results 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-I [87]. We proposed a model in which sustained physical exercise during pregnancy increases IGF-I in the mother, promoting placental transfer of nutrients to the fetus; this would in turn lead to increased amounts of IGF-I autonomously produced by the fetus, resulting in the accelerated development detectable at retinal level (Figure 2). The influence exerted by maternal enrichment during pregnancy on the fetus is not restricted to the visual system. The hippocampus of pups born from enriched mothers, indeed, displays increased expression of BDNF [88] and increased proliferation of progenitor cells in the granule layer [89], resulting in improved cognitive functions when the animals reach adult ages [90].

3. Impact of EE on adult visual system plasticity

3.1. Amblyopia recovery in enriched animals

When visual functions mature up to their adult-like levels, the critical period for plasticity in the visual cortex closes and the possibility to induce further functional and structural changes by manipulating sensory experience abruptly wanes. This poses enduring brakes to the potential for recovery from defective development and for functional rehabilitation. Overcoming the obstacles which limit plasticity in the adult brain is a fundamental goal of both basic and clinical research in Neuroscience [91].

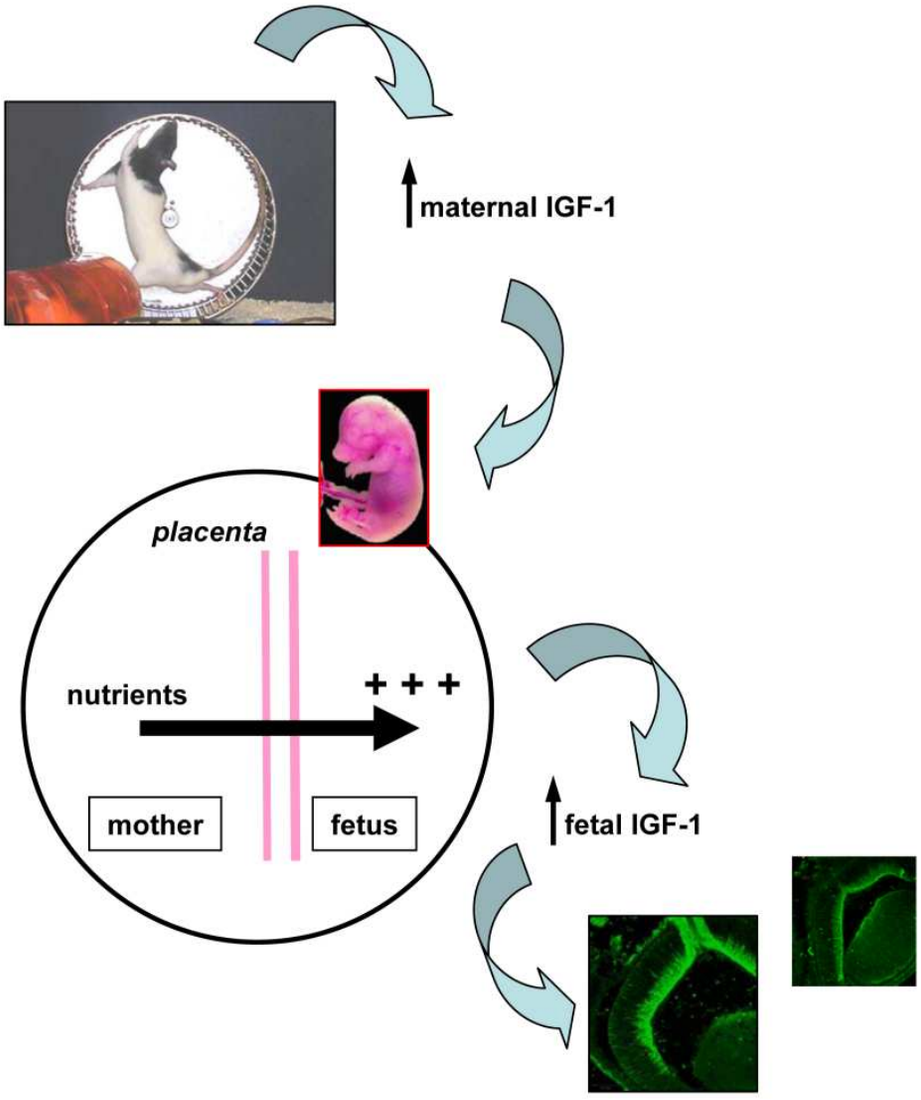

Figure 2. Prenatal enrichment modulates retinal development in the fetus. The figure depicts a possible explicative model for the effects elicited by maternal enrichment during pregnancy on retinal development. Increased levels of physical exercise in gestating dams lead to higher amounts of circulating IGF-I 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 fetal tissues, with an increased expression detectable in the ganglion cell layer of the retina. IGF, in turn, stimulates the maturation of retinal circuitries. The photographs depict two examples of one enriched (left) and one non-enriched (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. Modified from Sale et al. [87].

The decay of plasticity levels in the adult visual system is not absolute, of course, but is dependent on the kind of stimuli and neural processes under investigation. A striking example of use-dependent plasticity in the adult visual cortex has been described in the work of Bear and colleagues which 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 [92]. Another well defined phenomenon is the shift in orientation or spatial frequency selectivity displayed by neurons in the cat primary visual cortex after a period of adaptation consisting in the presentation of a stimulus at non-preferred orientations or spatial frequencies [93, 94]. Despite these and other [95] remarkable examples of adult V1 plasticity, however, the possibility of recovery from the consequences of an altered visual experience extending beyond the end of critical periods is extremely limited. One paradigmatic example of an enduring loss of visual abilities which is still orphan of treatment is amblyopia (lazy eye), a severe condition with an estimated prevalence of 1-5% in the total world population [96]. Amblyopia is caused by a marked functional