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Insights into Visual Cortex Plasticity: Interaction Between Genes and Sensory Experience

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1. Introduction

The central nervous system architecture is highly dynamic and continuously modified by sensory experience through processes of neuronal plasticity. Interactions with the external world, mediated by sensory input, update and modify the structural and functional architecture of the nervous system, particularly during short-term sensitive periods in early life (critical period (CP) for brain plasticity) during which experience drives the consolidation of synaptic circuitries (Katz & Shatz 1996; Berardi et al., 2000; Levelt & Hubener 2012). However, experience-dependent reorganization of neuronal circuitries continues in adult life, at least to some extent.

The visual cortex (VC) is a classical model to examine the influence of sensory experience on brain structure and function. Early electrophysiological studies demonstrated that occlusion of one eye (monocular deprivation, MD) during the CP leads to an ocular dominance (OD) shift of visual cortical neurons, i.e., a decrease in the number of cells responding to the deprived eye that is accompanied by an increment of cells driven by the open eye (Wiesel & Hubel 1963; Hubel & Wiesel 1970; Frenkel & Bear 2004). In addition, the deprived eye becomes amblyopic: its spatial acuity and contrast sensitivity are markedly impaired. At structural level, unilateral eyelid suture causes a reduction in the arborisation of geniculocortical terminals that serve the deprived eye, which parallels an increased spread of terminals serving the open eye (Antonini & Stryker 1993). Because MD does not cause amblyopia in adult life this is a typical example of a CP. These findings highlight the notion that sensory experience is critical for normal development of the nervous system.

The importance of sensory experience in development of the human brain is well exemplified by cases of strabismic or anisometric children that underwent no clinical treatment during early development. In either pathological condition proper visual experience is altered, causing a marked impairment of normal visual functions (amblyopia)

that is irreversible if not treated before 8 years of age (Holmes & Clarke 2006; Friedman et al., 2009; Maurer & Hensch 2012). A similar phenomenon is described by clinical observations of children born with congenital cataracts, a pathological condition in which the lens of the eye becomes milky and therefore no longer permits images to form on the retina (Lloyd et al., 2007; Milazzo et al., 2011). The recovery of normal visual functions after long-term sensory deprivation has long been a subject of study with the prospect of finding therapies for human amblyopia. Although amblyopia can be prevented by different strategies that restore the formation of proper retinal images or by eye patching in early life, such treatments are normally ineffective in adulthood. These observations indicate that proper sensory experience during early stages of development is necessary for normal visual perception and also point towards the enhancement of neuronal plasticity as a strategy for brain repair in adult life.

2. Sensory experience triggers the maturation of inhibitory circuitries that control the time-course of the CP

Among the different factors that regulate the CP for VC plasticity, inhibitory processes seem to play a critical role. Visual experience seems to signal the time-course of the CP by promoting the transfer of the protein Otx2 from the retina to the VC, where Otx2 gradually promotes the maturation of parvalbumin-positive GABAergic interneurons (Sugiyama et al., 2008). An initial threshold of inhibition then triggers the CP in which neural networks are highly susceptible to sensory experience (Hensch et al., 1998; Fagiolini & Hensch 2000), while a second inhibitory threshold signals the end of this phase of enhanced plasticity (Huang et al., 1999). A direct demonstration that GABAergic inhibition is a crucial brake limiting VC plasticity derives from the recent observation that a pharmacological reduction of inhibitory transmission effectively restores OD plasticity in adulthood (Harauzov et al., 2010). This is consistent with the fact that experimental paradigms such as dark exposure (He et al., 2006), environmental enrichment (Baroncelli et al., 2010; Sale et al., 2010), food restriction (Spolidoro et al., 2011), long-term fluoxetine (FLX) administration (Maya-Vetencourt et al., 2008; Chen et al., 2011; Maya-Vetencourt et al., 2011), and exogenous IGF-I administration (Maya-Vetencourt et al., 2012), all promote plasticity late in life by reducing the intracortical inhibitory/excitatory (I/E) ratio. This has prompted the search for endogenous factors with the potential to enhance plasticity in adult life by modulating the intracortical I/E balance.