imbalance between the two eyes occurring early in development and due to an unequal refractive power in the two eyes (anisometropia), an abnormal alignment of ocular axes (strabismus) or visual clouding caused, for instance, by congenital cataract [97]. If the cause of visual impairment is not rapidly removed, amblyopic subjects develop a dramatic degradation of visual acuity and contrast sensitivity in the anisometropic, strabismic or cataract affected eye and experience a broad range of other perceptual deficits, including stereopsis defects [96, 98, 99]. These deficits are attributed to the alteration in ocular dominance and binocularity of neurons in the developing visual cortex caused by the imbalance between the inputs form the two eyes.

While it is generally accepted that recovery of visual functions is possible only if normal visual experience is re-established early in development, recent studies in rodents have shown new therapeutic possibilities for the treatment of adult subjects [100]. In animal models like rats and mice, amblyopia can be easily induced by imposing a long-term occlusion of vision through one eye by an enduring MD procedure starting at the peak of plasticity early in development and protracted until adulthood. In the effort to challenge the critical period dogma, we showed that adult amblyopic rats transferred to an EE setting for three weeks undergo a full recovery of visual functions [101]. Immediately before starting the EE procedure, all rats were subjected to reverse suture, which consists in the re-opening of the long-term deprived (amblyopic) eye and the concomitant closure of the eyelids in the fellow eye, a procedure that, analogously to the so-called patching therapy in humans [102], is aimed at penalizing the preferred eye and forcing the brain to use visual inputs carried by the amblyopic eye. Reverse suture is very effective in promoting recovery form amblyopia if performed during the critical period but it is ineffective in adult subjects. On the contrary, reverse suture in animals exposed to EE was found to promote a complete rescue of ocular dominance and visual acuity, with beneficial effects detectable at both the electrophysiological and behavioral level and outlasting the end of the treatment for at least ten days. Recovery of plasticity in enriched animals was accompanied by a three-fold reduction in GABA-release detected in the visual cortex contralateral to the previously deprived eye by means of in vivo brain microdialysis, without any significant change in the release of glutamate. Moreover, the beneficial effects elicited by EE were totally counteracted by intracortical infusion of the benzodiazepine Diazepam, revealing a key role for decreased GABAergic transmission in

driving amblyopia rescue in enriched animals. This was one of the first demonstrations that reducing the inhibition-excitation balance reinstates plasticity in the adult brain [103], as subsequently confirmed by another study in which a pharmacological reduction of inhibition through intracortical infusion of either MPA (an inhibitor of GABA synthesis) or picrotoxin (a GABAA antagonist) was reported to reactivate plasticity in response to MD in adult rats [104] (Figure 3).

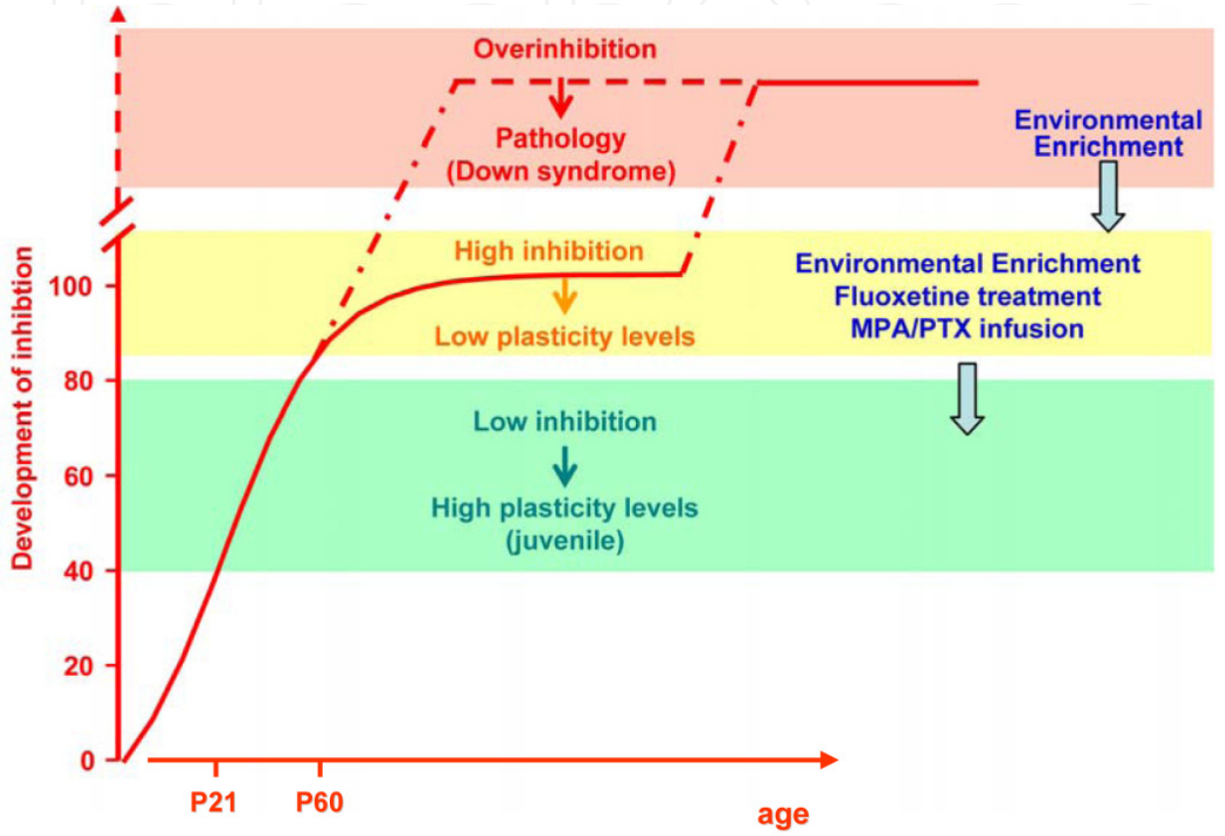

Figure 3. Developmental increase of brain GABAergic inhibition levels is paralleled by a progressive reduction of experience-dependent plasticity. Plasticity is high during early development (green block) and very low in the adult brain (yellow block). Anomalous increases in the strength of inhibitory neural circuits may lead to overinhibition linked to permanent deficits in synaptic plasticity and neural development, like in the Down syndrome. Reducing GABAergic inhibition with environmental enrichment, fluoxetine or pharmacological treatments (blockers of GABA synthesis or GABA receptor antagonists) can increase plasticity in the adult brain, enabling plasticity in V1 and favoring recovery from amblyopia. The capability of EE to reduce GABAergic inhibition makes this paradigm eligible for therapeutic applications also in the treatment of developmental intellectual disabilities. Plasticity levels have been normalized to the normal adult values (red curve). Modified from Sale et al. [113].