3. Long-distance projection systems regulate plasticity in the visual system

The major modulatory systems in the brain (i.e., noradrenaline, dopamine, histamine, acetylcholine, serotonin) regulate complex functions of the central nervous system such as cognition, behaviour, and neuronal plasticity. Experience-dependent modifications of cortical circuitries are not determined solely by local correlations of electrical activity but are

also influenced by attentional mechanisms (Singer 1995). Sensory signals, for instance, promote marked modifications of neural circuitries only when animals attend to the sensory input and use this information for the control of behaviour (Singer 1990, 1995). Early studies performed in cats demonstrated that changes of visual cortical circuitries in response to experience during early life, are lessened when noradrenergic (Kasamatsu & Pettigrew 1979; Bear & Singer 1986), cholinergic (Gu & Singer 1993) and serotonergic (Gu & Singer 1995; Wang et al., 1997) projections to the cortex are inactivated. Moreover, there is evidence that these neuromodulatory systems mediate forms of plasticity in the adult visual system of cats (Pettigrew & Kasamatsu 1978; Kasamatsu et al., 1979; Kasamatsu et al., 1985; Imamura & Kasamatsu 1991; Mataga et al., 1992) and rodents (Maya-Vetencourt et al., 2008; Baroncelli et al., 2010; Maya-Vetencourt et al., 2011).

Advances in the understanding of mechanisms by which neuromodulatory systems modulate experience-dependent plasticity derive from *in vitro* studies of synaptic plasticity. There is ample evidence that noradrenaline, acetylcholine and serotonin modulate two different forms of activity-dependent synaptic modifications: long-term potentiation (LTP) and long-term depression (LTD) (Kirkwood 2000). In the visual system, LTP and LTD can be induced by different patterns of electrical stimulation. Brief and strong episodes of high frequency stimulation promote LTP while prolonged low-frequency stimulation yields LTD. In the rodent VC, upon administration of noradrenaline and acetylcholine, weaker tetanic stimulation is required to induce LTP and shorter episodes of low frequency stimulation are needed to drive LTD (Brocher et al., 1992; Kirkwood et al., 1999). Likewise, serotonin facilitates the induction of both LTP and LTD in layer IV of the kitten VC (Kojic et al., 1997). Taken together, these findings are consistent with a role for neuromodulatory systems as enabling factors for visual cortical plasticity and indicate that activation of noradrenergic, cholinergic, and serotonergic receptors lowers the threshold of activity required for the induction of LTP and LTD. Intracellular mechanisms whereby neuromodulatory systems facilitate these forms of synaptic plasticity have been subject of extensive study. In the VC, the induction of LTP and LTD requires the activation of N-methyl-D-aspartate (NMDA) receptors together with a postsynaptic rise in intracellular calcium. The available evidence is consistent with a model in which the magnitude and duration of the calcium signal determines the magnitude of the synaptic modification (Bear 1996). Brief and large calcium influxes induce LTP, whereas smaller and prolonged calcium increases yield LTD. Of note, receptors of these three major neuromodulatory systems are able to activate the IP3 second messenger pathway, which can induce calcium release from intracellular stores and therefore modulate plasticity.

Because the intracortical inhibitory/excitatory (I/E) ratio is critical for the induction of neuronal plasticity in the visual system (Jiang et al., 2005; Sale et al., 2010), the neuromodulators-mediated fine-tuning of the I/E balance may also play a critical role for the induction of experience-dependent plasticity. In line with this, the enhanced action of serotonin and/or acetylcholine decreases the intracortical I/E balance in the rodent visual system (Amar et al., 2010; Moreau et al., 2010).

4. Non-visual components of the environment alter visual system development

In addition to MD, another classical paradigm used to assess the impact of experience in the functional maturation of the visual system is dark rearing (i.e., rearing animals in total darkness from birth). When dark-reared animals are brought back into the light, they turn out to be blind or, at least, display marked impairments of normal visual functions (Fagiolini et al., 1994). Total absence of visual experience delays the functional maturation of the striate cortex; an event that seems to be mediated by a down-regulation of BDNF expression (Castren et al., 1992), which results in a retarded maturation of GABAergic circuitries (Morales et al., 2002). The spatial resolution of visual cortical neurons is, in fact, reduced in dark-reared animals, this phenomenon being accompanied by longer latencies of responses to visual stimuli (Blakemore & Price 1987; Fagiolini et al., 1994). Moreover, visual cortical neurons have larger receptive field sizes and show alterations in the density of dendritic spines, which are shorter and fewer in dark-reared animals as compared to normally reared counterparts (Wallace & Bear 2004). Noteworthy, rearing animals in complete darkness extends the critical period far beyond its normal limits (Hensch 2005).