In amblyopia, one case of particularly relevant clinical interest is that of those patients who loose their better eye due to an accident or ocular illnesses, thus becoming severely visually impaired. It has been reported that the visual acuity of the amblyopic eye can display partial spontaneous recovery following loss of vision in the fellow eye [105-109], but the occurrence of this fortunate response is unpredictable and which factors promote improvement under

similar circumstances remains totally unknown. 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 (non amblyopic) eye due to optic nerve dissection [110]. While no spontaneous rescue of visual abilities was detected in animals reared under standard environmental conditions, a full recovery of visual acuity was achieved in monocular rats exposed to EE, an effect accompanied by lower numbers of GAD67+ cells and increased BDNF in the visual cortex. Thus, an enhanced environmental stimulation can promote visual cortex plasticity and functional recovery even in a condition in which competition between the two eyes is completely suppressed. However, this effect fits also well with a competition-based model, because stronger inputs from the fellow eye could mask activity in the weaker connections from the amblyopic eye until they are selectively silenced by optic nerve dissection.

Since it is currently thought that the inhibition-excitation balance is also impaired during development in amblyopic human subjects and that excessive inhibition levels are involved in the degradation of their spatial vision abilities [111, 112], EE appears as a very promising strategy to counteract visual impairments in amblyopia. Application to clinics of these results obtained in animal models requires the ability to transfer the EE paradigm in the much more complicated and variegated dimension of human life. A fruitful approach might be that of investigating the role of various independent EE components (e.g. social, sensory, motor) in reproducing the beneficial effects elicited by the entire enriched experience, and then designing therapeutic approaches based on the most promising and effective variables.

Recently, we followed this route by separately assessing the efficacy of physical exercise, increased levels of social interaction and enhanced visual stimulation for their potential in promoting recovery from amblyopia in adult rats [114]. Our results show a full recovery of ocular dominance and visual acuity either in both animals experiencing high levels of voluntary motor activity in a running wheel and in rats exposed to a protocol of visual enrichment inside a rotating fluorescent drum specifically designed to maximize stimulation of V1 cortical neurons (Figure 4). The strong involvement of visual experience in the recovery process was further indicated by the demonstration that amblyopic animals placed under classic EE conditions, but completely deprived from visual stimulation, failed to recover normal visual functions, and that using EE in no-reverse sutured animals in which the long-term deprived eye was maintained closed, prevented the animals to differentiate their visual function abilities from untreated controls. In contrast to motor and visual enrichment, enhancing social stimulation alone was not able to induce restoration of normal visual acuity and ocular dominance (Figure 4). 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 components typically present in EE is able to reproduce the effect of visual function recovery from amblyopia previously reported in classically-enriched animals [101, 114]. These findings should

encourage 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.

3.2. Visual perceptual learning and amblyopia

The possibility to reinstate plasticity in the adult visual cortex by using a non-invasive procedure such as EE is appealing. A growing body of evidence in humans shows that experimental paradigms akin to EE, such as playing videogames or practicing visual perceptual learning (PL), are effective in promoting recovery from amblyopia in adulthood [115-118].