Although early studies of the visual system showed that sensory experience after eye opening is necessary for the functional maturation of the VC (Wiesel & Hubel 1963, 1963; Hubel & Wiesel 1970; LeVay et al., 1980), the notion that non-visual components of the environment can influence the structural and functional development of the visual system has been increasingly appreciated in the last few years. Experiments in dark-reared transgenic mice overexpressing BDNF, revealed a remarkable and unexpected finding: visual cortical neurons in these animals responded normally to visual stimuli, indicating that transgenic animals could see well despite the lack of visual experience during the CP (Gianfranceschi et al., 2003). This result was the first demonstration of a gene that could substitute for functional aspects caused by experience in the nervous system. These observations are in consonance with the fact that environmental enrichment, an experimental condition characterized by an increased exploratory behavior and sensory-motor stimulation, which increases BDNF signaling and enhances GABAergic inhibition during early stages of development, prevents the effects of dark rearing in the visual system (Bartoletti et al., 2004). Of note, environmental enrichment in normally reared animals accelerates the functional development of the VC, this phenomenon being accompanied by alterations in the expression of BDNF and GABA synthesizing enzymes well before eye opening (Cancedda et al., 2004). These findings further suggest that environmental influences on visual system development may be, at least in part, independent of visual experience.

5. Inter-hemispheric projections control visual cortical maturation and plasticity

Recent studies in the rodent VC have demonstrated a key role for inter-hemispheric, transcallosal projections in processes of visual cortical development and plasticity. In

rodents, as in other mammals, callosal terminals are particularly concentrated in the area of primary VC mapping the central part of the visual field (Mizuno et al., 2007), thus contributing to binding together the two representations of the visual hemifields in the two hemispheres. A crucial role for callosal input activity in the functional maturation of the VC was indicated by experiments in which activity was unilaterally blocked in the striate cortex during the CP. Transient blockade of synaptic activity arrested maturation of visual acuity not only in the treated, but also in the contralateral hemisphere (Caleo et al., 2007). The CP for plasticity was also extended in both hemispheres (Caleo et al., 2007). These findings indicate that maturation of the blocked cortex is superimposable to that of the opposite side. Since the contralateral hemisphere maintains normal vision through the retinogeniculate pathway and only lacks callosal input, these data point towards a fundamental role for callosal linkages in regulating the process of cortical maturation. Similar conclusions have been drawn from experiments in knockout mice with reduced callosal connectivity; when tested as adults, these animals display a reduced visual acuity and a persistent OD plasticity (Pinto et al., 2009). The notion that inter-hemispheric callosal projections play a key role in the maturation of visual functions is exemplified by experimental observations in cats and humans. Early sections of the callosum in kittens, indeed, cause a reduction in the behavioural measure of visual acuity (Elberger 1984). Consistently, patients with hemianopia show impairments in figure detection tasks also in the intact hemifield, suggesting that these deficits may be caused by the loss of inter-hemispheric interactions (Paramei & Sabel 2008).

Other studies have indicated a role for the callosum in determining both normal binocularity and the shift of OD that follows a period of monocular eyelid suture in juvenile rats. In rodents, retinogeniculate afferent input to the cortex from the contralateral eye is much stronger than that from the ipsilateral eye. Indeed, over 95% of retinal fibers decussate at the chiasm. However, cells mapping the central part of the visual field are highly binocular, and experiments support the view that callosal afferents contribute to this binocularity by providing input from the ipsilateral eye. In particular, acute inactivation of transcallosal input activity in rats shifts OD towards the contralateral eye (Diao et al., 1983), due to a loss of ipsilateral eye responses (Restani et al., 2009). In a complementary experiment, binocularity was recorded before and after acute inactivation of thalamocortical input to isolate visual responses driven exclusively by callosal afferents in young rats (Cerri et al., 2010). After blockade of the ipsilateral thalamus, cortical neurons display a dramatic loss of contralateral eye driven responses, while ipsilateral eye driven responses are reduced to a less extent (Cerri et al., 2010). These experiments indicate that in rats, a substantial fraction of the influence of the ipsilateral eye on cortical responses arrives via callosal connections from the opposite hemisphere, where it is the dominant eye.

Not only normal binocularity, but also the shift of OD that follows MD appears to depend on the function of callosal fibers. In particular, acute inactivation of transcallosal input activity restores binocularity after MD in juvenile rats (Restani et al., 2009). This recovery of binocularity following callosal silencing is due to an unexpected and selective increase in the strength of the deprived eye. Thus, acute removal of callosal influence following MD

unmasks deprived eye inputs. These data highlight the notion that callosal afferents act primarily to inhibit closed eye inputs during visual deprivation (Restani et al., 2009).