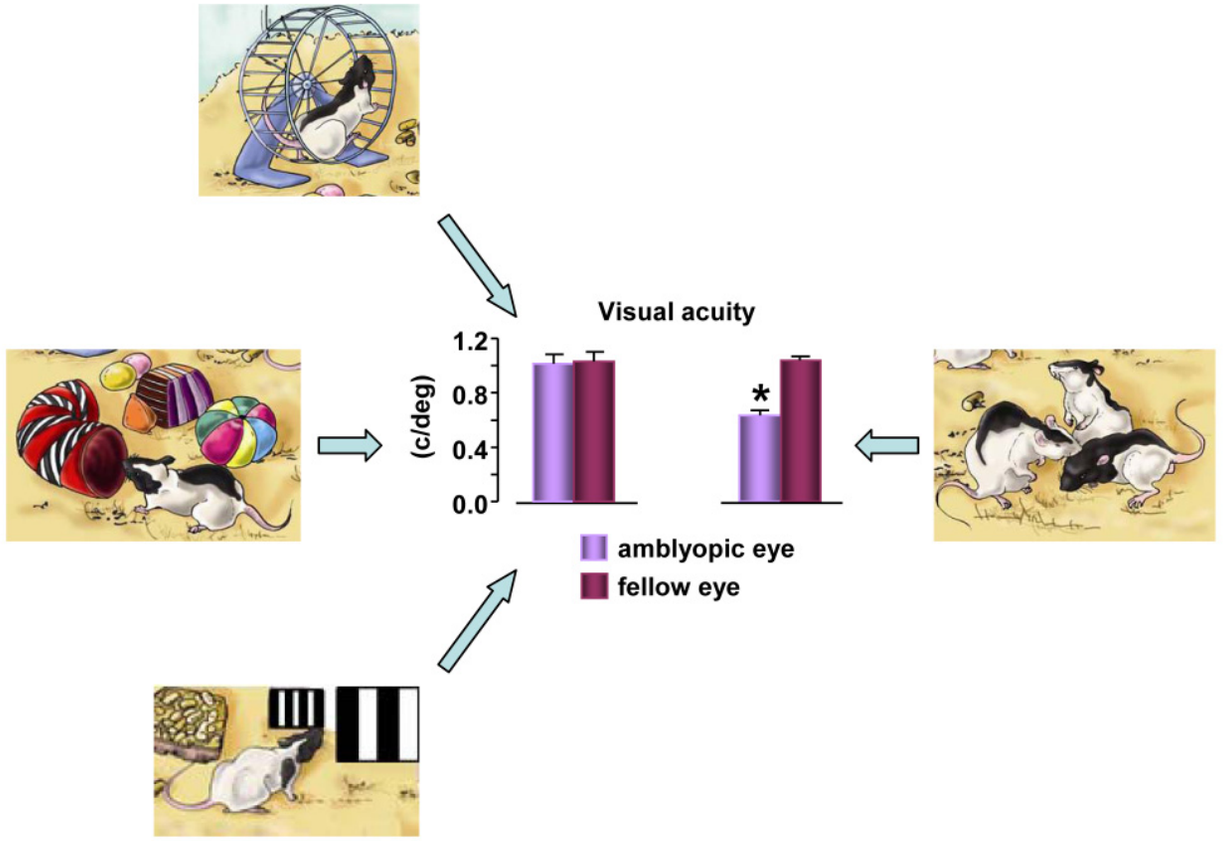

Figure 4. Impact of motor, social and sensory components on recovery from amblyopia in adult rats. Adult amblyopic rats were subjected for three weeks to either motor enrichment (consisting of a standard cage equipped with a running wheel connected to an automatic device recording the number of wheel turns), visual enrichment (consisting of a standard cage positioned at the centre of a rotating fluorescent drum where specific visual patterns were drawn), social stimulation (consisting of a slightly bigger standard cage where numerous rats where housed together), or visual perceptual learning (see Figure 5 for more details). A complete rescue of visual acuity in the amblyopic eye was achieved by rats performing physical exercise on a running wheel, in animals exposed to visual enrichment and in animals engaged in visual perceptual learning. This effect was also accompanied by a reduced inhibition/excitation balance in the visual cortex. In contrast, no recovery occurred in socially enriched rats or in animals practicing a purely associative visual task. Asterisk indicates statistical significance. Data replotted from Baroncelli et al. [114].

The cellular and molecular mechanisms underlying PL effects are still scarcely known. We reported that visual PL induces long-term potentiation (LTP) of intracortical synaptic responses in rat V1 [119], in agreement with Cooke and Bear [120]. 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 5A). This task requires activation of V1 circuitries, as indicated by the strong selectivity of PL for the orientation of gratings employed during training (Figure 5B). Control animals only learned the association task, i.e. they were only required to discriminate between a grating and a homogeneous grey panel, matching the overall swim time and number of training days in the water maze with those of PL rats (Figure 5A). Within 1 h 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 stimulating at the level of horizontal connections (stimulating electrode placed in layer II/III) (Figure 5A). Moreover, a significant shift toward increased amplitude of fEPSPs was found in the input/output curves of trained animals compared to controls. Thus, the data fulfill two of the most commonly accepted criteria used to relate LTP with learning, i.e.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 for LTP in mediating learning processes previously reported in other brain areas such as the amygdala, the hippocampus and the motor cortex [122-124]. 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 [125], 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 evidence on human subjects, 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, i.e. 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 [114] (Figure 5A). Recovery of visual abilities in PL animals was accompanied by a robust decrease of the inhibition-excitation balance, which could pave the way for future therapeutic attempts in humans based on a manipulation of the GABAergic tone. In line with this, repetitive transcranial magnetic stimulation, a treatment increasing cortical excitability, transiently improves contrast sensitivity in adult amblyopes [126].