6. Structural plasticity in the visual system

Experience-dependent functional modifications in the visual system are accompanied by a structural remodeling of synaptic connectivity, in terms of growth and loss of dendritic spines. Dendritic spines in pyramidal neurons are markedly sensitive to experience as indicated by the observation that total lack of visual experience in early life induces modifications in spine morphology and density, both of which are partially reversible by light exposure (Wallace & Bear 2004). This is consistent with the observation that monocular deprivation in early life alters the motility, turnover, number and morphology of dendritic spines in the VC (Majewska & Sur 2003; Mataga et al., 2004; Hofer et al., 2009; Tropea et al., 2010).

Structural plasticity *in vivo* studies, using two-photon imaging, indicate that dendritic spine dynamics is high during early postnatal life but decreases thereafter, in parallel to the time-course of CP plasticity over development (Fu & Zuo 2011). This suggests that, despite the absence of large-scale remodeling of dendrites, the reorganization of cortical connections in terms of growth and loss of dendritic spines may be the structural substrate for experience-dependent plasticity. Notably, chronic imaging experiments have recently demonstrated that changes in VC responsiveness after monocular deprivation during the CP correlate with structural modifications in terms of dendritic spines across the binocular VC; these two features being reversed when the deprived eye was reopened. After brief periods of MD, spine turnover increased significantly, with a larger percentage of spines being lost rather than gained, whereas after a 24-hours period of recovery (visual experience) the baseline number of dendritic spines was gained again (Yu et al., 2011). Interestingly, increasing the density and dynamics of spines by intracortical infusion of the bacterial toxin CNF1, restores a degree of plasticity in the mature cortex that is similar to that observed during early postnatal life (Cerri et al., 2011).

It is worth mentioning that new synapses formation may increase memory storage capacity of the brain and that new dendritic spines may serve as structural traces for earlier memories, enabling the brain for faster adaptations to similar future experiences (Hofer et al., 2009; Xu et al., 2009). Recent experiments carried out using the MD paradigm seem to confirm this notion. Modifications of dendritic spines caused by a first experience of unilateral eyelid suture persist even after restoration of binocular vision and may therefore be involved in the enhancement of plasticity observed after a second episode of visual deprivation (Hofer et al., 2009).

The imaging studies mentioned above raise the question of whether structural modifications of dendritic spines represent functional changes of synaptic transmission. Electrophysiological experiments in hippocampal slice cultures indicate that AMPA- and NMDA-type glutamate receptor currents of newborn spines resemble that of mature synaptic contacts (Zito et al., 2009). Interestingly, it has been recently demonstrated that

dendritic spine dynamics regulate the stability of synaptic plasticity. The relationship between Calcium influx and spine size actually determines the long-term synaptic stability and synaptic strength distribution, at least in synapses of hippocampal CA3-CA1 pyramidal neurons (O'Donnell et al., 2011).

7. Epigenetics of visual cortex plasticity

Plasticity is achieved by a complex interplay of environmental influences and physiological mechanisms that ultimately set in motion intracellular signal transduction pathways directly regulating gene expression. Processes of chromatin remodeling that modulate gene transcription are, in fact, conserved mechanisms by which the mammalian's nervous system accomplishes adaptive behavioral responses upon environmental demands. In rodents, for instance, maternal care seems to influence behavioral and endocrine responses to stress in the offspring by modifying chromatin susceptibility to transcription (Francis et al., 1999).

The reorganization of cortical circuitries during early development requires the activation of sensory transduction pathways, which eventually mediate the expression of genes that act as downstream effectors of plastic phenomena. Studies performed in cats and rodents during the CP indicate that electrical activity and experience-dependent expression of neurotrophins cooperate to set in motion different protein kinases: extracellular-signal-regulated kinase (ERK1/2) (Di Cristo et al., 2001), cAMP-dependent protein kinase (PKA) (Beaver et al., 2001), and calcium/calmodulin-dependent protein kinase II (CaMKII) (Taha et al., 2002). The activation of these intracellular signal transduction pathways promotes the up-regulation of transcription factors that, in turn, mediate gene expression. A very well known activity-dependent mechanism is the activation of the transcription factor CREB, which triggers the expression of genes under control of the cAMP-response element (CRE) promoter, thus allowing phenomena of plasticity to occur (Pham et al., 1999). These findings are in consonance with the recent observation that visual experience during development promotes modifications of chromatin structure that are permissive for transcription, whereas a developmental down-regulation of histone post-translational modifications regulates the closure of the CP in the mouse visual system (Putignano et al., 2007).