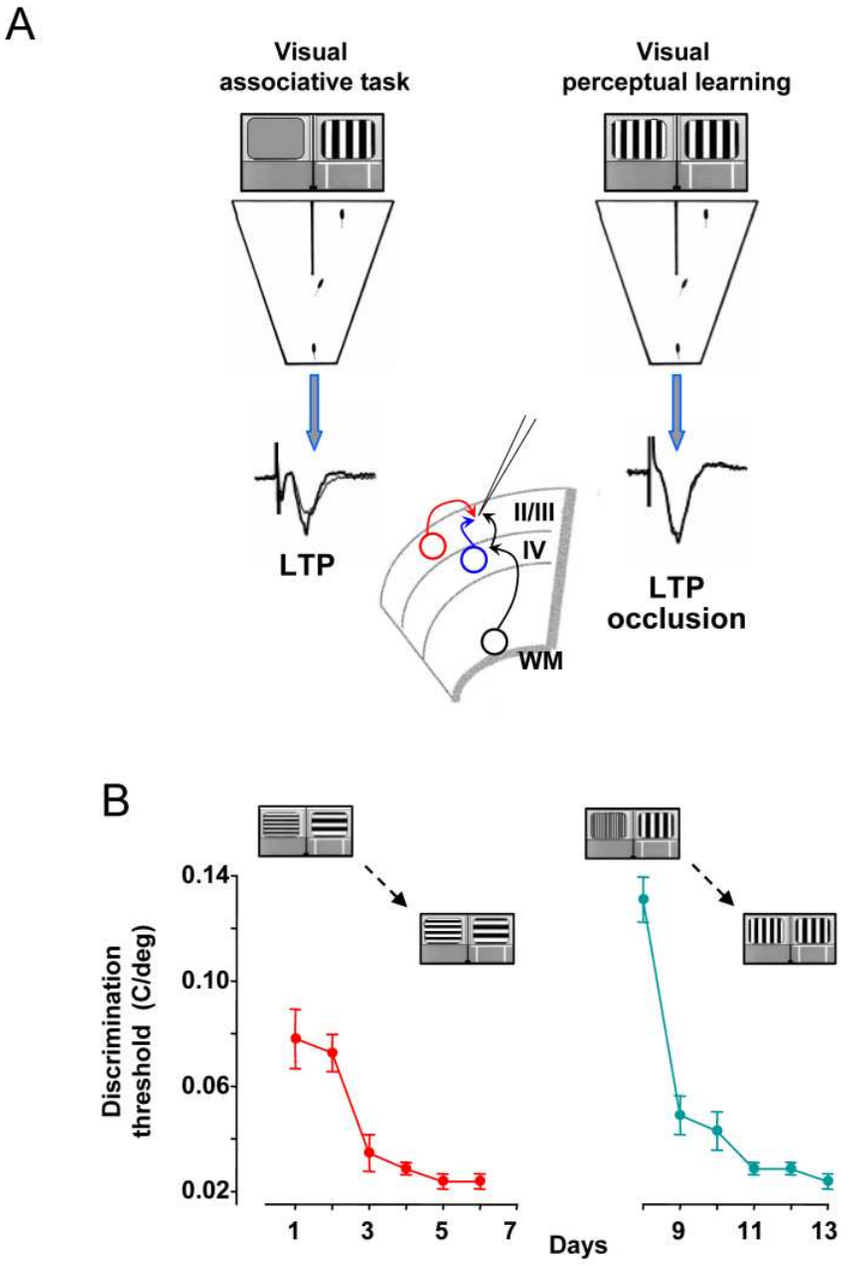

Figure 5. Visual perceptual learning induces long-term potentiation in the primary visual cortex. A) A modified version of the visual water box task [57, 121] was used to induce visual perceptual learning in a group of adult rats that were first trained to distinguish a low 0.117 cycles per degree (c/deg) 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 grey (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 min before (thin line) and 25 min 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. Data replotted from Sale et al. [119].

3.3. Serotonin: A master regulator of adult neural plasticity

The capability of EE to reinstate juvenile-like plasticity in the adult brain is not limited to its effects on amblyopia. Indeed, the visual cortex of enriched rats displays a remarkable reactivation of ocular dominance plasticity in response to MD [127, 128]. The ocular dominance shift of cortical neurons is detectable using both VEPs and single-unit recordings. While, also in this case, recovery of plasticity is paralleled by a marked reduction of the inhibitory tone and an increase in the number of BDNF-expressing neurons in the visual cortex, a crucial role for the neurotransmitter serotonin in triggering the plastic changes elicited by exposure to EE has been identified. Indeed, EE elicits a twofold enhancement of serotoninergic transmission in the visual cortex and infusion of a serotonin synthesis inhibitor not only blocks plasticity in response to MD but also completely counteracts the effects produced by EE on GABAergic inhibition and BDNF [127]. This led us to put forward a model in which serotonin, probably enhanced by a more sustained attention and arousal level promoted by living in the enriched condition, is the first trigger in the chain of plastic changes set in motion by EE, eliciting the decrease of GABA-mediated intracortical inhibition and, in parallel or in series, the enhancement of BDNF levels (Figure 6).

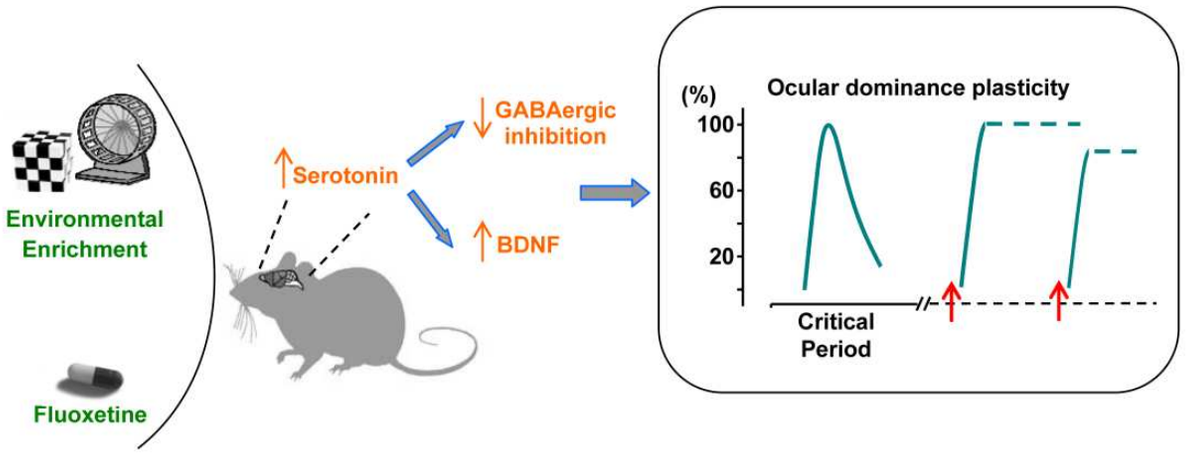

Figure 6. A critical role for serotonin in restoring ocular dominance plasticity in the adult visual cortex. Enhancing serotonergic transmission through exposure to environmental enrichment or administration of a chronic treatment with fluoxetine reinstates ocular dominance plasticity in adult rats. We propose a model in which serotonin drives a reduction of GABAergic inhibition and an increase in BDNF levels in the visual cortex. The graph on the right depicts the time course of the critical period for plasticity in response to monocular deprivation in rodents, and the reopening of plasticity achievable, though to a slightly reduced extent, at multiple distinct ages in adulthood (red arrows). Ocular dominance plasticity is normalized to the critical period peak's level.