In line with this notion, previous studies have demonstrated that the process of plasticity reactivation in the adult visual system is a multifactorial event that comprises the action of different cellular and molecular mechanisms, working in parallel or in series, the sum of which results in the activation of intracellular signal transduction pathways regulating the expression of plasticity genes (Putignano et al., 2007; Maya-Vetencourt et al., 2008; Bavelier et al., 2010; Morishita et al., 2010; Silingardi et al., 2010; Maya-Vetencourt et al., 2011; Maya-Vetencourt et al., 2012). Experimental paradigms based upon the manipulation of environmental stimulation levels, genetic manipulations, and pharmacological treatments in rodents have revealed that a complex interplay between the enhanced action of long-distance projection systems (e.g., serotonergic and cholinergic transmission) and IGF-I signaling seems to modulate the intracortical inhibitory/excitatory balance in favour of excitation (Amar et al., 2010; Moreau et al., 2010; Maya-Vetencourt et al., 2012), which, in

turn, set in motion cellular and molecular events that eventually mediate the expression of genes associated with functional modifications in the adult visual system. The reinstatement of adult VC plasticity caused by serotonergic transmission, for instance, is mediated by 5-HT_{1A} receptors signaling and accompanied by a transitory increment of BDNF expression. This is paralleled by an enhanced histone acetylation status at the activity-dependently regulated BDNF promoter regions and by a decreased expression of histone deacetylase enzymes (HDACs) (Maya-Vetencourt et al., 2011). In keeping with this, long-term treatment with HDACs inhibitors (e.g., Trichostatin-A, Valproic Acid and Sodium Butyrate) not only reinstates OD plasticity in adulthood (Putignano et al., 2007; Maya-Vetencourt et al., 2011) but also promotes full recovery of visual functions in adult amblyopic animals (Silingardi et al., 2010).

8. Cross-modal plasticity: Adaptive reorganization of neural networks

Sensory deprivation in one modality during early stages of development can have marked effects on the development of the remaining modalities. This phenomenon is known as cross-modal plasticity and is particularly epitomized by cases of congenital blindness or deafness from birth. In such instances, processes of cross-modal plasticity strengthen other sensory systems to compensate for the lack of vision or hearing.

Although clinical studies of deaf and blind humans have clearly demonstrated increased functional capabilities and compensatory expansion in the remaining sensory modalities (Bavelier & Neville 2002), the neurological bases for these plastic phenomena remain poorly understood. It has been reported that congenitally blind subjects show better sound localization abilities as compared to sighted individuals (Roder et al., 1999) and display better two-point tactile discrimination skills as well (Bavelier & Neville 2002). Moreover, studies that combine Braille reading and functional brain imaging revealed that early blind individuals show a strong activation of the primary VC during the Braille reading task (Sadato et al., 1996). Remarkably, the inactivation of the VC by means of transcranial electrical stimulation in blind people during Braille reading not only distorts tactile perceptions of blind subjects but also induces errors in Braille reading. These findings indicate that the VC seems to be recruited to process somatosensory information after congenital blindness (Cohen et al., 1997). Recent experimental evidence also suggests that congenital blindness enables visual circuitries to contribute to language processing (Bedny et al., 2011).

The question of whether there is a CP for cross-modal plasticity has also been addressed by examining the activation of visual cortical areas by Braille reading in early and late-onset blind individuals (blindness after 14 years of age). It has been reported that VC responsiveness to somatosensory stimuli is higher in congenitally blind and early-onset subjects as compared to the late-onset blind group (Cohen et al., 1999). These data indicate that there is a CP for the visual system to be recruited to a role in the processing of somatosensory information, which does not extend beyond 14 years of age in humans.

Phenomena of cross-modal plasticity have also been observed in the brain of deaf subjects. Functional magnetic resonance imaging studies have demonstrated that early deaf individuals use the primary auditory cortex alongside the visual system when they observe sign language (Lambertz et al., 2005). Although there is no hearing component to sign language, the auditory cortex is instead used to assist with visual and language processing. The effects of cochlear implants also provide another strategy to assess cross-modal plasticity in the deaf. Early deaf individuals, but not late-onset deaf subjects, actually display impairments in their ability to process language using a cochlear implant in adult life as the auditory cortex has been reshaped to deal with visual information and therefore it cannot deal as well with the new sensory input that the implant provides (Doucet et al., 2006).

There is evidence for potent cross-modal plastic interactions even during normal development. A recent series of experiments have demonstrated that enhancement of somatosensory stimulation in terms of body massage, affects development of another sensory modality, the visual system (Guzzetta et al., 2009). It has been reported that an enriched environment accelerates the structural and functional development of the rodent VC (Cancedda et al., 2004) and that enriching the environment in terms of tactile stimulation (body massage with a soft toothbrush) in rat pups effectively mimics the effects of enrichment on visual system development (Guzzetta et al., 2009). The massage protocol in the offspring of rats accelerated the maturation of visual functions and increased circulating levels of insulin-like growth factor 1 (IGF-I), whereas antagonizing IGF-I signaling by systemic injections of an IGF-I receptor antagonist prevented the effects of massage (Guzzetta et al., 2009). In keeping with this, enriching the environment in terms of body massage in human preterm infants accelerates the maturation of the visual system as indicated by an enhanced development of spatial acuity and, as in the offspring of rats, this phenomenon is accompanied by high IGF-I levels (Guzzetta et al., 2009). Taken together, these findings indicate that processes of cross-modal plasticity may be involved in the effects caused by environmental enrichment in VC development and portray the well-characterized visual system as a model to investigate the functional integration of two or more sensory modalities.

9. Achieving the recovery of sensory functions after long-term sensory deprivation

The recovery of normal visual functions after long-term sensory deprivation has long been a subject of study with the prospect of finding therapies for human amblyopia. In this context, perceptual learning has long been used to improve spatial acuity in adult amblyopic patients (Levi & Li 2009). Systematic training of patients with unilateral amblyopia (secondary to strabismus and anisometropia) in simple visual tasks revealed a 2-fold increase of contrast sensitivity and improved performance in letter-recognition tests (Polat et al., 2004). Likewise, Snellen acuities in anisometric amblyopes improved after intensive training in a Vernier acuity task. Moreover, video game playing appears to promote a significant rescue of visual functions in adult amblyopic patients. Playing video games for a short period of time using the amblyopic eye actually improves visual functions such as

spatial acuity and stereopsis (Li et al., 2011). The improvement of performance seen in perceptual learning is proportional to the number of trials taken, although performance eventually reaches an asymptote with no further progress (Huang et al., 2008). Unfortunately, the extent to which acuity improvements occur is limited by the task specificity of perceptual learning (Crist et al., 1997). In most instances of perceptual learning, attention to the trained stimulus is necessary for improvements of vision to occur (Ahissar & Hochstein 1993). This observation is particularly important as it epitomizes the role of diffuse projection systems in the physiological state of arousal, which regulates mechanisms of attention and information processing that may contribute to functional changes of neural circuitries in the adult brain. Such notion points toward the possibility to pharmacologically enhance plasticity as a strategy for brain repair, which could facilitate restructuring of mature circuitries impaired by damage or disease.

10. Conclusion

The ability of the brain to change functionally in response to experience is most active during early stages of development but it decreases later in life when major alterations in neuronal network structures no longer take place in response to experience. For decades it has been believed that the plastic potential of the adult nervous system is insufficient to allow the recovery of lost sensory functions following long-term deprivation. Therefore, treatments for human amblyopia were generally not undertaken in older children and adults. However, novel experimental data obtained in animal models have demonstrated the effectiveness of different pharmacological treatments and experimental paradigms based upon manipulation of environmental input levels in restoring plasticity to the adult nervous system. In light of these findings, one can speculate that the beneficial effects exerted by these treatments could be exploited for clinical application. Since deterioration in functional plasticity contributes to the pathogenesis of several brain diseases, environmental enrichment (Baroncelli et al., 2010), food restriction (Spolidoro et al., 2011), brief dark exposure (He et al., 2006), long-term fluoxetine treatment (Maya-Vetencourt et al., 2008; Chen et al., 2011; Maya-Vetencourt et al., 2011) and exogenous IGF-I administration (Maya-Vetencourt et al., 2012), all of which reactivate adult brain plasticity, arise as potential therapeutic strategies for pathological conditions, such as human amblyopia, in which reorganization of neural circuitries would be beneficial in adult life. These therapeutic approaches bear some similarity to the interventions that have proved successful in promoting recovery from other pathological conditions such as stroke (Maurer & Hensch 2012). Fluoxetine treatment, indeed, enhances the effects of rehabilitation in the recovery from motor deficits after ischaemic stroke in humans (Chollet et al., 2011).

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