The central role of serotonin in promoting adult visual cortex plasticity has been further demonstrated in animals chronically treated with fluoxetine, a selective serotonin reuptake inhibitor (SSRI) widely prescribed in the treatment of depression and various psychiatric disorders. The authors showed that fluoxetine delivered in the drinking water induces a full reinstatement of ocular dominance plasticity in response to MD (Figures 3 and 6) and a

complete recovery of visual functions from amblyopia. As found for enriched rats, these functional effects are associated with a marked reduction of GABAergic inhibition and are completely prevented by cortical Diazepam administration [129]. The reduction of inhibition triggered by fluoxetine provides a permissive environment for structural changes, such as the addition of new synapse-bearing branch spine tips [130]. In light of these promising results, fluoxetine appears to behave as a powerful enviromimetic [131], a drug that can be successfully exploited, alone or in combination with EE, to reproduce or to strengthen the positive effects elicited by the environment on brain health and plasticity.

4. Life-long beneficial outcome of EE: from developmental disorders to the aging brain

As underscored by the effects on amblyopia, the non invasive nature of EE makes this paradigm eligible for application in the domain of brain dysfunctions. The beneficial impact of EE does not only apply to the case of diseases deriving form alterations of sensory experience, but it also extends to genetically programmed states of brain disability.

One paradigmatic example is that of Down syndrome, the most common genetic cause of mental retardation [76] caused by triplication of chromosome 21. People with Down syndrome have a marked cognitive impairment [132, 133], and a number of attention and visual deficits [134-136] together with various disturbances in learning and memory abilities [132, 133]. The most widely animal study of Down syndrome is the Ts65Dn mouse, which carries triplication of a segment of Chr16, syntenic with human Chr21 [137, 138]. This model recapitulates the main hallmarks of the syndrome phenotype, including craniofacial abnormalities, impaired learning abilities and attention and visual function deficits (e.g., [139-141]. Moreover, in vivo cellular analyses, which are of course prevented in humans but easily conducted in the animal model, have allowed a substantial advancement in our knowledge concerning the mechanisms underlying neural impairments in Ts65Dn mice. In particular, a critical role for excessive levels of brain inhibition emerges, with an ensuing failure of long-term synaptic plasticity in the hippocampus [142-145]. This is in agreement with results obtained in post-mortem tissue from people with Down syndrome, which displays an impaired balance between excitatory and inhibitory systems (see [146]. The central role of overinhibition in Down syndrome pathogenesis is confirmed by the demonstration that administration of non-competitive antagonists of GABA-A receptors reverses spatial learning disabilities and LTP deficits in Ts65Dn mice [146]. Since EE is effective in reducing GABAergic inhibition, we have tested its potential for therapeutic application in the Ts65Dn model of the 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 [147].

On the opposite end of lifetime, severe functional deterioration can also occur during the aging process, across multiple systems including cognitive and sensory-motor domains. These deficits can, at least in part, be attributed to a progressive decay of neural plasticity in the elderly [148]. Interestingly, an enhanced environmental stimulation is able to restore ocular dominance plasticity not only in young adults [127], but also in the aging visual cortex, though to a slightly lower extent [149]. Plasticity in response to one week of MD is detectable at both the level of subthreshold modifications of postsynaptic potentials (by means of VEPs) and that of spike properties of cortical neurons (by means of single-unit recordings). In agreement to our previous results in younger animals, the number of GAD67+ cells was decreased while density of extracellular matrix PNNs increased in the visual cortex of aged enriched rats compared to age-matched standard-reared animals, demonstrating that the brain retains its capacity to undergo plastic changes elicited by a rich environmental experience without substantial changes in the underlying molecular machinery. This effect on neural plasticity offers an attractive explanation for the well known positive effects elicited by EE in the aging brain (e.g. [40, 148, 150]. Accordingly, intervention protocols aimed at promoting an active lifestyle in aging people should be encouraged.

5. Concluding remarks and future research lines

The data reviewed in this chapter have shown that EE is a powerful tool to modulate the development of the central nervous system and to boost plasticity in the adult cerebral cortex. The great success of this approach should not be hailed as a miracle, as it stands on the reliable EE ability to impact at multiple molecular substrate levels in the brain, including stimulation of maturational processes by enhanced activation of growth factors, reopening of plasticity windows through reduced intracortical inhibition and upregulation of plastic structural and functional changes by neurotrophin increments, which could in turn promote the expression of genes specifically involved in brain plasticity. We believe that the combination of a proper pharmacotherapy with non invasive strategies of environmental stimulation aimed at enhancing the spontaneous reparative potential held by the brain might emerge as the election curative approach for several neurological diseases.

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